Dehydropeptides Related to β-Lactam Antibiotics: a Scheme for the Biosynthesis of Penicillins and Cephalosporins

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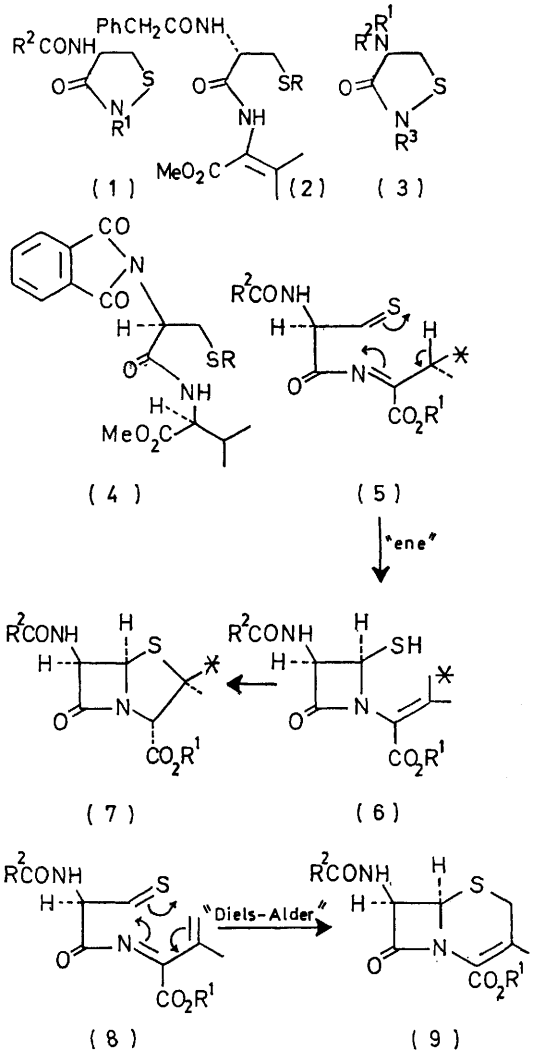
Summary Cystinylvaline and cysteinyldehydrovaline derivatives have been oxidised to isothiazolidinones, a new group of peptide derivatives; a chemically reasonable scheme for the biosynthesis of β-lactam antibiotics is presented.

IN studies connected with the biosynthesis of β-lactam antibiotics[1] we have examined the chemical oxidation of a number of cysteinyl peptides and have observed the formation of a new group of peptide derivatives, namely those containing an isothiazolidinone residue (**1**).[2] Thus, con-

version of the cysteinyldehydrovaline (**2**; R = H)[3] into the corresponding thioselenide (**2**; R = SePh), m.p. 162—163°,† was readily achieved by means of phenylselenyl bromide (1 equiv.) in pyridine. This substance was transformed to the corresponding isothiazolidinone by two procedures, *i.e.*



treatment with excess of phenylselenyl bromide in pyridine or by sequential oxidation (*m*-chloroperbenzoic acid) followed by ammonia at −60° in methylene chloride. The product [**3**; R^1 = H, R^2 = phenylacetyl, R^3 = α-(methyl-β-methylcrotonoyl)] was obtained as an oil, after purification by chromatography over silica gel, $[\alpha]_D$ + 19° (*c* 0·47, $CHCl_3$), whose spectral properties unambiguously proved its structure. A new carbonyl absorption, ν_{max} 1790 cm^{-1} (isothiazolidinone[2]), was present in the i.r. spectrum. The n.m.r. spectrum ($CDCl_3$, 100 MHz) indicated an intact methyl-β-methylcrotonoyl residue, δ 1·82 and 2·18 (each 3H, s), and 3·65 (3H, s), the methine hydrogen at C-4 appeared as a multiplet (δ 4·7) coupled to the amide hydrogen (δ 6·4, *J* 3 Hz), and the non-equivalent C-5 methylene protons appeared as two double doublets, δ 3·41 (1H, dd, *J* 10 and 12 Hz), and 3·95 (1H, dd, *J* 10 and 7 Hz). The mass spectrum exhibited a parent peak at *m/e* 348.

