Preparation of 6α-Monosubstituted and 6,6-Disubstituted Penicillanates from 6-Diazopenicillanates: Reactions of 6-Diazopenicillanates with Alcohols, Thiols, Phenylseleninyl Compounds, and Allylic Sulphides, and their Analogues

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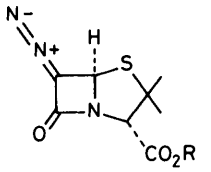
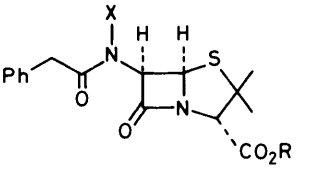
Reactions of 6-diazopenicillanates (1) and (2) with a range of compounds, in some cases catalysed by BF_3–Et_2O or $Cu(acac)_2$, have been investigated, and found to be useful for the synthesis of 6α-monosubstituted and 6,6-disubstituted penicillanates. Thus the 6α-alkoxy- and 6α-alkylthio-penicillanates (7)—(15), the 6-phenylselenopenicillanates (26)—(32), and the 6-allyl-6-alkylthio- and 6-allyl-6-phenylseleno-penicillanates (39)—(46), were obtained from reactions between 6-diazopenicillanates (1) and (2) and alcohols, thiols, phenylselenol, diphenyl diselenide, phenylseleninyl chloride, allylic sulphides, and allylic selenides. Reactions between 6-diazopenicillanates (1) and (2) and carboxylic acid derivatives and ethers were also briefly examined.

The structure of 2,2,2-trichloroethyl 6α-allyl-6β-phenylthiopenicillanate (39) was confirmed by a single-crystal *X*-ray study.

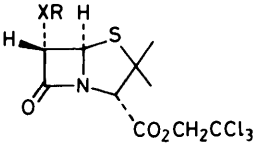
Interest in the chemistry of β-lactam antibiotics continues unabated.[1] In 1974 Sheehan described the isolation of the first crystalline 6-diazopenicillanate, the 2,2,2-trichloroethyl ester (1),[2] and since that time aspects of the chemistry of 6-diazopenicillanates have been studied.[3–5] We here describe reactions of 6-diazopenicillanates with a range of compounds including alcohols, thiols, phenylseleninyl compounds, and allylic sulphides and related compounds.[6] Some of our results complement other recent studies,[5,7] and provide efficient syntheses of 6α-monosubstituted, and 6,6-disubstituted penicillanates.



(1) R = CH_2CCl_3
(2) R = CH_2Ph



(3) R = CH_2CCl_3, X = H
(4) R = CH_2Ph, X = H
(5) R = CH_2CCl_3, X = NO
(6) R = CH_2Ph, X = NO



(7) R = Me, X = O
(8) R = Bu^t, X = O
(9) R = $PhCH_2$, X = O
(10) R = $HOCH_2CH_2OCH_2CH_2$, X = O
(11) R = $HO(CH_2)_4$, X = O
(12) R = Et, X = O
(13) R = $PhCH_2$, X = S
(14) R = Et, X = S
(15) R = Bu^i, X = S
(16) R = $PhCH_2CO$, X = O
(17) R = CH_3CO, X = S

Results and Discussion

2,2,2-Trichloroethyl and benzyl 6-diazopenicillanates (1) and (2) were prepared from the 6β-phenylacetamidopenicillanates (3) and (4) using a slightly modified version of the published procedure.[2] In particular, less dinitrogen tetroxide was used for *N*-nitrosation and the thermal decomposition of the intermediate *N*-nitroso-amides (5) and (6) was carried out by heating in dichloromethane under reflux, no pyridine being required.

Reactions of 6-Diazopenicillanates with Alcohols, Thiols, and their Derivatives.—Reactions of alcohols with diazo-compounds[8,9] are well known. Usually an acid catalyst is required, *e.g.* BF_3·Et_2O was used for the preparation of α-alkoxyacetophenones from diazoacetophenone.[10] It was found that 6-diazopenicillanate (1) reacts rapidly with methanol, t-butyl alcohol, and benzyl alcohol, in the presence of BF_3·Et_2O, to give 6α-alkoxypenicillanates (7)—(9). Nitrogen evolution was rapid on addition of the BF_3·Et_2O, and the reactions were complete within a few minutes at room temperature. Similar results were obtained with diols; thus diethylene glycol and butane-1,4-diol gave 6α-substituted products (10) and (11). Product (10) was also obtained, but less efficiently (15%), by treatment of a solution of 6-diazopenicillanate (1) in dioxan with BF_3·Et_2O. Similar treatment of a tetrahydrofuran (THF) solution of 6-diazopenicillanate (1) did not give an appreciable yield of product (11), but 6α-ethoxypenicillanate (12) was obtained (26%) when BF_3·Et_2O was added to a solution of 6-diazopenicillanate (1) in anhydrous diethyl ether.

Reactions of α-diazocarbonyl compounds with thiols are not well documented, although in the presence of a copper

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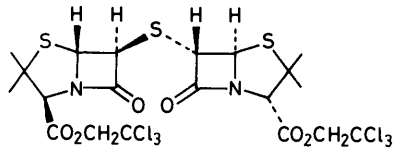

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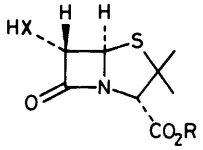
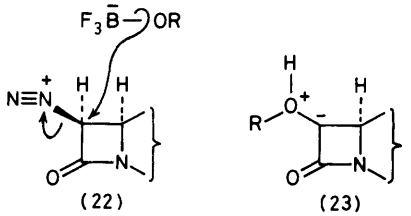


(19) X = O, R = CH_2CCl_3
(20) X = S, R = CH_2CCl_3
(21) X = S, R = Me



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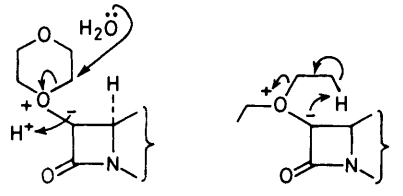


(24) (25)

catalyst, diazoacetophenone reacts with thiophenol to give α-phenylthioacetophenone.[11] Preliminary studies of the reaction between 6-diazopenicillanate (1) and toluenethiol in the presence of toluene-*p*-sulphonic acid or anhydrous copper(II) chloride, were not encouraging, but it was found that when $BF_3{\cdot}Et_2O$ was added to a solution of an excess of toluenethiol and diazopenicillanate (1) in dichloromethane, a rapid evolution of nitrogen occurred, and 6α-benzylthiopenicillanate (13) could be isolated (54%). Similarly ethanethiol and isobutanethiol gave 6α-alkylthiopenicillanates (14) and (15). An excess of thiol is required in these reactions. When a stoicheiometric amount of toluenethiol was used, a lower yield (37%) of 6α-benzylthiopenicillanate (13) was obtained and a second product, identified as the dimeric sulphide (18) was isolated (26%). Thioether (18) was also prepared (47%) by treatment of 6α-benzylthiopenicillanate (13) with 1 equiv. of 6-diazopenicillanate (1) and $BF_3{\cdot}Et_2O$ in dichloromethane.

6-Diazopenicillanate (1) was found to be stable to phenylacetic acid in dichloromethane, but on addition of $BF_3{\cdot}Et_2O$, nitrogen was evolved, and 6α-phenylacetoxypenicillanate (16) was obtained. Similarly 6-diazopenicillanate (1) reacted with thioacetic acid, although only a low yield (6%) of the 6α-acetylthiopenicillanate (17) was isolated after column chromatography.

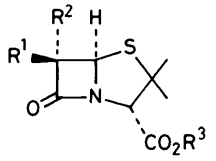
The α-configuration at C-6 was assigned to products (7)—(17) on the basis of their small H(5)–H(6) coupling constants.[12] In addition, 6α-methoxypenicillanate (7) was prepared from the known 6α-hydroxypenicillanate (19)[2] by treatment with diazomethane–$BF_3{\cdot}Et_2O$.

As a chemical correlation of the products, the 6α-acetylthiopenicillanate (17) was converted into 6α-benzylthiopenicillanate (13). Treatment of the thioester (17) with NaOMe–MeOH at −78 °C gave a mixture of the 6α-thiol 2,2,2-trichloroethyl and methyl esters (20) and (21) which were separated by column chromatography, and the trichloroethyl ester alkylated using benzyl bromide in ethanol containing triethylamine. Other reactions of the thiol (20) were not investigated.

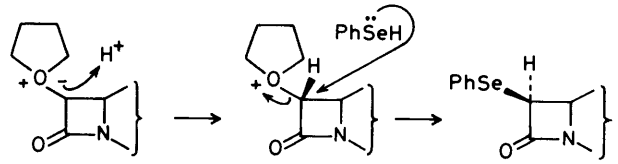
The clean formation of 6α-substituted penicillanates (7)—(15) in reactions between 6-diazopenicillanate (1) and alcohols and thiols in the presence of $BF_3{\cdot}Et_2O$, contrasts with the predominant rearrangement to thiazepines which occur on treatment with an alcohol and $Cu(acac)_2$,[5] and with the selective formation of 6β-isomers in the photochemical reactions of thiols and 6-diazopenicillanates.[7] Several mechanisms have been proposed for $BF_3{\cdot}Et_2O$ catalysed reactions between alcohols and diazo-compounds which are consistent with kinetic formation of the 6α-isomers.[9] The $BF_3{\cdot}Et_2O$ may co-ordinate with the alcohol (thiol) to form a species which protonates the 6-diazo-compound from the less hindered α-face.[13] Subsequent displacement of nitrogen, as in (22), gives the observed 6α-product. Alternatively, the ylide (23), possibly co-ordinated with BF_3, may be an intermediate.[5] The reactions between 6-diazopenicillanate (1) and dioxan and diethyl ether, could involve analogous ylide intermediates. Hydrolysis of the ylide (24) would give the dioxan product (10), and elimination of ethene from the ylide (25) would account for 6α-ethoxy-penicillanate (12).

