Determination of the Stereochemistry of the Product of Rearrangement of Penicillin G with Methyl Chloroformate by Total Synthesis

By **Christopher J. Veal** and **Douglas W. Young,*** School of Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ

Separate stereospecific syntheses of the product [4-isopropylidene-2-(2-methylthio-1-phenylacetamidovinyl)-oxazol-5(4*H*)-one] from the rearrangement of penicillin G with methyl chloroformate and of its geometric isomer have defined the former as the *Z*-isomer.

THE β-lactam antibiotics of the penicillin and cephalosporin series undergo many interesting rearrangements.[1,2] For example, treatment of penicillin V (1; R = PhO·CH_2·CO) with methyl chloroformate and triethylamine in dimethylformamide gives the oxazolones (2; R = PhO·CH_2·CO) and (3). We have treated penicillin G (1; R = $PhCH_2CO$) with this combination of reagents and obtained anhydropenicillin G (4) and a compound whose spectral and analytical data are consistent with the oxazolone structure (2; R = $PhCH_2$·CO). Only one of the two possible geometric isomers of (2; R = $PhCH_2$·CO) was present,† in contrast to the reported related rearrangement of penicillin V (1; R = PhO·CH_2·CO) with acetic anhydride,[3,4] which gave both geometric isomers of (5).

Our starting point for the synthesis of the oxazolone (2; R = $PhCH_2$·CO) was the thiazepine (6; R = Me).[5] This compound underwent base-catalysed ring-opening [6] (Scheme 1) to yield the enethiolate (7; R = Me). When we treated the thiazepine (6; R = Me) with 1 mol. equiv. of sodium methoxide in methanol for 30 min and then quenched the resultant enethiolate (7; R = Me) with benzyl bromide or methyl iodide, we obtained the products (8; R^1 = Me, R^2 = $PhCH_2$) and (8; R^1 = R^2 = Me), respectively. In each case only one geometric isomer was obtained † and it at first seemed that, since the enethiolate (7; R = Me) had been left in methanolic solution for 30 min, the observed stereospecificity must be the result of thermodynamic control. When, however, the enethiolate ion (7; R = Me) was left for 24 h before quenching with methyl iodide, a mixture of both geometric isomers was obtained. The second isomer was identical with a sample synthesised independently as described later. The products from the reactions in which the enethiolate (7; R = Me) was quenched after 30 min were, therefore, the kinetically preferred products and so must have the *E*-stereochemistry defined by the original thiazepine (6).

The ester (8; R^1 = R^2 = Me) is obviously related to the required oxazolone (2), and to complete a synthesis of (2; R = $PhCH_2$·CO) the acid (8; R^1 = H, R^2 = Me) was required. The ester (6; R = Me) was, therefore, hydrolysed with lithium iodide in pyridine. Attempts to convert the resulting acid (6; R = H) into (8; R^1 = H, R^2 = Me) by the sequence outlined in Scheme 1 failed, owing to inability to achieve base-catalysed ring-opening This is presumably due to the proximity of the acidic proton H_A in (6; R = H) to the carboxylate anion. The carboxylic acid (6; R = H) was, therefore, converted into the t-butyl ester (6; R = Bu^t) with t-butyl acetate and perchloric acid. The ester (6; R = Bu^t) readily underwent the retro-Michael reaction of Scheme 1, and the resultant enethiolate anion (7; R = Bu^t) was quenched after 30 min with methyl iodide to yield the single isomer (8; R^1 = Bu^t, R^2 = Me).† That this was the *E*-isomer was implied by analogy with the corresponding reaction of (6; R = Me) and by the similarity of the u.v. spectrum to those of (8; R^1 = Me, R^2 = $PhCH_2$) and (8; R^1 = R^2 = Me).

The t-butyl ester (8; R^1 = Bu^t, R^2 = Me) was cleaved with hydrogen chloride in methylene chloride to give the acid (8; R^1 = H, R^2 = Me), which was cyclised to the oxazolone (9) with acetic anhydride. The oxazolone (9) was different from the product (2; R = $PhCH_2$·CO) from the rearrangement of penicillin G with methyl chloroformate; it was thus evident that a stereospecific synthesis of the *Z*-isomer (10) was required.

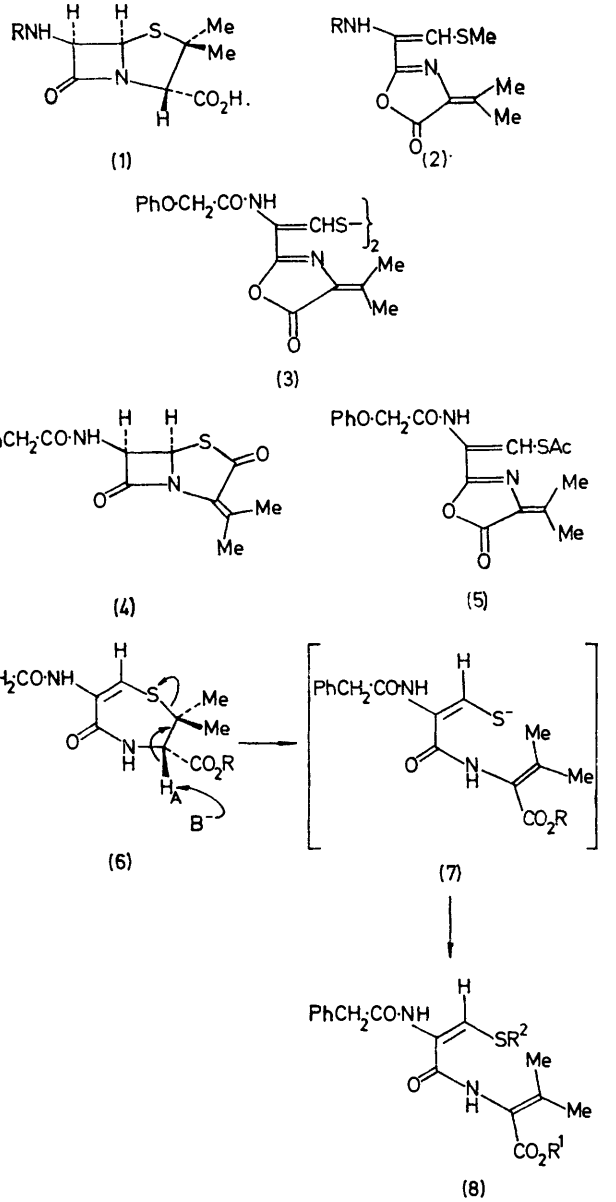
The aldehyde (11; R = Me) [7] could be converted into a series of dithioacetals (12; R^1 = Me, R^2 = Me, Et, $PhCH_2$, or Ph) by reaction with the appropriate thiol in the presence of boron trifluoride. Treatment of the dibenzyl dithioacetal (12; R^1 = Me, R^2 = $PhCH_2$) with sodium methoxide in methanol resulted in stereospecific elimination of the thiol to yield (13; R^1 = Me, R^2 = $PhCH_2$), which was isomeric with but different from the compound (8; R^1 = Me, R^2 = $PhCH_2$) prepared from the thiazepine (6; R = Me). Base-catalysed elimination of methanethiol from the dithioacetal (12; R^1 = R^2 = Me) was not stereospecific. The minor isomer (9%) proved to be (8; R^1 = R^2 = Me), identical with the compound prepared from the thiazepine (6; R = Me), and the major isomer (28%) was the *Z*-isomer (13; R^1 = R^2 = Me).

