Transformations of Penicillins: Novel Ring-opening Reactions of a Penicillin-derived Sulphimide[1]

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(2*S*,4*R*,6*S*,7*S*)-Methyl 3,3-dimethyl-8-oxo-7-phenoxacetamido-5-*p*-tolylsulphoryl-4-thia-1,5-diazabicyclo-[4.2.0]octane-2-carboxylate *S*-*p*-tolylsulphonylimide was thermolysed in refluxing toluene to afford quantitatively (3*S*,4*S*)-1-(1-methoxycarbonyl-2-methylprop-2-enyl)-3-phenoxyacetamido-4-[*N*-(*p*-tolylsulphonylaminothio)-*p*-tolylsulphonylamino]azetidin-2-one, by a β-elimination mechanism. Treatment of the monocyclic azetidinone with triphenylphosphine afforded methyl *N*-(α-phenoxyacetamido-β-*p*-tolylsulphonylacryloyl)-βγ-didehydrovalinate, which underwent addition of alcohols to the enamine double bond to form *gem*-alkoxy-amine dipeptides. The reduction of both the monocyclic azetidinone and the enamine dipeptide with sodium borohydride is described.

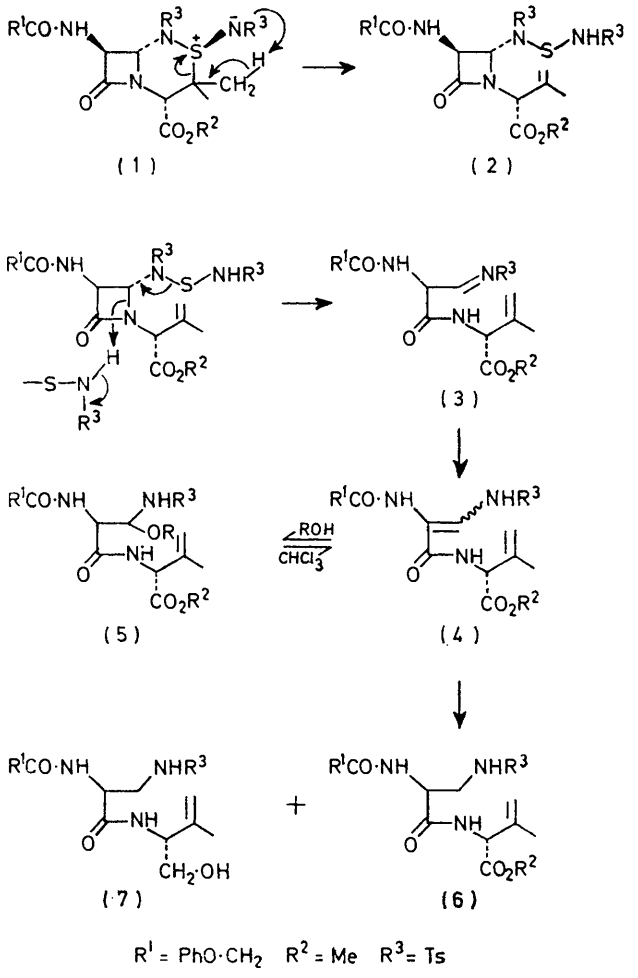
An earlier publication [2] described the formation and identification of the β-lactam-fused heterocyclic sulphimide (1). This paper describes the thermal electrocyclic rearrangement of compound (1) to a novel *trans*-disubstituted monocyclic azetidinone (2), which in turn undergoes a series of reactions with nucleophiles, leading to β-lactam-cleaved enamine dipeptides and derived products.

The sulphimide (1) in refluxing toluene was rapidly and quantitatively transformed into a single product (2). The i.r. spectrum indicated the presence of a β-lactam (1783 cm^{-1}), and showed that although tosylamino-groups were present the original *S*-tosylimide group had been altered. The n.m.r. spectrum pointed to a *trans*-configuration of the β-lactam protons (τ 4·23 and 4·62, *J* 2 Hz), a βγ-didehydrovalinate group, and two tosyl units. The product was isomeric with (1) and from consideration of spectroscopic data together with its mode of formation and chemical reactivity was assigned structure (2) with stereochemistry as depicted.

