Synthesis of Penicillanate Dimers: An *X*-Ray Crystal Structure of a Penicillanylidene-penicillanate

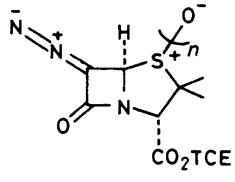
Barbara Hanlon and D. Ivor John *,†
Department of Chemistry, University of London, King's College, Strand, London WC2R 2LS
David J. Williams
The Chemical Crystallography Laboratory, Imperial College of Science and Technology, South Kensington, London SW7 2AY

On treatment with copper bis(acetoacetonate) in dichloromethane, 2,2,2-trichloroethyl 6-diazopenicillanate (**1**), and its (1*S*)-*S*-oxide and *S*,*S*-dioxide (**2**) and (**3**), were found to lose nitrogen and dimerize to give mixtures of (*E*)- and (*Z*)- alkenes (**5**)—(**10**), in which the (*E*)-isomers (**5**)—(**7**) predominated. The structure of the minor dimer from the 6-diazopenicillanate (**1**) was established as (**8**) by *X*-ray crystallography.

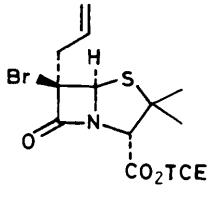
During the course of earlier studies on the reaction between the 6-diazopenicillanate (**1**) and allyl bromide it was noticed that if the reaction was carried out using only a slight excess of allyl bromide in dichloromethane with copper bis(acetoacetate) as catalyst, then two minor side-products were formed (*ca.* 9%) in addition to the 6-allyl-6-bromopenicillanate (**4**).[1] On the basis of their ^{1}H n.m.r. and mass spectra, these new products were tentatively identified as the penicillanylidene-penicillanates (**5**) and (**8**).[2] We now describe details of the preparation and characterization of these compounds, and of their *S*-oxides and *S*,*S*-dioxides.

Results and Discussion

It was found that column chromatography of the mixture of products formed by treatment of the 6-diazopenicillanate (**1**)[3]



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

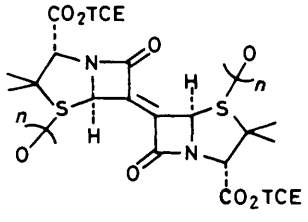


(**4**)

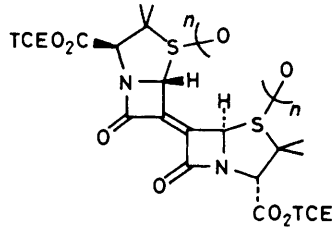
with copper bis(acetoacetonate) in dichloromethane, led to the isolation of two products, in yields of 13 and 8%, which were identified as 6-penicillanylidene dimers. The major, less polar isomer, showed molecular ion peaks at *m*/*z* 622, 660, and 658, in its mass spectrum, and had an ^{1}H n.m.r. spectrum consistent with the presence of the penicillanate nucleus. Similar spectroscopic data were obtained for the minor isomer, but the available data did not establish the alkene geometry.

The structure and stereochemistry of the minor dimer were established by *X*-ray diffraction. The *X*-ray diffraction study showed the presence of two crystallographically independent molecules‡ [Figures 1 and 2] both possessing (*Z*)-alkene geometry as depicted in formula (**8**). The major product was therefore identified as (**5**).

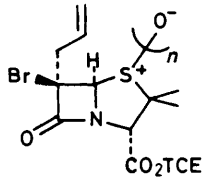
Similar results were obtained when the 6-diazopenicillanate sulphoxide (**2**) and sulphone (**3**) were treated with copper bis(acetoacetonate) in dichloromethane.[4] From the sulphoxide reaction two dimeric products were isolated in yields of 36 and 9%, whereas the sulphone gave two products in 28 and 16% yields. In each case the major product was identified as the (*E*)-isomer by comparison of spectroscopic and physical data with those of the sulphide dimers (**5**) and (**8**) (see Table 1). The major product from each reaction was found to have the higher melting point, the lower frequency carbonyl absorption in its i.r. spectrum, and the less shielded 5-H proton in its ^{1}H n.m.r. spectrum. Although not conclusive, these trends suggest that the



