Transformations of Penicillins. Part VII.[1a] Vinylic Sulphoxides from Penicillins and their Reactions

By **Derek H. R. Barton, Ian H. Coates,** and **Peter G. Sammes,*** Chemistry Department, Imperial College, London SW7 2AY
Caroline M. Cooper, Glaxo Research Limited, Greenford, Middlesex

The sulphenic acid intermediates produced thermally from penicillin *S*-oxides undergo addition to acetylenic esters to produce conjugated sulphoxides in good yields. These vinylic sulphoxides are subject to nucleophilic addition reactions. with, for example. diethyl sodiomalonate, which proceed in a stereoselective manner. Intramolecular addition reactions have also been observed.

THE formation and chemistry of vinylic sulphoxides has recently attracted attention.[2] An important property of these systems is the ease with which they undergo Michael-type addition reactions.[3] Furthermore, because of the chirality of the sulphoxide function, kinetically controlled addition reactions proceed in a stereoselective manner.[4] A method for the formation of vinylogous sulphoxides from penicillin derivatives was recently reported by us[5] and an alternative route to similar systems has also been described.[6] In this paper some

[1] (*a*) Part VI, R. D. Allan, D. H. R. Barton, M. Girijavallabha, and P. G. Sammes, preceding paper; (*b*) Part V, I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, 1187.

[2] G. A. Russell and L. Ochrymowycz, *J. Org. Chem.*, 1970, **35**, 2106; D. J. Abott, S. Colonna, and C. J. M. Stirling, *Chem. Comm.*, 1971, 471; D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Amer. Chem. Soc.*, 1972, **94**, 2891; E. Block, *ibid.*, p. 642; F. A. Carey and O. Hernandez, *J. Org. Chem.*, 1973, **38**, 2670.

[3] G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Letters*, 1973, 323.

[4] G. Tsuchihashi, S. Mitamura, and K. Ogura, *Tetrahedron Letters*, 1973, 323.

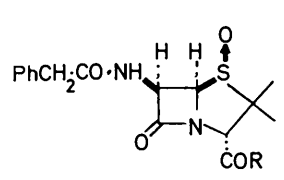
[5] D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J.C.S. Chem. Comm.*, 1973, 303.

[6] J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57.

further examples of this method are described and some of the reactions of these systems are noted.

In an examination of the chemistry of penicillin *S*-oxides [7] the trichloroethyl ester (1; R = O·CH_2·CCl_3) was found to react with dimethyl butynedioate in benzene at reflux to give a mixture of two compounds which could not be separated by preparative t.l.c. Although treatment of the mixture with either triethylamine or alumina only afforded the cyclisation product (2; R = CH_2·CCl_3), prior reduction of the sulphoxide

In contrast to the trichloroethyl ester (1; R = O·CH_2·CCl_3), trapping of the intermediate from the corresponding methyl ester (1; R = OMe) gave the initial adducts (7; R = OMe) and (8; R = OMe), which could be isolated in a ratio of *ca.* 1 : 1. The former isomer was unstable and slowly produced the cyclic adduct (2; R = Me) on treatment with either silica or triethylamine. Treatment of the latter isomer (8; R = OMe) with triethylamine did not effect cyclisation but instead led to formation of the conjugated



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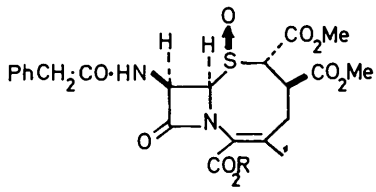

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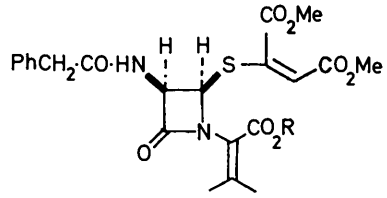

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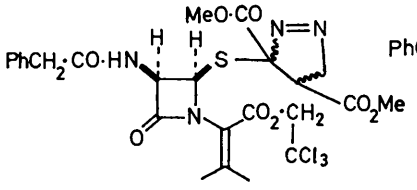

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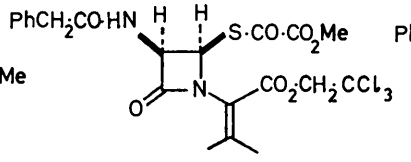

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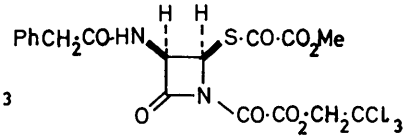

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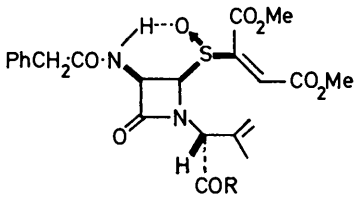

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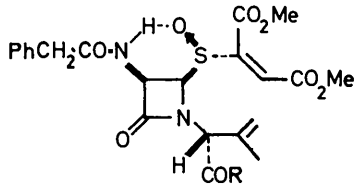


(8)

function in the crude reaction product, with potassium iodide and acetyl chloride in dimethylformamide, followed by reaction with triethylamine, gave a good yield of the uncyclised sulphide (3; R = CH_2·CCl_3). Some comparative reactions of the two unsaturated ester functions in this product were investigated. For example, addition of diazomethane proceeded rapidly (within 1 h) to give the epimeric adducts (4). Reaction of the remaining dimethylacrylic ester system with diazomethane is known to be a much slower process.[8] Ozonolysis occurred preferentially at the vinylic sulphide bond, to form the thio-oxalate ester (5). Further ozonolysis afforded the expected oxamide (6).

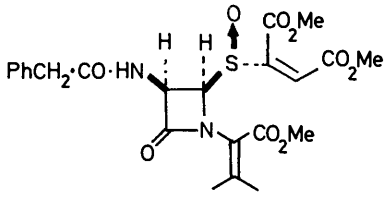
isomer (9). Configurational assignments previously made to the adducts (7; R = OMe) and (8; R = OMe) [5] relied on the assumptions that the addition of the sulphenic acid intermediate across the acetylenic bond proceeds in a *cis*-manner and that the resulting sulphoxide oxygen atom remains hydrogen-bonded to the side chain phenylacetamido-group as indicated. The unstable adduct (7; R = OMe) must have the *S*-configuration at the trigonal sulphur atom, in which the maleic ester residue is held in a favourable position for cyclisation. In the stable, *R*-isomer (8; R = OMe) the maleic ester group is held away from the adjacent isopentenoyl residue.

[7] D. H. R. Barton and P. G. Sammes, *Proc. Roy. Soc.*, 1971, *B*, **179**, 345.

[8] R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, *J.C.S. Perkin I*, 1973, 1182.

Further stereochemical evidence for the *cis*-addition of the sulphenic acid across the acetylenic bond was obtained from the reaction of the sulphoxide (1; R = OMe) with ethyl propiolate, which again formed two isomeric adducts; the n.m.r. spectrum of each showed the presence of two *trans*-disposed hydrogen atoms (J_{trans} 15 Hz). Treatment of the major isomer (10), which could be isolated by direct crystallisation from the reaction mixture, with triethylamine gave a quantitative yield of the conjugated derivative (11).

Although selective ozonolysis of the nitrogen substituent in the azetidinone sulphides (3; R = Me) had failed, isolation of the stable sulphoxide (9) from the methyl ester series allowed a further attempt at this process. It was anticipated that the sulphoxide group



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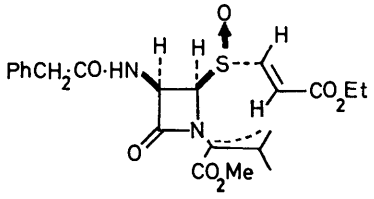
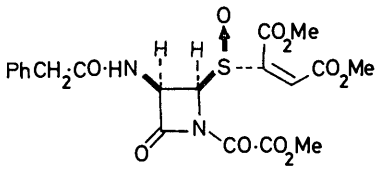


(10) βγ-isomer
(11) αβ-isomer



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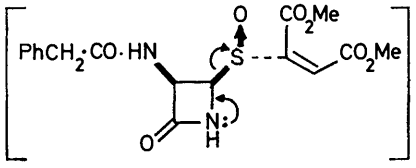

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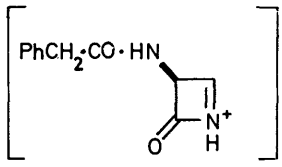

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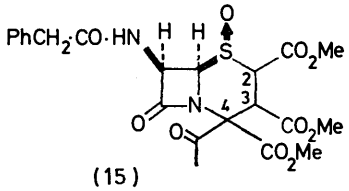


(15)

would deactivate the adjacent double bond and hence favour attack on the remaining conjugated double bond. In the event, the oxamide (12) was formed selectively by ozonolysis in dichloromethane at −78°.[9] However, attempted hydrolysis of this compound, under a variety of conditions, gave a mixture of products in which the β-lactam group had been destroyed. Since it is known that oxamides of the type (12), but in the sulphide series, can be hydrolysed to liberate the azetidinone nucleus, it is assumed that the sulphoxide residue is too good a departing group under the conditions of solvolysis tried and that the expected product (13) reacts further to produce the azetone intermediate (14), which collapses by further hydrolysis.