Reactions of 6-Diazopenicillanates with Phenylseleninyl Compounds.—Until recently reactions between diazo-compounds and organoselenium compounds had scarcely been mentioned in the literature,[8,14] but the successful reactions described above encouraged us to examine the analogous reaction with phenylselenol.

Treatment of 6-diazopenicillanate (1) with phenylselenol (prepared by reduction of diphenyl diselenide with hypophosphorous acid, followed by extraction into dichloromethane and concentration *in vacuo*[15]) and $BF_3{\cdot}Et_2O$ in dichloromethane, gave rise to rapid nitrogen evolution and led to the



(26) R^1 = H, R^2 = SePh, R^3 = CH_2CCl_3
(27) R^1 = SePh, R^2 = H, R^3 = CH_2CCl_3
(28) R^1 = R^2 = SePh, R^3 = CH_2CCl_3
(29) R^1 = R^2 = SePh, R^3 = CH_2Ph
(30) R^1 = SePh, R^2 = Cl, R^3 = CH_2CCl_3
(31) R^1 = SePh, R^2 = Cl, R^3 = CH_2Ph
(32) R^1 = R^2 = Br, R^3 = CH_2CCl_3



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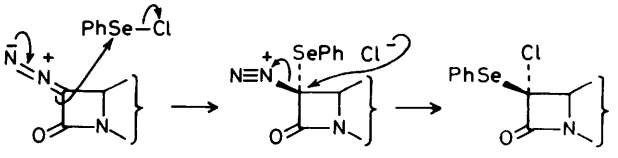


(34)

formation of 6α-phenylselenopenicillanate (26) which was isolated in 57% yield. Although the formation of the 6α-isomer is consistent with the analogous reactions described above, during preliminary studies an unexpected solvent effect was observed. If THF was added to the reaction mixture before the addition of the BF_3·Et_2O a second product was formed which was isolated and identified as the 6β-phenylselenopenicillanate (27). The reaction under these conditions was not as clean as in the absence of THF, but the ratio of the 6α : 6β epimers (26) and (27) did appear to depend upon the amount of THF present. In exceptional cases the ratio of the 6α-isomer (26) to the 6β-isomer (27) was 1 : 7, and the pure 6β-isomer could be isolated by fractional crystallization.

No further studies were carried out to explain the influence of the THF. One explanation is that THF competes with phenylselenol for the diazo-compound so generating the ylide (33) which on protonation from the β-side, followed by nucleophilic displacement with inversion, gives the product (27).

Next BF_3·Et_2O-catalysed reactions between the 6-diazopenicillanates (1) and (2) and diphenyl diselenide were examined.* It was found that under the usual conditions clean reactions took place, and the 6,6-bis(phenylseleno)penicillanates (28) and (29) could be isolated. In contrast benzene seleninyl chloride was found to react with the 6-diazopenicillanates in the absence of catalyst † to give 6α-chloro-6β-phenylselenopenicillanates (30) and (31). The C-6 configurations of these products were not unambiguously defined, but electrophilic attack by the phenyl seleninyl chloride on the 6-diazopenicillanates should give intermediates (34) which by S_N1 (least hindered approach) or S_N2 (inversion) reaction with chloride should give the 6α-chloro-6β-phenylseleno isomers shown (at least kinetically). Preliminary attempts to effect the analogous reactions with phenylselenenyl bromide were not promising; BF_3·Et_2O was required to initiate nitrogen loss, and complex product mixtures were obtained from which only 6,6-dibromopenicillanate (32) was isolated.

Reactions of 6-Diazopenicillanates with Allylic Sulphides, Selenides, and Bromides.—During the course of the work described above, participation of oxygen ylides (24), (25), and (33) was invoked to explain some of the results. Preliminary attempts to trap these ylides using methyl iodide or bromine were unsuccessful, but there remained the possibility that an intramolecular trap would be more effective. In particular an allylic ether should give the ylide (35), which would be expected to rearrange *via* a 2,3-shift to the 6,6-disubstituted penicillanate (36). Indeed the analogous nitrogen ylide (37), generated from the corresponding ammonium salt, does rearrange to the 6α-allyl-6β-dimethylaminopenicillanate (38).[18] However, when BF_3·Et_2O was added to a solution of 6-diazopenicillanate (1) in either 3-methoxy- or 3-phenoxy-propene, nitrogen was evolved, but only a complex mixture of products was obtained. Since sulphides are more nucleophilic than ethers, and since 2,3-sigmatropic rearrangements of allylic sulphonium ylides are well known,[19] we next investigated reactions between diazopenicillanates (1) and (2) and allylic sulphides.

Addition of BF_3·Et_2O to a solution of 6-diazopenicillanate (1) and an excess of allyl phenyl sulphide in anhydrous dichloromethane resulted in the rapid evolution of nitrogen, and led to the formation of three products which were separated

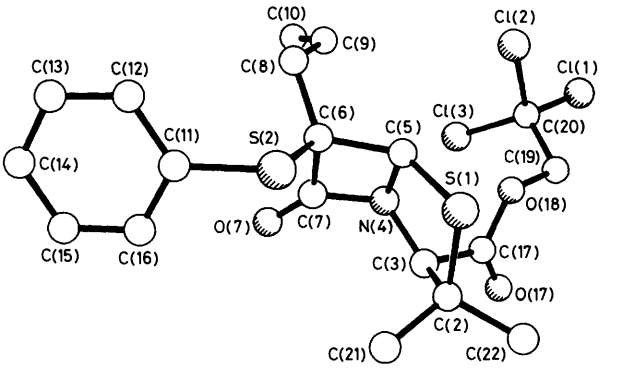
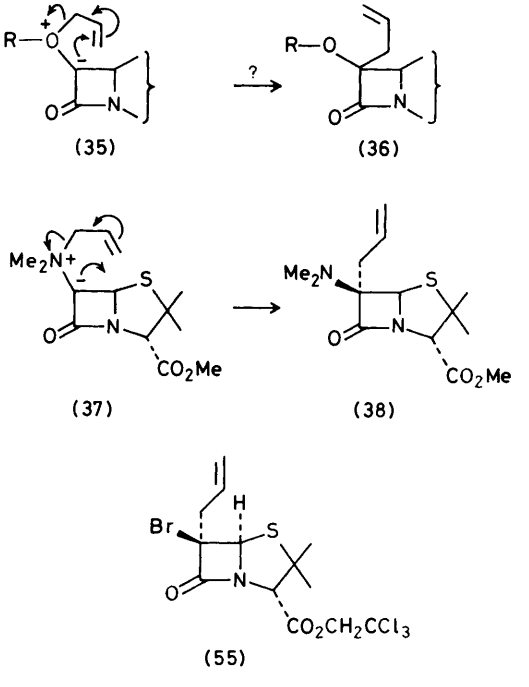


Figure. *Molecular structure of the major allyl phenyl sulphide product (39) showing crystallographic numbering scheme used*

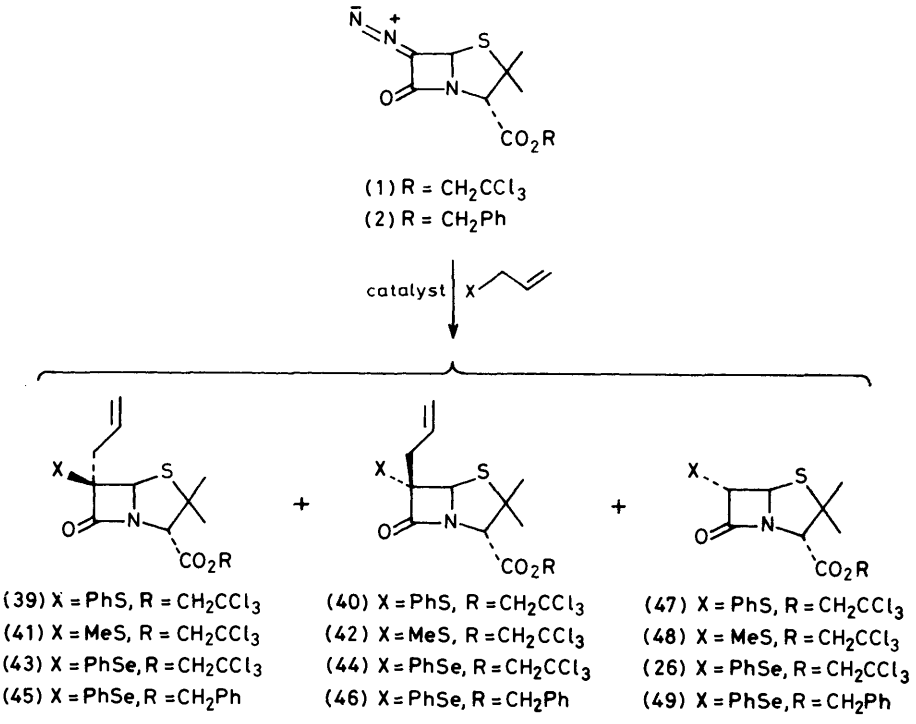
and identified as the two C-6 epimers of 6-allyl-6-phenylthiopenicillanate (39) and (40), together with 6α-phenylthiopenicillanate (47). Similarly 6-diazopenicillanate (1) and allyl methyl sulphide gave 6-allyl-6-methylthiopenicillanates (41) and (42) together with 6α-methylthiopenicillanate (48). This reaction was applied to allylic selenides. Thus 6-diazopenicillanates (1) and (2) and allyl phenyl selenide gave 6-allyl-6-phenylselenopenicillanates (43)—(46) together with 6α-phenylselenopenicillanates (26) and (49). (These products are shown in Scheme 1, and their yields in Table 1.) Subsequently it was found that the formation of the 6α-monosubstituted products (26) and (47)—(49), could be avoided by using $Cu(acac)_2$ as the catalyst.[4] Under these conditions the yields of the 6,6-disubstituted products were increased (Table 1.)

