Aspects of the Chemistry of 6-Diazopenicillanate *S*-Oxide and *S,S*-Dioxide

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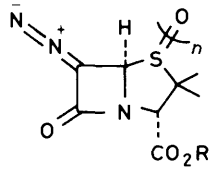
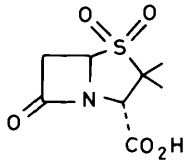
Procedures are developed for the preparation of 6-diazopenicillanate *S*-oxides and *S,S*-dioxides from the corresponding 6-phenylacetamidopenicillanates by *N*-nitrosation and thermal decomposition of the intermediate *N*-nitroso amides. The chemistry of these 6-diazopenicillanate *S*-oxides and *S,S*-dioxides was then briefly investigated, their reactions with pseudohalogens, alcohols, thiols, phenylseleno compounds, and aromatic aldehydes being examined. In some cases the products from these reactions were rearranged into the corresponding cepham or cephem derivatives.

The chemistry of 6-diazopenicillanates (**1**) has been widely studied and found to provide synthetically useful routes to a range of novel penicillanates with a wide variety of substituents at C-6.[1] We now report some preliminary results on the chemistry of 6-diazopenicillanate *S*-oxides (**2**) and *S,S*-dioxide (**3**). This investigation was carried out for two reasons. First, it was envisaged that a study of the chemistry of the 6-diazo *S*-oxide (**2**) would provide a range of novel 6-substituted



(**1**) *n* = 0
(**2**) *n* = 1
(**3**) *n* = 2



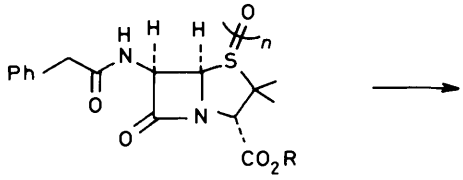
(**4**)

penicillanate *S*-oxides which could be rearranged to provide new cephalosporanates.[2] Secondly it was hoped to prepare a range of 6-substituted penicillanate *S,S*-dioxides whose biological activity would be of interest in view of the β-lactamase inhibition activity of the parent system (**4**).[3]

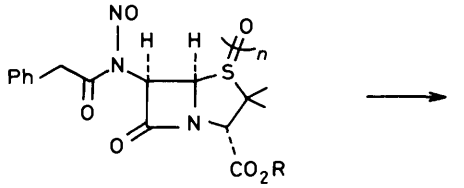
preparation of 2,2,2-trichloroethyl 6-diazopenicillanate (**1**; R = CH_2CCl_3) a practical route to the 6-diazo *S*-oxides and *S,S*-dioxides, would be *via* *N*-nitrosation of the analogous 6-phenylacetamidopenicillanates,[5] although earlier attempts at this procedure had not been encouraging.[6]

Results and Discussion

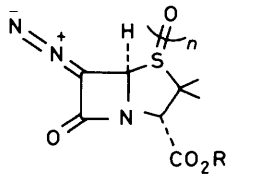
It was found that the 6β-phenylacetamidopenicillanate (1*S*)-*S*-oxides (**5**) and (**6**), and the analogous sulphone (**7**), could be nitrosated efficiently by adding a solution of dinitrogen tetraoxide in dichloromethane batchwise to a solution of the penicillanate in dichloromethane at −5 °C buffered by sodium acetate. The *N*-nitroso amides (**8**)—(**10**) were not isolated; instead after removal of excess of dinitrogen tetraoxide the dichloromethane solution of the *N*-nitroso compound was heated under reflux to effect decomposition. The 6-diazopenicillanates (**11**)—(**13**) were then isolated in good overall yields as crystalline products and characterized spectroscopically. Their i.r. spectra all showed characteristic diazo stretching absorption bands at *ca.* 2 200 cm^{-1} and of some interest was the chemical shift of 5-H in their ^1H n.m.r. spectra. It was observed that this proton was shielded along the series sulphide (**1**; R = CH_2CCl_3) δ 6.22, sulphoxide (**11**) δ 5.85, and sulphone (**13**) δ 5.48 p.p.m. The reactions of the 6-diazo-



(**5**) *n* = 1, R = TCE
(**6**) *n* = 1, R = Me
(**7**) *n* = 2, R = TCE



(**8**) *n* = 1, R = TCE
(**9**) *n* = 1, R = Me
(**10**) *n* = 2, R = TCE



(**11**) *n* = 1, R = TCE
(**12**) *n* = 1, R = Me
(**13**) *n* = 2, R = TCE

Pivaloyloxymethyl 6-diazopenicillanate (**1**; R = CH_2OCOBu^t) has been oxidized using *m*-chloroperoxybenzoic acid to provide the diazo *S*-oxides (**2**; R = CH_2OCOBu^t), but the oxidation was not stereoselective, a 1 : 1 mixture of the (1*R*)- and (1*S*)-*S*-oxides being obtained.[4] The 1β-*S*-oxide of the *p*-nitrophenyl 6-diazopenicillanate (**2**; R = *p*-$NO_2C_6H_4$) has been described as crystalline, but no details of its preparation are available.[5] It was felt that by analogy with the efficient penicillanates (**11**)—(**13**) with alcohols and thiols were then investigated.

Initial studies on the decomposition of the 6-diazopenicillanate sulphoxide (**11**) in methanol using boron trifluoride–diethyl ether and copper bis(acetoacetonate) as catalysts gave a complex mixture of products.[7] However when rhodium acetate was used as the catalyst in the presence of a base (1,5-diazabicyclo[4.3.0]non-5-ene), a modest yield (18%) of the 6α-methoxypenicillanate (**14**) was obtained. Under these conditions in ethanol, a better yield (49%) of the analogous 6α-ethoxypenicillanate (**15**) was also isolated. These 6α-alkoxypenicillanates were identified from spectroscopic data, the 6α-configuration being assigned on the basis of the

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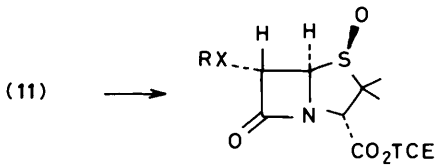
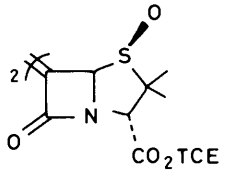


