Synthesis and Reactions of Thioaldehyde Dehydropeptides Related to β-Lactam Antibiotics

By JOHN CHENEY, CLIVE J. MOORES, JAMES A. RALEIGH, A. IAN SCOTT,†* and DOUGLAS W. YOUNG*
(*School of Molecular Sciences, University of Sussex, Falmer, Brighton* BN1 9QJ)

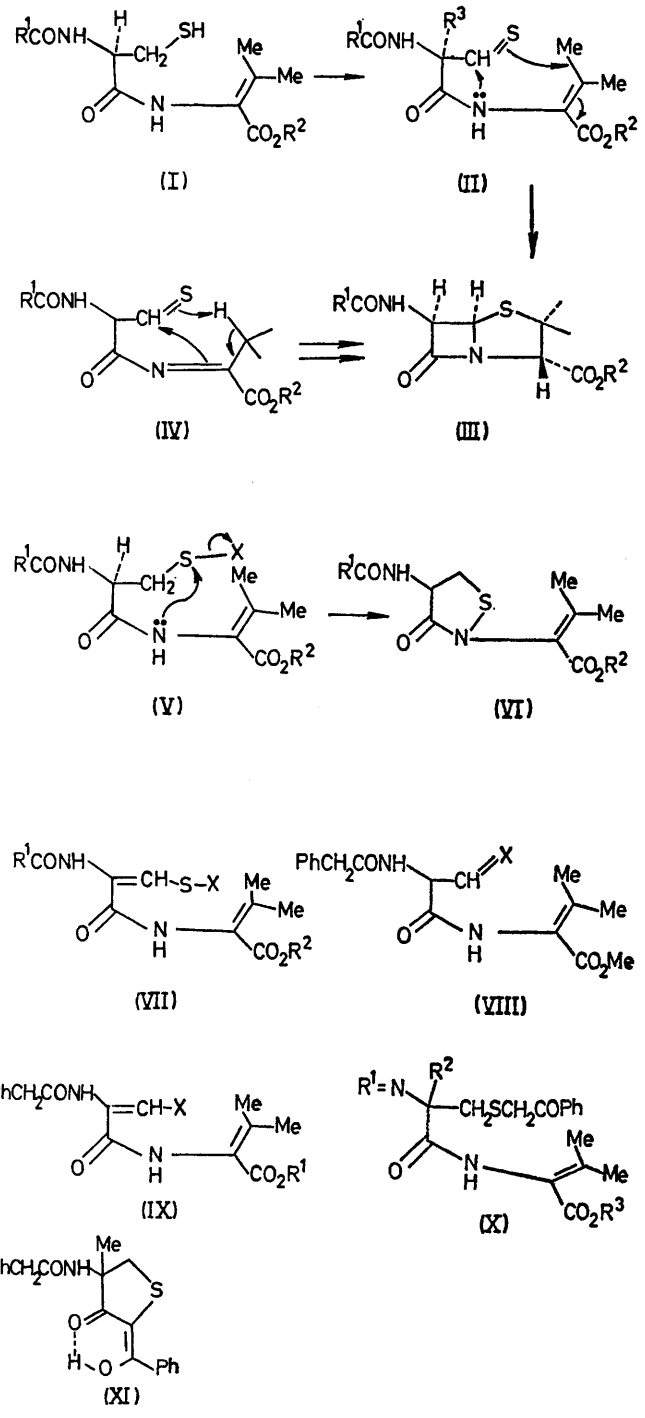
Summary Thioaldehyde dehydropeptides (II; R^3= H) related to β-lactam antibiotics have been synthesised; at room temperature these unstable compounds polymerise while at lower temperatures the thioenols are stabilised; when thioenolisation is prevented by the presence of an α-methyl substituent polymerisation is the only observable reaction.

IT has been suggested that penicillin (III) is synthesised in nature by oxidation of a cysteinyldehydrovaline dipeptide (I) to a thioaldehyde (II, R^3 = H) followed by cyclisation.[1] Recently, Baldwin[2] has reported studies of the oxidation of cysteinylvaline derivatives (V) in which a leaving group on sulphur is attacked by the nucleophilic amide nitrogen to yield isothiazolidinone products (VI) in much the same way as Leonard[3] found the unstable dehydro-analogues (VII) to react. Baldwin[2] has further suggested the interesting alternative to Arnstein's mechanism, in which the β-lactam of penicillin can be formed by an "ene" reaction of precursor (IV). We report a synthesis of thioaldehydes (II) which are the postulated intermediates in Arnstein's[1] mechanism and which, by simple tautomerism, would afford the intermediate in Baldwin's mechanism.