(**5**) *n* = 0
(**6**) *n* = 1
(**7**) *n* = 2



(**8**) *n* = 0
(**9**) *n* = 1
(**10**) *n* = 2



(**11**) *n* = 1
(**12**) *n* = 2

† Deceased 8th December, 1984. Please send correspondence on this paper to: Dr. E. J. Thomas, The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY

‡ It can be seen that the gross conformations of the two independent molecules differ significantly (Figures 1 and 2), the most pronounced differences being in the relative orientations of the trichloroethyl esters and in the folding of one of the thiazolidine rings (*cf.* [N(14)–C(18)] in molecules 1 *vs.* [N(35)–C(31)] in molecule 2). The folding of the thiazolidine ring in Figure 2 was also accompanied by a marked distortion from planarity of the associated β-lactam ring. An additional feature was an observed torsion angle for the C(11)–C(12) bond of 19(5)° in molecule 1, an angle expected to be near zero as a result of the extended conjugation of the O(10) to O(13) system. The equivalent C(37)–C(38) torsion angle in molecule 2 was 2(4)°.

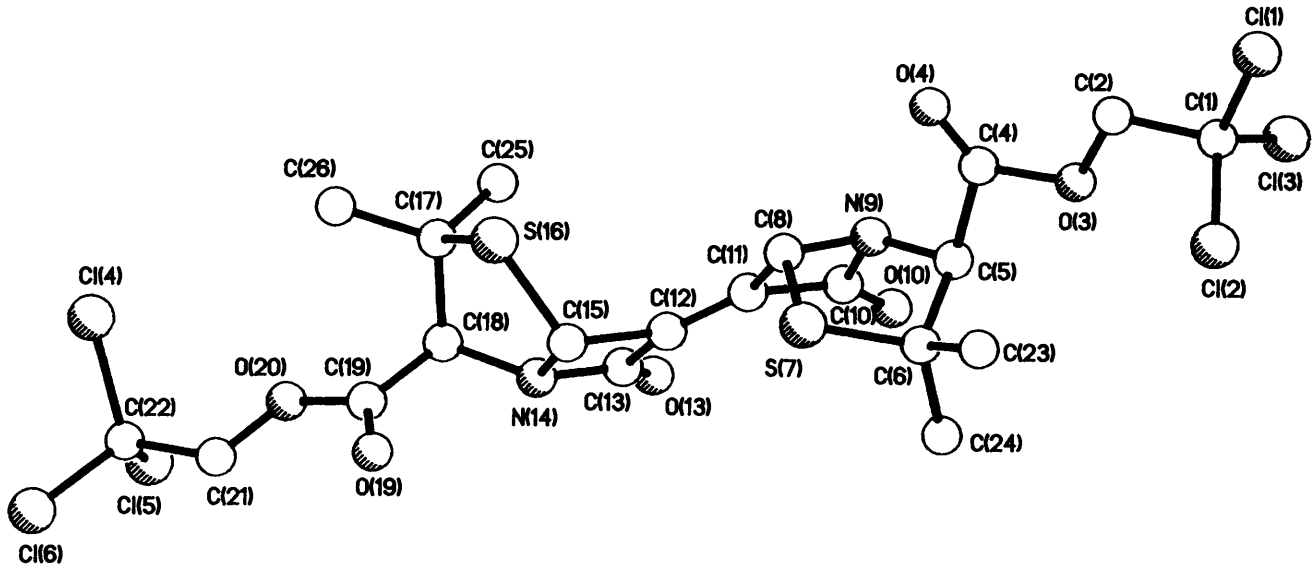


Figure 1. Molecular structure of compound (**8**) (first crystallographically independent molecule).