The acetal (14; R = Me) [7] was converted into the acid (14; R = H) by lithium iodide in pyridine, and this acid was converted into the aldehyde (11; R = H) and thence into the dithioacetal (12; R = H, R^2 = Me) by acidic hydrolysis followed by treatment with methane-

† After completion of the synthesis of both geometric isomers, which were readily distinguishable by t.l.c.; t.l.c. of the mixture gave no indication of the presence of the second isomer.

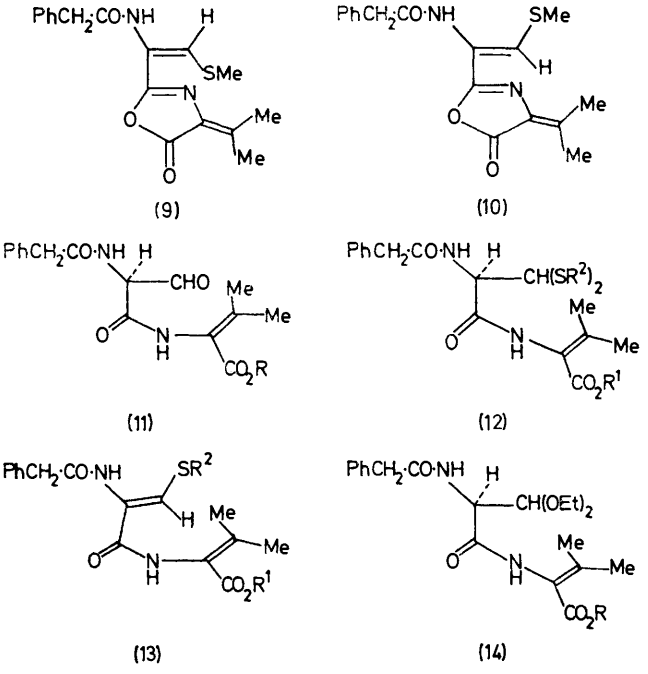
[1] R. D. G. Cooper and D. O. Spry in 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 183.
[2] R. J. Stoodley, *Progr. Org. Chem.*, 1973, **8**, 102.
[3] S. Kukolja, R. D. G. Cooper, and R. B. Morin, *Tetrahedron Letters*, 1969, 3381.
[4] S. Wolfe, C. Ferrari, and W. S Lee, *Tetrahedron Letters*, 1969, 338.
[5] N. J. Leonard and G. E. Wilson, *J. Amer. Chem. Soc.*, 1964, **86**, 530.
[6] N. J. Leonard and R. Y. Ning, *J. Org. Chem.*, 1967, **32**, 677.
[7] J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, *J.C.S. Chem. Comm.*, 1974, 47; *J.C.S. Perkin I*, 1974, 986.

thiol and boron trifluoride. When the base-catalysed thiol elimination was performed on the dithioacetal (12; $R^1 = H$, $R^2 = Me$), the reaction was stereospecific, and the product (13; $R^1 = H$, $R^2 = Me$) was isomeric with but different from the *E*-enethiol ether (8; $R^1 = H$, $R^2 = Me$) prepared from the thiazepine (6; $R = Bu^t$). Whereas the conversion of the acid (12; $R^1 = H$, $R^2 = Me$) into the enethiol thioether (13; $R^1 = H$, $R^2 = Me$) is stereospecific, the corresponding reaction of the methyl ester (12; $R^1 = R^2 = Me$) is not. This seems to indicate that the carboxylate anion exerts more stereochemical control on the reaction than



SCHEME 1

does the ester group, and this fact can best be rationalised if the expected product from either a kinetically or a thermodynamically controlled reaction is the *Z*-stereoisomer (13). This is shown in Scheme 2, where the sequence A is much preferred to B in which the electronegative thioether group remains close to the carboxylate



anion throughout the reaction. Further, product (8B; $R^1 = H$, $R^2 = Me$) will have the electronegative thioether and carboxylate groups eclipsed and so (13A) will be the thermodynamically preferred product.

The *Z*-oxazolone (10) was prepared from the acid (13; $R^1 = H$, $R^2 = Me$) with acetic anhydride, and was identical with the product of rearrangement of penicillin G with methyl chloroformate; thus the *Z*-stereochemistry of the latter is defined.