Ozonolysis of the initial mixture of unconjugated adducts (7; R = OMe) and (8; R = OMe) also proceeded smoothly. The product ketones were themselves unstable but, either on treatment with triethylamine or on silica gel chromatography, gave, amongst other products, a moderate yield of the cyclised product (15), as a mixture of two epimers. The n.m.r. spectra of both epimers showed the signals of the protons at positions 2 and 3 as a pair of doublets, J 12 Hz, indicating that the stereochemistry at these positions was similar in both isomers. Since intramolecular hydrogen bonding between the phenylacetamido-group and the sulphoxide system was apparent in both isomers, they are assumed to be epimeric about position 4, and to arise from cyclisation of the ketone derived from the (*S*)-sulphoxide adduct (7; R = OMe).

Intramolecular cyclisation of the type (7) ⟶ (2) can be avoided, in principle, by using penicillanic acid derivatives in which the acidity of the proton at position 3 is reduced. In earlier work it has been shown that amide derivatives fulfill this criterion.[10] Since hydrazides should behave similarly and since carboxylic acid protecting groups based on substituted hydrazide systems have been developed,[11] the use of the *NN'*-diisopropylhydrazide (1; R = NPr^i·NHPr^i) in the trapping reactions with dimethyl butynedioate was explored, The trapping reaction rapidly afforded the desired products (7; R = NPr^i·NHPr^i) and (8; R = NPr^i·NHPr^i). The relative ease and efficiency of this particular reaction (reaction time less than 16 h; for the esters, reaction times *ca.* 30 h) implies that the hydrazide group is intimately involved in the sulphoxide ⟶ sulphenic acid process. We suggest that this is due to a steric effect of the isopropyl substituents buttressing the methyl groups at position 2 and hence facilitating the sigmatropic proton transfer step. A similar rate enhancement has been observed in certain reactions when the side-chain amide substituent, a phenoxyacetyl residue, is replaced by the bulkier phthalimido-group.[12] The adducts (7; R = NPr^i·NHPr^i) and (8; R = NPr^i·NHPr^i) were unaffected by treatment with triethylamine. The assignments of configuration at the sulphur atom were made by a comparison of the chemical shifts of the vinylic sulphoxide protons with those in the methyl ester series. Ozonolysis of the (*S*)-sulphoxide (7; R = NPr^i·NHPr^i) did not afford the expected

[9] R. D. G. Cooper and F. L. Jose, *J. Amer. Chem. Soc.*, 1972, **94**, 1021.

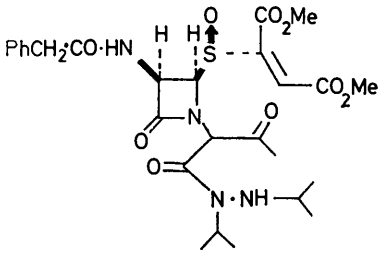
[10] D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

[11] D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 929.

[12] R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1970, **92**, 5010.

ketone (16) but instead gave a good yield of the pyrazolinone (17).

The availability of the base-stable adducts (7; R = $NPr^{i}{\cdot}NHPr^{i}$) and (8; R = $NPr^{i}{\cdot}NHPr^{i}$) allowed a study of addition reactions across the conjugated sulphoxide bond. Michael-type addition of diethyl sodiomalonate to the sulphoxide (8; R = $NPr^{i}{\cdot}NHPr^{i}$) occurred in dry benzene to give an almost quantitative yield of an adduct (18), isolated as a crystalline solid. N.m.r. spectroscopy established that only one of the eight possible stereoisomers had been formed. A similar result was obtained with ethyl sodioacetoacetate, to give the adduct (19). These results are consistent with the work of Tsuchihashi *et al.*, who established the mode of anionic additions to simple αβ-unsaturated sulphoxides.[4] Such additions, when carried out under the irreversible conditions described here, proceed in a kinetically controlled manner. Treatment of the adduct (19) with diazomethane in methanol gave the vinyl ether (20; R = $NPr^{i}{\cdot}NHPr^{i}$) as a mixture of the geometrical isomers (n.m.r. analysis). We hoped to be able to use such derivatives by effecting oxidation across the vinylic ether bond to give an α-keto-ester and subsequent cyclisation across the liberated β-lactam nitrogen atom. Thus, oxidation of the hydrazide function with lead tetra-acetate and pyridine in dry benzene at room temperature gave a mixture of the corresponding acids (20; R = OH) which were methylated with diazomethane, treated with triethylamine in order to effect conjugation [to give (21)], and ozonised in dichloromethane. Hydrolysis of the resulting oxamide (22) with dilute phosphoric acid in aqueous tetrahydrofuran produced the free azetidinone (23). Further ozonolysis of this, or its oxamide precursor, led to extensive decomposition. The azetidinones proved to be unstable and decomposed on heating in benzene solution at reflux or on treatment with tertiary bases at room temperature. Again azetone intermediates of the type (14) are suspected. Attempted reduction of the free azetidinone (23) with phosphorus tribromide in dimethylformamide [13] did not give the expected sulphide but, instead, a product, $C_{12}H_{10}N_2O_3$. This material contained an intact β-lactam ring ($\nu_{max.}$ 1800 cm^{-1}), which was *cis*-substituted [τ 3·72 and 4·38 (doublets, J_{cis} 4 Hz)], and a formyl group, incorporated from the solvent. Two possible structures are (24) and (25). The lack of any aldehyde absorptions at 2720—2820 cm^{-1} in the i.r. spectrum, together with the presence of only one exchangeable proton and the mass spectral fragmentations indicated, supports the former structure (24). This compound must be formed by intramolecular cyclisation of an azetone intermediate followed by formylation by the phosphorus tribromide–dimethylformamide reagent.



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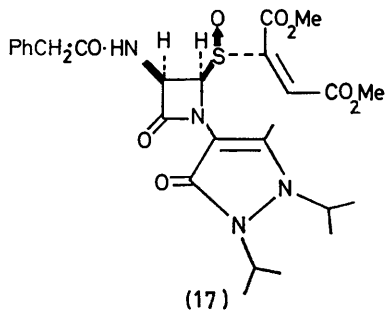

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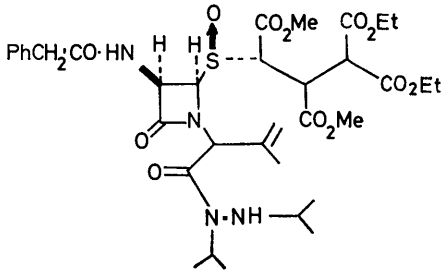

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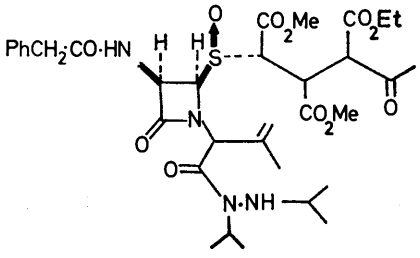

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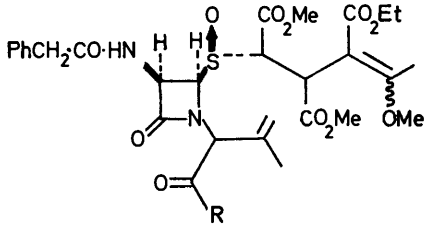