(14) R = Me, X = O
(15) R = Et, X = O
(16) R = $PhCH_2CO$, X = O
(17) R = Et, X = S
(18) R = $PhCH_2$, X = S

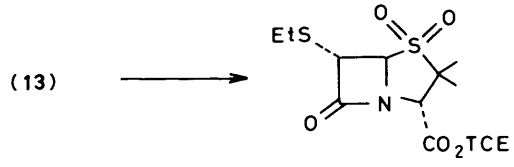


(19)

small 5-H,6-H proton coupling constant *ca.* 2 Hz. When the reaction in methanol was carried out in the absence of base, a different product was isolated in low yield, and identified as a penicillanate *S*-oxide dimer (**19**). More efficient routes to this compound, together with structural data, are presented in the following paper.[8]

The 6-diazopenicillanate *S*-oxide (**11**) was also found to react with phenylacetic acid under the same conditions as with alcohols, to afford a low yield (10%) of the 6α-phenylacetoxypenicillanate *S*-oxide (**16**) together with the penicillanate *S*-oxide dimer (**19**) (22%). Similarly the reactions with thiols, *e.g.* ethanethiol and toluenethiol, gave 6α-alkylthiopenicillanates (**17**) (52%) and (**18**) (23%), although it was not necessary to add base to these reactions.[7]

The ethanethiol reaction was also applied to the 6-diazopenicillanate *S,S*-dioxide (**13**). In this case a single β-lactam was isolated and identified as the 6α-ethylthiopenicillanate *S,S*-dioxide (**20**) (40%).



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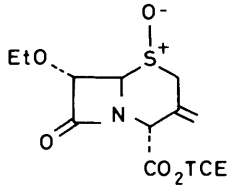

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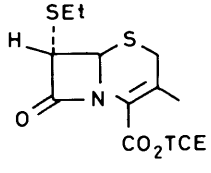
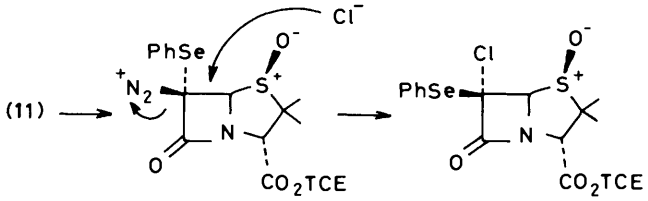


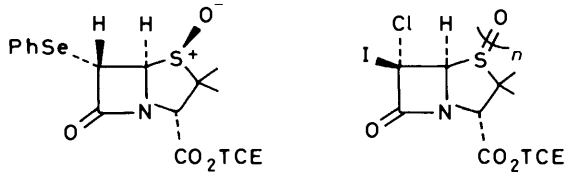
(22)

Ring expansion reactions of the 6α-ethoxy- and 6α-ethylthiopenicillanate *S*-oxides (**15**) and (**17**) were then briefly examined. It was found that on treatment with *N*-chlorosuccinimide and stannic chloride in carbon tetrachloride, the 6α-ethoxypenicillanate *S*-oxide (**15**) rearranged to provide the 2,2,2-trichloroethyl 7α-ethoxy-3-methylenecepham *S*-oxide (**21**) (64%).[9] A single *S*-oxide isomer was isolated but the available data did not establish the *S*-oxide configuration. In contrast treatment of the 6α-ethylthiopenicillanate *S*-oxide (**17**) with *N*-chlorosuccinimide and stannic chloride in carbon tetrachloride did not afford the expected 3-methylenecepham. However ring-expansion of this compound was achieved by heating it with excess of acetic anhydride under reflux in dimethylformamide.[10] A single β-lactam product was isolated and identified as the 7α-ethylthiocephem (**22**) (57%).

The next reactions of the 6-diazopenicillanate *S*-oxide (**11**) to be investigated were those with phenylseleno compounds and with mixed halogens, since it was hoped that the reduction of the 6-substituted products so obtained using tributyltin hydride would provide novel 6β-substituted penicillanate *S*-oxides.[11] Benzeneselenenyl chloride was found to react cleanly with the 6-diazopenicillanate *S*-oxide (**11**) even in the absence of catalyst. A single product was isolated and identified as the 6-chloro-6-phenylselenopenicillanate *S*-oxide (**24**) (65%). The C-6 configuration of this product was not established, but that shown is consistent with stereoselective attack of the benzeneseleno chloride on the less hindered α-face of the diazo-compound, followed by loss of nitrogen with inversion of configuration at C-6, see (**23**). The 6-diazopenicillanate *S*-oxide (**11**) was also found to react with benzeneselenol in the presence of a rhodium acetate catalyst, to provide the 6α-phenylselenopenicillanate (**25**) (32%), the C-6-configuration in this case being assigned on the basis of the 5-H,6-H proton coupling, *ca.* 2 Hz. Finally it was found that treatment of the 6-diazopenicillanate *S*-oxide (**11**) with iodine monochloride gave a mixture of the 6-chloro-6-iodopenicillanate *S*-oxide (**26**) (49%) and the corresponding sulphide (**27**) (8%) which would appear to have been formed by reduction of the sulphoxide by ICl. This minor product was



(23) (24)

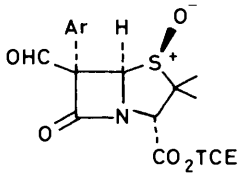


(25) (26) *n* = 1 (27) *n* = 0

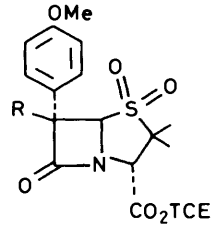
prepared more efficiently by treatment of the trichloroethyl 6-diazopenicillanate (**1**; R = CH_2CCl_3) with iodine monochloride. Again the configurations of these products at C-6 were not formally established, but that shown is consistent with attack of iodine monochloride onto the less hindered α-face of the 6-diazopenicillanates, followed by loss of nitrogen with inversion of configuration as C-6, *cf.* (**23**). The corresponding 6-chloro-6-iodopenicillanic acid has been prepared from 6-APA, sodium nitrite, and ICl, and its methyl ester is also known.[12]