Products (39)—(49) were all separated and purified by column chromatography except for 6β-allyl-6α-methylthiopenicillanate (42) which could not be obtained completely free of the major isomer (41). The configuration at C-6 of the major 6,6-disubstituted product from the reaction between 6-diazopenicillanate (1) and allyl phenyl sulphide, was established as that shown in formula (39), by an *X*-ray diffraction study. The Figure shows a projection which clearly defines the



* Since our work was completed the reactions of ethyl diazoacetate and dimethyl diazomalonate with diphenyl diselenide have been reported.[16]

† After our preliminary communication on this work, the reaction between α-diazocyclohexanone and benzeneseleninyl chloride was described.[17]



Scheme 1

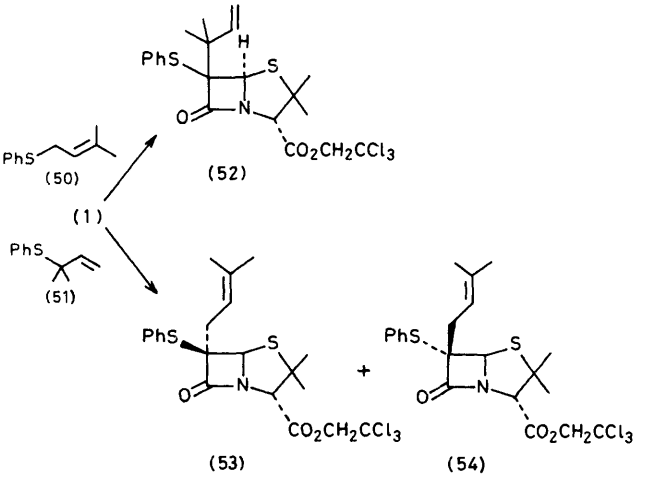
Table 1.

Starting 6-diazo-penicillanate	X	Catalyst	Yield of 6,6-disubstituted product (%)	Ratios of 6,6-disubstituted products	Yield of 6α-monosubstituted product
(1)	PhS	$BF_3{\cdot}Et_2O$	47	(39) : (40) = 56 : 44	3
(1)	MeS	$BF_3{\cdot}Et_2O$	49	(41) : (42) = 80 : 20	16
(1)	PhSe	$BF_3{\cdot}Et_2O$	48	(43) : (44) = 66 : 34	15
(2)	PhSe	$BF_3{\cdot}Et_2O$	33	(45) : (46) = 63 : 37	7
(1)	PhS	$Cu(acac)_2$	65	(39) : (40) = 87 : 13	0
(1)	MeS	$Cu(acac)_2$	60	(41) : (42) = 80 : 20	0
(1)	PhSe	$Cu(acac)_2$	64	(43) : (44) = 50 : 50	0

configuration at C-6. The configurations at C-6 of the other C-6 disubstituted penicillanates (41)—(46) were assigned by analogy, and were consistent with their relative ^1H n.m.r. chemical shifts. These assignments are consistent with those of Baldwin who assigned the analogous configuration to (38), the product of rearrangement of the ammonium ylide (37).[18]

The formation of 6,6-disubstituted penicillanates (39)—(46) is consistent with the participation of allylic sulphonium and selenonium ylides which rearrange by 2,3-sigmatropic shifts. To confirm this mechanism, 6-diazopenicillanate (1) was treated with α,α-dimethyl- and γ,γ-dimethyl-allyl phenyl sulphides (50) and (51) in the presence of $Cu(acac)_2$. The major products obtained, shown in Scheme 2, are consistent with the 2,3-sigmatropic shift pathway. Structures were assigned to products (52)—(54) on the basis of spectroscopic data. The configurations at C-6 for compounds (53) and (54) were assigned by analogy with the reactions discussed above and are consistent with their ^1H n.m.r. chemical shifts; from the data available it was not possible to assign the C-6 configuration of compound (52) with absolute certainty since only one product was isolated in this case.

Finally it was found that addition of $Cu(acac)_2$ to a solution



Scheme 2

of diazopenicillanate (1) in freshly distilled allyl bromide led to the formation of an unstable product which was purified by rapid chromatography on neutral alumina and identified as 6α-allyl-6β-bromopenicillanate (55) (48%). The ^{1}H n.m.r. spectrum of the product suggested that it was a single isomer; the configuration at C-6 was assigned by analogy.

Experimental

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. spectra were measured on a Perkin-Elmer 257 spectrophotometer and n.m.r. spectra on Perkin-Elmer R12B and Bruker HFX 90 spectrometers. A Perkin-Elmer 142 polarimeter was used for optical activity measurements. Short-column chromatography was used for preparative purposes using Hopkin and Williams silica gel for t.l.c. (2—50 mesh, MFC without binder), eluted with ethyl acetate–light petroleum (b.p. 60—80 °C). All solvents were dried and distilled before use.

Several compounds characterised had three or more chlorine atoms and one or two selenium atoms per molecule. For these compounds, characteristic isotope peaks were observed in their mass spectra; only the dominant peaks are reported here.

2,2,2-*Trichloroethyl* 6-*Diazopenicillanate* (1).—Dinitrogen tetraoxide (18 g) was dissolved in anhydrous dichloromethane (200 ml). Half of this solution was added to a mixture of 2,2,2-trichloroethyl 6β-phenylacetamidopenicillanate (3) (28 g) and anhydrous sodium acetate (98 g) in dichloromethane (350 ml), and the mixture stirred for 1.5 h at −5 °C, the remaining dinitrogen tetraoxide being added after 1 h. Excess of dinitrogen tetraoxide was destroyed by adding the reaction mixture slowly (0.5 h) to a solution of sodium hydrogencarbonate (60 g) in water (500 ml). The organic phase was separated, washed with aqueous sodium hydrogencarbonate and water, dried over $MgSO_4$, and concentrated under reduced pressure to give a solution of the *N*-nitroso-amide (5) in dichloromethane (*ca.* 350 ml) (**CARE**: *the* N-*nitroso-amide was assumed to be extremely toxic*) which was heated under reflux for 4 h. After being washed with aqueous sodium hydrogencarbonate and water, the yellow dichloromethane solution was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude 6-diazopenicillanate (1) (20.7 g). Trituration with ethanol gave yellow crystals of 6-diazopenicillanate (1) (11.4 g), m.p. 103—104 °C (lit.,[2] 103.5—104 °C).

Benzyl 6-*Diazopenicillanate* (2).—Using the procedure described above, benzyl 6β-phenylacetamidopenicillanate (4) (21 g) gave crude 6-diazopenicillanate (2) (14.6 g) which was chromatographed to give benzyl 6-diazopenicillanate (2) (5.8 g),[20] a yellow oil; $\nu_{max.}$ (film) 2 100 (N=N=C) and 1 740 cm^{-1} (C=O); δ ($CDCl_3$) 1.35 and 1.55 (each 3 H, s, 2 × Me), 4.40 (1 H, s, $CHCO_2$), 5.15 (2 H, s, CH_2Ph), 6.15 (1 H, s, 5-H), and 7.35 (5 H, s, aromatic H).

General Procedure for 6-Diazopenicillinate Decompositions.—The 6-diazopenicillanate (1) or (2) was dissolved in anhydrous dichloromethane under a dry nitrogen atmosphere. Addition of the reagent, often in excess, followed by catalyst (BF_3·Et_2O; 10% molar equiv.) initiated nitrogen evolution. After being stirred for 0.25—0.5 h at 20 °C the reaction mixture was diluted with dichloromethane, washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated under reduced pressure to give crude product which was purified by short-column chromatography on silica gel under slight pressure [eluted with ethyl acetate–light petroleum (60—80 °C)]. Using this general procedure, the following compounds were prepared: yields refer to chromatographed products.

2,2,2-*Trichloroethyl* 6α-*methoxypenicillanate* (7) (60%), a colourless oil, homogeneous by t.l.c.; $[\alpha]_D$ +130° (1% in $CHCl_3$); $\nu_{max.}$ 1 760 br cm^{-1} (2 × C=O); δ ([$^2H_6$]acetone) 1.57 and 1.63 (each 3 H, s, 2 × Me), 3.51 (3 H, s, OMe), 4.66 (1 H, d, *J* 1.46 Hz, 6-H), 4.69 (1 H, s, 3-H), 4.99 (2 H, s, CH_2CCl_3), and 5.37 (1 H, d, *J* 1.46 Hz, 5-H); *m/z* 365, 363, 361 (M^+) and 294, 292, 290 (M^+ − MeOC=C=O) (Found: M^+, 360.9714. $C_{11}H_{14}{}^{35}Cl_3NO_4S$ requires *M*, 360.9709). An identical sample was prepared by treatment of 6α-hydroxypenicillanate (19) (150 mg)[2] with diazomethane and BF_3·Et_2O in dichloromethane under the standard conditions described above (yield 60 mg).