[1] Preliminary communication, M. M. Campbell, and G. Johnson, *J.C.S. Chem. Comm.*, 1974, 974.

[2] Preliminary communication, M. M. Campbell, G. Johnson, A. F. Cameron, and I. S. Cameron, *J.C.S. Chem. Comm.*, 1974, 868.

Penicillin *S*-oxides [3] are known to undergo thermal β-elimination reactions leading to rearranged products.



Instances have been reported of the isoelectronic penicillin *S*-imides [4] and also penicillin S^+–C^- ylides [4,5] rearranging by electrocyclic reactions. There is therefore ample precedent for a mechanism in which the β-oriented *S*-tosylimide group in (1) participates in electrocyclic ring opening with H-transfer, perhaps from the adjacent β-methyl group.

The reaction of the azetidinone (2) with triphenylphosphine was investigated with the objective of desulphurizing the N–S–N group at C-4, but at 0 °C cleavage occurred with formation of triphenylphosphine sulphide and an optically active crystalline non-β-lactam product. Elemental and spectroscopic analysis indicated structure (4) for this compound, although it was not possible rigorously to assign *E*- or *Z*-stereochemistry. Detailed n.m.r. analysis (220 MHz) allowed assignment of all protons, including the single vinylic proton at τ 2·96, coupling with the tosylamino-proton (10 Hz). The latter was more rapidly exchanged in D_2O than either of the amide protons, reflecting its greater acidity. In $CDCl_3$–C_5D_5N the n.m.r. spectrum of an equilibrium mixture of the *E*- and *Z*-isomers was observed, presumably equilibrating through the imine (3). The u.v. spectrum of (4) was similar to those of structurally related enamines.[6] Addition of a trace amount of alkali to the solution afforded a new chromophore (298 nm) possibly a delocalized *N*-anion. The mass spectrum of (4) showed structurally informative ions at *m/e* 155 and 346 (Scheme). Compound (4) is of interest in the light of its structural relationship to dipeptides recently postulated [6a,7] as intermediates in the biosynthesis of penicillins. We suggest that (4) is formed by nucleophilic attack of triphenylphosphine on (2), followed by tautomerism of the intermediate imine (3). The organophosphorus residue left after isolation of (4) was highly unstable and was not characterized.

Solutions of both the β-lactam (2) and the enamine (4) in ethanol deposited white crystals, $[\alpha]_D^{20}$ −41° (*c* 1·00 in dioxan), shown to be the homogeneous ethanolamine (5; R = Et) formed by Michael addition to the acryloyl group [or nucleophilic addition to the imine (3)]. Only one of the possible ethanolamine diastereoisomers crystallised from the reaction. The n.m.r. spectrum (220 MHz) showed the MeCH_2·O signal as an ABX_3 system (J_{AB} 9 Hz). Reactions of compounds (2) and (4) in methanol afforded the corresponding homogeneous *gem*-methanolamine (5; R = Me) in which the methoxy-signal appeared as a singlet in the n.m.r. spectrum.

By-products of the reaction of the azetidinone (2) with ethanol were *NN'*-thiobis(toluene-*p*-sulphonamide) [8] and elemental sulphur. These may be accounted for in terms of disproportionation of an intermediate such as *NN'*-dithiobis(toluene-*p*-sulphonamide). The *gem*-alkoxy-amines (5) slowly reverted to the enamine dipeptide (4) in dry chloroform.