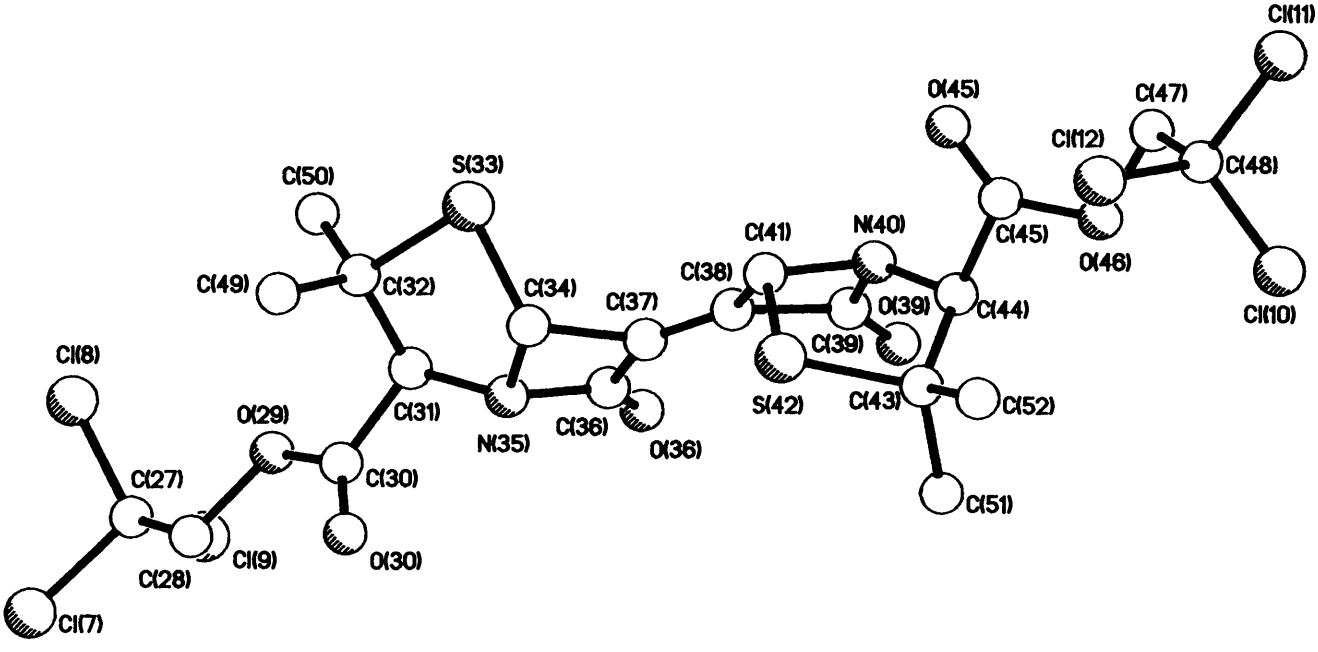


Figure 2. Molecular structure of compound (**8**) (second crystallographically independent molecule).

Table 1. Selected data for penicillanate dimers

Dimer	Yield (%)	M.p. (°C)	$\nu_{max.}$(C=O) cm^{-1}	δ_H(5-H) (p.p.m.)
(**5**)	13	63—65	1 770br	5.98
(**8**)	8	54—56	1 790, 1 770	5.83
(**6**)	36	163—164.5	1 780	5.70
(**9**)	9	139—141	1 795, 1 760	5.51
(**7**)	28	144—146	1 780	5.41
(**10**)	16	115—117	1 810, 1 770	5.26

major isomer in each case has the same double-bond geometry, and so the major dimeric products from the *S*-oxide and *S,S*-dioxide reactions were identified as the (*E*)-isomers (**6**) and (**7**).

Finally, since the penicillanate dimers (**5**) and (**8**) were first detected in reactions between the 6-diazopenicillanate (**1**) and allyl bromide,[2] it was of interest to examine the reactions between allyl bromide and the 6-diazo *S*-oxide (**2**) and the *S,S*-dioxide (**3**). However when catalysed by copper bis(acetoacetonate), only a single β-lactam product was isolated from each of these reactions, a result consistent with the reported reaction between benzyl 6-diazopenicillanate *S*-oxide (**2**; R=CH_2Ph) and allyl bromide.[5] These were identified as the 6-allyl-6-bromopenicillanate *S*-oxide (**11**) and *S,S*-dioxide (**12**).