The stereochemical assignments for all the enethiol thioethers in this study have been deduced from consideration of the methods used in the synthesis of the two series of geometric isomers (8) and (13). U.v. spectral data for the two series to which *Z*- and *E*-stereochemistry have been assigned are summarised in the Table. In the *Z*-series, where the chromophore is

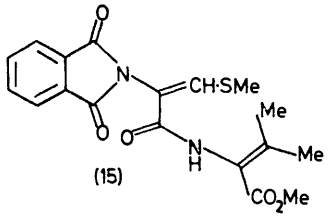
			Z-Series [(13) or (10)]		*E*-Series [(8) or (9)]	
Compounds	R^1	R^2	$\lambda_{max.}$/nm	ε	$\lambda_{max.}$/nm	ε
(13) or (8)	Me	$PhCH_2$	288	18 300	299	15 700
(13) or (8)	Me	Me	285	19 200	297	10 500
(13) or (8)	H	Me	285	13 600	298	6 985
(10) or (9)			333	35 600	348	6 000
(15) [a]			286	18 400	295	16 600

[a] The *E*-isomer of compound (15) was synthesised by base-catalysed ring opening and alkylation of the corresponding thiazepine, which was prepared by the method of ref. 15. The *Z*-isomer was obtained from the *E*-isomer by photolysis. These experiments are described in the Experimental section.

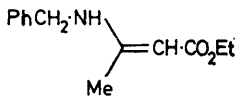
trans, the ε value is higher than in the *E*-series, where the chromophore is *cis*. This seems to be in keeping with the general expectation.[8] Further the series assigned

[8] A. E. Gilham and E. S. Stern, 'An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry,' Arnold, London, 1958, p. 267.

the *trans*-chromophore invariably absorbs at lower wavelength than the series assigned the *cis*-chromophore. The best analogy which we have been able to find for our system in this context is the pair of enamine esters (16): the compound with the *trans*-chromophore has

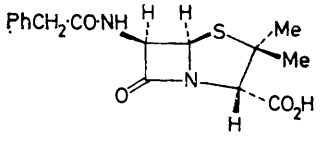


(15)

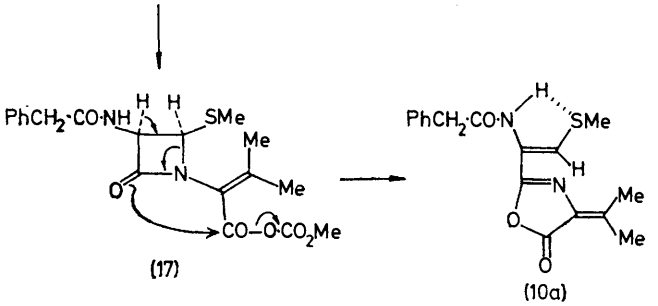


(16)

absorption 11 nm lower than the compound with the *cis*-chromophore.[9]



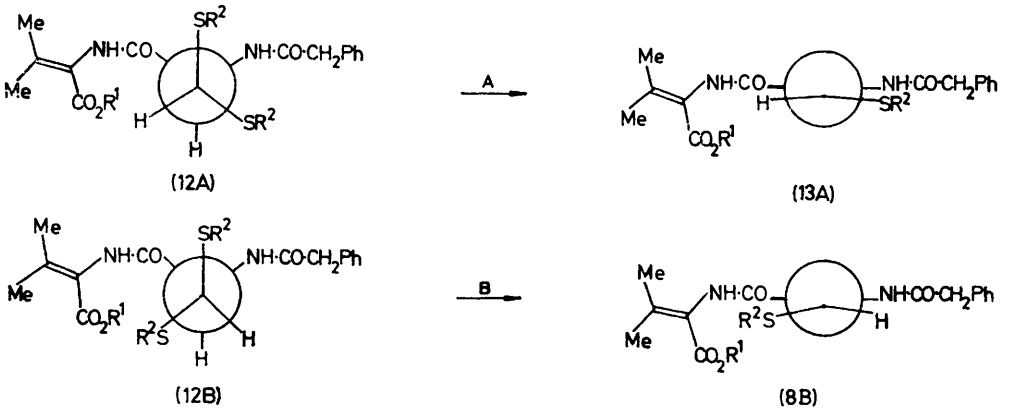
(1A)



(17) (10a)

SCHEME 3

Our studies have shown that rearrangement of penicillin G with methyl chloroformate (Scheme 3) is stereospecific and that the resultant oxazolone (10) has the geometry with the phenylacetamido side-chain *cis* to the sulphur atom, as is the case in the starting penicillin G.* If the β-lactam (17) is indeed an intermediate in the rearrangement, as has been suggested,[1] then, if C–N cleavage is concerted with loss of the C-6 proton, the observed stereochemistry would be expected for the oxazolone (10). Work on epimerisation of penicillins [10–12] implies that when the β-lactam ring is intact, the steric repulsion between the sulphur and the side chain nitrogen atom is important for thermodynamic control but it is just possible that hydrogen bonding as shown in (10A) may allow the *Z*-stereochemistry to be thermodynamically preferred.



(12A) (13A) (12B) (8B)

SCHEME 2

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 237 or 257 instrument and u.v. spectra with a Unicam SP 800 spectrophotometer. N.m.r. spectra were recorded with a Varian T60, A60, EM360, or HA100 instrument, and mass spectra with a Hitachi RMU-6 or A.E.I. MS9 instrument. T.l.c. was carried out with Kieselgel G (Merck) in 0.25 mm layers for analytical work and 0.75 mm layers for preparative work. Microanalyses were performed by Mr. and Mrs. A. G. Olney and mass spectroscopy was carried out by Mr. A. Greenway.

Reaction of Penicillin G with Methyl Chloroformate and Triethylamine.—Penicillin G (10.1 g) was isolated [13] as a foam from the potassium salt and dissolved in dry dimethylformamide (500 ml) containing dry triethylamine (4.2 ml). Redistilled methyl chloroformate (9.17 ml) in dry dimethylformamide (10 ml) was added slowly with stirring and stirring was continued at room temperature for a further 2 h. The solution was added to crushed ice and extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield a tar which exhibited two spots on t.l.c. [ethyl acetate–chloroform

* E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday (*J.C.S. Perkin I*, 1975, 652) have recently obtained the phenoxyacetyl analogue of (13; $R^1 = R^2 = Me$) by rearrangement of penicillin V with methyl iodide and base. They have assigned the stereochemistry by analogy with a similar rearrangement. The reported u.v. spectrum of this compound is in good agreement with those of compounds of the *Z*-series in the present paper.

