FACILE DIKETOPIPERAZINE FORMATION FROM DIPEPTIDES CONTAINING α-AMINOISOBUTYRIC ACID. CONFORMATIONAL FACTORS INFLUENCING CYCLISATION[+]

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Diketopiperazines were formed in good yields
on deprotection of N-protected dipeptide esters
containing α-aminoisobutyric acid residues.
Cyclisation is likely to be favoured by confor-
mational constraints introduced by the gem di-
alkyl groups.

Diketopiperazine formation from dipeptides requires
moderately vigorous conditions like heating the dipeptide
esters in toluene[1] or the free dipeptide in phenol.[2] However
cyclisation occurs readily in dipeptides containing imino
acids like proline or sarcosine,[3] presumably as a consequence
of the higher probability of occurrence of the cis peptide
conformation. The fragmentation of tri and tetrapeptides

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to yield cyclic dipeptides under alkaline conditions has also been observed.[4] In this communication we wish to report the facile formation of diketopiperazines from dipeptides of α-aminoisobutyric acid (Aib) and to discuss the role of the free dipeptide conformation in favouring cyclisation.

The removal of the t-butoxycarbonyl (Boc) or benzyloxy-carbonyl (Z) amino protecting groups, from dipeptides containing Aib residues at either position resulted only in the isolation of the corresponding diketopiperazine (Equation 1)


(1)
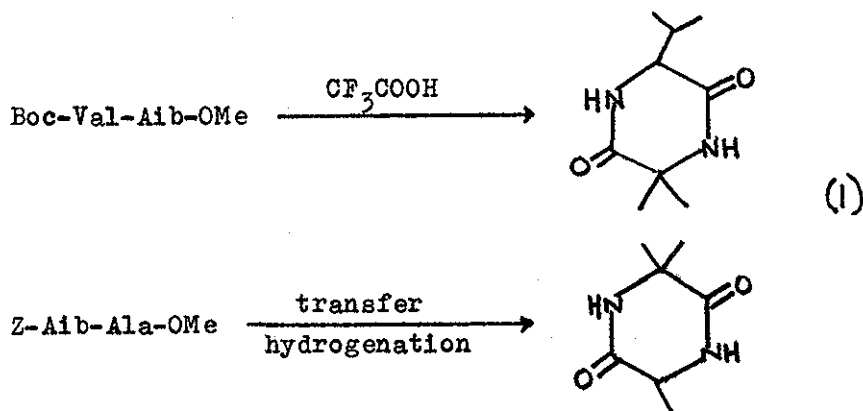
The results of deprotection reactions on four dipeptides containing Aib residues are summarised in Table I.

TABLE I

Starting peptide	Deprotection procedure	Product	Yield	MP °C	$[\alpha]_D^{25}$
Z-Aib-Ala-OMe	transfer hydrogenation	c(Aib-Ala)	68%	270	+3.8°
Z-Aib-Aib-OMe	"	c(Aib-Aib)	10%	300	-
Boc-Val-Aib-OMe	CF$_3$COOH	c(Val-Aib)	60%	210	+3.25°
Boc-Ile-Aib-OMe	"	c(Ile-Aib)	70%	252	+4.65°

The cyclic products are the only readily isolable
compounds after deprotection, except in the case of
Z-Aib-Aib-OMe. In this case the reported yield in Table I
corresponds to the amount isolated immediately after de-
protection. However on standing the dipeptide methyl ester
cyclises slowly. A report on the difficulty of cyclising
the dipeptide trichlorophenyl ester has appeared.[3]