2,2,2-*Trichloroethyl* 6α-*t-butoxypenicillanate* (8) (72%) was prepared using t-butyl alcohol as solvent, a sample being crystallized from ethanol–water, m.p. 85—86 °C; $[\alpha]_D$ +80° (1% in $CHCl_3$); $\nu_{max.}$ (Nujol) 1 790 (β-lactam C=O) and 1 755 cm^{-1} (ester C=O); δ ($CDCl_3$) 1.26 (9 H, s, Me_3C), 1.55 and 1.62 (each 3 H, s, 2 × Me), 4.63 (1 H, s, 3-H), 4.70 (1 H, d, *J* 1.47 Hz, 6-H), 4.78 (2 H, s, CH_2CCl_3), and 5.22 (1 H, d, *J* 1.47 Hz, 5-H); *m/z* 350, 348, 346 (M^+ − 57), and 294, 292, 290 (M^+ − Bu^{t}OC=C=O) (Found: C, 41.5; H, 4.95; Cl, 26.5; N, 3.75; S, 8.2. $C_{14}H_{20}Cl_3NO_4S$ requires C, 41.54; H, 4.98; Cl, 26.28; N, 3.46; S, 7.92%).

2,2,2-*Trichloroethyl* 6α-*benzyloxypenicillanate* (9) (40%), a sample was recrystallized from ethanol–water, m.p. 54—55 °C; $[\alpha]_D$ +133° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 780 br cm^{-1} (2 × C=O); δ ([$^2H_6$]acetone) 1.53 and 1.60 (each 3 H, s, 2 × Me), 4.68 (1 H, s, 3-H), 4.70 and 4.81 (each 1 H, d, *J* 11.4 Hz, CH_2CCl_3), 4.79 (1 H, d, *J* 1.17 Hz, 6-H), 4.96 (2 H, s, CH_2Ph), 5.16 (1 H, d, *J* 1.17 Hz, 5-H), and 7.39 (5 H, m, aromatic H); *m/z* 441, 439, 437 (M^+), 350, 348, 346 (M^+ − $PhCH_2$), and 294, 292, 290 (M^+ − $PhCH_2OC$=C=O).

2,2,2-*Trichloroethyl* 6α-[2-(2-*hydroxyethyloxy*) *ethoxy*]-*penicillanate* (10) (58%), a pale yellow oil, homogeneous by t.l.c.; $[\alpha]_D$ +94° (1% in $CHCl_3$); $\nu_{max.}$ (film) 3 500 (OH) and 1 775 br cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.55 and 1.61 (each 3 H, s, 2 × Me), 2.39br (1 H, s, OH), 3.5—3.95 (8 H, m, 4 × OCH_2), 4.62 (1 H, s, 3-H), 4.73 (1 H, d, *J* 1.47 Hz, 6-H), 4.79 (2 H, s, CH_2CCl_3), and 5.36 (1 H, d, *J* 1.47 Hz, 5-H); *m/z* 439, 437, 435 (M^+), 350, 348, 346 (M^+ − $HOCH_2CH_2OCH_2CH_2$) and 294, 292, 290 (M^+ − $HOCH_2CH_2OCH_2CH_2OC$=C=O) (Found: M^+, 435.0087. $C_{14}H_{20}{}^{35}Cl_3NO_6S$ requires *M*, 435.0078). Treatment of a solution of 6-diazopenicillanate (1) (500 mg) in dioxan (5 ml) with BF_3·Et_2O (160 mg) gave the 6α-substituted penicillanate (10) (91 mg) after column chromatography.

2,2,2-*Trichloroethyl* 6α-(*hydroxybutyloxy*)*penicillanate* (11) (43%), an oil, homogeneous by t.l.c.; $[\alpha]_D$ +105° (1% in $CHCl_3$); $\nu_{max.}$ (film) 3 450 br (OH) and 1 770 br cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.55 and 1.62 (each 3 H, s, 2 × Me), 1.58 (1 H, s, OH), 1.4—1.8 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.65—3.75 (4 H, m, $CH_2CH_2CH_2CH_2$), 4.63 (1 H, s, 3-H), 4.65 (1 H, d, *J* 1.47 Hz, 6-H), 4.79 (2 H, s, CH_2CCl_3), and 5.33 (1 H, d, *J* 1.47 Hz, 5-H); *m/z* 423, 421, 419 (M^+), 350, 348, 346 (M^+ − $HOCH_2CH_2CH_2CH_2$), and 294, 292, 290 [M^+ − $HO(CH_2)_4OC$=C=O] (Found: M^+, 419.0124. $C_{14}H_{20}{}^{35}Cl_3NO_5S$ requires *M*, 419.0128).

2,2,2-*Trichloroethyl* 6α-*ethoxypenicillanate* (12) (26%), was prepared using diethyl ether as solvent, a colourless oil; $[\alpha]_D$ +123° (0.8% in $CHCl_3$); $\nu_{max.}$ (film) 1 770 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.27 (3 H, t, *J* 7.04 Hz, CH_2CH_3), 1.55 and 1.62 (each 3 H, s, 2 × Me), 3.6—3.9 (2 H, m, CH_2CH_3) 4.62 (1 H, s, 3-H), 4.64 (1 H, d, *J* 1.47 Hz, 6-H), 4.78 (2 H, s, CH_2CCl_3), and 5.33 (1 H, d, *J* 1.47 Hz, 5-H); *m/z* 379, 377, 375 (M^+), 350, 348, 346 (M^+ − Et), and 294, 292, 290 (M^+ − EtOC=C=O) (Found: M^+, 374.9870. $C_{12}H_{16}{}^{35}Cl_3NO_4S$ requires *M*, 374.9866).

2,2,2-*Trichloroethyl* 6α-*ethylthiopenicillanate* (14) (50%), a

colourless oil, $[\alpha]_D$ +107° (2% in $CHCl_3$); $\nu_{max.}$ (film) 1 770 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.32 (3 H, t, *J* 7.34 Hz, CH_2CH_3), 1.56 and 1.68 (each 3 H, s, 2 × Me), 2.72 (2 H, q, *J* 7.34 Hz, CH_2CH_3), 4.23 (1 H, d, *J* 1.76 Hz, 6-H), 4.66 (1 H, s, 3-H), 4.74 and 4.83 (each 1 H, d, *J* 12.03 Hz, CH_2CCl_3), and 5.26 (1 H, d, *J* 1.76 Hz, 5-H); *m/z* 395, 393, 391 (M^+), and 294, 292, 290 (M^+ − EtSC=C=O) (Found: M^+, 390.9657.$C_{12}H_{16}{}^{35}Cl_3NO_3S_2$ requires *M*, 390.9637).

2,2,2-*Trichloroethyl* 6α-*isobutylthiopenicillanate* (15) (50%), a colourless oil, $[\alpha]_D$ +117° (2% in $CHCl_3$); $\nu_{max.}$ 1 780 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.01 (6 H, d, *J* 6.45 Hz, Me_2CH), 1.55 and 1.67 (each 3 H, s, 2 × Me), 1.78 (1 H, m, Me_2CH), 2.57 (2 H, d, *J* 7.04 Hz, $CHCH_2$), 4.21 (1 H, d, *J* 1.75 Hz, 6-H), 4.66 (1 H, s, 3-H), 4.72 and 4.84 (each 1 H, d, *J* 12.7 Hz, CH_2CCl_3), and 5.24 (1 H, d, *J* 1.75 Hz, 5-H); *m/z* 423, 421, 419 (M^+), and 294, 292, 290 (M^+ − Me_2CHCH_2SC=C=O) (Found: M^+, 418.9951. $C_{14}H_{20}{}^{35}Cl_3NO_3S_2$ requires *M*, 418.9950).

2,2,2-*Trichloroethyl* 6α-*phenylacetoxypenicillanate* (16) (40%), a pale yellow oil, $[\alpha]_D$ +128° (1% in $CHCl_3$); $\nu_{max.}$ (film) 1 750 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.54 and 1.64 (each 3 H, s, 2 × Me), 3.73 (2 H, s, $PhCH_2$), 4.65 (1 H, s, 3-H), 4.78 (2 H, s, CH_2CCl_3), 5.25 (1 H, d, *J* 1.47 Hz, 5-H), 5.60 (1 H, d, *J* 1.47 Hz, 6-H), and 7.31 (5 H, s, aromatic H); *m/z* 469, 467, 465 (M^+), 351, 349, 347 (M^+ − $PhCH_2CO$) and 294, 292, 290 (M^+ − $PhCH_2CO_2C$=C=O)(Found: C, 46.55; H, 4.15; Cl, 22.5; N, 3.05; S, 6.8. $C_{18}H_{18}Cl_3NO_5S$ requires C, 46.31; H, 3.89; Cl, 22.79; N, 3.00; S, 6.87%).