The C-6 configuration of these products could not be established by ^{1}H n.m.r., no useful n.O.e. enhancements being observed, but that shown is consistent with the stereoselectivity of reaction of 6-diazopenicillanates and allylic sulphides.[1]

Experimental

For details of general procedures see the first paper in this series.

Preparation of 6-Penicillanylidenepenicillanates.—From 6-diazopenicillanate (**1**). Copper bis(acetoacetonate) (20 mg, 0.07 mmol) was added to a solution of 2,2,2-trichloroethyl 6-diazopenicillanate (**1**) (250 mg, 0.7 mmol)[3] in dichloromethane (20 ml), and the mixture stirred at room temperature for 45 min. It was washed with dilute aqueous HCl (0.1 M, 2 × 10 ml), saturated aqueous sodium hydrogen carbonate (2 × 10 ml), and water (2 × 10 ml), and dried ($MgSO_4$). Concentration under reduced pressure gave an oil which was chromatographed on silica using ethyl acetate and light petroleum (1:9) as eluant. The first eluted product was identified as the (*E*)-*dimer* (**5**) (30 mg, 13%), m.p. 63—65 °C (from ethyl acetate–light petroleum); $\nu_{max.}$($CHCl_3$) 1 770 cm^{-1}; δ_H($CDCl_3$) 1.56 and 1.64 (each 6 H, s, 2 × Me), 4.73 (2 H, s, 2 × 3-H) 4.77 and 4.83 (each 2 H, d, *J* 12 Hz, 2 × HC*H*CCl_3), and 5.98 (2 H, s, 2 × 5-H); $\lambda_{max.}$ 231 nm (ε 12, 620) and 293 nm (ε 4 496); *m*/*z* 661. The second eluted product was identified as the (*Z*)-*dimer* (**8**) (19 mg, 8%), m.p. 54—56 °C (from ethyl acetate–light petroleum); $\nu_{max.}$($CHCl_3$) 1 790 and 1 770 cm^{-1}; δ_H($CDCl_3$) 1.59 and 1.67 (each 6 H, s, 2 × Me), 4.78 (2 H, s, 2 × 3-H), 4.81 (4 H, s, 2 × CH_2CCl_3), and 5.83 (2 H, s, 2 × 5-H); $\lambda_{max.}$ 233 nm (ε 15 900) and 285 nm (ε 31 85); *m*/*z*, 589.

From 6-Diazopenicillanate Sulphoxide (**2**). Following the procedure outlined above, 2,2,2-trichloroethyl 6-diazopenicillanate (1*S*)-*S*,*S*-dioxide (**2**) (200 mg, 0.53 mmol)[4] and copper bis(acetoacetonate) (15 mg, 0.053 mmol) gave two products which were separated by chromatography on silica using chloroform as eluant. The first eluted product was identified as the (E)-*dimer* (**6**) (66 mg, 36%), m.p. 163—164 °C (from ethyl acetate–light petroleum) (Found: M^+, 689.8800. $C_{20}H_{20}{}^{35}Cl_6N_2O_8S_2$ requires *M*, 689.8792); $\nu_{max.}$($CHCl_3$) 1 780, and 1 060 cm^{-1}; δ_H($CDCl_3$) 1.36 and 1.80 (each 6 H, s, 2 × Me), 4.68 and 5.07 (each 2 H, s, *J* 12 Hz, 2 × HC*H*CCl_3), 4.89 (2 H, s, 2 × 3-H), and 5.70 (2 H, s, 2 × 5-H); *m*/*z* 690 (M^+). The second eluted product was identified as the (*Z*)-*dimer* (**9**) (17 mg, 9%), m.p. 139—141 °C (from ethyl acetate–light petroleum) (Found: M^+, 689.8802. $C_{20}H_{20}{}^{35}Cl_6N_2O_8S_2$ requires *M*, 689.8792); $\nu_{max.}$($CHCl_3$) 1 795, 1 760, and 1 050 cm^{-1}, δ_H($CDCl_3$) 1.38 and 1.82 (each 6 H, s, 2 × Me), 4.69 and 5.06 (each 2 H, d, *J* 12 Hz, 2 × HC*H*CCl_3), 4.88 (2 H, s, 2 × 3-H), and 5.51 (2 H, s, 2 × 5-H); *m*/*z*, 690 (M^+).