[9] H. P. Schad, *Helv. Chim. Acta*, 1955, **38**, 1117.
[10] B. G. Ramsay and R. J. Stoodley, *Chem. Comm.*, 1971, 450.
[11] D. H. R. Barton, I. H. Coats, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599.
[12] G. A. Koppel, *Tetrahedron Letters*, 1973, 4233.
[13] 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton 1949, p. 91.

(1 : 1)]. Preliminary purification by chromatography on silica gel (chloroform) yielded an orange solid. A portion of this (70 mg) was purified by preparative t.l.c. [ethyl acetate–chloroform (1 : 1)]. A fraction of R_F 0.59 crystallised from acetone and water as needles (24 mg) of *anhydropenicillin G*, m.p. 150—152° (lit.,[14] 156—158°), $\lambda_{max.}$ (MeOH) 272 nm, $\nu_{max.}$ ($CHCl_3$) 3 390 (NH), 1 790 (β-lactam), 1 685 (amide), and 1 640 cm^{-1} (amide), τ ($CDCl_3$) 8.03 (3 H, s, MeC=), 7.93 (3 H, s, MeC=), 6.50 (2 H, s, $PhCH_2$), 4.60 (1 H, d, *J* 4 Hz, CHS), 4.25 (1 H, q, *J* 4 and 8 Hz, NHC*H*·CHS), 3.63br (1 H, d, *J* 8 Hz, NH), and 2.80 (5 H, s, Ph). A fraction of R_F 0.52 solidified on trituration with diethyl ether and was recrystallised from chloroform and diethyl ether to give *4-isopropylidene-2-(2-methylthio-1-phenylacetamidovinyl)oxazol-5(4H)-one* (2; R = $PhCH_2$·CO) (20 mg), m.p. 145—150°, $\nu_{max.}$ (Nujol) 1 790 and 1 770 (oxazolone) and 1 660 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 271 and 334 nm (log ε 3.83 and 4.55), $\lambda_{max.}$ (OH^-) 286 nm (Found: C, 61.65; H, 5.7; N, 8.2. $C_{17}H_{18}N_2O_3S$ requires C, 61.8; H, 5.5; N, 8.5%), τ ($CDCl_3$) 7.83 (3 H, s, MeC=), 7.68 (3 H, s, MeC=), 7.56 (3 H, s, SMe), 6.25 (2 H, s, $PhCH_2$), 3.14br (1 H, s, NH), 2.80 (1 H, s, olefinic), and 2.63 (5 H, s, Ph).

Methyl 2-(3-Benzylthio-2-phenylacetamidoacrylamido)-3-methylbut-2-enoate (8; R^1 = Me, R^2 = $PhCH_2$).—This compound was prepared in 50% yield by the method of Leonard;[6] m.p. 150—152° (lit.,[6] 154—155°), $\lambda_{max.}$ (MeOH) 299 nm. T.l.c. of the crude mixture showed no trace of the geometric isomer.

Methyl 3-Methyl-2-(3-methylthio-2-phenylacetamidoacrylamido)but-2-enoate (8; R^1 = R^2 = Me).—The thiazepine (6; R = Me) [5] (50 mg) was dissolved in redistilled methanol (5 ml) and sodium methoxide (8 mg) was added. The mixture was stirred at room temperature for 30 min, methyl iodide (0.1 ml) was added, and the mixture was left for a further 30 min at room temperature. The solvent was removed *in vacuo* and chloroform was added. The organic suspension was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a white solid in good yield, m.p. 130—135° (from chloroform—diethyl ether), *m/e* 362, $\lambda_{max.}$ (MeOH) 230sh and 297 nm (log ε 4.1 and 4.02), $\nu_{max.}$ ($CHCl_3$) 1 720 (ester) and 1 655 cm^{-1} (amide), τ ($CDCl_3$) 8.15 (3 H, s, MeC=), 7.84 (3 H, s, MeC=), 7.54 (3 H, s, SMe), 6.36 (2 H, s, $PhCH_2$), 6.26 (3 H, s, OMe), 2.68 (5 H, s, Ph), 2.01 (1 H, s, olefin), and 1.8br (2 H, NH, exchangeable with D_2O) T.l.c. indicated the presence of one geometric isomer only.

Second Reaction of the Enethiolate (7; R = Me) *with Methyl Iodide*.—The thiazepine (6; R = Me) (30 mg) was dissolved in methanolic sodium methoxide as above and stirred at room temperature for 24 h before quenching with an excess of methyl iodide. Work-up as above gave a pale yellow solid which exhibited two spots on t.l.c. corresponding to the geometric isomers (8) and (13) (R^1 = R^2 = Me), prepared independently. Preparative t.l.c. [EtOAc–$CHCl_3$ (1 : 1)] afforded the isomer (13; R^1 = R^2 = Me), identical with a sample prepared from the thioacetal (12; R^1 = R^2 = Me). This was the major product.

(3S)-2,3,4,5-Tetrahydro-2,2-dimethyl-5-oxo-6-phenylacetamido-1,4-thiazepine-3-carboxylic Acid (6; R = H) *and its t-Butyl Ester* (6; R = Bu^t).—The thiazepine (6; R = Me) (50 mg) was dissolved in redistilled pyridine (20 ml) and fused lithium iodide (200 mg) was added. The mixture was refluxed under nitrogen for 4 h. Chloroform was added and the mixture was extracted with aqueous 10% sodium hydrogen carbonate. The extracts were acidified with 5N-hydrochloric acid and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield a pale yellow oil which crystallised to give the *acid* on trituration with diethyl ether; yield 35 mg, m.p. 96—100° (Found: M^+, 334.099 04. $C_{16}H_{18}N_2O_4S$ requires *M*, 334.098 72), $\lambda_{max.}$ (MeOH) 232 and 307 nm (log ε 3.91 and 3.62), $\nu_{max.}$ ($CHCl_3$) 3 350 (NH), 1 710 (acid), and 1 640 cm^{-1} (amide), τ ($CDCl_3$) 8.66 (3 H, s, Me), 8.38 (3 H, s, Me), 6.37 (2 H, s, $PhCH_2$), 5.87 (1 H, d, *J* 6 Hz, C*H*·CO_2H; singlet in D_2O), 2.72 (5 H, s, Ph), 2.36 (1 H, s, olefin), and 1.96 and 1.50 (3 H, s + br, d, *J* 6 Hz, NH and CO_2H, exchangeable with D_2O).