Reduction of the monocyclic azetidinone (2) with borohydride gave, as minor products, toluene-*p*-sulphonamide and, surprisingly, the enamine dipeptide (4). The latter may arise by hydride ion attack at sulphur with formation of the intermediate imine (3) and thence the more highly resonance-stabilised compound (4). The major product was the reduced dipeptide (6). N.m.r. analysis (60 MHz) indicated that (6) was possibly

[3] See, for example, R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Accounts Chem. Res.*, 1973, **6**, 32; D. H. R. Barton, *Pure Appl. Chem.*, 1973, **33**, 1; J. H. C. Nayler, *Adv. Drug. Res.*, 1973, **7**, 1; T. S. Chou, J. R. Burgtof, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *J. Amer. Chem. Soc.*, 1974, **5**, 1609; T. S. Chou, *Tetrahedron Letters*, 1974, 725; and references cited in these papers.

[4] M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Letters*, 1972, 5097.

[5] M. Yoshimoto, S. Ishihara, E. Nakayama, and N. So ma, *Tetrahedron Letters*, 1972, 2923; M. Yoshimoto, S. Ishihara, E. Nakayama, E. Shoji, H. Kuwano, and N. Soma, *ibid.*, p. 4387.

[6] (*a*) J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, *J.C.S. Perkin I*, 1974, 986; (*b*) R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, *ibid.*, 1973, 1182; (*c*) R. J. Stoodley and N. S. Watson, *ibid.*, 1974, 252.

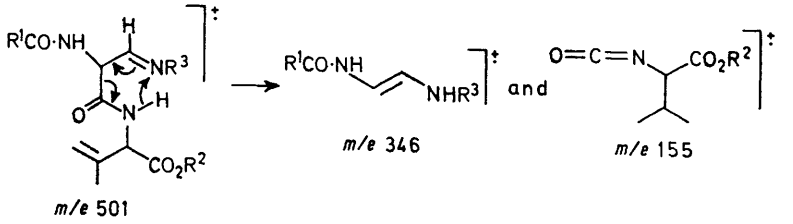
[7] H. R. V. Arnstein and J. C. Grawhill, *Biochem. J.*, 1957, **67**, 180; P. A. Lemke and D. R. Brannon, 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 370; J. E. Baldwin, S. B. Haber, and J. Kitchin, *J.C.S. Chem. Comm.*, 1973, 790; D. J. Aberhart and J. Y.-R. Chu, *ibid.*, 1974, 564.

[8] M. M. Campbell and G. Johnson, preceding paper.

a single diastereoisomer, but it was not possible to assign the absolute stereochemistry at the phenoxyacetamido-site. It was subsequently shown that the enamine dipeptide (4) could be reduced by sodium borohydride to give (6), together with a small quantity of the ester-reduced dipeptide (7), the structure of which was suggested by i.r. and n.m.r. spectroscopy.

Other nucleophiles, *e.g.* acetate or a catalytic trace of thiocyanate, rapidly reacted with the azetidinone (2) to give complex mixtures from which small quantities of (4) could be isolated. No β-lactam product indicative of nucleophilic attack at C-4 was observed. Room temperature treatment of (2) with triethylamine did not isomerise the βγ-didehydrovalinate group. Under more forcing conditions the azetidinone was degraded into a complex mixture of compounds.

The transformation of penicillins into *S*-imides such as (1) which can readily be rearranged to enamines (4) represents a new method of opening up the penam nucleus.



SCHEME

EXPERIMENTAL

General experimental details are as described in the preceding paper.[8]