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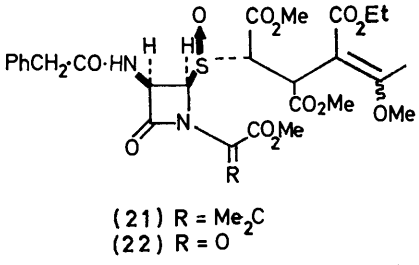


(21) R = Me_2C
(22) R = O

One further series of reactions involving use of the efficient trapping of sulphenic acids by acetylene esters has been tried. The availability of the *o*-nitrobenzoate (26) [1] allowed an examination of its reaction with dimethyl butynedioate. From the mixture of products, one major adduct was isolated, which was not the expected compound (27) but instead was the isomer (28), in which the ester system had undergone an allylic rearrangement reaction [see arrows, formula (27)]. A similar rearrangement takes place on heating the *o*-nitrobenzoate (26) in the absence of a trapping agent;

[13] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683.

two of the products are the isothiazolinones (29) and (30), the latter arising on further heating of the unrearranged isomer. Small amounts of these isothiazolinones were also produced in the trapping reactions of the ester (26) with the acetylene derivative. Both could be reduced with zinc dust and ammonium chloride to give the same product, shown to be the dihydrothiazinone (31), possibly formed by preferential reduction of the nitrogen–sulphur bond to give intermediates of the type (32), followed either by intramolecular displacement of the aromatic ester group as indicated, or by prior formation of the acylimine species (33) before addition of the thiol group across the imine function. Two other compounds also isolated from the thermolysis of the *o*-nitrobenzoate (26) were the cephem derivatives (34) and (35). These must arise by a nucleophilic reaction of the sulphenic acid intermediate (36) as indicated. Nucleophilic reactions of sulphenic acids have precedent.[14]

Although selective ozonolysis of the derivative (28) proceeded smoothly to give the formyl derivative (37) and the acetone derivative (38), the formyl group of the former (37) was not removed by hydrolysis under the conditions reported by Heusler.[15] Osmylation of the ester (28) with osmium tetroxide in benzene,[16] followed by treatment with sodium disulphite, gave an unstable product which did not collapse to the expected azetidinone (13) but instead gave the cyclised product (39) as a single compound, identified by its spectral properties and analytical figures.

To conclude, the vinylogous sulphoxides produced by the trapping of the penicillin *S*-oxides with dimethyl

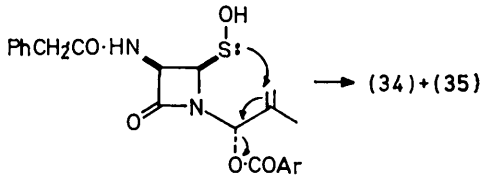
[14] R. D. G. Cooper and D. O. Spry, ' Cephalosporin and Penicillin, Chemistry and Biology,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 183.

[15] K. Heusler, *Helv. Chim. Acta*, 1972, **55**, 388.

[16] R. Criegee, *Annalen*, 1936, **522**, 75.

butynedioate readily undergo addition reactions allowing formation of a variety of new *S*-substituted derivatives. However, although removal of the nitrogen substituent on the resulting azetidinone is possible, elimination of the sulphur groups in the sulphoxide series tends to compete with intramolecular cyclisation.

In a previous paper [17] we reported the use of the *o*-nitrobenzoate group for protecting alcohols and phenols. Whilst the general procedure reported is often adequate, the method is not suitable for certain fattier alcohols. In these cases, the intermediate *o*-hydroxylamino-benzoates formed in the reduction



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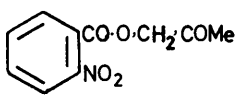

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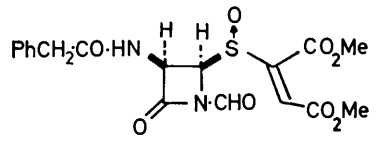

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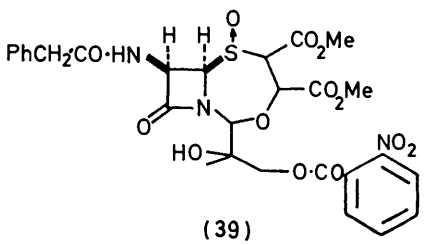

(39)

require a modified work-up with mild base to liberate the alcohol. An example of this procedure is reported in the Experimental section for the *o*-nitrobenzoate of cholesterol.

EXPERIMENTAL

For general procedures, see preceding paper. Mass spectra were determined with an A.E.I. MS9 machine.

Trapping Reactions of the Ester (1; R = O·CH_2·CCl_3) *with Dimethyl But-2-ynedioate.*—The sulphoxide (1; R = O·CH_2·CCl_3) was trapped with dimethyl butynedioate in benzene as described previously.[1b] The resulting crude mixture of sulphoxides (0·62 g) was immediately dissolved in dimethylformamide (10 ml) and treated with acetyl chloride (0·5 ml) and potassium iodide (0·5 g) at 0° for 45 min. The mixture was then poured into ice-cold, saturated aqueous sodium hydrogen carbonate and the iodine was neutralised with sodium thiosulphate. The mixture was extracted with ethyl acetate (5 × 50 ml) and the organic layer washed with water (2 × 50 ml), dried, and evaporated. The residue was dissolved in ethyl acetate (10 ml) and dry triethylamine (0·2 ml) and kept for 30 min at room temperature. The resulting red solution was extracted with 20% phosphoric acid (10 ml) and water (2 × 10 ml), dried, and evaporated to dryness to give (3R,4R)-4-[1,2-*bis*(*methoxycarbonyl*)*vinylthio*]-1-[2-*methyl*-1-(2,2,2-*trichloroethoxycarbonyl*)*prop*-1-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (3; R = CH_2·CCl_3) (0·50 g, 84%) as an amorphous foam. A pure sample was prepared for characterisation by preparative t.l.c. (1 : 1 benzene–ethyl acetate); $[\alpha]_D^{20}$ −5·6° (*c* 1·2 in $CHCl_3$), $\lambda_{max.}$ 280 nm (ε 8760), $\nu_{max.}$ ($CHBr_3$) 3340 (NH), 1776 (β-lactam), 1730 (CO_2R), 1690, and 1518 cm^{-1} (amide), τ 2·67 (5H, s, Ph), 3·33 (1H, d, *J* 9 Hz, NH), 4·07 (1H, d, C*H*·CO_2Me), 4·34 (1H, d, *J* 5 Hz, 4-H), 4·70 (1H, dd, *J* 5 and 9 Hz, 3-H), 5·09 and 5·27 (2H, ABq, *J* 12 Hz, CH_2·CCl_3), 6·18 and 6·29 (2 × CO_2Me), 6·34 (2H, s, CH_2Ph), and 7·64 and 7·84 (6H, s, Me_2C) (Found: C, 46·5; H, 4·2; N, 4·2; S, 5·0. $C_{24}H_{25}Cl_3N_2O_8S$,0·5H_2O requires C, 46·7; H, 4·3; N, 4·2; S, 5·2%).

Reactions of the Sulphide (3; R = CH_2·CCl_3).—(a) *Addition of diazomethane.* The sulphide (0·62 g) in ethyl acetate (1·0 ml) was treated with an excess of diazomethane in ether at 0°. After 45 min, the remaining diazomethane was removed under reduced pressure to give, as an inseparable, epimeric mixture, amorphous (3R,4R)-4-[3,4-*bis*(*methoxycarbonyl*)-Δ¹-*pyrazolin*-3-*ylthio*]-1-[2-*methyl*-1-(2,2,2-*trichloroethoxycarbonyl*)*prop*-1-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (4) (0·65 g, 100%), $\nu_{max.}$ ($CHCl_3$) 3500 (NH), 1770 (β-lactam), 1735 (CO_2R), 1680, and 1570 cm^{-1} (CONH), τ 2·72 (5H, s, Ph), 3·62 (1H, m, 3-H), 3·86 and 3·90 (1H, two d, *J* 5 Hz in both epimers, 4-H), 5·54 (2H, ABq, *J* 18 Hz, CH_2·N=N), 5·22 (2H, s, CH_2·CCl_3), 6·37 (6H, s, CO_2Me), 6·42 (2H, s, CH_2Ph), 7·80 (6H, 2s, Me_2C), 7·72 (3H, s), and 7·94 (3H, s) (Found: C, 45·9; H, 4·2; Cl, 16·0; N, 8·6; S, 4·9. $C_{25}H_{27}Cl_3N_4O_8S$ requires C, 46·0; H, 4·0; Cl, 16·3; N, 8·6; S, 4·9%).

