General Synthesis of Didehydroamino-acids and Peptides

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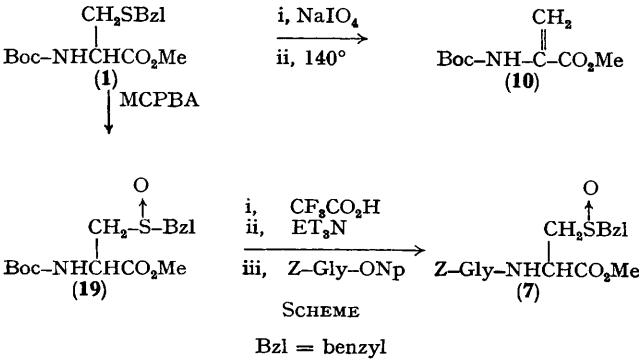
Summary Thermolysis of β-alkylsulphinyl derivatives of amino-acids and peptides gives αβ-didehydroamino-acids and peptides.

SEVERAL methods[1,2] for the synthesis of the αβ-didehydroamino-acid unit have been developed for use in studies of the role of didehydropeptides in the biosynthesis[3] and mechanism of action[4] of microbial peptides. Additional synthetic methods are needed to prepare complex didehydropeptides containing hydroxy-amino-acids or peptide bonds susceptible to base-catalysed rearrangements. We report here the synthesis of didehydropeptides by thermolysis of β-alkylsulphinyl derivatives of amino-acids (Scheme).

Heating the sulphoxides (**1**)—(**8**) in refluxing xylene under nitrogen for 6—10 h gave the corresponding didehydro-compounds (**10**)—(**17**) which were isolated in good yield after chromatography on silica gel (Table). Elimination of the sulphoxide group was facilitated by replacement of the amide hydrogen of the sulphoxide-containing amino-acid with a methyl group. The tertiary amide sulphoxide (**9**) was transformed in high yield into the didehydropeptide (**18**) within 48 h at room temperature in chloroform.



SCHEME

Bzl = benzyl

Ionization of the α-proton in acylated secondary amino-acids has been reported to be suppressed by competing ionization of the more acidic amide N–H bond.[5]

The sulphoxides (**1**)—(**9**) were prepared by oxidation of the corresponding sulphides with sodium periodate in aqueous methanol or with *m*-chloroperbenzoic acid in chloroform. Peptide sulphoxides can also be synthesized stepwise using preformed protected β-S-alkylsulphinyl derivatives of amino-acid and peptides. *E.g.*, oxidation of the β-*S*-benzylcysteinate (**1**) gave the sulphoxide (**19**) which after treatment with CF_3CO_2H followed by neutralization with Et_3N and reaction with *p*-nitrophenyl *N*-benzyloxycarbonylglycinate gave the dipeptide sulphoxide (**7**) in 70% yield (Scheme).

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TABLE†

Sulphoxide		Didehydropeptide		Yield (%)
(**1**)	Boc-Cys(OBzl)-OMe	(**10**)	Boc-Δ-Ala-OMe	85
(**2**)	Boc-But(3SOBzl)-OMe[a,b]	(**11**)	Boc-ΔBut-OMe[b,c]	81
(**3**)	Boc-Val(3SOBzl)-OMe	(**12**)	Boc-ΔVal-OMe	89
(**4**)	Boc-Ala-Phe(3SOBzl)-OMe[a]	(**13**)	Boc-Ala-ΔPhe-OMe[c]	78
(**5**)	Z-Cys(OBzl)-Gly-OEt	(**14**)	Z-ΔAla-Gly-OEt	75
(**6**)	Ac-Gly-Cys(OBzl)-OMe	(**15**)	Ac-Gly-ΔAla-OMe	80
(**7**)	Z-Gly-Cys(OBzl)-OMe	(**16**)	Z-Gly-ΔAla-OMe	60
(**8**)	Boc-MeAla-Leu-Phe(3SOBzl)-Gly-OMe[a]	(**17**)	Boc-MeAla-Leu-ΔPhe-Gly-OEt[c]	65
(**9**)	Boc-MePhe(3SOBzl)-Gly-MeAla-Leu-OMe[a]	(**18**)	Boc-NMeΔPhe-Gly-MeAla-Leu-OMe[c]	95

[a] The β-*S*-benzylamino-acid used to prepare the sulphoxides was a mixture of both *threo*- and *erythro*-diastereoisomers. [b] But = β-methylalanine. [c] The product obtained was a mixture of E and Z isomers.

† Satisfactory microanalysis, t.l.c., n.m.r., and i.r. data were obtained.

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