From 6-diazopenicillanate S,S-dioxide (**3**). Following the procedure outlined above, 2,2,2-trichloroethyl 6-diazopenicillanate *S*,*S*-dioxide (**3**) (200 mg, 0.51 mmol)[4] and copper bis(acetoacetonate) (15 mg, 0.05 mmol) gave two products which were separated by chromatography on silica using dichloromethane as eluant. The first eluted product was identified as the (Z)-*dimer* (10) (30 mg, 16%), m.p. 115—117 °C (from ethyl acetate–light petroleum) (Found: M^+, 721.8696. $C_{20}H_{20}N_2O_{10}S_2{}^{35}Cl_6$ requires *M*, 721.8690), $\nu_{max.}$($CHCl_3$) 1 810, 1 770, 1 340, and 1 120 cm^{-1}; δ_H($CDCl_3$) 1.56 and 1.71 (each 6 H, s, 2 × Me), 4.73 and 5.02 (each 2 H, d, *J* 12 Hz, 2 × HC*H*CCl_3), 4.75 (2 H, s, 2 × 3-H), and 5.26 (each 2 H, s, 2 × 5-H); *m*/*z* 722 (M^+). The second eluted product was identified as the (E)-*dimer* (**7**) (52 mg, 28%), m.p. 144—146 °C (from ethyl acetate–light petroleum) (Found: M^+, 721.8697. $C_{20}H_{20}{}^{35}Cl_6N_2O_{10}S_2$ requires *M*, 721.8690); $\nu_{max.}$($CHCl_3$) 1 780, 1 330, and 1 120 cm^{-1}; δ_H($CDCl_3$) 1.55 and 1.71 (each 6 H, s, 2 × Me), 4.71 and 5.02 (each 2 H, d, *J* 12 Hz, 2 × HC*H*CCl_3), 4.75 (2 H, s, 2 × 3-H), and 5.41 (2 H, s, 2 × 5-H); *m*/*z* 722 (M^+).

2,2,2-Trichloroethyl 6α-Allyl-6β-bromopenicillanate (1S)-S-*Oxide* (**11**).—Allyl bromide (320 mg, 2.67 mmol) and copper bis(acetoacetonate) (15 mg, 0.053 mmol) were added to the 6-diazopenicillanate *S*-oxide (**2**) (200 mg, 0.53 mmol) in dichloromethane (10 ml) at room temperature, and the mixture stirred for 30 min. The reaction was then washed with dilute aqueous HCl, saturated sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Concentration under reduced

Table 2. Atom co-ordinates (× 10^4) for compound (**8**)