The next group of reactions of the 6-diazopenicillanate *S*-oxide (**11**) and *S,S*-dioxide (**13**) to be investigated were those with aldehydes and ketones. Boron trifluoride-catalysed reactions with aromatic aldehydes were found to follow those of the analogous 6-diazo sulphide.[1] Thus on addition of boron trifluoride–diethyl etherate to a solution of the diazo *S*-oxide

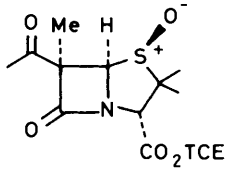
(**11**) and 4-methoxybenzaldehyde in dichloromethane, rapid evolution of nitrogen was observed and the 6β-formylpenicillanate (**28**) could be isolated (35%). The diazo *S,S*-dioxide (**13**) similarly gave the 6β-formylpenicillanate *S,S*-dioxide (**30**) (35%), which was reduced using sodium borohydride to the corresponding alcohol (**31**), but only in modest yield (12%). The 6-diazo *S*-oxide (**11**) was also treated with furfuraldehyde and with acetone in the presence of boron trifluoride–diethyl ether to give the 6β-formyl-6α-furylpenicillanate (**29**) (39%), and the 6β-acetyl-6α-methylpenicillanate (**32**) (10%), respectively. These 6-acylpenicillanate *S*-oxides and *S,S*-dioxide (**28**)—(**32**) were found to be more stable than the corresponding sulphides.



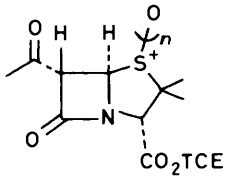
(**28**) Ar = 4-$MeOC_6H_4$
(**29**) Ar = 2-furyl



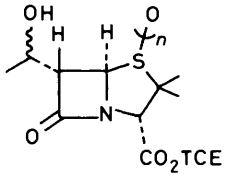
(**30**) R = CHO
(**31**) R = CH_2OH



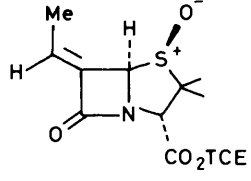
(**32**)



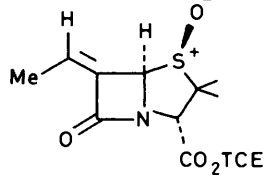
(**33**) *n* = 0
(**34**) *n* = 1



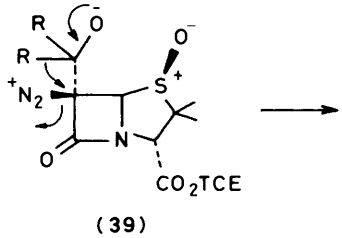
(**35**) *n* = 0
(**36**) *n* = 1



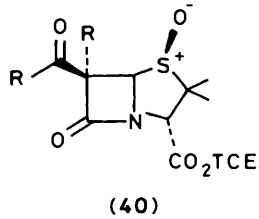
(**37**)



(**38**)



(**39**)



(**40**)

However treatment of the 6-diazopenicillanate *S*-oxide (**11**) with acetaldehyde in the presence of anhydrous zinc chloride, a procedure known to be effective for the preparation of the 6α-acetylpenicillanate (**33**) from the diazo sulphide (**1**; R = CH_2CCl_3),[13] was not successful, no identifiable products being obtained. The 6α-acetylpenicillanate *S*-oxide (**34**) was prepared however by peracid oxidation of the sulphide (**33**). This oxosulphide was also reduced using an excess of dimethylamine–borane in the presence of magnesium bis(trifluoroacetate) to give an inseparable mixture of the 6-hydroxyethylpenicillanates (**35**), ratio, 1.2:1, which was oxidized to provide the *S*-oxides (**36**) (84%), and the hydroxy sulphoxides dehydrated (mesyl chloride, triethylamine; K_2CO_3) to give the 6-ethylidenepenicillanate *S*-oxides (**37**) and (**38**) ratio *ca.* 4:1.

Mechanistic aspects of these 6-diazo *S*-oxide and *S,S*-dioxide reactions were not investigated. The boron trifluoride–diethyl ether-catalysed reactions with aromatic aldehydes and acetone may involve rearrangement of an intermediate zwitterion as shown in (**39**). These reactions appeared to be quite stereoselective, only the 6β-acyl products being isolated.

Experimental

For general experimentals details see the first full paper in this series.

2,2,2-*Trichloroethyl* 6-*Diazopenicillanate* (1S)-S-*Oxide* (**11**).—Dinitrogen tetraoxide (1.92 g, 21 mmol) was solidified at −78 °C and dissolved in dichloromethane (30 ml). Half of this solution was added to trichloroethyl 6β-phenylacetamidopenicillanate (1*S*)-*S*-oxide (**5**) (3.35 g, 7 mmol) and anhydrous sodium acetate (6.28 g, 76 mmol) in dichloromethane (50 ml), and the mixture stirred for 2 h at −5 °C. The remaining dinitrogen tetraoxide was then added, and the stirring continued for a further 2.5 h at −5 °C. The mixture was then added slowly to an aqueous solution of rapidly stirred sodium hydrogen carbonate (8.4 g, 0.1 mol) over a period of 30 min. The organic layer was then separated, washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml) and water (1 × 100 ml), dried ($MgSO_4$), and concentrated under reduced pressure to *ca.* 50 ml. This solution of nitrosated penicillanate (**8**) was then heated under reflux for 3 h, cooled, washed with saturated aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). Concentration under reduced pressure gave 2,2,2-*trichloroethyl* 6-*diazopenicillanate* (1S)-S-*oxide* (**11**) (2.27 g, 84%), yellow crystals, m.p. 144—146 °C (Found: M^+, 372.9455. $C_{10}H_{10}{}^{35}Cl_3N_3O_4S$ requires *M*, 372.9457); $\nu_{max.}$($CHCl_3$) 2 220, 1 760, 1 740, and 1 060 cm^{-1}; δ_H($CDCl_3$) 1.35 and 1.78 (each 3 H, s, Me), 4.52 (1 H, s, 3-H), 4.65 and 5.07 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), and 5.85 (1 H, s, 5-H); *m/z* 373 (M^+).