Thermolysis of the Sulphimide (1).—A suspension of the sulphimide (0·03 g) in toluene (5 ml) was refluxed until a clear solution was obtained. T.l.c. showed complete conversion into a single, less polar product. Evaporation *in vacuo* gave a white solid foam (0·03 g), m.p. *ca.* 80°, $[\alpha]_D^{20}$ −112° (*c* 1·00 in $CHCl_3$), which could not be crystallized from a variety of solvents. (3S,4S)-1-(1-*methoxycarbonyl*-2-*methylprop*-2-*enyl*)-3-*phenoxyacetamido*-4-[N-(p-*tolylsulphonylaminothio*)-p-*tolylsulphonylamino*]*azetidin*-2-*one* (2) showed $\nu_{max.}$ (film) 3360 (amide NH), 3200 (amide NH), 1783 (β-lactam C=O), 1745 (ester C=O), 1685 (amide C=O), and 1355, 1165, and 1085 cm^{-1} (tosyl [9]), τ 8·16 (3H, s, *Me*C=), 7·70 (3H, s, tosyl Me), 7·62 (3H, s, tosyl Me), 6·30 (3H, s, MeO), 5·60 (2H, s, PhOCH_2), 5·35 (1H, s, α-methine H), 5·10br (1H, s, =C*H*H), 4·96 (1H, s, =CH*H*), 4·62 (1H, m, 3-H coupling with NH), 4·23 (1H, d, *J* 2 Hz, 4-H coupling with 3-H), 3·20—1·90 (14H, m, aromatic and NH), and 1·98br (1H, s, tosyl NH, exchanged by D_2O) (Found: C, 53·2; H, 5·1; N, 7·2; S, 13·4. $C_{31}H_{34}N_4O_9S_3$ requires C, 53·0; H, 4·9; N, 7·9; S, 13·6%).

Thermolysis of the Sulphimide (1; R^1 = $PhCH_2$).—The sulphimide (1·0 g) was treated as above, yielding as a solid foam which resisted crystallization, (3*S*,4*S*)-1-(1-methoxycarbonyl-2-methylprop-2-enyl)-3-phenylacetamido-4-[*N*-(*p*-tolylsulphonylaminothio)-*p*-tolylsulphonylamino]azetidin-2-one, $[\alpha]_D^{20}$ −73° (*c* 1·00 in $CHCl_3$), m.p. indeterminate, $\nu_{max.}$ (film) 3250 (amide NH), 1790 (β-lactam C=O), 1760 (ester C=O), 1670 (amide C=O), and 1360, 1170, and 1092 cm^{-1} (tosyl), τ 8·15 (3H, s, MeC=), 7·60 (6H, s, two tosyl Me), 6·34 (2H, s, PhCH_2), 6·26 (3H, s, MeO), 5·30 (1H, s, α-methine H), 5·05br (1H, s, =C*H*H), 4·90 (1H, s, =CH*H*), 4·64 (1H, m, 3-H coupling with NH), 4·30 (1H, d, *J* 2 Hz, 4-H coupling with 3-H), and 2·70—1·90 (15H, m, aromatic and 2 × NH).