The acid (6; R = H) (33 mg) was dissolved in t-butyl acetate (5 ml) and aqueous 60% perchloric acid (0.1 ml) was added. The mixture was left for 4 h at room temperature, chloroform was added, and the organic solution was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The residual pale yellow solid *ester* was recrystallised from diethyl ether–hexane; yield 30 mg, m.p. 138—143° (Found: M^+, 390.161 318. $C_{20}H_{26}N_2O_4S$ requires *M*, 390.161 33), $\lambda_{max.}$ (MeOH) 233 and 306 nm (log ε 3.98 and 3.65), $\lambda_{max.}$ (OH^-) 252 and 330 nm (log ε 4.08 and 4.00), $\nu_{max.}$ ($CHCl_3$) 3 360 (NH), 1 720 (ester), and 1 650 cm^{-1} (amide), τ ($CDCl_3$) 8.72 (3 H, s, MeC), 8.53 (9 H, s, Me_3C), 8.48 (3 H, s, MeC), 6.37 (2 H, s, $PhCH_2$), 6.00 (1 H, d, *J* 7 Hz, C*H*·CO_2Bu^t, singlet on adding D_2O), 2.70 (5 H, s, Ph), 2.24 (1 H, s, olefin), and 2.14br (1 H, s, NH, exchanged with D_2O).

t-Butyl 3-Methyl-2-(3-methylthio-2-phenylacetamidoacrylamido)but-2-enoate (8; R^1 = Bu^t, R^2 = Me) *and the Corresponding Acid* (8; R^1 = H, R^2 = Me).—The thiazepine (6; R = Bu^t) (80 mg) was dissolved in redistilled methanol (40 ml) and sodium methoxide (22 mg) was added. The mixture was stirred at room temperature for 30 min, methyl iodide (0.1 ml) was added, and the solution was stirred for a further 30 min at room temperature. The methanol was removed *in vacuo*, chloroform was added, and the organic solution was washed with water, dried ($MgSO_4$), and evaporated to yield an oil. This solidified on trituration with diethyl ether and was recrystallised from chloroform–diethyl ether to give the *butenoate* (60 mg), m.p. 182—184° (Found: M^+, 404.175 457. $C_{21}H_{28}N_2O_4S$ requires *M*, 404.176 967), $\lambda_{max.}$ (MeOH) 298 nm (log ε 4.00), $\nu_{max.}$ ($CHCl_3$) 1 710 (ester) and 1 650 cm^{-1} (amide), τ ($CDCl_3$) 8.56 (9 H, s, Me_3C), 8.19 (3 H, s, MeC=), 7.85 (3 H, s, MeC=), 7.56 (3 H, s, SMe), 6.36 (2 H, s, $PhCH_2$), 2.70 (5 H, s, Ph), 2.00 (1 H, s, olefin), and 1.76br (2 H, NH).

The ester (8; R^1 = Bu^t, R^2 = Me) (20 mg) dissolved in dry dichloromethane (7 ml) was cooled to 0 °C and saturated with dry gaseous hydrogen chloride. The solution was stirred at 0 °C for 4 h and chloroform was added. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to a white solid which was washed with ethyl acetate (5 ml). The solid *acid* (15 mg) could not be crystallised; m.p. 201—203° (Found: M^+, 348.114 570. $C_{17}H_{20}N_2O_4S$ requires *M*, 348.114 38), $\lambda_{max.}$ (MeOH) 298 nm (log ε 3.84), $\nu_{max.}$ (MeCN) 1 720 (acid), 1 680, and 1 655 cm^{-1} (amide), τ [$(CD_3)_2SO$] 8.37 (3 H, s, MeC=), 7.98 (3 H, s, MeC=), 7.78 (3 H, s, SMe), 6.44 (2 H, s, $PhCH_2$), 3.23 (1 H, s, olefin), and 2.72 (5 H, s, Ph).

(E)-4-Isopropylidene-2-(2-methylthio-1-phenylacetamidovinyl)oxazol-5(4H)-one (9).—The acid (8; R^1 = H, R^2 = Me) (10 mg) was dissolved in acetic anhydride (10 ml) and left for 12 h at room temperature. The solvent was removed

[14] S. Wolfe, J. C. Godfrey, C. T. Holrege, and Y. G. Perron, *Canad. J. Chem.*, 1968, **46**, 2549.

to yield a pale yellow *solid* which was recrystallised from diethyl ether–pentane; yield 8 mg, m.p. 168—172° (Found: C, 60.5; H, 5.55; N, 8.1%; M^+, 330.103 949. $C_{17}H_{18}N_2O_3S$ requires C, 61.8; H, 5.5; N, 8.5%; *M*, 330.103 943), $\lambda_{max.}$ (MeOH) 273 and 348 nm (log ε 3.91 and 3.78), $\lambda_{max.}$ (OH^-) 298 nm, $\nu_{max.}$ ($CHCl_3$) 1 790 and 1 770 (oxazolone), and 1 660 cm^{-1} (amide), τ ($CDCl_3$) 7.90 (3 H, s, MeC=), 7.71 (3 H, s, MeC=), 7.61 (3 H, s, SMe), 6.34 (2 H, s, PhCH_2), 2.70 (5 H, s, Ph), and 1.92 (1 H, s, olefin).