An important structural requirement for diketopiperazine
formation is the presence of the cis peptide conformer. The
energy difference between the trans and cis conformers of the
model amide, N-methylacetamide have been reported at various
times,[5] as between 1.5 and 2.5 kcal mole^{-1}. While experimental
detection of less than 1% of the cis form may be difficult, it
is clear that the cis conformer may be present in small but
finite amounts. A recent theoretical study[5] estimating the
cis form of N-methylacetamide at 5.5×10^{-4}% is not borne out
by proton nmr measurements, where at least 0.5% is detectable.[6]
In peptides therefore the cis form may be present in amounts
sufficient to allow specifically favoured reaction paths to
proceed via this conformer. The presence of the gem dialkyl
group in α-aminoisobutyric acid imposes considerable conforma-
tional restrictions about the C^{α}—C' (ψ) and N—C^{α} (∅) bonds.[7]
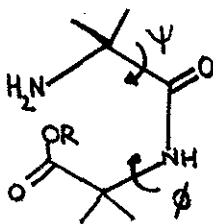
Cyclisation reactions may then follow from the proximity of the amino and ester functions. For Aib at the N-terminal restriction of ψ results while Aib at the C-terminal restricts the range of Ø. The slow rate of cyclisation for Aib-Aib-OMe results from the sluggish formation of a peptide bond between two sterically hindered residues. We have also observed the formation of a diacylated diketopiperazine in the attempted coupling of Boc-Val-Aib-OH or Z-Val-Aib-OH to Aib-OMe using DCC (Equation 2)

X-Val-Aib-OH ⟶

X = Boc or Z

(2)
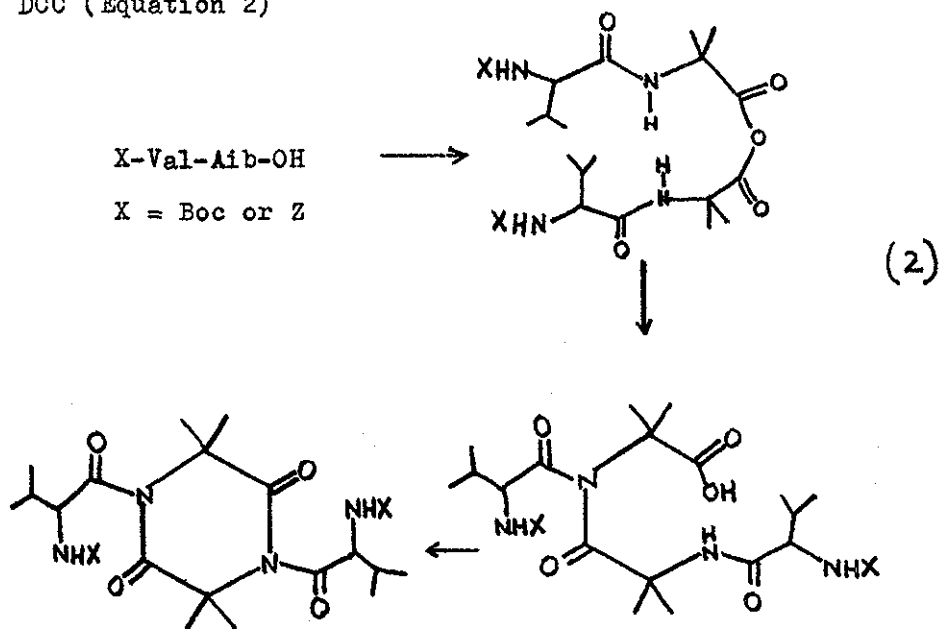
Diketopiperazine formation presumably results via rearrangement of the symmetrical anhydride. The ready formation of cyclic dipeptides even from tripeptides containing Aib residues explains the difficulties encountered in the deprotection of the

amino group in Z-Mea-Pro-Trp-OMe[8] and the formation of a bicyclic imidazolone and tricyclic imidazolone on attempted cyclisation of Aib-Aib-Aib-Aib-COCl in pyridine.[3a]

EXPERIMENTAL   a) Removal of the Boc group.   1g of the Boc dipeptide ester was treated with 2ml TFA for five hours at room temperature.   After removal of the TFA the residue was dissolved in water and extracted with ethyl acetate.   The aqueous solution was then made mildly alkaline with $NaHCO_3$, upon which the diketopiperazine crystallised out.

b) Removal of the Z group.[9]   1g of the Z-dipeptide ester was dissolved in 10ml ethanol.   5ml cyclohexene (freshly distilled and peroxide free) and 0.5g 10% palladium/charcoal were added and the mixture refluxed for 1 hour.   The catalyst was filtered and the ethanol solution evaporated to yield the diketopiperazine.

All the compounds obtained were characterised by IR, NMR in TFA and elemental analysis.

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