(b) *Ozonolysis.* The sulphide (0·43 g) in dry dichloromethane (50 ml) at −78° was treated with ozone until a faint blue colour persisted. The solution was then purged with nitrogen at −78°. The product was washed with aqueous sodium disulphite (2 × 50 ml) and brine (50 ml), and the aqueous phase was back-extracted with dichloromethane (50 ml). The organic layer was washed with water (50 ml), dried, and evaporated to give (3R,4R)-4-(*methoxyoxaloylthio*)-3-*phenylacetamido*-1-(2,2,2-*trichloroethoxyoxaloyl*)*azetidin*-2-*one* (6) (0·39 g, 100%) as a white foam, $[\alpha]_D^{20}$ +14·5° (*c* 1·2 in $CHCl_3$), $\lambda_{max.}$ 258 and 323 nm (ε 4650 and 5900), $\nu_{max.}$ ($CHBr_3$) 3450 (NH), 1830, 1765, 1740, and 1710 (β-lactam, oxamide, and CO_2Me), and 1690 and 1518 (CONH) cm^{-1}, τ 2·75 (5H, s, Ph), 3·44 (1H, d, *J* 8 Hz, NH), 3·96 (1H, d, *J* 6 Hz, 4-H), 4·78 (1H, m, 3-H), 5·04 and 5·19 (2H, ABq, *J* 12 Hz, CH_2·CCl_3), 6·10 (3H, s, CO_2Me), and 6·39 (2H, s, PhCH_2) (Found: C, 41·2; H, 2·9; N, 5·3; S, 6·1. $C_{18}H_{15}Cl_3N_2O_8S$ requires C, 41·1; H, 2·9; N, 5·3; S, 6·1%).

Ozonolysis of a similar sample of the sulphide at −78° in dichloromethane, but with only 1 equiv. of ozone, resulted

[17] D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599.

in a quantitative yield of the keto-ester (5), $[\alpha]_D^{20}$ +19° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3450 (NH), 1780 (β-lactam), 1740 (CO_2R), 1708 (CO), 1690, and 1510 cm^{-1} (CONH), τ 2·74 (5H, s, Ph), 3·28 (1H, d, *J* 7 Hz, NH), 3·91 (1H, d, *J* 5 Hz, 4-H), 4·90 (1H, dd, *J* 5 and 7 Hz, 3-H), 5·15 and 5·32 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·12 (3H, s, CO_2Me), 6·40 (2H, s, $PhCH_2$), and 7·74 and 7·90 (6H, 2s, Me_2C). Ozonolysis of this ester produced the oxamide (6) in high yield.

Trapping Reaction of the Methyl Ester (1; R = OMe) *with Dimethyl But-2-ynedioate*.—Methyl (1*S*,3*R*,6*R*)-2,2-dimethyl-6-phenylacetamidopenam-3-carboxylate 1-oxide (5·0 g) in dry benzene (750 ml) was heated to reflux under nitrogen with dimethyl butynedioate (10 ml) for 30 h. The mixture was evaporated to *ca.* 25 ml under reduced pressure, then poured into rapidly stirred light petroleum. The precipitate was redissolved in the minimum quantity of benzene and reprecipitated in a similar manner a further two times to give a mixture of the (*R*)- and (*S*)-sulphoxides (4·0 g). A sample of the latter sulphoxide was prepared by silica gel chromatography (1 : 4 ethyl acetate–benzene) as a white foam, and identified as (3R,4R)-4-[1,2-*bis*(*methoxycarbonyl*)*vinylthio*]-1-(1-*methoxycarbonyl*-2-*methylprop*-2-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (S)-S-*oxide* (7; R = OMe) (2·5 g, 40%), $[\alpha]_D^{20}$ −26° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ ($CHBr_3$) 3400 (NH), 1780 (β-lactam), 1740 (CO_2Me), 1680, and 1510 cm^{-1} (CONH), τ 2·64 (5H, s, Ph), 2·93 (1H, d, *J* 9 Hz, NH), 3·13 (1H, s, $=CH{\cdot}CO_2Me$), 4·10 (1H, dd, *J* 5 and 9 Hz, 3-H), 4·49 (1H, d, *J* 6 Hz, 4-H), 4·93, 5·11, and 5·30 (3H, m, $CH_2{=}C$, NCHR), 6·17 and 6·28 (9H, 3 × Me), 6·37 (2H, s, CH_2Ph), and 8·19 (3H, s, $CHMe$) (Found: C, 52·9; H, 5·0; N, 5·0; S, 6·1. $C_{23}H_{26}N_2O_9S,H_2O$ requires C, 52·7; H, 5·3; N, 5·3; S, 6·0%).

The corresponding (*R*)-sulphoxide (8; R = OMe) was not isolated in an analytically pure state. A partially purified sample showed $\nu_{max.}$ ($CHBr_3$) 3400 (NH), 1780 (β-lactam), 1740 (CO_2Me), 1680, and 1510 cm^{-1} (CONH), τ 2·64 (5H, s, Ph), 2·82 (1H, d, *J* 9 Hz, NH), 3·54 (1H, d, $=CH{\cdot}CO_2Me$), 3·95 (1H, dd, *J* 5 and 9 Hz, 3-H), 5·48 (1H, d, *J* 5 Hz, 4-H), 4·79, 4·92, and 4·98 (3H, m, $CH_2{=}C$, NCHR), 6·17 and 6·31 (9H, 3 × Me), 6·40 (2H, s, CH_2Ph), and 8·08 (3H, s, Me).

Treatment of the crude mixture (*ca.* 1 : 1) of isomers (7) and (8) (1·0 g) with dry triethylamine (0·1 ml) in ethyl acetate (50 ml) at room temperature for 30 min afforded two new products, separated by preparative t.l.c. (1 : 2 ethyl acetate–benzene). The more polar compound was (3R,4R)-4-[1,2-*bis*(*methoxycarbonyl*)*vinylthio*]-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (R)-S-*oxide* (9) (0·32 g, 32%), isolated as a foam, $[\alpha]_D^{20}$ −125° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ 3400 (NH), 1785 (β-lactam), 1735 (CO_2Me), 1685, and 1510 cm^{-1} (CONH), τ 2·66 (5H, s, Ph), 3·48 (1H, s, $=CH{\cdot}CO_2Me$), 3·96 (1H, dd, *J* 4 and 10 Hz, 3-H), 4·72 (1H, d, *J* 4 Hz, 4-H), 6·13 and 6·20 (9H, 3 × CO_2Me), 6·38 (2H, s, CH_2Ph), 7·70 and 7·85 (6H, s, Me_2C) (Found: C, 52·0; H, 5·05; N, 5·0; S, 6·2. $C_{23}H_{26}N_2O_9S,H_2O$ requires C, 52·5; H, 5·35; N, 5·3; S, 6·1%).

The less polar product, obtained as a white foam was *trimethyl* (3R,4R)-3-*methyl*-10-*oxo*-9-*phenylacetamido*-7-*thia*-1-*azabicyclo*[6.2.0]*dec*-9-*ene*-2,5,6-*tricarboxylate* (S)-S-*oxide* (2; R = Me) (0·37 g, 37%), $[\alpha]_D^{20}$ +76° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3400 (NH), 1785, 1785 (β-lactam), 1735 (CO_2Me), 1680, and 1510 cm^{-1} (CONH), τ 2·76 (5H, s, Ph), 3·24 (1H, d, *J* 10 Hz, NH), 5·92 (1H, d, *J* 12 Hz, $SCH{\cdot}CO_2Me$), 6·21 and 6·26 (3 × CO_2Me), 6·30 (1H, m, $CH_2{\cdot}CH{\cdot}CO_2Me$), 6·38 (2H, s, CH_2Ph), 6·30 and 7·44 (2H, m, $CH_2{\cdot}CH$), and 7·87 (3H, s, Me) (Found: C, 52·7; H, 5·1; N, 5·1; S, 5·9. $C_{23}H_{26}N_2O_9S,H_2O$ requires C, 52·7; H, 5·3; N, 5·3; S, 6·1%).