Methyl 2-(3,3-Bismethylthio-2-phenylacetamidopropionamido)-3-methylbut-2-enoate (12; $R^1 = R^2 =$ Me) *and the Corresponding Diethyl* (12; $R^1 =$ Me, $R^2 =$ Et), Diphenyl ($R^1 =$ Me, $R^2 =$ Ph), and Dibenzyl ($R^1 =$ Me, $R^2 =$ $PhCH_2$) *Dithioacetals*.—(i) The aldehyde [7] (11; R = Me) (37 mg) was dissolved in dichloromethane (15 ml) containing boron trifluoride–ether complex (2 drops) and methanethiol (3 drops). The mixture was stirred at room temperature for 12 h and chloroform was added. The organic solution was washed with water, dried (Na_2SO_4), and evaporated to leave a white *solid* (12; $R^1 = R^2 =$ Me), which was recrystallised from chloroform; yield 40 mg, m.p. 212—214° (Found: C, 55.65; H, 6.2; N, 6.75. $C_{19}H_{26}N_2O_4S_2$ requires C, 55.6; H, 6.4; N, 6.85%), $\nu_{max.}$ (Nujol) 3 250 (NH), 1 720 (ester), and 1 665 and 1 645 cm^{-1} (amide), τ ($CDCl_3$) 8.17 (3 H, s, MeC=), 7.83br (9 H, s, MeC= and 2 × SMe), 6.36 (2 H, s, PhCH_2), 6.30 (3 H, s, OMe), 5.84 [1 H, d, *J* 6 Hz, C*H*$(SMe)_2$], 5.22 [1 H, m, C*H*·CH$(SMe)_2$], 2.68 (5 H, s, Ph), and 2.24br (1 H, s, NH).

(ii) The aldehyde [7] (11; R = Me) (100 mg) was dissolved in chloroform (10 ml) containing boron trifluoride–ether complex (5 drops) and ethanethiol (0.3 ml). The mixture was stirred at room temperature for 12 h and the solvent was removed in a stream of nitrogen to yield a gum which solidified on trituration with diethyl ether and was recrystallised from chloroform–diethyl ether to give the *dithioacetal* (12; $R^1 =$ Me, $R^2 =$ Et) (65 mg), m.p. 179—180° (Found: C, 57.35; H, 7.0; N, 6.1. $C_{21}H_{30}N_2O_4S_2$ requires C, 57.5; H, 6.9; N, 6.4%), $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 3 300 (NH), 1 715 (ester), and 1 680 and 1 660 cm^{-1} (amide), τ ($CDCl_3$) 8.81 and 8.72 (6 H, 2 × t, *J* 7 Hz, S·CH_2·CH_3), 8.16 (3 H, s, MeC=), 7.85 (3 H, s, MeC=), 7.39 and 7.27 (4 H, 2 × q, *J* 7 Hz, S·CH_2·CH_3), 6.37 (2 H, s, PhCH_2), 6.30 (3 H, s, OMe), 5.70 [1 H, d, *J* 4 Hz, C*H*$(SEt)_2$], 5.20 (1 H, q, *J* 4 and 8 Hz, C*H*), 3.30br (1 H, d, *J* 8 Hz, NH), 2.70 (5 H, s, Ph), and 2.12br (1 H, s, NH).

(iii) The same method as in (ii) but with benzenethiol gave the dithioacetal (12; $R^1 =$ Me, $R^2 =$ Ph) (20%), m.p. 171—174° (from chloroform–diethyl ether), $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 1 715 (ester), and 1 680 and 1 660 cm^{-1} (amide), *m/e* 534, τ ($CDCl_3$) 8.12 (3 H, s, MeC=), 7.81 (3 H, s, MeC=), 6.43 (2 H, s, PhCH_2), 6.28 (3 H, s, OMe), 5.09 [2 H, m, C*H*·C*H*(SPh_2)], 3.34br (1 H, d, *J* 6 Hz, NH), 2.71 (15 H, m, Ph), and 2.23br (1 H, s, NH).

(iv) A similar reaction with phenylmethanethiol gave the *dithioacetal* (12; $R^1 =$ Me, $R^2 =$ $PhCH_2$) (23%), m.p. 194—198° (from chloroform–diethyl ether) (Found: C, 65.7; H, 6.4; N, 5.1. $C_{31}H_{34}N_2O_4S_2$ requires C, 66.2; H, 6.1; N, 5.0%), $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 1 715 (ester), and 1 675 and 1 655 cm^{-1} (amide), τ ($CDCl_3$) 8.24 (3 H, s, MeC=), 7.90 (3 H, s, MeC=), 6.59 (2 H, s, PhCH_2), 6.36 (3 H, s, O*Me*), 6.43, 6.40, 6.22, and 6.19 (4 H, SCH_2Ph), 6.03 [1 H, d, *J* 4 Hz, C*H*$(SCH_2Ph)_2$], 5.18 [1 H, q, *J* 4 and 7 Hz, NH·C*H*·CH$(SCH_2Ph)_2$; d in D_2O], 3.54br (1 H, d, *J* 7 Hz, NH, exchangeable in D_2O), 2.74 (15 H, m, Ph), and 2.37br (1 H, s, NH, exchangeable in D_2O).

Methyl 2-(3-Benzylthio-2-phenylacetamidoacrylamido)-3-methylbut-2-enoate (13; $R^1 =$ Me, $R^2 =$ $PhCH_2$).—The dibenzyl dithioacetal (12; $R^1 =$ Me, $R^2 =$ $PhCH_2$) (150 mg) was dissolved in dry methanol (30 ml) and sodium methoxide (75 mg) was added. The solution was refluxed under nitrogen for 4 h, then cooled, and chloroform was added. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to yield a white solid which exhibited three spots on t.l.c. [ethyl acetate–chloroform (1 : 1)]. Preparative t.l.c. in the same system yielded starting material (80 mg), m.p. 194—196°, and a fraction of R_F 0.45, which was recrystallised from benzene to give the *product* (13; $R^1 =$ Me, $R^2 =$ $PhCH_2$) (40 mg), m.p. 182—184° (Found: C, 65.95; H, 6.15; N, 6.55. $C_{24}H_{26}N_2O_4S$ requires C, 65.75; H, 6.0; N, 6.4%), $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 1 720 (ester), and 1 690—1 660 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 288 nm (log ε 4.26), τ ($CDCl_3$) 8.20 (3 H, s, MeC=), 7.86 (3 H, s, MeC=), 6.29 (5 H, s, OMe and PhCH_2), 6.01 (2 H, s, PhCH_2S), 3.43br (1 H, s, NH, exchangeable with D_2O), 2.69 (5 H, s, Ph), and 2.65 (5 H, s, Ph). A third compound (5 mg) isolated from the plate was neither (13; $R^1 =$ Me, $R^2 =$ $PhCH_2$) nor its geometric isomer.