Methyl 6-*Diazopenicillanate* (1S)-S-*Oxide* (**12**).—Methyl 6β-phenylacetamidopenicillanate *S*-oxide (**6**) (2.2 g, 6 mmol) was nitrosated using dinitrogen tetraoxide (1.67 g, 18 mmol) following the procedure described above, except that the reaction was carried out over a period of 8.5 h. The nitrosation was worked up as described above, and the solution of the *N*-nitrosopenicillanate (**9**) in dichloromethane heated under reflux for 3 h. Work-up as above gave *methyl* 6-*diazopenicillanate* (1S)-S-*oxide* (**12**) (1.23 g, 79%), yellow crystals, m.p. 119—121 °C (Found: M^+, 257.0469. $C_9H_{11}N_3O_4S$ requires *M*, 257.0469); $\nu_{max.}$($CHCl_3$) 2 100, 1 770, 1 750, and 1 060 cm^{-1}; δ_H($CDCl_3$) 1.27 and 1.69 (each 3 H, s, Me), 3.82 (3 H, s, OMe), 4.39 (1 H, s, 3-H), and 5.83 (1 H, s, 5-H); *m/z* 257 (M^+).

2,2,2-*Trichloroethyl* 6-*Diazopenicillanate* S,S-*Dioxide* (**13**).—The 6β-phenylacetamidopenicillanate *S,S*-dioxide (**7**) (0.69 g, 1.39 mmol) was nitrosated as above using dinitrogen tetraoxide (0.5 g, 5.43 mmol) over a period of 6.5 h. The intermediate *N*-nitroso compound was decomposed in dichloromethane, and heated under reflux for 3 h to provide 2,2,2-*trichloroethyl* 6-

diazopenicillanate S,S-*dioxide* (**13**) (0.45 g, 80%), pale yellow crystals, m.p. 133—135 °C; $\nu_{max.}$($CHCl_3$) 2 200, 1 810, 1 760, 1 280, and 1 160 cm^{-1}; δ_H($CDCl_3$) 1.53 and 1.70 (each 3 H, s, Me), 4.38 (1 H, s, 3-H), 4.67 and 5.03 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), and 5.48 (1 H, s, 5-H); *m/z* 325 ($M^+ - SO_2$).

2,2,2-*Trichloroethyl* 6α-*Methoxypenicillanate* (1S)-S-*Oxide* (**14**).—Diazabicyclo[4.3.0]non-5-ene (6 mg, 0.04 mmol) and rhodium acetate (few crystals) in methanol (2 ml) was added to the 6-diazopenicillanate *S*-oxide (**11**) (150 mg, 0.4 mmol) in dichloromethane (5 ml) and methanol (10 ml). Nitrogen was evolved, and after 1 h, the solution was concentrated under reduced pressure to give an oil which was chromatographed on silica, using ethyl acetate–light petroleum (1:1) as eluant, to provide 2,2,2-*trichloroethyl* 6α-*methoxypenicillanate* (1S)-S-*oxide* (**14**) (27 mg, 18%), m.p. 95—97 °C (from ethyl acetate–light petroleum) (Found: M^+, 376.9658. $C_{11}H_{14}{}^{35}Cl_3NO_5S$ requires *M*, 376.9658); $\nu_{max.}$($CHCl_3$) 1 790, 1 770, and 1 060 cm^{-1}; δ_H($CDCl_3$) 1.34 and 1.76 (each 3 H, s, Me), 3.59 (3 H, s, OMe), 4.63 (1 H, s, 3-H), 4.67 and 5.03 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), and 5.0 (2 H, overlapping, d, *J* 1.8 Hz, 5- and 6-H); *m/z* 377 (M^+).

2,2,2-*Trichloroethyl* 6α-*Ethoxypenicillanate* (1S)-S-*Oxide* (**15**).—6-Diazopenicillanate (**11**) (200 mg, 0.53 mmol) in dichloromethane (10 ml) was treated with ethanol (10 ml) diazabicyclo[4.3.0]non-5-ene (8 mg, 0.05 mmol), and rhodium acetate (few crystals), in ethanol (3 ml) as above to give 2,2,2-*trichloroethyl* 6α-*ethoxypenicillanate* (1S)-S-*oxide* (**15**) (102 mg, 49%), m.p. 129—130 °C (from ethyl acetate–light petroleum) (Found: M^+, 390.9833. $C_{12}H_{16}NO_5S^{35}Cl_3$ requires *M*, 390.9814); $\nu_{max.}$($CHCl_3$) 1 780, 1 760, and 1 040 cm^{-1}; δ_H($CDCl_3$) 1.33 and 1.76 (each 3 H, s, Me), 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2), 3.8 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.62 (1 H, s, 3-H), 4.67 and 5.03 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), 4.98 (1 H, d, *J* 2 Hz, 6-H), and 5.02 (1 H, d, *J* 2 Hz, 5-H); *m/z* 391 (M^+).

2,2,2-*Trichloroethyl* 6α-*Phenylacetoxypenicillanate* (1S)-S-*Oxide* (**16**).—6-Diazopenicillanate (**11**) (150 mg, 0.4 mmol), phenylacetic acid (272 mg, 2 mmol), rhodium acetate (a few crystals), and diazabicyclo[4.3.0]non-5-ene (6 mg, 0.04 mmol) in dichloromethane (2 ml) gave, following the procedure described above, a yellow oil which was separated into two products using chromatography on silica gel. The less polar product was identified as 2,2,2-*trichloroethyl* 6α-*phenylacetoxypenicillanate* (1S)-S-*Oxide* (**16**) (18 mg, 10%), a colourless oil; $\nu_{max.}$($CHCl_3$) 1 800, 1 750, and 1 050 cm^{-1}; δ_H($CDCl_3$) 1.30 and 1.76 (each 3 H, s, Me), 3.72 (2 H, s, PhCH_2), 4.66 and 5.05 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), 4.67 (1 H, s, 3-H), 4.97 (1 H, d, *J* 2 Hz, 6-H), 5.81 (1 H, d, *J* 2 Hz, 5-H), and 7.3 (5 H, m, ArH); *m/z* 481. The more polar product was identified as the dimer (**19**) (22 mg, 16%).[8]