Trapping Reaction of the Methyl Ester (1; R = OMe) *with Ethyl Propiolate*.—The sulphoxide (5·0 g) in dry benzene (250 ml) was heated to reflux with ethyl propiolate (10 ml) for 30 h; the mixture was then evaporated to small bulk. Although n.m.r. analysis indicated the presence of a mixture of isomeric sulphoxides only the major isomer crystallised out, (3R,4R)-4-(2-*ethoxycarbonylvinylthio*)-1-(1-*methoxycarbonyl*-2-*methylprop*-2-*enyl*)-3-*phenylacetamidoazetidin*-3-*one* (R)-S-*oxide* (10) (3·2 g, 50%), m.p. 180—181° $[\alpha]_D^{20}$ +53° (*c* 1·3 in dioxan), $\nu_{max.}$ 3410 (NH), 1780 (β-lactam), 1720 (CO_2Me), 1708 (CO_2Et), 1690, and 1510 cm^{-1} (amide), τ [$(CD_3)_2SO$] 0·73 (1H, d, *J* 10 Hz, NH), 2·16 (1H, d, *J* 15 Hz, $SCH{=}$), 2·67 (5H, s, Ph), 3·64 (1H, d, *J* 15 Hz, $=CH{\cdot}CO_2Et$), 4·38 (1H, dd, *J* 5 and 10 Hz, 3-H), 4·62 (1H, d, *J* 5 Hz, 4-H), 4·96 and 5·10 (2H, m, $CH_2{=}$), 5·32 (1H, s, $CH{\cdot}CO_2Me$), 5·71 and 5·85 (2H, ABq, *J* 7 Hz, CH_2Me), 6·27 (3H, s, CO_2Me), 6·33 and 6·47 (2H, ABq, *J* 14 Hz, CH_2Ph), 8·21 (3H, s, $MeCH{=}$), and 8·74 (3H, t, *J* 7 Hz, $Me{\cdot}CH_2$) (Found: C, 57·2; H, 5·6; N, 6·0; S, 7·0. $C_{22}H_{26}N_2O_7S$ requires C, 57·0; H, 5·6; N, 6·0; S, 6·7%).

Treatment of this product with triethylamine in ethyl acetate for 30 min at room temperature afforded the conjugated derivative quantitatively, isolated directly as an amorphous foam. (3R,4R)-4-(2-*Ethoxycarbonylvinylthio*)-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (R)-S-*oxide* (11) had $[\alpha]_D^{20}$ +263° (*c* 1·3 in $CHCl_3$), $\nu_{max.}$ 3450 (NH), 1780 (β-lactam), 1720 (CO_2Et), 1708 (CO_2Me), 1690, and 1510 cm^{-1} (CONH), τ 2·60 (1H, d, *J* 15 Hz, SCH), 2·67 (5H, s, Ph), 3·06 (1H, d, *J* 9 Hz, NH), 3·53 (1H, d, *J* 15 Hz, $=CH{\cdot}CO_2Et$), 4·14 (1H, dd, *J* 5·9 Hz, 3-H), 4·73 (1H, d, *J* 5 Hz, 4-H), 5·70—5·85 (2H, m, CH_2Me), 6·26 (3H, s, CO_2Me), 6·35 (2H, s, CH_2Ph), 7·88 and 7·91 (6H, 2 × Me), 8·71 (3H, t, *J* 7 Hz, $MeCH_2$) (Found: C, 56·6; H, 5·7; N, 6·0; S, 6·8. $C_{22}H_{26}N_2O_7S$ requires C, 57·0; H, 5·7; N, 6·0; S, 6·7%).

Ozonolysis of the Sulphoxide (9).—A sample of the sulphoxide was ozonised with 1 equiv. of ozone at −78° in dichloromethane. After 30 min the solution was worked up in the normal manner to give, as a crude product, the oxamide (12), $\nu_{max.}$ 3450, 1830, 1765, and 1730 cm^{-1}. This material was immediately treated with 1 : 5 aqueous 20% phosphoric acid–dioxan for 2 h at room temperature. Extraction with chloroform gave a mixture which showed no β-lactam i.r. absorption.

Ozonolysis of the Adducts (7; R = OMe) *and* (8; R = OMe).—The initial mixture of adducts (1·0 g) from a trapping reaction was dissolved in dichloromethane and ozonised at −78° until a faint blue colour persisted. The excess of ozone was then purged from the solution with nitrogen at −78°. The solution was warmed to ambient temperature, washed with sodium disulphite solution (2 × 50 ml) and water (2 × 50 ml), dried, and evaporated to produce a colourless foam. Preparative t.l.c. afforded two isomers of (6R,7R)-4-acetyl-2,3,4-trismethoxycarbonyl-7-phenylacetamidocepham 1-oxide (15). The *major isomer* (0·20 g, 20%) had m.p. 196—198° (decomp.) (from methanol) $[\alpha]_D^{20}$ +79·5° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ (Nujol) 3400 (NH), 1790 (β-lactam), 1740 (CO_2Me), 1685, and 1510 cm^{-1} (CONH), τ 2·70 (5H, s, Ph), 3·12 (1H, d, *J* 10 Hz, NH), 4·10 (1H, dd, *J* 4 and 10 Hz, 7-H), 5·18 (1H, d, *J* 4 Hz, 5-H), 5·70 and 6·08 (2H, dd, *J* 12 Hz, 2-H and 3-H), 6·18, 6·23, and 6·34 (3 × CO_2Me), 6·43 (2H, s, CH_2Ph), and 7·46 (3H, s, COMe) (Found: C, 51·8; H, 4·8; N, 5·5; S, 6·4.

$C_{22}H_{24}N_2O_{10}S$ requires C, 52·0; H, 4·8; N, 5·5; S, 6·3%). The *minor isomer* was obtained as an amorphous solid (0·14 g, 14%), $[\alpha]_D^{25}$ +149° (*c* 1·5 in $CHCl_3$), $\nu_{max.}$ 3400 (NH), 1788 (β-lactam), 1740 (CO_2Me), 1720 (COMe), 1680, and 1502 cm^{-1} (CONH), τ 2·76 (5H, s, Ph), 2·82 (1H, d, *J* 9 Hz), 4·18 (1H, dd, *J* 4 and 9 Hz, 7-H), 5·34 (1H, d, *J* 4 Hz, 6-H), 5·78 and 6·16 (2H, dd, *J* 12 Hz, 2-H and 3-H), 6·13, 6·28, and 6·44 (3 × CO_2Me), 6·47 (2H, s, CH_2Ph), and 7·76 (3H, s, COMe) (Found: C, 51·8; H, 4·8; N, 5·6; S, 6·2. $C_{22}H_{24}N_2O_{10}S$ requires C, 52·0; H, 4·8; N, 5·5; S, 6·3%).

Trapping Reaction of the Hydrazide (1; R = Pr^i·NHPr^i) *with Dimethyl But-2-ynedioate*.—The sulphoxide (4·7 g) in dry benzene (100 ml) was heated to reflux under dry nitrogen in the presence of dimethyl butynedioate for 16 h. The solution was evaporated to 40 ml; precipitation from light petroleum, redissolution in the minimum volume of benzene, and reprecipitation from light petroleum gave a mixture of sulphoxide adducts (5·3 g, 90%). Chromatography through silica gel (benzene–ethyl acetate mixtures) gave the separated (3*R*,4*R*)-4-[1,2-bis(methoxycarbonyl)-vinylthio]-1-[1-(*NN'*-di-isopropylhydrazinocarbonyl)-2-methylprop-2-enyl]-3-phenylacetamidoazetidin-2-one *S*-oxides. The major (R)-*isomer* (8; R = NPr^i·NHPr^i), which could also be crystallised out directly from the trapping reaction products, crystallised from benzene; m.p. 140—141°, $[\alpha]_D^{20}$ −214° (*c* 1·4 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1770 (β-lactam), 1730 (CO_2Me), 1680, 1510 (CONH), and 1660 cm^{-1} (CON<), τ 2·63 (5H, s, Ph), 2·83 (1H, d, *J* 10 Hz, NH), 3·55 (1H, s, C=C*H*CO_2Me), 3·89 (1H, dd, *J* 4 and 10 Hz, 3-H), 4·37 (1H, d, CH·CON), 4·39 (1H, d, *J* 4 Hz, 4-H), 4·90 and 5·01 (2H, m, CH_2), 5·78 (1H, m, C*H*Me_2), 6·14 (2 × MeO), 6·44 (2H, s, CH_2Ph), 6·68 (1H, m, C*H*Me_2), 8·01 (3H, s, Me), and 8·67—8·96 (4 × *Me*CH) (Found: C, 58·5; H, 6·5; N, 8·8; S, 4·9. $C_{28}H_{38}N_4O_8S$,-0·33C_6H_6 requires C, 58·5; H, 6·5; N, 9·0; S, 5·2%).