2,2,2-*Trichloroethyl* 6α-*acetylthiopenicillanate* (17) (6%), an oil,$[\alpha]_D$ +128° (1% in $CHCl_3$); $\nu_{max.}$ (film) 1 785 br (2 × C=O) and 1 700 cm^{-1} (C=O); δ ($CDCl_3$) 1.56 and 1.71 (each 3 H, s, 2 × Me), 2.42 (3 H, s, MeCO), 4.67 (1 H, s, 3-H), 4.78 (2 H, s, CH_2CCl_3), and 4.92 and 5.18 (each 1 H, d, *J* 1.76 Hz, 6-H and 5-H); *m/z* 409, 407, 405 (M^+) and 294, 292, 290 (M^+ −CH_3COSC=O=O) (Found: M^+, 404.9437. $C_{12}H_{14}{}^{35}Cl_3NO_4S_2$ requires *M*, 404.9430).

2,2,2-*Trichloroethyl* 6α-*phenylselenopenicillanate* (26) (65%), recrystallised from ethyl acetate–light petroleum (51%), colourless crystals, m.p. 51—52 °C; $[\alpha]_D$ +137.5° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (2 × C=O) and 1 575 cm^{-1} (aromatic); δ ($CDCl_3$) 1.49 and 1.65 (each 3 H, s, 2 × Me), 4.51 (1 H, d, *J* 1.76 Hz, 6-H), 4.58 (1 H, s, 3-H), 4.69 (2 H, s, CH_2CCl_3), 5.23 (1 H, d, *J* 1.76 Hz, 5-H), and 7.26—7.68 (5 H, m, ArH); *m/z* 489, 487, 485 (M^+), and 294, 292, 290 (M^+ − PhSeC=C=O) (Found: C, 39.45; H, 3.35; Cl, 22.1; N, 2.75; S, 6.45. $C_{16}H_{16}Cl_3NO_3SSe$ requires C, 39.40; H, 3.31; Cl, 21.81; N, 2.87; S, 6.58%). Chromatography of the product mixtures from 6-diazopenicillanate (1)–phenylselenol reactions in dichloromethane–THF gave mixtures of 6α- and 6β-phenylselenopenicillanate (26) and (27). Fractional crystallization of one such mixture gave 2,2,2-*trichloroethyl* 6β-*phenylselenopenicillanate* (27) (16%), m.p. 109—110 °C; $[\alpha]_D$ +14° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (2 × C=O) and 1 575 cm^{-1} (aromatic); δ ([$^2H_6$]acetone) 1.59 and 1.74 (each 3 H, s, 2 × Me), 4.69 (1 H, s, 3-H), 4.99 (2 H, s, CH_2CCl_3) 5.17 (1 H, d, *J* 4.40 Hz, 6-H), 5.74 (1 H, d, *J* 4.40 Hz, 5-H), and 7.30—7.7 (5 H, m, aromatic H); *m/z* 489, 487, 485 (M^+), and 294, 292, 290 (M^+ − PhSeC=C=O) (Found: C, 39.7; H, 3.4; Cl, 21.75; N, 2.95; S, 6.50%).

2,2,2-*Trichloroethyl* 6,6-*bis*(*phenylseleno*)*penicillanate* (28) (43%), recrystallized from ethyl acetate–light petroleum (33%), m.p. 127 °C; $[\alpha]_D$ +88° (0.8% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 765 (2 × C=O) and 1 575 cm^{-1} (aromatic); δ ($CDCl_3$) 1.48 and 1.79 (each 3 H, s, 2 × Me), 4.53 (1 H, s, 3-H), 4.49 and 4.75 (each 1 H, d, *J* 11.74 Hz, CH_2CCl_3), 5.46 (1 H, s, 5-H), and 7.30—7.95 (10 H, m, aromatic H); *m/z* 489, 487, 485 (M^+ − PhSe), 415, 413, 411 [$(PhSe)_2C$=$CHSCMe_2$], 357, 355, 353 [$(PhSe)_2CHC$=O], 294, 292, 290 [M^+ −$(PhSe)_2C$=C=O] (Found: C, 41.4; H, 3.15; Cl, 16.55; N, 2.2; S, 4.75. $C_{22}H_{20}Cl_3NO_3SSe_2$ requires C, 41.11; H, 3.14; Cl, 16.55; N, 2.18; S, 4.99%).

Benzyl 6,6-*bis*(*phenylseleno*)*penicillanate* (29) (35%), recrystallized from ethyl acetate–light petroleum (25%), m.p. 105—106 °C; $[\alpha]_D$ +120° (0.8% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (β-lactam C=O), 1 740 (ester C=O), and 1 570 (aromatic) cm^{-1}; δ($CDCl_3$) 1.33 and 1.72 (each 3 H, s, 2 × Me), 4.40 (1 H, s, 3-H), 4.95 and 5.1 (each 1 H, *J* 12.3 Hz, CH_2Ph), 5.38 (1 H, s, 5-H), and 7.1—7.9 (15 H, m, aromatic H); *m/z* 603, 601, 599 (M^+) (Found: C, 53.85; H, 4.35; N, 2.1; S, 5.1. $C_{27}H_{25}NO_3SSe_2$ requires C, 53.90; H, 4.15; N, 2.35; S, 5.35%).

2,2,2-*Trichloroethyl* 6α-*chloro*-6β-*phenylselenopenicillanate* (30), was prepared from phenylseleninyl chloride (1 equiv.) and diazopenicillanate (1) in dichloromethane. Nitrogen evolution occurred immediately on addition of the phenylseleninyl chloride to the diazopenicillanate solution, no $BF_3{\cdot}Et_2O$ being required. The crude product was recrystallized from ethyl acetate–light petroleum to give 6α-*chloro*-6β-*phenylselenopenicillanate* (30) (64%), m.p. 115—115.5 °C; $[\alpha]_D$ +90° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 780 (β-lactam C=O), 1 760 (ester C=O), and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.58 and 1.83 (each 3 H, s, 2 × Me), 4.69 (1 H, s, 3-H), 4.79 (2 H, s, CH_2CCl_3), 5.68 (1 H, s, 5-H), and 7.25—7.85 (5 H, m, aromatic H); *m/z* 523, 521, 519 (M^+).

Benzyl 6α-*chloro*-6β-*phenylselenopenicillanate* (31), from phenylseleninyl chloride (1 equiv.) and diazopenicillanate (2) in dichloromethane, no catalyst being required. Recrystallization from ethyl acetate–light petroleum gave 6α-*chloro*-6β-*phenylselenopenicillanate* (31) (26%), colourless crystals, m.p. 103—104 °C; $[\alpha]_D$ +106° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 780 (β-lactam C=O), 1 745 (ester C=O), and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.41 and 1.76 (each 3 H, s, 2 × Me), 4.57 (1 H, s, 3-H), 5.19 (2 H, s, CH_2Ph), 5.64 (1 H, s, 5-H), and 7.3—7.85 (10 H, m, aromatic H); *m/z* 483, 481, 479 (M^+) (Found: C, 52.2; H, 4.35; Cl, 7.3; N, 2.85; S, 6.7. $C_{21}H_{20}ClNO_3SSe$ requires C, 52.45; H, 4.19; Cl, 7.37; N, 2.91; S, 6.67%).

2,2,2-*Trichloroethyl* 6α-*Benzylthiopenicillanate* (13).—Addition of $BF_3{\cdot}Et_2O$ (79 mg, 0.56 mmol) to a solution of 6-diazopenicillanate (1) (2 g, 5.6 mmol) and toluenethiol (690 mg, 5.6 mmol) in dichloromethane (30 ml) initiated nitrogen evolution. The mixture was then stirred at 20 °C for 15 min. Work-up in the usual way gave a mixture of two products which were separated by column chromatography. The less polar material, isolated as an oil (930 mg), was crystallized from ethyl acetate–light petroleum to give 2,2,2-*trichloroethyl* 6α-*benzylthiopenicillanate* (13) (583 mg, 23%), m.p. 59—61 °C; $[\alpha]_D$ +119° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.49 and 1.63 (each 3 H, s, 2 × Me), 3.87 (2 H, s, $PhCH_2S$), 4.17 (1 H, d, *J* 1.46 Hz, 6-H), 4.61 (1 H, s, 3-H), 4.75 (1 H, s, CH_2CCl_3), 4.94 (1 H, d, *J* 1.46 Hz, 5-H), and 7.32 (5 H, m, aromatic H); *m/z* 457, 455, 453 (M^+), 294, 292, 290 (M^+ − $PhCH_2SC$=C=O) (Found: C, 44.8; H, 3.95; Cl, 23.35; N, 3.0; S, 13.90. $C_{17}H_{18}Cl_3NO_3S_2$ requires C, 44.89; H, 3.98; Cl, 23.39; N, 3.08; S, 14.10%). The more polar material was isolated as an oil, and identified as the *thiobis*(*penicillanate*) (18) (500 mg), $[\alpha]_D$ +142° (1% in $CHCl_3$); $\nu_{max.}$ (film) 1 770 br cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.55 and 1.67 (each 3 H, s, 2 × Me), 4.39 (1 H, d, *J* 1.76 Hz, 6-H), 4.66 (1 H, s, 3-H), 4.79 (2 H, s, CH_2CCl_3), and 5.27 (1 H, d, *J* 1.76 Hz, 6-H); *m/z* 696, 694, 692 (M^+) (Found: M^+, 691.8781. $C_{20}H_{22}{}^{35}Cl_6N_2O_6S_3$ requires *M*, 691.8772.

The formation of the thiobis(penicillanate) (18) could be avoided by using an excess of toluenethiol (5—10 equiv.). Treatment of 6α-benzylthiopenicillanate (13) with 6-diazopenicillanate (1) under the usual conditions gave the penicillanate sulphide (18) (47%) after column chromatography.