Atom	*x*	*y*	*z*
Cl(1)	2 950(5)	8 033	8 399(4)
Cl(2)	3 357(8)	10 137(7)	8 085(5)
Cl(3)	1 963(5)	9 095(9)	7 041(5)
C(1)	2 918(18)	8 967(24)	7 623(14)
C(2)	3 558(17)	8 553(18)	7 221(12)
O(3)	3 568(9)	9 268(11)	6 585(8)
C(4)	4 114(13)	8 952(19)	6 132(10)
O(4)	4 495(10)	8 202(10)	6 176(8)
C(5)	4 121(15)	9 985(16)	5 603(10)
C(6)	4 763(13)	10 871(14)	6 011(10)
S(7)	5 724(4)	10 458(5)	5 940(3)
C(8)	5 270(12)	9 653(17)	5 076(11)
N(9)	4 412(11)	9 615(13)	4 949(9)
O(10)	4 254(12)	10 136(12)	4 212(9)
C(10)	3 612(9)	10 498(12)	3 819(7)
C(11)	5 130(13)	10 070(16)	4 260(11)
C(12)	5 618(14)	10 394(19)	3 825(12)
C(13)	5 492(11)	10 760(18)	2 930(12)
O(13)	4 910(9)	10 924(13)	2 407(8)
N(14)	6 329(13)	10 733(12)	3 047(10)
C(15)	6 568(15)	10 360(18)	3 931(11)
S(16)	7 064(5)	9 090(6)	3 913(4)
C(17)	6 882(15)	9 027(19)	2 807(12)
C(18)	6 794(13)	10 211(17)	2 540(11)
C(19)	7 623(17)	10 733(20)	2 694(15)
O(19)	8 004(12)	11 283(16)	3 291(11)
O(20)	7 941(10)	10 627(15)	2 074(9)
C(21)	8 660(16)	11 132(24)	2 136(15)
C(22)	8 955(20)	10 836(23)	1 353(18)
C(23)	4 808(15)	10 978(17)	6 897(11)
C(24)	4 452(16)	11 931(15)	5 625(12)
C(25)	6 042(15)	8 520(20)	2 419(13)
C(26)	7 623(16)	8 507(20)	2 639(14)
Cl(4)	9 170(5)	9 397(9)	1 464(6)
Cl(5)	8 295(7)	11 148(10)	597(5)
Cl(6)	9 962(7)	11 456(12)	1 522(8)
Cl(7)	2 095(5)	7 924(8)	14 999(4)
Cl(8)	1 109(6)	8 327(10)	13 445(5)
Cl(9)	1 833(7)	6 315(7)	13 836(6)
C(27)	1 975(15)	7 666(20)	13 964(12)
C(28)	2 724(15)	7 982(21)	13 821(11)
O(29)	2 597(11)	7 809(15)	12 946(9)
C(30)	3 269(18)	7 983(18)	12 715(12)
O(30)	3 950(11)	8 235(13)	13 137(8)
C(31)	3 043(13)	7 924(18)	11 819(11)
C(32)	2 589(13)	8 898(20)	11 410(11)
S(33)	2 950(4)	9 028(6)	10 494(3)
C(34)	3 978(14)	8 599(17)	11 019(11)
N(35)	3 842(12)	7 780(14)	11 590(10)
C(36)	3 989(19)	6 925(21)	11 141(14)
O(36)	3 847(14)	6 009(13)	11 178(11)
C(37)	4 350(16)	7 670(20)	10 648(12)
C(38)	4 728(14)	7 622(17)	10 089(11)
C(39)	4 970(18)	6 648(21)	9 622(14)
O(39)	5 010(13)	5 699(13)	9 672(10)
N(40)	5 235(12)	7 355(16)	9 188(11)

pressure gave an oil, which was chromatographed on silica using ethyl acetate–light petroleum (1:1) as eluant, to give 2,2,2-*trichloroethyl* 6α-*allyl*-6β-*bromopenicillanate* (1S)-S-*oxide* (**11**) (54 mg, 22%), m.p. 136—138 °C (from ethyl acetate–light petroleum); $\nu_{max.}(CHCl_3)$ 1 790, 1 765, and 1 050 cm^{-1}; $\delta_H(CDCl_3)$ 1.32 and 1.76 (each 3 H, s, Me), 2.78 (1 H, dd, *J*, 5, 15 Hz, HC*H*), 3.53 (1 H, dd, *J* 8, 15 Hz, HCH), 4.69 and 5.04 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 4.75 (1 H, s, 3-H), 4.85 (1 H, s, 5-H), 5.41 (2 H, m, vinylic H), and 5.98 (1 H, m, vinylic H); *m/z* 468 (M^+).