2,2,2-*Trichloroethyl* 6α-*Ethylthiopenicillanate* (1S)-S-*Oxide* (**17**).—Ethanethiol (207 mg, 3.34 mmol) and rhodium acetate (a few crystals) were added to the 6-diazopenicillanate (**11**) (250 mg, 0.67 mmol) in dichloromethane (20 ml). After 1 h the mixture was washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give an oil, which was purified by chromatography on silica using ethyl acetate–light petroleum (3:7) as eluant, to give 2,2,2-*trichloroethyl* 6α-*ethylthiopenicillanate* (1S)-S-*oxide* (**17**) (142 mg, 52%), a colourless oil (Found: M^+, 406.9596. $C_{12}H_{16}NO_4S_2{}^{35}Cl_3$ requires *M*, 406.9586); $\nu_{max.}$($CHCl_3$) 1 790, 1 770, and 1 040 cm^{-1}; δ_H($CDCl_3$) 1.33 and 1.78 (each 3 H, s, Me), 1.36 (3 H, t, *J* 8 Hz, CH_3CH_2), 2.77 (2 H, q, *J* 8 Hz, CH_3CH_2), 4.52 (1 H, d, *J* 2 Hz, 6-H), 4.66 (1 H, s, 3-H), 4.67 and 5.00 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), and 4.89 (1 H, d, *J* 2 Hz, 5-H); *m/z* 407 (M^+).

2,2,2-*Trichloroethyl* 6α-*Benzylthiopenicillanate* (1S)-S-*Oxide* (**18**).—Following the procedure outlined above, 6-diazopenicillanate (**11**) (200 mg, 0.53 mmol) and toluenethiol (34 mg, 2.67 mmol) gave, after chromatography, 2,2,2-*trichloroethyl* 6α-*benzylthiopenicillanate* (1S)-S-*oxide* (**18**) (58 mg, 23%), a colourless oil (Found: M^+, 468.9753. $C_{17}H_{18}{}^{35}Cl_3NO_4S_2$ requires *M*, 468.9742); $\nu_{max.}$($CHCl_3$) 1 790, 1 770, and 1 050 cm^{-1}; δ_H($CDCl_3$) 1.35 and 1.72 (each 3 H, m, Me), 3.91 (2 H, s, PhCH_2), 4.32 (1 H, d, *J* 2 Hz, 6-H), 4.49 (1 H, d, *J* 2 Hz, 5-H), 4.61 (1 H, s, 3-H), 4.65 and 5.03 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), and 7.36 (5 H, m, ArH); *m/z* 469 (M^+).

2,2,2-*Trichloroethyl* 6α-*Ethylthiopenicillanate* S,S-*Dioxide* (**20**).—Following the procedure outlined above, 6-diazopenicillanate sulphone (**13**) (210 mg, 0.53 mmol) and ethanethiol (166 mg, 2.67 mmol) gave, after chromatography, 2,2,2-*trichloroethyl* 6α-*ethylthiopenicillanate* S,S-*dioxide* (**20**) (91 mg, 40%), a colourless oil (Found: M^+, 422.9540. $C_{12}H_{16}{}^{35}Cl_3NO_5S_2$ requires *M*, 422.9534); $\nu_{max.}$($CHCl_3$) 1 800, 1 770, 1 330, and 1 160 cm^{-1}; δ_H($CDCl_3$) 1.51 and 1.68 (each 3 H, s, Me), 1.35 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.74 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.55 (1 H, s, 3-H), 4.55 (1 H, d, *J* 1.5 Hz, 6-H), 4.63 (1 H, d, *J* 1.5 Hz, 5-H), and 4.69 and 4.97 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$); *m/z* 423 (M^+).

2,2,2-*Trichloroethyl* 7α-*Ethoxy*-3-*methylenecepham* S-*Oxide* (**21**).—*N*-Chlorosuccinimide (140 mg, 1.04 mmol) was added to 2,2,2-trichloroethyl 6α-ethoxypenicillanate *S*,*S*-oxide (**15**) (237 mg, 0.7 mmol) in carbon tetrachloride (20 ml), and the mixture heated under reflux for 5 h before being cooled and filtered. Stannic chloride (272 mg, 1.04 mmol) was added to the filtrate and the solution was stirred for 17 h. The mixture was then washed with water extracted into $CHCl_3$, and dried ($MgSO_4$). The solution was concentrated under reduced pressure to leave a white solid (175 mg, 64%) which was recrystallized to give 2,2,2-*trichloroethyl* 7α-*ethoxy*-3-*methylenecepham* S-*oxide* (**21**) (135 mg, 49%), m.p. 129—130 °C (from chloroform–cyclohexane) (Found: M^+, 388.9656. $C_{12}H_{14}{}^{35}Cl_3NO_5S$ requires *M*, 388.9656); $\nu_{max.}$($CHCl_3$) 1 760 and 1 040 cm^{-1}; δ_H($CDCl_3$) 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2), 3.73 (4 H, m, CH_3CH_2 + SCH_2), 4.72 (1 H, d, *J* 2 Hz, 7-H), 4.78 and 4.89 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$), 4.89 (1 H, d, *J* 2 Hz, 6-H), 5.31 (1 H, s, 4-H), and 5.49 and 5.77 (each 1 H, d, *J* 1.4 Hz, vinylic H); δ_C($CDCl_3$) 15.14 (q, CH_3CH_2), 50.30 (t, 2-C), 56.03 (d, 7-C), 66.88 (t, CH_3CH_2), 67.85 (d, 4-C), 74.57 (t, CH_2CCl_3), 84.30 (d, 6-C), 94.23 (s, CCl_3), 122.05 and 127.01 (s, t, vinylic C), and 166.32 and 166.39 (each S, carbonyl C); *m/z* 389 (M^+).

2,2,2-*Trichloroethyl* 7α-*Ethylthioceph*-3-*em* (**22**).—Acetic anhydride (112 mg, 1.1 mmol) was added to a solution of 6α-ethylthiopenicillanate *S*-oxide (**17**) (86 mg, 0.22 mmol) in dimethylformamide (1 ml), and the mixture heated under reflux for 1 h. The mixture was then concentrated under reduced pressure, the residue dissolved in benzene, and the benzene solution washed with water and dried ($MgSO_4$). Removal of the benzene under reduced pressure gave an oil which was chromatographed on silica gel using ethyl acetate–light petroleum (1:1) as eluant, to provide 2,2,2-*trichloroethyl* 7α-*ethylthioceph*-3-*em* (**22**) (49 mg, 57%), a colourless oil (Found: M^+, 389.9554. $C_{12}H_{15}{}^{35}Cl_3NO_3S_2$ requires *M*, 389.9558); $\nu_{max.}$($CHCl_3$) 1 780 cm^{-1}; δ_H($CDCl_3$) 1.32 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.20 (3 H, s, 3-CH_3), 2.74 (2 H, m, CH_3CH_2), 3.28 and 3.50 (each 1 H, d, *J* 18 Hz, SHC*H*), 4.05 (1 H, d, *J* 2 Hz, 7-H), 4.65 (1 H, d, *J* 2 Hz, 6-H), and 4.78 and 5.04 (each 1 H, d, *J* 12 Hz, *H*$CHCCl_3$).