The minor (S)-*isomer* (7; R = NPr^i·NHPr^i) was isolated as a white foam, $[\alpha]_D^{20}$ +99° (*c* 1·2 in $CHCl_3$), $\nu_{max.}$ 3430 (NH), 1776 (β-lactam), 1736 (CO_2Me), 1680, 1660, and 1508 cm^{-1} (CON<), τ 2·73 (5H, s, Ph), 3·18 (1H, s, =C*H*·CO_2Me), 4·06 and 4·13 (2H, m, 3-H and 4-H), 4·41 (1H, s, CH·CON), 6·19 (2 × CO_2Me), 6·39 (2H, s, CH_2Ph), 6·74 (1H, m, C*H*Me_2), 8·16 (3H, s, Me), and 8·74 and 9·00 (4 × *Me*CH) (Found: C, 56·3; H, 6·5; N, 9·3; S, 5·2. $C_{28}H_{38}N_4O_8S$ requires C, 56·9; H, 6·5; N, 9·5; S, 5·4%).

Both isomers were unaffected by treatment with triethylamine in ethyl acetate.

Ozonolysis of the Sulphoxide Adduct (7; R = NPr^i·NHPr^i).—The sulphoxide (0·59 g) was ozonised in dry dichloromethane (50 ml) at −78° until a faint blue colour persisted. Work-up in the normal manner gave (3R,4R)-4-[1,2-*bis*-(*methoxycarbonyl*)*vinylthio*]-1-(1,2-*di-isopropyl*-3-*methyl*-5-*oxo*-Δ^3-*pyrazolin*-4-*yl*)-3-*phenylacetamidoazetidin*-2-*one* (S)-S-*oxide* (17) (0·52 g, 91%). A sample purified by preparative t.l.c. had $[\alpha]_D^{20}$ −24° (*c* 1·4 in $CHCl_3$), $\nu_{max.}$ 3410 (NH), 1774 (β-lactam), 1738 (CO_2Me), 1655, 1510 (CONH), and 1660 cm^{-1} (CON), $\lambda_{max.}$ 267 nm (ε 11,500), τ 2·69 (5H, s, Ph), 3·18 (1H, d, *J* 10 Hz, NH), 3·29 (1H, s, =C*H*·CO_2Me), 3·94 and 4·05 (2H, m, 3-H and 4-H), 5·92 (2H, m, C*H*Me_2), 6·17 and 6·28 (2 × CO_2Me), 6·36 (2H, s, CH_2Ph), 7·80 (3H, s, Me), and 8·63—8·73 (4 × *Me*CH) (Found: C, 56·3; H, 6·1; N, 9·7; S, 5·0. $C_{22}H_{34}N_4O_8S$ requires C, 56·4; H, 6·0; N, 9·7; S, 5·5%).

Addition Reactions of the Vinyl Sulphoxide (8; R = NPr^i·NHPr^i).—(a) *With diethyl sodiomalonate*. The sulphoxide (0·59 g) in dry benzene (10 ml) was treated with the freshly prepared sodium salt (0·36 g) in benzene (30 ml) at 25°. After 5 min the red solution was poured into 20% phosphoric acid (30 ml) and extracted with ethyl acetate (30 ml). The organic phase was washed with water (30 ml), dried, and evaporated. Precipitation of the oily product from light petroleum (×2) afforded (3R,4R)-4-[3,3-*bis*-(*ethoxycarbonyl*)-1,2-*bis*(*methoxycarbonyl*)*propylthio*]-1-(1-NN'-*di-isopropylhydrazinocarbonyl*-2-*methylprop*-2-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (R)-S-*oxide* (18) (0·67 g, 89%), $[\alpha]_D^{20}$ −183° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ ($CHBr_3$) 3370 (NH), 1770 (β-lactam), 1760, 1730 (CO_2R), 1685, 1502 (CONH), and 1660 cm^{-1} (CON), τ 2·40 (1H, d, *J* 10 Hz, NH), 2·70 (5H, s, Ph), 3·83 (1H, dd, *J* 5 and 10 Hz, 3-H), 4·26 (1H, d, *J* 5 Hz, 4-H), 4·34 (1H, s, NCHCO), 4·94 and 5·03 (2H, 2s, $=CH_2$), 5·85 (6H, m), 6·20 and 6·77 (2 × Me), 6·25 (2H, m), 6·42 (2H, s, CH_2Ph), 6·70 (1H, m, NCH), 8·04 (3H, s, =CH*Me*), *ca.* 8·70 (12H, 4 × *Me*CH), and 8·92 (6H, t, *J* 7 Hz, 2 × *Me*CH_2) (Found: C, 55·7; H, 6·6; N, 7·7; S, 4·3. $C_{35}H_{50}N_4O_{12}S$ requires C, 56·0; H, 6·7; N, 7·5; S, 4·3%).

(b) *With ethyl sodioacetoacetate*. In a similar manner the sulphoxide (0·59 g) was treated with the sodioacetoacetate to give (as an amorphous solid) (3R,4R)-4-[1,2-*bis*(*methoxycarbonyl*)-3-*ethoxycarbonyl*-4-*oxopentylthio*]-1-(1-NN'-*di-isopropylhydrazinocarbonyl*-2-*methylprop*-2-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (R)-S-*oxide* (19) (0·66 g, 92%), $[\alpha]_D^{24}$ −104° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ ($CHBr_3$), 3370 (NH), 1778 (β-lactam), 1738 (CO_2R, COR), 1680, 1508 (CONH), and 1660 cm^{-1} (CON), $\lambda_{max.}$ 253 nm (ε 8600), τ 2·30 (1H, d, *J* 10 Hz, NH), 2·68 (5H, s, Ph), 3·90 (1H, dd, *J* 5 and 10 Hz, 3-H), 4·42 (1H, s, C*H*·CON), 4·62 (1H, d, *J* 5 Hz, 4-H), 5·10 and 5·20 (2H, s, CH_2=), 5·5—6·0 (6H, m), 6·18 and 6·32 (2 × CO_2Me), 6·36 (2H, s, CH_2Ph), 6·70 (1H, m, N·C*H*Me_2), 7·80 (3H, s, COMe), 8·11 (3H, s, MeC=), and 8·5—9·0 (15H, m, 4 × *Me*CH and *Me*CH_2) (Found: C, 56·5; H, 6·7; N, 7·7; S, 4·4. $C_{34}H_{48}N_4O_{11}S$ requires C, 56·6; H, 6·7; N, 7·8; S, 4·4%).

Reactions of the Adduct (19).—The sulphoxide (1·0 g) in methanol (30 ml) was treated with an excess of diazomethane in ether for 45 min at 0° and any remaining diazomethane was destroyed with glacial acetic acid. Ethyl acetate (60 ml) was added and the organic layer was extracted with aqueous sodium hydrogen carbonate (2 × 30 ml) and water (30 ml), dried, and evaporated to give (3*R*,4*R*)-4-[1,2-bis(methoxycarbonyl)-3-ethoxycarbonyl-4-methoxypent-3-enylthio)-1-(1-*NN'*-di-isopropylhydrazinocarbonyl-2-methylprop-2-enyl)-3-phenylacetamidoazetidin-2-one (*R*)-oxide (20) as a mixture of *cis*- and *trans*-isomers, $\nu_{max.}$ ($CHBr_3$) 3370 (NH), 1770 (β-lactam), 1730 (CO_2Me), 1688 (conj. CO_2Et), 1660, and 1500 cm^{-1} (amide), $\lambda_{max.}$ 249 nm (ε 11,500). A sample was separated by preparative t.l.c. The less polar material had $[\alpha]_D^{24}$ −121° (*c* 1·1 in $CHCl_3$), and the more polar isomer, $[\alpha]_D^{24}$ −87° (*c* 1·3 in $CHCl_3$).