Benzylpenaldic acid diethyl acetal[4] was condensed with methyl α-amino-ββ-dimethylacrylate[5] to yield the acetal [VIII, X = $(OEt)_2$]‡ which could be hydrolysed to the aldehyde (VIII, X = O). Reaction of the aldehyde (VIII, X = O) with ethylamine, aniline, or urea gave the enamines (IX; X = NHEt, NHPh, and $NHCONH_2$) and reaction of these enamine dipeptides with hydrogen sulphide and acid followed by trapping of the intermediate thioaldehyde (II, R^1 = $PhCH_2$, R^2 = Me R^3 = H) with base and 1-chloro-2,4-dinitrobenzene yielded the geometrically isomeric thioethers (VII, X = 2,4-dinitrophenyl), one of which was identical in every respect with a sample prepared by the method of Leonard.[6]

Generation of the thioaldehyde under a variety of conditions failed to yield β-lactam derivatives and since the method of synthesis of this unstable intermediate might not specifically generate the thioaldehyde rather than the thioenol tautomer, we determined to ensure that thioaldehyde was indeed the first-formed tautomer by application of Woodward's ingenious use of the Norrish type II reaction.[7]

Reduction of *NN'*-bisphenylacetyl-L-cystine with sodium in liquid ammonia followed by *in situ* reaction of the resultant thiolate with phenacyl chloride gave *N*-phenylacetyl-*S*-phenacyl-L-cysteine and this was condensed with methyl α-amino-ββ-dimethylacrylate to yield the peptide (X; R^1 = $PhCH_2CO$, H, R^2 = H, R^3 = Me). The peptides (X; R^1 = Bu^tOCO, H, R^2 = H, R^3 = Me) and (X; R^1 = phthaloyl, R^2 = H, R^3 = Me) could be synthesised in a like manner and photolysis of these at room temperature generated products with spectral data and osmometric molecular weights compatible with their being polymers of the



† Present address: Sterling Chemical Laboratory, Yale University, 225 Prospect Street, New Haven, Conn., U.S.A.
‡ All new compounds have been characterised by analytical and spectral data.

desired thioaldehydes (II, $R^3 = H$). Low-temperature photolysis gave a solution with λ_{max} *ca.* 300 nm, λ_{max} (OH^-) = 335 nm, compatible with the presence of the thioenol tautomer, and trapping experiments using base and 1-chloro-2,4-dinitrobenzene or benzyl bromide yielded the geometrically isomeric sulphides (VII, X = 2,4-dinitrophenyl) and (VII, X = CH_2Ph) respectively. Generation of the thioaldehyde under a large variety of conditions gave no β-lactam products.

Since generation of the thioaldehyde at low temperatures had yielded the thioenol tautomer and not β-lactams, we attempted the synthesis of the "blocked" thioaldehydes (II, R^3 = Me) by Norrish type II photolysis of thioethers (X, R^2 = Me). *N*-Phenylacetyl-*S*-phenacyl-α-methylcysteine‡ could readily be prepared from *S*-benzyl-α-methylcysteine[8] by phenylacetylation followed by reduction and *in situ* reaction with phenacyl chloride. The condensation reaction proved troublesome, as might be expected for α-methyl amino acids,[9] a further complication in this case being self-condensation of *N*-phenylacetyl-*S*-phenacyl-α-methylcysteine to yield the β-diketone (XI). We were, however, able to obtain some of the desired sulphide (X, $R^1 = PhCH_2CO$, H; $R^2 = R^3$ = Me) and photolysis under a variety of conditions yielded polymeric thioaldehydes.

We have therefore been able to synthesise the tautomeric thioaldehyde system (II) ⇌ (IV) which is central to both Arnstein's[1] and Baldwin's[2] suggested biogenetic pathways to penicillin. However, we have been unable to convert this key intermediate *in vitro* into the antibiotic.

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