Reaction of the Azetidinone (2) *with Triphenylphosphine.*—A solution of the azetidinone (1·0 g, 1·43 mmol) in toluene (40 ml) was cooled to 0 °C and triphenylphosphine (0·39 g, 1·48 mmol) was added. The solution was stirred for 1·5 h, then evaporated to low bulk *in vacuo* and filtered. The filtrate was adsorbed directly on a silica gel column, which was eluted with petroleum–ethyl acetate (3 : 1) giving triphenylphosphine sulphide (m.p.; i.r., n.m.r., and mass spectroscopy) and then *methyl* N-(α-*phenoxyacetamido*-β-p-*tolylsulphonylacryloyl*)-βγ-*didehydrovalinate* (4) (0·5 g), m.p. 124—126°, $[\alpha]_D^{22}$ −44° (*c* 1·00 in dioxan), $\nu_{max.}$ (KBr) 3320 (amide NH), 1735 (ester C=O), 1678 (amide C=O), 1620 (acryloyl C=C), 1530, 1495, 1155, and 1080 cm^{-1}, τ (dry $CHCl_3$; 220 MHz) 8·25 (3H, s, MeC=), 7·62 (3H, s, tosyl Me), 6·26 (3H, s, MeO), 5·49 (2H, s, PhOCH_2), 4·98 (1H, d, *J* 7·5 Hz, α-methine H in βγ-didehydrovalinate), 4·96 (2H, s, CH_2=C), 3·25 (1H, d, *J* 7·5 Hz, amide NH coupling with α-methine H), 2·96 (1H, d, *J* 10 Hz, β-H of acryloyl), 3·12—2·18 (9H, m, aromatic), 1·03 (1H, s, phenoxyacetamido NH), and 0·28 (1H, d, *J* 10 Hz, tosylamino NH, rapidly exchanged by D_2O). Spin decoupling confirmed assignments of isopropenyl protons and also tosylamino and vinyl protons. After addition of [$^2H_5$]pyridine to the solution the spectra of *E*- and *Z*-isomers were observed: τ (minor isomer) 8·36 (3H, s, MeC=), 7·68 (3H, s, tosyl Me), 6·35 (3H, s, MeO), 5·44 (2H, s, PhOCH_2), 5·10 (1H, s, =C*H*H), 5·06 (1H, s, =CH*H*), 4·92 (1H, d, *J* 7·5 Hz, α-methine H), 3·16—2·25 (10H, m, aromatic and amide NH), 2·13 (1H, d, *J* 7·5 Hz, amide NH), 1·40 (1H, s, phenoxyacetamido NH), and 0·58 (1H, s, tosyl NH); τ (major isomer) 8·31 (3H, s, MeC=), 7·68 (3H, s, tosyl Me), 6·35 (3H, s, MeO), 5·80 (2H, s, PhOCH_2), 5·10 (1H, s, *H*CH=C), 5·06 (1H, s, HC*H*=C), 4·92 (1H, d, *J* 7·5 Hz, α-methine H), 3·25—2·10 (9H, m, aromatic), 2·13 (1H, d, *J* 7·5 Hz, amide NH), 1·41 (1H, s, phenoxyacetamido NH), and 0·68 (1H, s, tosyl NH); $\lambda_{max.}$ (EtOH) 220 (ε 17,900), 262 (16,900), 268 (16,150), and 275 nm (13,300); after addition of a trace of sodium hydroxide $\lambda_{max.}$ 220 (ε 17,900) and 298 nm (17,900); original u.v. spectrum re-formed by addition of dilute hydrochloric acid (Found: C, 57·5; H, 5·6; N, 8·5; S, 6·6%; M^+, 501·1582. $C_{24}H_{27}N_3O_7S$ requires C, 57·5; H, 5·4; N, 8·2; S, 6·4%; *M*, 501·1570); *m/e* 501, 394, 346, 291, 171, 155, 107, and 91.

Reaction of the Enamine Dipeptide (4) *with Ethanol.*—A

[9] L. J. Bellamy, 'Advances in Infrared Group Frequencies,' Methuen, London, 1968.