The ether (20) (7·3 g) in dry benzene (30 ml) was treated with freshly crystallised lead tetra-acetate (5·3 g, 1·2 equiv.) and anhydrous pyridine (0·95 g, 1·2 equiv.) at 25°. The solution was stirred for 10 min, then treated with sodium hydrogen carbonate solution (3 × 60 ml). The combined aqueous fractions were washed once with dichloromethane, acidified with 20% phosphoric acid, and re-extracted with ethyl acetate. The acid obtained (4·2 g was immediately treated with diazomethane and then with triethylamine to give the conjugated ester (21), as a mixture of two isomers, $\nu_{max.}$ ($CHBr_3$) 3380 (NH), 1780 (β-lactam),

1736 (CO_2Me), 1700 (conjugated ester), 1692, and 1502 cm^{-1} (CONH), $\lambda_{max.}$ 238 (ε 15,800). The major isomer was separated by preparative t.l.c. and used in subsequent transformations.

The sulphoxide (21) (0·65 g) in dichloromethane (50 ml) was treated with ozone at −78° until a faint blue colour persisted. The solution was worked up in the usual manner to afford the oxamide (22) as a foam (0·58 g, 95%), $\nu_{max.}$ ($CHCl_3$) 1840 and 1760 cm^{-1}. This was dissolved in tetrahydrofuran (30 ml) and treated with 10% phosphoric acid (10 ml) at room temperature for 20 min before extraction with ethyl acetate (100 ml) and washing with brine (2 × 30 ml). The organic phase was dried and evaporated to give (3R,4R)-4-[1,2-*bis*(*methoxycarbonyl*)-3-*ethoxycarbonyl*-4-*methoxypent*-3-*enylthio*]-3-*phenylacetamidoazetidin*-2-*one* (R)-*oxide* (23) as a white foam (0·30 g, 56%), $[\alpha]_D^{24}$ −122° (*c* 1·1 in $CHCl_3$), $\lambda_{max.}$ 249 nm (ε 11,000), $\nu_{max.}$ ($CHBr_3$) 3390 (NH), 1788 (β-lactam), 1732 (CO_2Me), 1700 (CO_2Et), 1690, 1505 (CONH), and 1042 cm^{-1} (*S*-oxide), τ 2·68 (5H, s, Ph), 2·86 (1H, d, *J* 9 Hz, NH), 4·49 (1H, dd, *J* 5 and 9 Hz, 3-H), 4·96 and 5·68 (2H, AXq, *J* 12 Hz, S·C*H*·C*H*·CO_2Me), 5·55 (1H, d, *J* 5 Hz, 4-H), 6·14 (3H, s, MeO), 6·20 and 6·30 (2 × CO_2Me), 5·80 (2H, m, CH_2·CH_3), 7·54 (3H, s, MeC=), and 8·78 (3H, t, *J* 7 Hz, CH_2·CH_3) (Found: C, 53·0; H, 5·8; N, 5·1; S, 5·67. $C_{24}H_{30}N_2O_{10}S$ requires C. 53·4; H, 5·6; N, 5·2; S, 5·9%).

Reduction of the Azetidinone (23).—The sulphoxide (0·54 g) in dry dimethylformamide (10 ml) was treated with phosphorus tribromide (1·1 g) at 0° with vigorous stirring for 15 min. The mixture was then poured into aqueous sodium hydrogen carbonate (30 ml) and ethyl acetate (100 ml). The organic layer was washed with water (6 × 30 ml), dried, and evaporated to give 3-*benzylidene*-2-*formyl*-2,6-*diaza*-4-*oxabicyclo*[3.2.0]*heptan*-7-*one* (24) (0·17 g, 74%), m.p. 163—164° (decomp.) (from chloroform), $[\alpha]_D^{24}$ +165° (*c* 0·8 in $CHCl_3$), $\nu_{max.}$ ($CHBr_3$) 3400 (NH), 1800 (β-lactam), 1690 (CHO), and 1670 cm^{-1} (C=C), $\lambda_{max.}$ 286 (ε 6500), τ [$(CD_3)_2SO$] 0·38 (1H, s, NH), 1·06 (1H, s, CHO), 2·40—2·90 (6H, m, Ph and CH=), 3·72 (1H, d, *J* 4 Hz, 5-H), and 4·38br (1H, 1-H) (Found: M^+, 230·0688. $C_{12}H_{10}N_2O_3$ requires *M*, 230·06191), *m/e* 202, 187, and 118.

Trapping of the o-*Nitrobenzoate* (26) *with Dimethyl But*-2-*ynedioate*.—The ester (4·71 g) in dry benzene (100 ml) was heated to reflux under nitrogen with dimethyl butynedioate (10 ml) in the presence of calcium carbonate (5·0 g) for 8 h. The inorganic salts were filtered off, the filtrate was evaporated to *ca.* 40 ml, and the product was precipitated with light petroleum. The precipitate was redissolved in the minimum quantity of benzene before reprecipitation from light petroleum. The resulting red oil was chromatographed through silica (1 : 6 ethyl acetate–benzene) to give, as the major product, amorphous (3R,4R)-4-[1,2-*bis*-(*methoxycarbonyl*)*vinylthio*]-1-[2-*methyl*-3-(o-*nitrobenzoyloxy*)-*prop*-1-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* S-*oxide* (28) (1·35 g, 22%), $[\alpha]_D^{20}$ +52° (*c* 1·2 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1780 (β-lactam), 1730 (ester), 1685, 1510 (CONH), 1545, and 1360 cm^{-1} (NO_2), τ 2·10—2·50 (4H, m, ArH), 2·74 (5H, s, Ph), 3·12 (1H, d, *J* 9 Hz, NH), 3·23 (1H, s, vinyl H), 4·20 (1H, dd, *J* 5 and 9 Hz, 3-H), 4·20br (1H, s, vinyl H), 4·77 (2H, s, CH_2Ph), and 8·17 (3H, s, Me) (Found: C, 54·8; H, 4·6; N, 6·9; S, 5·4. $C_{28}H_{27}N_3O_{11}S$ requires C, 54·8; H, 4·4; N, 6·9; S, 5·2%).

Thermolysis of the Sulphoxide (26).—The ester (4·71 g) was heated in benzene (100 ml) at reflux under nitrogen with calcium carbonate (60 g) for 8 h. The inorganic salts were filtered off and the filtrate was evaporated to *ca.* 40 ml. Precipitation from light petroleum (×2) gave a solid which was chromatographed through silica gel (1 : 6, then 1 : 1 ethyl acetate–benzene). Preparative t.l.c. of the eluted product gave the following compounds in order of increasing polarity: 2-[2-*methyl*-1-(o-*nitrobenzoyloxy*)*prop*-2-*enyl*]-4-*phenylacetamido*-Δ⁴-*isothiazolin*-3-*one* (29) (0·78 g, 18%), m.p. 157—158° (from methanol), $[\alpha]_D^{26}$ ±0° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1740 (ArCO·O), 1660 (CON), 1540, and 1360 cm^{-1} (NO_2), $\lambda_{max.}$ 296 nm (ε 11,300), τ 1·40 (1H, s, 5-H), 1·70 (1H, s, NH), 2·30 (4H. m, ArH), 2·78 (5H, s, Ph), 4·60br and 4·76br (2H, 2s, CH_2=), 6·20 (2H, s, CH_2Ph), and 8·20 (3H, s, Me) (Found: C, 58·1; H, 4·4; N, 9·1; S, 7·3. $C_{22}H_{19}N_3O_6S$ requires C, 58·3; H, 4·2; N, 9·3; S, 7·1%); 2-[2-*methyl*-3-(o-*nitrobenzoyloxy*)-*prop*-1-*enyl*]-4-*phenylacetamido*-Δ⁴-*isothiazolin*-3-*one* (30) (0·68 g, 15%), m.p. 170—172° (from methanol), $[\alpha]_D^{26}$ ±0° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1735 (ArCO·O), 1660 (CON), 1545, and 1360 cm^{-1} (NO_2), τ 1·40 (1H, s, 5-H), 1·62 (1H, s, NH), 2·28 (4H, m, ArH), 2·69 (5H, s, Ph), 3·20 (1H, s, vinyl H), 5·19 (2H, s, CH_2O), 6·22 (2H, s, CH_2Ph), and 8·00 (3H, s, Me) (Found: C, 58·3; H, 4·2; N, 9·4; S, 7·3. $C_{22}H_{19}N_3O_6S$ requires C, 58·3; H, 4·2; N, 9·3; S, 7·1%); (1*S*,6*R*,7*R*)-3-methyl-7-phenylacetamidoceph-3-em 1-oxide (34) (0·33 g, 11%), m.p. 213—215°, identical (m.p. 213—214°; t.l.c. and spectral properties) with authentic material; * (1*R*,6*R*,7*R*)-3-methyl-7-phenylacetamidoceph-3-em 1-oxide (35) (0·37 g, 12%), as a white foam, $[\alpha]_D^{20}$ −182° (*c* 0·8 in $CHCl_3$), identical (t.l.c. and spectral properties) with an authentic sample.*