2,2,2-*Trichloroethyl* 6-*Chloro*-6-*phenylselenopenicillanate* S,S-*Dioxide* (**24**).—Benzeneselenenyl chloride (127 mg, 0.67 mmol) in dichloromethane (10 ml) was added dropwise to a solution of the 6-diazopenicillanate *S*-oxide (**11**) (250 mg, 0.67 mmol) in dichloromethane (30 ml). After 30 min the solvent was removed under reduced pressure, and the residue recrystallized from ethyl acetate–light petroleum to give 2,2,2-*trichloroethyl* 6-*chloro*-6-*phenylselenopenicillanate* (**24**) (235 mg, 65%), m.p. 151—153 °C (Found: M^+, 535.8689. $C_{16}H_{15}{}^{35}Cl_4NO_4SSe$ requires *M*, 535.8681); $\nu_{max.}$(CHCl$_3$) 1 790, 1 770, and 1 040 cm^{-1}; δ_H(CDCl$_3$) 1.34 and 1.80 (each 3 H, s, Me), 4.68 and 5.06 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 4.84 (1 H, s, 3-H), 5.14 (1 H, s, 5-H), and 7.54 (5 H, m, ArH); *m*/*z* 536 (M^+).

2,2,2-*Trichloroethyl* 6α-*Phenylselenopenicillanate* (1S)-S-*Oxide* (**25**).—Freshly prepared benzeneselenenol (144 mg, 0.92 mmol) in dichloromethane (4 ml) and rhodium acetate (a few crystals) were added to the 6-diazopenicillanate (**11**) (200 mg, 0.53 mmol) in dichloromethane (20 ml). After 30 min the solution was concentrated under reduced pressure to give a residue which was chromatographed on silica, using ethyl acetate–light petroleum (1:1), as eluant, to provide diphenyl diselenide followed by 2,2,2-*trichloroethyl* 6α-*phenylselenopenicillanate* (1S)-S-*oxide* (**25**) (45 mg, 17%), a colourless oil (Found: M^+, 501.9733. $C_{16}H_{16}{}^{35}Cl_3NO_4S^{80}Se$ requires *M*, 501.9764); $\nu_{max.}$(CHCl$_3$) 1 790 and 1 060 cm^{-1}; δ_H(CDCl$_3$) 1.22 and 1.74 (each 3 H, s, Me), 4.60 (1 H, s, 3-H), 4.62 and 4.93 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 4.75 (1 H, d, *J* 2 Hz, 6-H), 4.78 (1 H, d, *J* 2 Hz, 5-H), and 7.49 (5 H, m, ArH); *m*/*z* 502 (M^+).

2,2,2-*Trichloroethyl* 6-*Chloro*-6-*iodopenicillanate* (1S)-S-*Oxide* (**26**).—Iodine monochloride (123 mg, 0.76 mmol) in dichloromethane (5 ml) was added dropwise to the 6-diazopenicillanate (**11**) (300 mg, 0.76 mmol) in dichloromethane. After 30 min the mixture was concentrated under reduced pressure, and the residue was chromatographed on silica using ethyl acetate–light petroleum (1:1) as eluant. The first eluted product was identified as 2,2,2-*trichloroethyl* 6-*chloro*-6-*iodopenicillanate* (**27**) (30 mg, 8%), an oil; $\nu_{max.}$(CHCl$_3$) 1 790 and 1 760 cm^{-1}; δ_H(CDCl$_3$) 1.54 and 1.72 (each 3 H, s, Me), 4.70 (1 H, s, 3-H), 4.79 (2 H, s, CH_2CCl_3), and 5.47 (1 H, s, 5-H). The second eluted product was identified as 2,2,2-*trichloroethyl* 6-*chloro*-6-*iodopenicillanate* (1S)-S-*oxide* (**26**) (189 mg, 49%), an oil (Found: M^+, 506.8143. $C_{10}H_{10}{}^{35}Cl_4NO_4IS$ requires *M*, 506.8130); $\nu_{max.}$(CHCl$_3$) 1 810, 1 760, and 1 020 cm^{-1}; δ_H(CDCl$_3$) 1.35 and 1.79 (each 3 H, s, Me), 4.82 (1 H, s, 3-H), 4.70 and 5.06 (each 1 H, d, *J* 12 Hz, HC*H*CCl$_3$) and 5.15 (1 H, s, 5-H); *m*/*z* 507 (M^+).

2,2,2-*Trichloroethyl* 6β-*Formyl*-6α-(4-*methoxyphenyl*)-*penicillanate* (1S)-S-*Oxide* (**28**).—4-Methoxybenzaldehyde (73 mg, 0.53 mmol) was added to a solution of the 6-diazopenicillanate (**11**) (200 mg, 0.53 mmol) in dichloromethane (10 ml) at 0 °C, followed by boron trifluoride diethyletherate (2 drops). After 30 min the mixture was concentrated under reduced pressure, and the residue chromatographed on silica using ethyl acetate–light petroleum (1:1), as eluant, to give 2,2,2-*trichloroethyl* 6β-*formyl*-6α-(4-*methoxyphenyl*)*penicillanate* (1S)-S-*oxide* (**28**) (97 mg, 38%), an oil (Found: M^+, 480.9931. $C_{18}H_{18}{}^{35}Cl_3NO_6S$ requires *M*, 480.9919); $\nu_{max.}$(CHCl$_3$) 1 790, 1 780, 1 720, and 1 050 cm^{-1}; δ_H(CDCl$_3$) 1.31 and 1.81 (each 3 H, s, Me), 3.82 (3 H, s, OMe), 4.81 (1 H, s, 3-H), 4.64 and 5.02 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 5.1 (1 H, s, 5-H), 7.41 and 6.96 (each 2 H, m, ArH), and 9.7 (1 H, s, CHO); δ_C(CDCl$_3$) 18.72, 19.59 and 55.43 (each q, CH_3), 65.06 (d, 3-C), 72.81 (s, 6-C), 72.98 (s, 2-C), 74.97 (t, CH_2CCl_3), 83.57 (d, 5-C), 94.02 (s, CCl_3), 115.14 and 128.45 (each d, ArC), 121.59 and 160.41 (both s, ArC), 166.58 and 169.46 (each s, carbonyl C), and 191.11 (d, CHO); *m*/*z* 481 (M^+).