Reaction of the Dimethyl Dithioacetal (12; $R^1 = R^2 =$ Me) *with Base*.—The dithioacetal (120 mg) was dissolved in dry redistilled methanol (80 ml) containing sodium methoxide (60 mg). The mixture was refluxed under nitrogen for 3.5 h and chloroform (100 ml) was added to the cooled solution. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to leave a white solid which exhibited three spots on t.l.c. [ethyl acetate–chloroform (1 : 1)]. Preparative t.l.c. in the same system gave a fraction of R_F 0.22, which was recrystallised from chloroform–diethyl ether to give the *enethiol methyl thioether* (13; $R^1 = R^2 =$ Me) (30 mg), m.p. 191—194° (Found: C, 59.4; H, 6.45; N, 7.55. $C_{18}H_{22}N_2O_4S$ requires C, 59.65; H, 6.1; N, 7.75%), $\nu_{max.}$ ($CHCl_3$) 3 350 (NH), 1 710 (ester), and 1 650 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 230sh and 285 nm (log ε 4.1 and 4.28), τ ($CDCl_3$) 8.21 (3 H, s, MeC=), 7.89 (3 H, s, MeC=), 7.63 (3 H, s, SMe), 6.29 (5 H, s, OMe and PhCH_2), 3.23 (1 H, s, NH, exchangeable with D_2O), 2.65 (5 H, s, Ph), 2.45br (1 H, s, NH, exchangeable with D_2O). A fraction of R_F 0.38, recrystallised from chloroform–diethyl ether (yield 10 mg), had m.p. 130—135° and was identical with compound (8; $R^1 = R^2 =$ Me) prepared from the thiazepine (6; R = Me). A third fraction (30 mg), m.p. 210—212°, proved to be starting material.

2-(3,3-Diethoxy-2-phenylacetamidopropionamido)-3-methylbut-2-enoic Acid (14; R = H).—The diethyl acetal [7] (14; R = Me) (300 mg) was dissolved in anhydrous pyridine (20 ml) and freshly fused lithium iodide (1.5 g) was added. The mixture was refluxed under nitrogen for 2 h and dichloromethane was added to the cooled solution. The organic solution was extracted with saturated aqueous sodium hydrogen carbonate and crushed ice was added to the extracts, which were neutralised with concentrated hydrochloric acid. The solution was extracted with dichloromethane and the extracts were washed with water, dried (Na_2SO_4), and evaporated to yield a solid. This was recrystallised from chloroform–diethyl ether to give the *acetal* (14; R = H) (120 mg), m.p. 175—180° (Found: C, 61.55; H, 6.85; N, 7.25. $C_{20}H_{28}N_2O_6$ requires C, 61.2; H, 7.2; N, 7.15%), $\nu_{max.}$ (Nujol) 3 260 (NH), 2 600br (OH), 1 685 (acid), and 1 630 cm^{-1} (amide), τ ($CDCl_3$) 8.92 and 8.79 (6 H, 2 × t, *J* 7 Hz, OCH_2·CH_3), 8.16 (3 H, s, MeC=), 7.80 (3 H, s, MeC=), 6.37 (2 H, s, PhCH_2), 6.30br (4 H, m,

$OCH_2{\cdot}CH_3$), 5.34 [1 H, q, *J* 2 and 7 Hz $CH{\cdot}CH(OEt)_2$], 5.21 [1 H, d, *J* 2 Hz, $CH(OEt)_2$], 3.30br (1 H, d, *J* 7 Hz, NH), 2.70 (5 H, s, Ph), 2.16br (1 H, s, NH), and 1.3br (1 H, CO_2H). The neutral extracts yielded starting material (65 mg), m.p. 185—186 (lit.,[7] 186°).

3-Methyl-2-(3-oxo-2-phenylacetamidopropionamido)but-2-enoic Acid (11; R = H).—The diethyl acetal (14; R = H) (40 mg) dissolved in acetonitrile (3 ml) was heated to reflux and 0.4N-hydrochloric acid (1 ml) was added. Refluxing was continued for 18 min and chloroform was added to the cooled solution. The aqueous layer was further extracted with chloroform and the combined organic extracts were dried ($MgSO_4$) and evaporated to yield an oil. This solidified on trituration with diethyl ether to give the *aldehyde* (30 mg), m.p. 90—106°, $\lambda_{max.}$ (OH^-) 280 nm, $\nu_{max.}$ ($CHCl_3$) 1 720sh (aldehyde), 1 700 (acid), and 1 670 cm^{-1} (amide), τ ($CDCl_3$) 8.26 (3 H, s, *Me*C=), 7.88 (3 H, s, *Me*C=), 6.39 (2 H, s, $PhCH_2$), 2.76 (5 H, s, Ph), and 0.53 (s, CHO). The *2,4-dinitrophenylhydrazone* had m.p. 222—224° (Found: C, 52.75; N, 5.0; N, 16.45. $C_{22}H_{22}N_6O_8$ requires C, 53.0; H, 4.45; N, 16.85%). The crude aldehyde was synthesised as required and used immediately.

2-(3,3-Bismethylthio-2-phenylacetamidopropionamido)-3-methylbut-2-enoic Acid (12; R^1 = H, R^2 = Me).—The aldehyde (11; R = H) (37 mg) was dissolved in dichloromethane (15 ml) and boron trifluoride–ether complex (2 drops) and methanethiol (3 drops) were added. The mixture was stirred at room temperature for 12 h and chloroform was added. The organic solution was washed with water, dried (Na_2SO_4), and evaporated to yield a pale yellow solid. This was recrystallised from chloroform–diethyl ether to give the *dithioacetal* (33 mg), m.p. 205—210° (Found: C, 54.4; H, 6.25; N, 7.1. $C_{18}H_{24}N_2O_4S_2$ requires C, 54.55; H, 6.1; N, 7.05%), $\nu_{max.}$ (Nujol) 3 260 (NH), 1 690 (acid), and 1 650 cm^{-1} (amide), τ [$(CD_3)_2SO$] 8.21 (3 H, s, MeC=), 7.91 and 7.87 (9 H, 2 × s, MeC= and SMe), 6.42 (2 H, s, $PhCH_2$), 5.91 [1 H, d, *J* 7 Hz, $CH(SMe)_2$], 5.16 (1 H, m, NHC*H*), 2.73 (5 H, s, Ph), 2.05 (1 H, d, *J* 10 Hz, NH), and 0.92 (1 H, s, CO_2H, exchangeable with D_2O).