2,2,2-*Trichloroethyl* 6α-*Thiopenicillanate* (20).—Sodium methoxide (20 mg) in methanol (10 ml) was added during 1 h to 6α-acetylthiopenicillanate (17) (150 mg) in methanol (15 ml) at −78 °C under nitrogen, and the mixture stirred for 3 h. The crude reaction mixture was washed with ice-cold dilute HCl, ice-cold aqueous sodium hydrogencarbonate, and ice-cold water, dried ($MgSO_4$), and concentrated under reduced pressure to give an oil (76 mg) which t.l.c. indicated to contain two major components. Chromatography on silica gel gave the less polar component, identified as 2,2,2-*trichloroethyl* 6α-*thiopenicillanate* (20) (22 mg), a colourless oil; $\nu_{max.}$ 2 560 (SH) and 1 780 cm^{-1} (β-lactam and ester C=O); δ ($CDCl_3$) 1.55 and 1.67 (each 3 H, s, 2 × Me), 2.34 (1 H, d, *J* 10.57 Hz, SH), 4.16 (1 H, dd, *J* 10.56 and 1.76 Hz, 6-H), 4.65 (1 H, s, 3-H), 4.78 (2 H, s, CH_2CCl_3), and 5.21 (1 H, d, *J* 1.76 Hz, 5-H); *m/z* 367, 365, 363 (M^+) and 294, 292, 290 (M^+ − HSC=C=O) (Found: M^+, 362.9329. $C_{10}H_{12}{}^{35}Cl_3NO_3S_2$ requires *M*, 362.9325). The more polar component was identified as *methyl* 6α-*mercaptopenicillanate* (21) (21 mg), a colourless oil; $\nu_{max.}$ (film) 2 540 (SH), 1 775 (β-lactam C=O), and 1 750 cm^{-1} (ester C=O); δ ($CDCl_3$) 1.46 and 1.62 (each 3 H, s, 2 × Me), 2.32 (1 H, d, *J* 10.5 Hz, SH), 3.79 (3 H, s, OMe), 4.12 (1 H, dd, *J* 10.56 and 1.76 Hz, 6-H), 4.51 (1 H, s, 3-H), and 5.18 (1 H, d, *J* 1.76 Hz, 5-H); *m/z* 247 (M^+) and 173 (M^+ − HS−C=C=O).

Benzyl bromide (36 mg) and triethylamine (19 mg) were added to 6α-mercaptopenicillanate (20) (70 mg) in ethanol under nitrogen, and the reaction mixture stirred for 0.5 h before being diluted with dichloromethane (20 ml), washed with water, and dried ($MgSO_4$). Concentration *in vacuo* and chromatography gave 6α-benzylthiopenicillanate (13) (23 mg) identical (^1H n.m.r., i.r., m.s.) with a sample prepared as described above.

Reaction of 6-*Diazopenicillanate* (1) *with Allyl Phenyl Sulphide*.—$BF_3{\cdot}Et_2O$ (10 mg) was added to a solution of 6-diazopenicillanate (1) (250 mg) and allyl phenyl sulphide (116 mg) in dichloromethane (10 ml) and the mixture stirred for 0.5 h. Work-up as usual gave an oil which was separated into three components by column chromatography. The first eluted product was crystallized from ethyl acetate–light petroleum to give 2,2,2-*trichloroethyl* 6α-*allyl*-6β-*phenylthiopenicillanate* (39) (92 mg), m.p. 87—88 °C; $[\alpha]_D$ +81° (1.6% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 760 (2 × C=O), 1 640 (C=C), and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.57 and 1.81 (each 3 H, s, 2 × Me), 2.55 (2 H, m, CH_2−CH=), 4.65 (1 H, s, 3-H), 4.73 and 4.82 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 4.95—5.30 (2 H, m, vinylic H), 5.43 (1 H, s, 5-H), 5.5—5.95 (1 H, m, vinylic H), and 7.26—7.76 (5 H, m, aromatic H); *m/z* 483, 481, 479 (M^+) (Found: M^+, 478.9950. $C_{19}H_{20}{}^{35}Cl_3NO_3S_2$ requires *M*, 478.9922). The second eluted material was crystallized from ethyl acetate–light petroleum to give 2,2,2-*trichloroethyl* 6β-*allyl*-6α-*phenylthiopenicillanate* (40) (65 mg), m.p. 58—59 °C; $[\alpha]_D$ +197° (1.6% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 760 (2 × C=O), and 1 640 (C=C), 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.49 and 1.63 (each 3 H, s, 2 × Me), 2.80 (2 H, m, CH_2−CH=), 4.44 (1 H, s, 3-H), 4.57 and 4.74 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 5.15 (2 H, m, vinylic H), 5.30 (1 H, s, 5-H), 5.75—6.15 (1 H, m, vinylic H), and 7.25—7.65 (5 H, m, aromatic H); *m/z* 483, 481, 479 (M^+) (Found: M^+, 478.9949). The third eluted product, a colourless oil was identified as 2,2,2-*trichloroethyl* 6α-*phenylthiopenicillanate* (47) (10 mg); $[\alpha]_D$ +114° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (2 × C=O) and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.50 and 1.65 (each 3 H, s, 2 × Me), 4.45 (1 H, d, *J* 2 Hz, 6-H), 4.59 (1 H, s, 3-H), 4.68 (2 H, s, CH_2CCl_3), 5.20 (1 H, d, *J* 2 Hz, 5-H), and 7.35 (5 H, m, aromatic H); *m/z* 443, 441, 439 (M^+) and 294, 292, 290 (M^+ − PhSC=C=O) (Found: M^+, 438.9653. $C_{16}H_{16}{}^{35}Cl_3NO_3S_2$ requires *M*, 438.9637).

Reaction of 6-*Diazopenicillanate* (1) *with Allyl Methyl Sulphide*.—$BF_3{\cdot}Et_2O$ (79 mg) was added to a solution of 6-diazopenicillanate (1) (2 g) and allyl methyl sulphide (1.2 g) in dichloromethane (60 ml) and the mixture stirred for 0.5 h. Work-up as usual gave an oil which was separated into two fractions by column chromatography. The first eluted material was a mixture of two compounds. Crystallization from ethyl acetate–light petroleum gave 2,2,2-*trichloroethyl* 6α-*allyl*-6β-*methylthiopenicillanate* (41) (694 mg), m.p. 104—104.5 °C; $[\alpha]_D$ +95° (1.2% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 765br cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.54 and 1.75 (each 3 H, s, 2 × Me), 2.26 (3 H, s, MeS), 2.79 (2 H, m, CH_2−CH=), 4.57 (1 H, s, 3-H), 4.72 and 4.81 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 5.21 (1 H, m, vinylic H), 5.28 (1 H, m, vinylic H), 5.34 (1 H, s, 5-H), and 5.65—6.1 (1 H, m, vinylic H); *m/e* 421, 419, 417 (M^+) (Found: C, 39.7; H, 4.2; N, 3.1. $C_{14}H_{18}Cl_3NO_3S_2$ requires C, 40.15; H, 4.33; N, 3.34%). The mother-liquor from this crystallization (169 mg) consisted of a mixture of the two C-6 epimers of 2,2,2-trichloroethyl 6-allyl-6-methylthiopenicillanate (41) and (42), ratio (41) : (42) = 30 : 70, respectively. From the ^1H n.m.r. spectrum of this mixture, the following peaks were assigned to the 6β-allyl-6α-methylthiopenicillanate (42), δ ($CDCl_3$) 1.56 and 1.69 (each 3 H, s, 2 × Me), 2.24 (3 H, s, SMe), 2.75—2.95 (2 H, m, CH_2−CH=), 4.58 (1 H, s, 3-H), 4.71 and 4.81 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 5.13 and 5.30 (each 1 H, m, vinylic H), 5.37 (1 H, s, 5-H), and 5.65—6.1 (1 H, m, vinylic H). The second eluted product was identified as 2,2,2-*trichloroethyl* 6α-*methylthiopenicillanate* (48) (110 mg), a colourless oil; $[\alpha]_D$ +103° (2% in $CHCl_3$); $\nu_{max.}$ (film) 1 780 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.56 and 1.68 (each 3 H, s, 2 × Me), 2.23 (3 H, s, MeS), 4.23 (1 H, d, *J* 2 Hz, 6-H) 4.67 (1 H, s, 3-H), 4.75 and 4.80 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), and 5.29 (1 H, d, *J* 2 Hz, 5-H); *m/z* 381, 379, 377 (M^+), 334, 332, 330 (M^+ − MeS) and 294, 292, 290 (M^+ − MeS−C=C=O).