2,2,2-*Trichloroethyl* 6β-*Formyl*-6α-(2-*furyl*)*penicillanate* (1S)-S-*Oxide* (**29**).—Following the procedure outlined above, 6-diazopenicillanate (**11**) (200 mg, 0.53 mmol) and furfuraldehyde (51 mg, 0.53 mmol) gave, after column chromatography, the 2,2,2-*trichloroethyl* 6β-*formyl*-6α-(2-*furyl*)*penicillanate* (1S)-S-*oxide* (**29**). (92 mg, 39%), white crystals, m.p. 139—140 °C (from ethyl acetate–light petroleum) (Found: M^+, 440.9612. $C_{15}H_{14}{}^{35}Cl_3NO_6S$ requires *M*, 440.9606); $\nu_{max.}$(CHCl$_3$) 1 800, 1 770, 1 720, and 1 060 cm^{-1}; δ_H(CDCl$_3$) 1.34 and 1.80 (each 3 H, s, Me), 4.68 and 5.04 (each 2 H, d, *J* 12 Hz, *H*CHCCl$_3$), 4.81 (1 H, s, 3-H), 5.25 (1 H, s, 5-H), 6.45 (2 H, m, ArH), 7.51 (1 H, d, *J* 0.8 Hz, ArH), and 9.74 (1 H, s, CHO); δ_C(CDCl$_3$) 18.70 and 19.39 (each q, CH_3), 65.43 (d, C-3), 68.80 (s, 6-C), 73.28 (s, 2-C), 75.13 (t, CH_2CCl_3), 82.03 (d, 5-C), 94.12 (s, CCl_3), 110.99 and 111.58 (each d, ArC), 142.29 (s, ArC), 144.98 (d, ArC), 166.59 and 166.93 (each s, C=O), and 189.04 (d, CHO); *m*/*z* 441 (M^+).

2,2,2-*Trichloroethyl* 6β-*Formyl*-6α-(4-*methoxyphenyl*)-*penicillanate* S,S-*Dioxide* (**30**).—Following the above procedure, the 6-diazopenicillanate (**13**) (400 mg, 1.02 mmol) and 4-methoxybenzaldehyde (140 mg, 1.02 mmol) gave after chromatography, on silica using ethyl acetate–light petroleum (1:9) as eluant, the 2,2,2-*trichloroethyl* 6β-*formyl*-6α-(4-*methoxyphenyl*)*penicillanate* S,S-*dioxide* (**30**) (180 mg, 35%), white needles, m.p. 156—157 °C (from ethyl acetate–light petroleum); $\nu_{max.}$(CHCl$_3$) 1 810, 1 770, 1 730, 1 350, and 1 160 cm^{-1}; δ_H(CDCl$_3$) 1.50 and 1.70 (each 3 H, s, Me), 3.83 (3 H, s, OMe), 4.69 (1 H, s, 3-H), 4.67 and 4.99 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 4.87 (1 H s, 5-H), 6.98 and 7.39 (each 2 H, m, ArH), and 9.68 (1 H, s, CHO); *m*/*z* 482 ($M^+ - CH_3$).

Sodium borohydride (14 mg, 0.36 mmol) was added to a solution of the 6β-formylpenicillanate *S*,*S*-dioxide (**30**) (180 mg, 0.36 mmol) in dioxane (12 ml) containing aqueous pH 7 buffer (6 ml). After 30 min a conventional work-up and preparative t.l.c. on silica using ethyl acetate–light petroleum 1:1 as solvent, gave 2,2,2-*trichloroethyl* 6β-*hydroxymethyl*-6α-(4-*methoxyphenyl*)*penicillanate* S,S-*dioxide* (**31**) (21 mg, 12%), an oil; $\nu_{max.}$(CHCl$_3$) 3 450, 1 800, 1 770, 1 350, and 1 160 cm^{-1}; δ_H(CDCl$_3$) 1.50 and 1.71 (each 3 H, s, Me), 3.83 (4 H, s, Me + OH), 4.07 and 4.63 (each 1 H, d, *J* 11 Hz, HC*H*OH), 4.67 and 4.99 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 4.71 (1 H, s, 3-H), 4.72 (1 H, s, 5-H), and 6.95 and 7.42 (each 2 H, m, ArH).

2,2,2-*Trichloroethyl* 6β-*Acetyl*-6α-*methylpenicillanate* (1S)-S-*Oxide* (**32**).—6-Diazopenicillanate (**11**) (200 mg, 0.53 mmol) and acetone (31 mg, 0.53 mmol) gave, following the above procedure, 2,2,2-*trichloroethyl* 6β-*acetyl*-6α-*methylpenicillanate* S-*oxide* (**32**) (23 mg, 10%), a colourless oil (Found: M^+, 402.9827. $C_{13}H_{16}{}^{35}Cl_3NO_5S$ requires *M*, 402.9815); $\nu_{max.}$(CHCl$_3$) 1 780, 1 760, 1 720, and 1 060 cm^{-1}; δ_H(CDCl$_3$) 1.30 and 1.78 (each 3 H, s, Me), 1.75 (3 H, s, 6-CH_3), 2.35 (3 H, s, $COCH_3$), 4.67 (1 H, s, 3-H), 4.66 and 5.02 (each 1 H, d, *J* 12 Hz, HCHCCl$_3$), and 4.85 (1 H, s, 5-H); *m*/*z* 403 (M^+).