Reduction of the Isothiazolinones (29) *and* (30). Treatment of either isothiazolinone (0·45 g) in tetrahydrofuran (10 ml) and water (5 ml) with ammonium chloride (0·33 g) and zinc dust (0·14 g) with vigorous stirring at 0° for 30 min, followed by treatment with ethyl acetate (50 ml) and extraction with water (2 × 10 ml) drying, and evaporation of the organic phase gave 2,3-dihydro-2-isopropenyl-5-phenylacetamido-1,3-thiazin-4-one (31) (0·21 g, 85%), m.p. 152—152·5° (from ethanol), identical with an authentic sample.*

Ozonolysis of the Adduct (28).—The sulphoxide (0·61 g) in dichloromethane (50 ml) was treated with ozone at −78° until a faint blue colour persisted. The solution was then purged with nitrogen, warmed to room temperature, and extracted with aqueous sodium disulphite (30 ml) and water (30 ml). The solution was evaporated to dryness and the resulting oil precipitated from cyclohexane. The precipitate was reprecipitated from more cyclohexane to give (3R,4R)-[1,2-*bis*(*methoxycarbonyl*)*vinylthio*]-1-*formyl*-3-*phenylacetamidoazetidin*-2-*one* S-*oxide* (37) (0·31 g, 72%) as a colourless foam, $[\alpha]_D^{24}$ −29° (*c* 0·2 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3420 (NH), 1815 (β-lactam), 1735 (ester), 1710 (CHO), 1695, and 1510 cm^{-1} (CONH), τ 1·17 (1H, s, CHO), 2·62 (5H, s, Ph), 2·83 (1H, d, *J* 10 Hz, NH), 3·06 (1H, s, =C*H*·CO_2Me), 3·82 (1H, dd, *J* 5 and 10 Hz, 3-H), 4·24 (1H, d, *J* 5 Hz, 4-H), 6·07 and 6·10 (CO_2Me), and 6·29 (2H, s, CH_2Ph) (Found: C, 48·9; H, 4·3; N, 5·9. $C_{18}H_{18}N_2O_6S$ requires C, 50·1; H, 4·3; N, 6·6%).

The cyclohexane triturates were evaporated to dryness to give a yellow oil which was distilled under reduced pressure to give, as an oil (0·11 g, 52%), 2-*oxopropyl* o-*nitrobenzoate*, b.p. (0·2 mmHg) 90°, $\nu_{max.}$ 1735 (ester), 1545. and

* We thank Glaxo Research Ltd., Greenford, for authentic samples of these compounds.

1360 cm^{-1} (NO_2), τ 1·9—2·5 (4H, m, aromatic), 5·10 (2H, s, CH_2), and 7·80 (3H, s, Me) (Found: C, 54·0; H, 4·4; N, 6·2. $C_{10}H_9NO_5$ requires C, 53·8; H, 4·1; N, 6·3%).

Osmylation of the Adduct (28).—The adduct (0·61 g) and osmium tetraoxide (0·30 g) were stirred in benzene (10 ml) at room temperature for 2 days. The mixture was then treated with aqueous sodium disulphite for 2 h. The inorganic material was filtered off and washed with ethyl acetate (20 ml). The organic phase was washed with water and then evaporated. The amorphous solid was purified by preparative t.l.c. to give *dimethyl* (7R,8R)-2-[1-*hydroxy*-1-*methyl*-2-(o-*nitrobenzoyloxy*)*ethyl*]-9-*oxo*-8-*phenylacetamido*-6-*thia*-3-*oxa*-1-*azabicyclo*[5.2.0]*nonane*-4,5-*dicarboxylate* S-*oxide* (39) (0·32 g, 49%) as an amorphous foam, $[\alpha]_D^{20}$ +119° (*c* 1·6 in $CHCl_3$), $\nu_{max.}$ 3550 (OH), 3300 (NH), 1780 (β-lactam), 1735 (CO_2R), 1680, 1510 (CONH), 1540, and 1360 cm^{-1} (NO_2), τ 2·27 (4H, m, aromatic), 2·69 (5H, s, Ph), 3·10 (1H, d, *J* 10 Hz, NH), 4·17 (1H, dd, *J* 4 and 10 Hz, 8-H), 4·55 (1H, d, *J* 4 Hz, 7-H), 4·90 (2H, s, CH_2), 5·28 (1H, s, NCHO), 5·65 (2H, ABq, *J* 12 Hz, S·C*H*·CH), 6·20 (6H, s, 2 × CO_2Me), 6·32 (2H, s, CH_2Ph), and 8·73 (3H, s, Me) (Found: C, 51·6; H, 4·8; N, 6·1; S, 4·9. $C_{28}H_{29}NO_{12}S$ requires C, 51·7; H, 4·5; N, 6·4; S, 4·9%).

Reduction of Cholest-5-en-3β-yl 2-Nitrobenzoate and Liberation of Cholesterol (*Modified Procedure*).—Cholesteryl 2-nitrobenzoate (0·54 g, 0·001 mol) in tetrahydrofuran (10 ml) was treated with ammonium acetate (0·8 g, 0·01 mol) in water (4 ml) at room temperature and zinc dust (0·4 g) was added in portions (100 mg) with stirring. The mixture was then stirred for a further 10 min. Reduction (as followed by t.l.c.) took 15—30 min in various runs, depending on the quality of the zinc dust employed. The mixture was filtered, the solids were washed with ethyl acetate, and the filtrate was poured into ethyl acetate (100 ml). After extraction with water (3 × 30 ml) the organic phase was dried and evaporated under reduced pressure to give a buff solid (0·51 g, 96%). Recrystallisation from methanol gave *cholest-5-en-3β-yl 2-hydroxylaminobenzoate*, m.p. 160—162° (decomp.), $\nu_{max.}$ ($CHBr_3$) 3500 (OH), 3320 (NH), and 1695 (ArCO) cm^{-1}, $\lambda_{max.}$ (3 : 2 methanol–dioxan) 233, 251, and 334 nm (ε 5950, 5550, and 2860), τ 0·5—2·5 (4H, m, C_6H_4), 4·45 (1H, m, CH), 455 (1H, m, =CH=), and 7·3—9·4 (remaining protons), *m/e* 521 (M^+), 519 ($M^+ - 2$), 505 ($M^+ - 16$), and 386 (Found: C, 78·4; H, 9·8; N, 2·3. $C_{34}H_{51}NO_3$ requires C, 78·3; H, 9·85; N, 2·7%).

Treatment of the hydroxylaminobenzoate (0·51 g) in tetrahydrofuran (5 ml) with 2N-sodium hydroxide (5 ml), with stirring, at room temperature for 20 min, followed by addition of ethyl acetate (100 ml) and extraction with dilute sodium hydroxide and water (3 × 30 ml) gave, after drying and evaporation, a pale yellow solid. Crystallisation from methanol gave cholesterol (0·21 g, 55%), m.p. 147—148°, identical (t.l.c., n.m.r., and i.r. comparison) with an authentic sample. A control experiment showed that cholest-5-en-3β-yl 2-nitrobenzoate was unaffected by a similar treatment with base.

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