Reaction of 6-*Diazopenicillanate* (1) *with Allyl Phenyl Selenide*.—$BF_3{\cdot}Et_2O$ (10 mg) was added to a solution of 6-diazopenicillanate (1) (250 mg) and allyl phenyl selenide (148 mg) [21] in dichloromethane (10 ml). After 0.5 h at 20 °C the reaction was worked up in the usual way to give a mixture of three major components (t.l.c.) which were separated by column chromatography. The first eluted product was crystallized from ethyl acetate–light petroleum to give 2,2,2-*trichloroethyl* 6α-*allyl*-6β-*phenylselenopenicillanate* (43) (114 mg), m.p. 105—106 °C; $[\alpha]_D$ +91° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 760 (2 × C=O), 1 640 (C=C), and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.55 and 1.84 (each 3 H, s, 2 × Me), 2.52 (2 H, m, CH_2−CH=), 4.65 (1 H, s, 3-H), 4.72 and 4.83 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 4.95—5.2 (2 H, m, vinylic H), 5.40 (1 H, s, 5-H), 5.55—5.95 (1 H, m, vinylic H), and 7.25—7.86 (5 H, m, aromatic H); *m/z* 531, 529, 527 (M^+) (Found: C, 43.35; H, 4.0; Cl, 20.05; N, 2.6; S, 5.85. $C_{19}H_{20}Cl_3NO_3SSe$ requires C, 43.24; H, 3.82; Cl, 20.15; N, 2.65; S, 6.08%). The second eluted component was crystallized from ethyl acetate–light petroleum to give 2,2,2-*trichloroethyl* 6β-*allyl*-6α-*phenylselenopenicillanate* (44) (62 mg), m.p. 80—81 °C; $[\alpha]_D$ +182.5° (1% in $CHCl_3$); $\nu_{max.}$ 1 765 (2 × C=O), 1 640 (C=C), and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.47 and 1.62 (each 3 H, s, 2 × Me), 2.84 (2 H, m, CH_2−CH=), 4.41 (1 H, s, 3-H), 4.53 and 4.76 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 5.16 (1 H, m, vinylic H), 5.30 (1 H, m, vinylic H), 5.35 (1 H, s, 5-H), 5.65—6.05 (1 H, m, vinylic H), and 7.25—7.75 (5 H, m, aromatic H); *m/z* 531, 529, 527 (M^+) (Found: C, 43.5; H, 3.85; Cl, 20.15; N, 2.6; S, 6.05%). The third eluted material was 6α-phenylselenopenicillanate (26) (56 mg) identical (^1H n.m.r., i.r., t.l.c.) with samples prepared as described above.

Reaction of 6-*Diazopenicillanate* (2) *with Allyl Phenyl Selenide*.—BF_3·Et_2O (45 mg) was added to a solution of 6-diazopenicillanate (2) (1 g) and allyl phenyl selenide (682 mg) [21] in dichloromethane (60 ml). After 0.5 h the reaction mixture was worked up as usual to give a mixture of three components (t.l.c.) which were separated by column chromatography. The first eluted product was crystallised from ethyl acetate–light petroleum to give *benzyl* 6α-*allyl*-6β-*phenylselenopenicillanate* (45) (250 mg), m.p. 112—113 °C; $[\alpha]_D$ +55° (0.8% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (β-lactam C=O), 1 745 (ester C=O), 1 640 (C=C), and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.41 and 1.77 (each 3 H, s, 2 × Me), 2.51 (2 H, m, CH_2–CH=), 4.54 (1 H, s, 3-H), 4.92—5.12 (2 H, m, vinylic H), 5.18 (2 H, s, CH_2Ph), 5.34 (1 H, s, 5-H), 5.55—5.85 (1 H, m, vinylic H), and 7.2—7.85 (10 H, m, aromatic H); *m/z* 489, 487, 485 (M^+) (Found: C, 58.85; H, 5.35; N, 2.85; S, 6.35. $C_{24}H_{25}NO_3SSe$ requires C, 59.25; H, 5.18; N, 2.85; S, 6.59%). The second eluted component was identified as *benzyl* 6β-*allyl*-6α-*phenylselenopenicillanate* (46) (111 mg), a colourless oil; $[\alpha]_D$ +173° (3.2% in $CHCl_3$); $\nu_{max.}$ (film) 1 770 (β-lactam C=O), 1 750 (ester C=O), 1 640 (C=C), and 1 580 and 1 500 cm^{-1} (aromatic); δ ($CDCl_3$) 1.31 and 1.55 (each 3 H, s, 2 × Me), 2.82 (2 H, m, CH_2–CH=), 4.30 (1 H, s, 3-H), 4.95 and 5.11 (each 1 H, d, *J* 12 Hz, CH_2Ph), 5.15 (2 H, m, vinylic H), 5.29 (1 H, s, 5-H), 5.6—5.9 (1 H, m, vinylic H), and 7.15—7.80 (10 H, m, aromatic H); *m/z* 489, 487, 485 (M^+) (Found: M^+, 487.0723. $C_{24}H_{25}NO_3{}^{78}Se$ requires *M*, 487.0718.) The third eluted component was crystallized from ethyl acetate–light petroleum to give *benzyl* 6α-*phenylselenopenicillanate* (49) (100 mg), m.p. 78—79 °C; $[\alpha]_D$ +149° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 775 (β-lactam C=O), 1 745 (ester C=O), and 1 580 and 1 500 cm^{-1} (aromatic); δ ($CDCl_3$) 1.34 and 1.58 (each 3 H, s, 2 × Me), 4.47 (1 H, s, 3-H), 4.48 (1 H, d, *J* 1.76 Hz, 6-H), 5.10 (2 H, s, CH_2Ph), 5.19 (1 H, d, *J* 1.76 Hz, 5-H), and 7.2—7.65 (10 H, m, aromatic H); *m/z* 449, 447, 445 (M^+) (Found: C, 56.25; H, 4.85; N, 3.05; S, 7.05. $C_{21}H_{21}NO_3SSe$ requires C, 56.50; H, 4.74; N, 3.14; S, 7.18%).

Reaction of 6-*Diazopenicillanate* (1) *with* γ,γ-*Dimethylallyl Phenyl Sulphide* (50).—$Cu(acac)_2$ (20 mg) was added to a solution of 6-diazopenicillanate (1) (250 mg) and γ,γ-dimethylallyl phenyl sulphide (50) (312 mg) [22] in dichloromethane (10 ml). After 0.5 h at 20 °C, the reaction mixture was diluted with dichloromethane (20 ml), washed with dilute HCl, aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated under reduced pressure to give an oil which t.l.c. showed to contain one major component. This product was purified by column chromatography to give 2,2,2-*trichloroethyl* 6α-(3-*methylbut*-1-*en*-3-*yl*)-6β-*phenylthiopenicillanate* (52) (193 mg), as a colourless oil; $[\alpha]_D$ +60° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (2 × C=O), 1 640 (C=C), and 1 580 and 1 520 cm^{-1} (aromatic); δ ($CDCl_3$) 1.26 (6 H, s, $-CMe_2$–CH=), 1.53 and 1.65 (each 3 H, s, 2 × Me), 4.41, (1 H, s, 3-H), 4.67 and 4.81 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 4.95—5.15 (2 H, m, vinylic H), 5.38 (1 H, s, 5-H), 5.7—6.1 (1 H, m, vinylic H), and 7.2—7.8 (5 H, m, aromatic H); *m/z* 511, 509, and 507 (M^+) (Found: M^+, 507.0258. $C_{21}H_{24}{}^{35}Cl_3NO_3S_2$ requires *M*, 507.0261).

Reaction of 6-*Diazopenicillanate* (1) *with* α,α-*Dimethylallyl Phenyl Sulphide* (51).—$Cu(acac)_2$ (20 mg) was added to a solution of 6-diazopenicillanate (1) (250 mg) and α,α-dimethylallyl phenyl sulphide (51) (312 mg) [22] in dichloromethane (10 ml). After 0.5 h at 20 °C the reaction mixture was worked up as described above to give an oil which t.l.c. indicated as containing two major components. These were separated by column chromatography. The first eluted product was identified as 2,2,2-*trichloroethyl* 6α-(3-*methylbut*-2-*en*-1-*yl*)-6β-*phenylthiopenicillanate* (53) (60 mg), a colourless oil, $[\alpha]_D$ +66° (1% in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 770 (2 × C=O) and 1 580 cm^{-1} (aromatic); δ ($CDCl_3$) 1.41 and 1.68 (each 3 H, s, 2 × Me), 1.56 and 1.81 (each 3 H, s, 2 × Me), 2.49 (2 H, m, CH_2–CH=), 4.65 (1 H, s, 3-H), 4.73 and 4.82 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 5.10 (1 H, m, vinylic H), 5.36 (1 H, s, 5-H), and 7.2—7.8 (5 H, aromatic H); *m/z* 511, 509, and 507 (M^+) (Found: M^+, 507.0226. $C_{21}H_{24}{}^{35}Cl_3NO_3S_2$ requires *M*, 507.0261). The second eluted product was identified as 2,2,2-*trichloroethyl* 6β-(3-*methylbut*-2-*en*-1-*yl*)-6α-*phenylthiopenicillanate* (54) (40 mg), a colourless oil; $[\alpha]_D$ +170° (1% in $CHCl_3$); $\nu_{max.}$ 1 770 cm^{-1} (2 × C=O); δ ($CDCl_3$) 1.48 and 1.62 (each 3 H, s, 2 × Me), 1.62 and 1.77 (each 3 H, s, 2 × Me), 2.71 (2 H, m, CH_2–CH=), 4.43 (1 H, s, 3-H), 4.57 and 4.73 (each 1 H, d, *J* 12 Hz, CH_2CCl_3), 5.20 (1 H, m, vinylic H), 5.27 (1 H, s, 5-H), and 7.2—7.7 (5 H, m, aromatic H); *m/z* 511, 509, and 507 (M^+) (Found: M^+, 507.0270).