2,2,2-*Trichloroethyl* 6α-*Acetylpenicillanate* S,S-*Dioxide* (**34**).—*m*-Chloroperoxybenzoic acid (60 mg, 0.35 mmol) in dichloromethane (10 ml) was added dropwise to the 6α-acetylpenicillanate (130 mg, 0.34 mmol)[13] in dichloromethane (10 ml) at 0 °C. After 1 h at 0 °C the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated under reduced pressure to provide the S-*oxide* (**34**) (96 mg, 72%), an unstable, colourless oil; $\nu_{max.}$(CHCl$_3$) 1 800, 1 770, 1 720, and 1 060 cm^{-1}; δ_H(CDCl$_3$) 1.37 and 1.80 (each 3 H, s, Me), 2.41 (3 H, s, $COCH_3$), 4.60 (1 H, d, *J* 2 Hz, 6-H), 4.62 (1 H, s, 3-H), 4.68 and 5.06 (each 1 H, d, *J* 12 Hz, HCHCCl$_3$), and 5.30 (1 H, d, *J* 2 Hz, 5-H).

2,2,2-*Trichloroethyl* 6α-*Hydroxyethylpenicillanate* S-*Oxides*

(**36**).—Magnesium bis(trifluoroacetate) (2.79 g, 11.15 mmol) and dimethylamine–borane (0.26 g, 4.46 mmol) were added to the 6α-acetylpenicillanate (**33**) (0.83 g, 2.23 mmol) in ether (80 ml) at 0 °C, and the mixture stirred at 0 °C for 2 h before being washed with dilute HCl and water, dried ($MgSO_4$), and concentrated under reduced pressure to provide an oil which on chromatography [silica, ethyl acetate–light petroleum (1:1)] gave the 6α-*hydroxyethylpenicillanates* (**35**) (0.5 g, 60%) as a mixture of diastereoisomers, ratio *ca.* 1.2:1 (Found: M^+, 374.9869. $C_{12}H_{16}{}^{35}Cl_3NO_4S$ requires *M*, 374.9864); $\nu_{max.}(CHCl_3)$ 3 450 and 1 760 cm^{-1}; $\delta_H(CDCl_3)$ major isomer, 1.36 (3 H, d, *J* 6 Hz, $CHCH_3$), 1.56 and 1.70 (each 3 H, s, Me), 3.35 (1 H, dd, *J* 2, 6 Hz, 6-H), 4.27 (2 H, m, $CHOH$), 4.60 (1 H, s, 3-H), 4.72 and 4.84 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 5.33 (1 H, d, *J* 2 Hz, 5-H); minor isomer, 1.39 (3 H, d, *J* 6 Hz, $CHCH_3$), 1.56 and 1.70 (each 3 H, s, Me), 3.44 (1 H, dd, *J* 2, 5 Hz, 6-H), 4.27 (2 H, m, $CHOH$), 4.62 (1 H, s, 3-H), 4.72 and 4.84 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 5.29 (1 H, d, *J* 2 Hz, 5-H).

The mixture of hydroxyethylpenicillanates (**35**) (155 mg) was treated with *m*-chloroperoxybenzoic acid (70 mg, 0.41 mmol) as above to give a mixture of the S-*oxides* (**36**) (135 mg, 84%), ratio 1.2:1; $\nu_{max.}(CHCl_3)$ 3 400, 1 790, 1 770, and 1 060 cm^{-1}; $\delta_H(CDCl_3)$ major isomer, 1.34 and 1.79 (each 3 H, s, Me), 1.39 (3 H, d, *J* 6 Hz, $CHCH_3$), 3.62 (1 H, dd, *J* 2, 6 Hz, 6-H), 4.44 (1 H, m, $CHOH$), 4.65 (1 H, s, 3-H), 4.65 and 5.04 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 5.04 (1 H, d, *J* 2 Hz, 5-H); minor isomer, 1.35 and 1.79 (each 3 H, s, Me), 1.46 (3 H, d, *J* 6 Hz, $CHCH_3$), 3.75 (1 H, dd, *J* 2, 4.5 Hz, 6-H), 4.44 (1 H, m, $CHOH$), 4.65 (1 H, s, 3-H), 4.65 and 5.04 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 4.98 (1 H, d, *J* 2 Hz, 5-H).

2,2,2-*Trichloroethyl* 6-*Ethylidenepenicillanate* S-*Oxides* (**37**) *and* (**38**).—Mesyl chloride (40 mg, 0.38 mmol), triethylamine (35 mg, 0.38 mmol), and dimethylaminopyridine (4 mg, 0.04 mmol), were added to a mixture of the hydroxypenicillanate *S*-oxides (**36**) (150 mg, 0.38 ml) in dichloromethane (10 ml). After 1 h, an aqueous work-up gave a mixture of mesylates (125 mg, 70%); $\nu_{max.}(CHCl_3)$ 1 790 and 1 060 cm^{-1}.

Anhydrous K_2CO_3 (104 mg, 0.75 mmol) was added to a solution of the above mesylates (88 mg, 0.2 mmol) in dichloromethane (10 ml), and the mixture stirred for 3 h. After being filtered, the mixture was concentrated under reduced pressure, and the residue chromatographed using methanol–chloroform (1:9) as eluant, to provide a mixture of the 6-*ethylidenepenicillanate* (1S)-*oxides* (**37**) and (**38**), as a colourless oil (Found: M^+, 372.9708. $C_{12}H_{14}{}^{35}Cl_3NO_4S$ requires *M*, 372.9708); $\nu_{max.}(CHCl_3)$ 1 780, 1 770, and 1 060 cm^{-1}; $\delta_H(CDCl_3)$ major isomer, 1.36 and 1.79 (each 3 H, s, Me), 1.93 (3 H, d, *J* 7 Hz, $CHCH_3$), 4.66 and 5.07 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), 4.70 (1 H, s, 3-H), 5.49 (1 H, br s, 5-H), and 6.7 (1 H, dq, *J* 1.5, 7 Hz, $CHCH_3$); minor isomer, 1.34 and 1.78 (each 3 H, s, Me), 2.17 (3 H, d, *J* 7 Hz, $CHCH_3$), 4.66 and 5.08 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), 4.70 (1 H, s, 3-H), 5.39 (1 H, br s, 5-H), and 6.13 (1 H, dq, *J* 1.1, 7 Hz, $CHCH_3$).

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