3-Methyl-2-(3-methylthio-2-phenylacetamidoacrylamido)but-2-enoic Acid (13; R^1 = H, R^2 = Me).—The dimethyl dithioacetal (12; R^1 = H, R^2 = Me) (40 mg) was dissolved in redistilled methanol (20 ml) containing sodium methoxide (40 mg). The mixture was refluxed for 8 h under nitrogen and methanol (10 ml) was distilled off. The residue was poured into water and the aqueous solution was washed with chloroform and acidified with dilute hydrochloric acid. The acidic solution was extracted with chloroform and the extracts were dried (Na_2SO_4) and evaporated to yield a pale yellow solid. This was recrystallised from chloroform–diethyl ether to yield the *product* (15 mg), m.p. 174—176° (Found: C, 58.55; H, 6.0; N, 7.95. $C_{17}H_{20}N_2O_4S$ requires C, 58.6; H, 5.8; N, 8.05%), $\lambda_{max.}$ (MeOH) 230 and 285 nm (log ε 3.89 and 4.13), $\nu_{max.}$ (Nujol) 1 700sh (acid), and 1 675 and 1 640 cm^{-1} (amide), τ (CD_3OD) 8.21 (3 H, s, MeC=), 7.85 (3 H, s, MeC=), 7.61 (3 H, s, SMe), 6.33 (2 H, s, $PhCH_2$), and 2.62 (6 H, m, Ph and olefinic H).

(Z)-4-Isopropylidene-2-(2-methylthio-1-phenylacetamidovinyl)oxazol-5(4H)-one (10).—The acid (13; R^1 = H, R^2 = Me) (8 mg) was dissolved in acetic anhydride (3 ml) and kept for 12 h at room temperature. The solvent was removed *in vacuo* to yield a pale yellow solid which was recrystallised from chloroform–diethyl ether (7 mg) to give material, m.p. 154—156°, identical with the product (2; R = $PhCH_2{\cdot}CO$) obtained from rearrangement of penicillin G with methyl chloroformate.

(3RS)-Methyl 2,3,4,5-Tetrahydro-2,2-dimethyl-5-oxo-6-phthalimido-1,4-thiazepine-3-carboxylate.—(3*RS*)-Methyl 2,2-dimethyl-6-phthalimido-5-oxoperhydro-1,4-thiazepine [15] (3.4 g) was dissolved in dichloromethane (100 ml) and the solution was cooled to −60 °C in acetone–solid CO_2. A solution of chlorine in carbon tetrachloride (0.693M; 14.4 ml) was added dropwise over 30 min and the reaction temperature (−60 ± 2 °C) was maintained for a further 2 h. The mixture was allowed to warm to room temperature overnight under a stream of nitrogen and the solvent was removed *in vacuo*. Ethyl acetate (50 ml) was added and the solution was left at −15 °C overnight. Starting material (100 mg) was filtered off and the solvent was removed *in vacuo* to yield a foam, which was separated into two fractions by preparative t.l.c. [ethyl acetate–chloroform (1 : 1)]. These were the desired compound [15] (600 mg) and the starting material (1.1 g).

Methyl 3-Methyl-2-(3-methylthio-2-phthalimidoacrylamido)-but-2-enoate (15) (E-*Isomer*).—The foregoing thiazepine (300 mg) was dissolved in dry methanol (20 ml) and sodium methoxide (90 mg) was added. The mixture was stirred at room temperature for 30 min. Methyl iodide (0.05 ml) was added and the mixture was stirred for a further 30 min at room temperature. The methanol was removed *in vacuo* and the residue was dissolved in chloroform. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to leave an oil. This solidified on trituration with diethyl ether and was recrystallised from chloroform–diethyl ether to give the *product* (300 mg), m.p. 193—195° (Found: C, 57.35; H, 4.9; N, 7.5. $C_{18}H_{18}N_2O_5S$ requires C, 57.75; H, 4.85; N, 7.5%), $\nu_{max.}$ ($CHCl_3$) 1 780 and 1 760 (phthalimide), 1 715 (ester), and 1 665 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 239sh and 295 nm (log ε 4.11 and 4.22), τ ($CDCl_3$) 8.12 (3 H, s, MeC=), 7.82 (3 H, s, MeC=), 7.56 (3 H, s, SMe), 6.28 (3 H, s, OMe), 3.05br (1 H, s, NH), 2.95 (1 H, s, olefinic), and 2.15 (4 H, m, ArH).

Irradiation of the Ester (15) (E-*Isomer*).—The ester (50 mg) was dissolved in dry pyridine (20 ml) in a quartz flask and thoroughly degassed. The solution was irradiated with a Philips 125 W high-pressure mercury arc under nitrogen for 16 h and the solvent was removed *in vacuo* to yield a black oil which exhibited three spots on t.l.c. [chloroform–ethyl acetate (1 : 1)]. Preparative t.l.c. (2 ×) in the same system yielded the starting *E*-isomer (17 mg), m.p. 193—195°, and the *Z*-isomer (20 mg), m.p. 158—160° (from chloroform–diethyl ether), *m/e* 374, $\nu_{max.}$ ($CHCl_3$) 3 410 (NH), 1 780 and 1 730 (phthalimide), 1 715 (ester), and 1 670 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 239 and 286 nm (log ε 4.17 and 4.26), τ ($CDCl_3$) 8.15 (3 H, s, MeC=), 7.82 (3 H, s, MeC=), 7.52 (3 H, s, SMe), 6.30 (3 H, s, OMe), 3.20br (1 H, s, NH, exchangeable with D_2O), and 2.1br (5 H, m, Ph and olefinic).

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