2,2,2-*Trichloroethyl* 6α-*Allyl*-6β-*bromopenicillanate* S,S-*Dioxide* (**12**).—Following the procedures outlined above, 6-diazopenicillanate sulphone (**3**) (200 mg, 0.51 mmol), copper bis(acetoacetonate) (15 mg, 0.051 mmol), and allyl bromide (322 mg, 2.67 mmol) gave, after chromatography on silica using dichloromethane as eluant, 2,2,2-*trichloroethyl* 6α-*allyl*-6β-*bromopenicillanate* S,S-*dioxide* (**12**) (95 mg, 39%), m.p. 109—110 °C (from ethyl acetate–light petroleum); $\nu_{max.}(CHCl_3)$ 1 810, 1 770, 1 330, and 1 120 cm^{-1}; $\delta_H(CDCl_3)$ 1.50 and 1.67 (each 3 H, s, Me), 2.84 (1 H, dd, *J* 6, 15 Hz, *H*CH), 3.50 (1 H, dd, *J* 8, 15 Hz, HC*H*), 4.62 (1 H, s, 3-H), 4.81 (1 H, s, 5-H), 4.70 and 5.01 (each 1 H, d, *J* 12 Hz, *H*CHCCl$_3$), 5.40 (2 H, m, vinylic H), and 5.92 (1 H, m, vinylic H); $\delta_C(CDCl_3)$ 17.73 and 20.22 (each q, CH_3), 35.22 (t, $CH_2CH{=}CH_2$), 62.68 (d, 5-C), 62.90 (s, 2-C), 64.86 (s, 6-C), 72.76 (d, 3-C), 75.22 (t, CH_2CCl_3), 93.79 (s, CCl_3), 121.64 (t, vinylic C), 130.11 (d, vinylic C), and 164.76 and 169.72 (each s, C=O); *m/z* 446 (M^+ − Cl).

Crystal Data for (**8**).—$C_{20}H_{20}Cl_6N_2O_6S_2$, M = 676.2*, monoclinic, a = 16.707(5), b = 12.585(4), c = 17.598(5) Å, β = 106.03(3)°, U = 3 556 Å^3, μ(Cu-K_α) = 59 cm^{-1}*, λ = 1.541 78 Å, space-group P_{11}, Z = 4, (2 crystallographically independent molecules in the asymmetric unit), D_c = 1.27 g cm^{-3}*, $F(000)$ = 1 378. Approximate crystal dimensions: 0.07 × 0.07 × 0.20 mm.

Data Collection and Processing.—3 170 Independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $\theta \leq 55°$] were measured on a Nicolet R3M diffractometer with Cu-K_α radiation (graphite monochromator) and using ω-scans.

Structural Analysis and Refinement.—The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically. The hydrogen atom positions were idealised (C–H = 0.96 Å), assigned isotropic thermal parameters [U(H) = 1.2U_{eq}(C)], and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares and converged to give R = 0.015, unit weights were used. The high value of R is a consequence of both poor crystal quality and disorder in the four CCl_3 groups and the presence of disordered solvent fragments. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

Fractional atomic co-ordinates for the non-hydrogen atoms are given in Table 2. Bond lengths, bond angles, the fractional co-ordinates of the hydrogen atoms, and the isotropic thermal parameters and the anisotropic thermal parameters for the non-hydrogen atoms are available on request from the Cambridge Crystallographic Data Centre.†

* Contains contributions from unidentified solvent fragments.

† See Instructions for Authors (1986), para. 5.6.3 in, *J. Chem. Soc., Perkin Trans. 1*, 1986, issue 1.

References

1 P. J. Giddings, D. I. John, E. J. Thomas, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2757.
2 P. J. Giddings, Ph.D. Thesis, University of London, 1979.
3 J. C. Sheehan, Y. S. Lo, J. Lölliger, and C. C. Podewell, *J. Org. Chem.*, 1974, **39**, 1444.
4 B. Hanlon and D. I. John, *J. Chem. Soc., Perkin Trans. 1*, 1986, preceding paper.
5 S. W. McCombie, U. S. Patent, 4 237 051, *Chem. Abstr.*, **94**, P175113*g*.

Received 20*th January* 1986; *Paper* 6/152