2,2,2-*Trichloromethyl* 6α-*Allyl*-6β-*bromopenicillanate* (55).—$Cu(acac)_2$ (20 mg) was added to a solution of 6-diazopenicillanate (1) (250 mg) in freshly distilled allyl bromide (3 ml). After 0.5 h at 20 °C the reaction mixture was worked up as usual, and the crude product rapidly chromatographed on neutral alumina with ethyl acetate–light petroleum (3 : 7) as eluant, to give 2,2,2-*trichloroethyl* 6α-*allyl*-6β-*bromopenicillanate* (55) (150 mg), as a pale green oil; $\nu_{max.}$ ($CHCl_3$) 1 780 (β-lactam C=O), 1 765 (ester C=O), and 1 640 cm^{-1} (C=C); δ ($CDCl_3$) 1.56 and 1.67 (each 3 H, s, 2 × Me), 2.89 (2 H, m, CH_2–CH=), 4.60 (1 H, s, 3-H), 4.79 (2 H, s, CH_2CCl_3), 5.19 (1 H, m, vinylic H), 5.35 (1 H, m, vinylic H), 5.63 (1 H, s, 5-H), and 5.7—6.0 (1 H, m, vinylic H); *m/z* 453, 451, 449 (M^+), and 294, 292, 290 (M^+ − CH_2=CH–CH_2CBr–C=O) (Found: M^+, 448.9045. $C_{13}H_{15}{}^{79}Br^{35}Cl_3NO_3S$ requires *M*, 448.9019).

Table 2. Fractional co-ordinates (× 10^4) for the non-hydrogen atoms with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
S(1)	5 978(1)	3 832(1)	1 686(2)
S(2)	4 398(1)	3 792(1)	3 094(2)
C(2)	5 895(2)	3 652(2)	−1 116(8)
C(3)	5 697(2)	4 446(2)	−2 037(7)
N(4)	5 300(2)	4 830(2)	−502(5)
C(5)	5 466(2)	4 699(2)	1 664(7)
C(6)	4 693(2)	4 718(2)	2 139(7)
C(7)	4 605(2)	4 790(2)	−190(8)
O(7)	4 144(2)	4 803(2)	−1 392(5)
C(8)	4 439(2)	5 395(2)	3 412(8)
C(9)	4 679(3)	6 149(3)	2 689(10)
C(10)	4 323(4)	6 668(4)	1 813(14)
C(11)	3 504(2)	3 904(2)	2 927(7)
C(12)	3 135(3)	4 198(3)	4 583(9)
C(13)	2 438(3)	4 264(3)	4 426(11)
C(14)	2 104(3)	4 010(3)	2 724(10)
C(15)	2 467(2)	3 704(3)	1 112(11)
C(16)	3 162(2)	3 653(3)	1 205(9)
C(17)	6 292(2)	4 931(3)	−2 731(7)
O(17)	6 494(2)	4 955(2)	−4 465(6)
O(18)	6 565(2)	5 314(2)	−1 155(5)
C(19)	7 069(2)	5 874(2)	−1 616(9)
C(20)	6 799(2)	6 650(3)	−1 060(9)
C(21)	5 334(3)	3 085(3)	−1 541(10)
C(22)	6 579(3)	3 354(3)	−1 897(10)
Cl(1)	7 440(1)	7 329(1)	−1 552(4)
Cl(2)	6 601(1)	6 679(1)	1 597(3)
Cl(3)	6 069(1)	6 861(1)	−2 497(4)

X-*Ray Structure Determination of Compound* (39).—Crystals

Table 3. Bond lengths with e.s.d.s in parentheses

S(1)–C(2)	1.854(5)	S(1)–C(5)	1.822(4)
S(2)–C(6)	1.828(4)	S(2)–C(11)	1.777(4)
C(2)–C(3)	1.562(6)	C(2)–C(21)	1.511(7)
C(2)–C(22)	1.532(7)	C(3)–N(4)	1.434(5)
C(3)–C(17)	1.516(6)	N(4)–C(5)	1.463(6)
N(4)–C(7)	1.386(5)	C(5)–C(6)	1.555(5)
C(6)–C(7)	1.528(7)	C(6)–C(8)	1.529(6)
C(7)–O(7)	1.198(6)	C(8)–C(9)	1.477(7)
C(9)–C(10)	1.281(9)	C(11)–C(12)	1.397(7)
C(11)–C(16)	1.377(7)	C(12)–C(13)	1.382(7)
C(13)–C(14)	1.361(9)	C(14)–C(15)	1.376(9)
C(15)–C(16)	1.374(7)	C(17)–O(17)	1.196(6)
C(17)–O(18)	1.337(6)	O(18)–C(19)	1.425(5)
C(19)–C(20)	1.501(6)	C(20)–Cl(1)	1.762(5)
C(20)–Cl(2)	1.770(6)	C(20)Cl(3)	1.755(5)

Table 4. Bond angles (°) with e.s.d.s in parentheses

C(2)–S(1)–C(5)	94.9(2)	C(6)–S(2)–C(11)	101.4(2)
S(1)–C(2)–C(3)	104.3(3)	S(1)–C(2)–C(21)	110.8(4)
C(3)–C(2)–C(21)	109.3(4)	S(1)–C(2)–C(22)	107.8(3)
C(3)–C(2)–C(22)	113.3(4)	C(21)–C(2)–C(22)	111.2(4)
C(2)–C(3)–N(4)	106.6(4)	C(2)–C(3)–C(17)	114.7(3)
N(4)–C(3)–C(17)	111.6(3)	C(3)–N(4)–C(5)	118.2(3)
C(3)–N(4)–C(7)	128.1(4)	C(5)–N(4)–C(7)	94.2(3)
S(1)–C(5)–N(4)	105.2(3)	S(1)–C(5)–C(6)	124.0(3)
N(4)–C(5)–C(6)	88.2(3)	S(2)–C(6)–C(5)	111.1(3)
S(2)–C(6)–C(7)	111.9(3)	C(5)–C(6)–C(7)	85.2(3)
S(2)–C(6)–C(8)	113.5(3)	C(5)–C(6)–C(8)	116.4(3)
C(7)–C(6)–C(8)	115.8(4)	N(4)–C(7)–C(6)	92.1(3)
N(4)–C(7)–O(7)	130.7(5)	C(6)–C(7)–O(7)	137.1(4)
C(6)–C(8)–C(9)	114.5(4)	C(8)–C(9)–C(10)	126.8(6)
S(2)–C(11)–C(12)	120.7(4)	S(2)–C(11)–C(16)	120.0(4)
C(12)–C(11)–C(16)	119.2(4)	C(11)–C(12)–C(13)	119.4(5)
C(12)–C(13)–C(14)	120.8(6)	C(13)–C(14)–C(15)	119.6(5)
C(14)–C(15)–C(16)	120.6(6)	C(11)–C(16)–C(15)	120.2(5)
C(3)–C(17)–O(17)	123.9(4)	C(3)–C(17)–O(18)	111.4(4)
O(17)–C(17)–O(18)	124.7(4)	C(17)–O(18)–C(19)	117.6(4)
O(18)–C(19)–C(20)	108.9(4)	C(19)–C(20)–Cl(1)	108.2(3)
C(19)–C(20)–Cl(2)	109.8(4)	Cl(1)–C(20)–Cl(2)	108.4(3)
C(19)–C(20)–Cl(3)	110.6(4)	Cl(1)–C(20)–Cl(3)	110.5(3)
Cl(2)–C(20)–Cl(3)	109.4(3)		

of (39), $C_{19}H_{20}Cl_3NO_3S_2$, $M = 480.86$, are fine colourless needles elongated along c; orthorhombic, $a = 19.710(3)$, $b = 17.486(3)$, $c = 6.496(1)$ Å, $U = 2\,239$ Å^3, $D_c = 1.43$ g cm^{-3}, $Z = 4$, space group P2,2,2.

Data for a crystal mounted along its c direction were measured on a Siemens off-line four-circle diffractometer using Ni-filtered Cu-K_α radiation. A total of 1 945 independent reflections were measured ($O \leqslant 60°$) using the θ—2θ scan technique with the 'five value' measuring procedure.[23] Of these 259 had $|F_o| < 3\sigma(|F_o|)$ and were classed as unobserved. The net count of the 1 100 reflections, measured as a reference every 50 reflections fell by *ca.* 20% during the period of the data collection (*ca.* 4 days) indicating that slow decomposition had occurred. The data were brought to a uniform arbitrary scale by use of this reflection and Lorentz and polarisation, but no absorption, corrections were applied. The structure was solved by direct methods by the application of the program MULTAN to 230 reflections with normalised structure factors (E's) $\geqslant 1.47$. An E-map computed for the phase solution with the highest 'combined figure of merit' gave plausible positions for a 13 atom fragment of the molecule. The remaining atoms were found in a difference electron-density map.

The non-hydrogen atoms were refined anisotropically. The hydrogen atoms, with the exception of the methyl groups which were refined as rigid bodies, were placed at calculated positions and allowed to ride on their parent carbons. Refinement was terminated at a final $R = 0.040$.

The absolute configuration was confirmed by refinement of a single 'free variable' η which multiples all f''.[24] This variable refined to a value of +1.05(6) indicating that the co-ordinate set was of the correct chirality.

Computations were carried out on the Imperial College Cyber 174, the University of London CDC 7600, and on the laboratory Eclipse S140 computers, using in the main programs belonging to the SHELX76 and SHELXTL program systems.

Table 2 lists the fractional atomic co-ordinates. Tables 3 and 4 give the bond lengths and valence angles respectively. The anisotropic temperature factors, the hydrogen co-ordinates, and the structure factors have been deposited as a Supplementary Publication [SUP. No. 23388 (13 pages)].*

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* For details of the Supplementary publications scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans.* 1, 1981, Index issue.

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