solution of (4) in ethanol afforded quantitatively white crystals of *methyl* N-[3-*ethoxy*-α-*phenoxyacetamido*-β-(p-*tolylsulphonylamino*)*propionyl*]-βγ-*didehydrovalinate* (5; R = Et), m.p. 156—157°, $[\alpha]_D^{20}$ −41° (*c* 1·00 in dioxan), $\nu_{max.}$ (KBr) 3280 (amide and tosylamino NH), 1740 (ester C=O), 1650 (amide C=O), 1540 (amide NH), and 1340, 1160, 1100, and 1050 cm^{-1} (tosyl); $\lambda_{max.}$ (EtOH) 225 nm (ε 10,900), τ ($CDCl_3$; 220 MHz) 8·78 (3H, t, *J* 7 Hz, CH_3·CH_2·O), 8·20 (3H, s, MeC=), 8·04 (3H, s, tosyl Me), 6·48 (1H, dq, *J* 7 and 9 Hz, Me*H*CH·O), 6·35 (1H, d, *J* 14 Hz, PhOCH_2), 6·05 (1H, dq, *J* 7 Hz and 9 Hz, MeHC*H*·O), 5·84 (1H, d, *J* 14 Hz, PhOCH_2), 5·41 (1H, dd, *J* 8 and 9 Hz, α-methine H in propionyl), 5·20 (1H, dd, *J* 8 and 10 Hz, β-methine H in propionyl; 10 Hz coupling disappeared in D_2O), 5·05 (1H, d, *J* 7·5 Hz, α-methine H in didehydrovalinate), 4·91 and 4·89 (each 1H, s, =CH_2), 3·54 (1H, d, *J* 10 Hz, TsNH, exchanged with D_2O), 3·22 (2H, d, *J* 9 Hz, tosyl aromatic), 2·53 (1H, d, *J* 8 Hz, phenoxyacetamido NH), 2·49 (1H, d, *J* 7·5 Hz, didehydrovalinate NH), 3·10—2·60 (5H, m, aromatic), and 2·34 (2H, d, *J* 9 Hz, tosyl aromatic) [Found: C, 57·0; H, 6·0; N, 7·4; S, 5·7%; $(M - EtOH)^+$, 501·1568. $C_{26}H_{33}N_3O_8S$ requires C, 57·0; H, 6·0; N, 7·7; S, 5·9%. $C_{24}H_{27}N_3O_7S$ requires 501·1570]; *m/e* 501, 469, 442, 394, 346, 252, 155, and 91.

Reaction of the Enamine Dipeptide (4) *with Methanol.*—A solution of (4) in methanol quantitatively afforded a crystalline precipitate of *methyl* N-[β-*methoxy*-α-*phenoxyacetamido*-β-(p-*tolylsulphonylamino*)*propionyl*]-βγ-*didehydrovalinate* (5; R = Me), m.p. 148—150°, $\nu_{max.}$ (KBr) 3280 (amide and tosylamino NH), 1740 (ester C=O), 1650 (amide C=O), 1540 (amide NH), and 1340, 1160, 1110, and 1050 cm^{-1} (tosyl), τ ($CDCl_3$; 60 MHz) 8·16 (3H, s, MeC=), 7·95 (3H, s, tosyl Me), 6·46 (3H, s, OMe), 6·16 (3H, s, CO_2CH_3), 6·06 (1H, s, PhOC*H*H), 5·79 (1H, s, PhOCH*H*), 5·30—4·80 (complex m, α- and β-methine protons in propionyl, =CH_2 in didehydrovalinate, α-methine H in didehydrovalinate), 3·36br (1H, d, *J* 8 Hz, tosyl NH), 3·06 and 2·15 (each 2H, d, *J* 9 Hz, tosyl aromatic), 2·36 (2H, 2 × d, phenoxyacetamido NH and didehydrovalinate NH), and 2·90—2·20 (5H, m, *Ph*OCH_2) (Found: C, 55·9; H, 5·9; N, 7·9; S, 6·0. $C_{25}H_{31}N_3O_8S$ requires C, 56·3; H, 5·9; N, 7·9; S, 6·0%).

Reactions of the Azetidinone (2) *with Ethanol and Methanol.*—The thermolysis product (2) (1·0 g, 1·4 mmol) dissolved in ethanol was set aside at room temperature for several days, affording a white crystalline solid (0·35 g, 49%), identical with the ethanolamine (5; R = Et) (m.p.; i.r. and n.m.r. spectra). The mother liquors were reduced in volume and subjected to column chromatography, affording more ethanolamine (5), together with *NN'*-thiobis(toluene-*p*-sulphonamide) and sulphur. A similar reaction occurred in methanol, affording the methanolamine (5; R = Me).

Conversion of the Ethanolamine (5; R = Et) *into the Enamine Dipeptide* (4).—A solution of the ethanolamine (1 mg) in chloroform (25 ml) was left at room temperature for 3 h, during which gradual build-up of the chromophore associated with the enamine dipeptide (4) was observed by u.v. spectroscopy. The u.v. spectrum was identical with that of an authentic sample of (4). A similar transformation was observed in the n.m.r. spectrum.