Similarly *N*-phthaloylcystinylvaline methyl ester was converted by sequential chlorination ($CHCl_3$, −25°) into the sulphenyl chloride (**4**; R = Cl), followed by potassium phthalimide into the sulphenimide (**4**; R = phthalimido). Chromatography of this latter compound over silica gel in chloroform–ethyl acetate gave directly the isothiazolidinone [**3**; R^1R^2 = phthaloyl, R^3 = $Me_2CHCH(CO_2Me)$-], $[\alpha]_D$ − 96° (*c* 0·26, $CHCl_3$), δ ($CDCl_3$) 1·05 (6H, d, *J* 6·5 Hz), 2·25 (1H, m), 3·48 (1H, dd, *J* 8 and 10 Hz), 3·81 (3H, s), 4·22 (1H, dd, *J* 10 and 12 Hz), 4·64 (1H, d, *J* 9 Hz), 5·35 (1H, m), and 7·81 (4H, m). The isothiazolidinone was also formed by treatment of the sulphenimide (**4**; R = phthalimido) with sodium acetate in aqueous tetrahydrofuran.

The apparently easy formation of such compounds during our attempts to oxidise the cysteinyl thiol function to thioaldehyde suggests the possible involvement of similar species in the biosynthetic pathway to β-lactam antibiotics.[4] In fact, biological conversion of such isothiazolidinones, derived from cysteinylvaline and cysteinyldehydrovaline peptides, into the next state of oxidation, *i.e.* the thioaldehyde level, provides a chemically reasonable pathway for the formation of the β-lactam nuclei, in the penicillins and cephalosporins, respectively. Thus, the isothiazolidinone from cysteinylvaline peptide could yield the thioaldehyde (**5**), which by "ene" reaction would provide the thiol (**6**). The *in vitro* Michael reaction of such a species (**6**) is already known to yield penicillins (**7**).[5] Furthermore, this process is in complete stereochemical accord (see starred atom) with the experiments recently conducted with chiral ^{13}C-valine as a precursor to penicillin V.[6] Finally, an isothiazolidinone from a cysteinyldehydrovaline peptide could, in a similar way, yield the thioaldehyde (**8**), which by Diels–Alder reaction provides a cephalosporin (**9**).‡

We thank the National Science Foundation, the Petroleum Research Fund sponsored by the American Chemical Society, and Eli Lilly and Company for their support, and the staff of the Lilly Research Laboratories and Professor R. Thomas for helpful discussions.

(*Received*, 30*th July* 1973; *Com.* 1103.)

† All new compounds have been characterized by analytical and spectral data.

‡ Examination of accurate models of the thioaldehydes for both the "ene" and "diene" reactions indicates that the correct orbital overlap and symmetry requirements are met in each case. Hence their description as "chemically reasonable." In each acylimine, (**5**) and (**8**), only the *cis* geometrical isomer, with respect to the C–N and C-2–C-3 valine bonds, can participate in the electrocyclic ene or diene reactions. This fact is not clearly represented in the planar structures written for (**5**) and (**8**).

[1] P. A. Lemke and D. R. Brannon in 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 370.

[2] Derivatives of the isothiazolidinone nucleus have been prepared by A. Leuttringhaus and R. Schneider, *Annalen*, 1964, **679**, 123. Such compounds have not yet been reported in nature.

[3] N. Leonard and R. Y. Ning, *J. Org. Chem.*, 1967, **32**, 677.

[4] Recently isothiazolones have been observed to convert into dehydropeptide derivatives, *cf.* R. B. Morin, E. M. Gordon, T. McGrath, and R. Shuman, *Tetrahedron Letters*, 1973, 2159.

[5] S. Wolfe, R. N. Bassett, S. M. Caldwell, and F. Nasson, *J. Amer. Chem. Soc.*, 1969, **71**, 7205.

[6] J. E. Baldwin, J. Löliger, W. Rastetter, N. Neuss, L. L. Huckstep, and N. De La Higuera, *J. Amer. Chem. Soc.*, 1973, **95**, 3796; N. Neuss, C. H. Nash, J. E. Baldwin, P. A. Lemke, and J. B. Cynatzue, *ibid.*, p. 3796.