Sodium Borohydride Reduction of the Azetidinone (2).—The azetidinone (2·0 g, 2·85 g mnol) was dissolved in methanol and cooled to 0°; solid sodium borohydride was gradually added with stirring until t.l.c. indicated complete consumption of starting material. The resultant solution was filtered, evaporated *in vacuo*, and chromatographed to give toluene-*p*-sulphonamide, followed by the enamine dipeptide (4) (0·15 g, 11%) and *methyl* N-[α-*phenoxyacetamido*-β-(p-*tolylsulphonylamino*)*propionyl*]-βγ-*didehydrovalinate* (6) (1·0 g, 70%) as a white crystalline solid, m.p. 153°, $[\alpha]_D^{20}$ −60° (*c* 1·00 in dioxan), $\nu_{max.}$ (film) 3300 (amide NH), 1740 (ester C=O), 1660 (amide C=O), and 1330, 1240, 1155, and 1090 cm^{-1} (tosyl), $\lambda_{max.}$ (EtOH) 230 nm (ε 11,500), τ ($CDCl_3$; 60 MHz) 8·21 (3H, s, MeC=), 7·62 (3H, s, tosyl Me), 6·71 (1H, d, *J* 8 Hz, CH*H*·NHTs), 6·61 (1H, d, *J* 8 Hz, C*H*H·NHTs), 6·26 (3H, s, CO_2CH_3), 5·46 (2H, s, PhOCH_2), 5·31 (1H, dt, *J* 4 and 5 Hz, α-methine H in propionyl), 5·03 (1H, d, *J* 6 Hz, α-methine H in didehydrovalinate), 4·93br (2H, d, C=CH_2), 4·06 (1H, t, *J* 8 Hz, TosN*H*, exchanged by D_2O), and 3·20—2·00 (11H, m, aromatic and 2 × NH) (Found: C, 56·7; H, 5·9; N, 8·2; S, 6·5%; M^+, 503·1728. $C_{24}H_{29}N_3O_7S$ requires C, 57·2; H, 5·8; N, 8·3; S, 6·4%; *M*, 503·1726).

Reduction of the Enamine Dipeptide (4) *with Sodium Borohydride.*—The enamine (4) (0·30 g, 0·6 mmol) was dissolved in methanol at 0 °C and an excess of sodium borohydride (150 mg) was added. The solution was allowed to attain room temperature, and t.l.c. then indicated partial reaction. The solution was filtered and evaporated *in vacuo*. Chromatography on silica gel (6 g) gave starting material (0·16 g, 54%), the reduction product (6) (0·05 g, 16%), and a more polar product (7) (0·02 g, 9%) as an oil, $\nu_{max.}$ (film) 3320 (amide NH and alcohol OH), 1660 (amide C=O), and 1330, 1150, and 1090 cm^{-1} (tosyl), τ ($CDCl_3$; 60 MHz) 8·20 (3H, s, MeC=), 7·54 (3H, s, tosyl Me), 6·60 (2H, m, CH_2·NHTs), 6·20 (2H, m, CH_2·OH), 5·40 (3H, m, α-methine H of propionyl and PhOCH_2), 5·15 (1H, m, methine H adjacent to CH_2·OH), 4·92 (2H, s, =CH_2), 3·50 (1H, m, amide NH), and 3·00—1·80 (10H, m, aromatic and OH).

Reaction of the Azetidinone (2) *with Potassium Thiocyanate.*—The azetidinone (2) (1·0 g, 1·42 mmol) in acetone was treated with three small crystals of potassium thiocyanate. After completion of the reaction (5 min) the solvent was evaporated off *in vacuo* and the residue chromatographed on silica gel, affording *NN'*-thiobis-(toluene-*p*-sulphonamide) (0·28 g, 96%) and the enamine dipeptide (4) (0·26 g, 36%), slightly contaminated with impurities of identical chromatographic retention characteristics. No β-lactam products were isolated.

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