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AMINO ACID DERIVATIVES THAT STABILIZE SECONDARY STRUCTURES OF POLYPEPTIDES—III. β-ENAMINONITRILES AS ANALOGS OF SECONDARY AMIDES. THE MCC GROUP—1-ACYLAMINO-2-AMINOALKYL-3-CYANO-2-CYCLOPENTENES AS AMINO ACID ANALOGS

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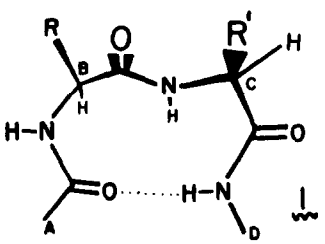
Abstract

The properties of β-cyanoenamines as analogs of amides are studied with derivatives of a rigid amino acid equivalent—Mcc = 1,2-diamino-3-cyanocyclopentene, prepared in two steps from methyl 2-(N-Boc-amino)-5-cyanopentanoate. Racemation of Mcc and incorporation into a cyclic pentapeptide are described.

Recently a variety of cyclic analogs of α-amino acids have been incorporated into linear or cyclic polypeptides with the aim of constraining the region near the analog to the conformation found in a β or γ-turn[1]. Most of these analogs are lactams in which the conformation of an amide residue is fixed by replacement of the hydrogen of a peptide secondary amide (e.g. the B-C amide of 1) by a carbon atom of a cyclic structure. Although such a substitution leaves the environment at the carbonyl of the B-C amide intact, it destroys the hydrogen-bonding capacity of the N-H function. In this and in the accompanying communication, we report results of our first effort to find a complementary tactic for bond fixation, in which the amide carbonyl is replaced by a cyanovinyl group as in 2.



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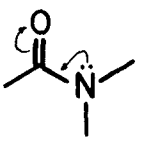
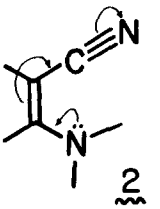
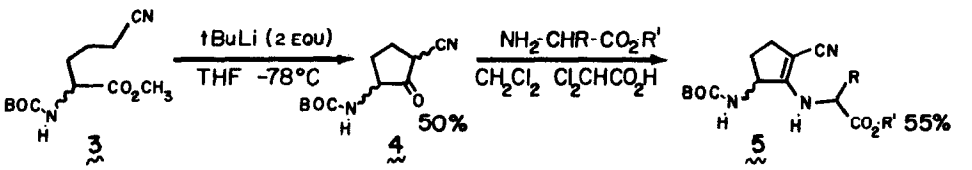




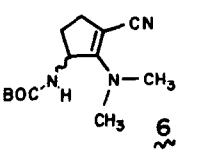
2

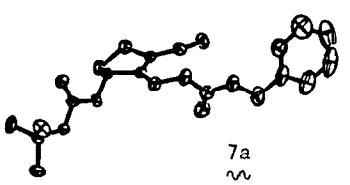
The β-enaminonitrile function was chosen over other amide vinylogues because of the compactness, the marginal hydrogen bonding tendency, and the edgewise thinness of the cyano

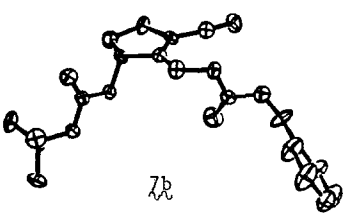
group. A natural first study involved 5 which is an analog of proline in which the amide-like NH rather than the amide carbonyl is left unchanged by the added atoms of the conformationally constraining five-membered ring. Once a satisfactory route is available, key points to be learned from a study of 5 are the barrier to rotation about the enamino C-N bond of 5, and the degree of planarity of the β-cyanoenamine function.

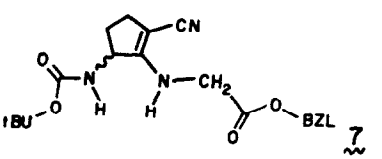


Preparation of the monocyclic analog 5 was conveniently achieved in two steps from the readily available 3[2,3]. Reaction of 4 with amino acid esters proceeds sluggishly and requires use of a weakly acidic catalyst of which dichloroacetic acid in CH_2Cl_2 was found to be optimal. A variable temperature ^1H NMR study of 6 demonstrated a rotational barrier for the C-N enamine bond of 12 kcal/mol, which may be compared with a range of 13-20 kcal/mol that is observed for amides[4,5]. An x-ray crystallographic analysis of 7 revealed two distinct conformations 7a and 7b within the unit cell that differ in the orientations of the side chain benzyl group and in the puckering of the cyclopentene ring, but which share a near-planar orientation of the β-enaminonitrile function. Thus like a secondary amide this function tends to be planar, has an s-trans-like conformation, and has a substantial torsional barrier.



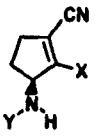






Compatibility with standard procedures of peptide synthesis and the preferred conformational bias of the cyclic function of 5 within peptide arrays are two key questions which we addressed through the synthesis of the diasteromeric cyclic peptide analogs of Scheme I. These materials were isolated as pure crystalline solids by reverse phase liquid chromatography on a preparative Vydac column[6]. Owing to problems with chiral instability of the Mcc derivatives the intermediates of the synthesis were carried forward as diastereomeric mixtures. A variety of cyclizing reagents were tried for the ring closure reaction 10 → 11, but diphenylphosphoryl azide gave a cleaner product in better yield.

SCHEME I Synthesis of cyclo(Pro-Gly-Pro-DLMcc-Gly)



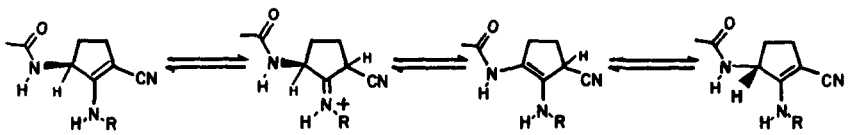
≡ LMcc

7 —(1.Tfa 2.Et$_3$N 3.Boc-Pro-OSu, 83%)→ Boc-Pro-DLMcc-Gly-OBzl (8) —(1.Tfa 2.Et$_3$N 3. Z-Pro-Gly-OSu)→

Z-Pro-Gly-Pro-DLMcc-Gly-OBzl (9, 61%) —(H_2-Pd, HOAc 93%)→ H-Pro-Gly-Pro-Mcc-Gly-OH (10)

10 —(Ph_3PN_3 Et_3N, DMF 60%)→ cyclo(Pro-Gly-Pro-DLMcc-Gly) (11)

The reactions of the Scheme established that the Mcc group is indeed compatible with the routine operations of peptide synthesis, including hydrogenolysis of benzyl groups, standard activation and coupling reactions, and trifluoroacetic acid-induced cleavage of t-butyl derived blocking groups. However, during the course of this synthesis it was noted that trifluoroacetic acid at 25°C for 1 h, and acids of comparable strength under similar conditions, results in rapid, complete epimerization of the Mcc function, doubtless through C-α deprotonation of an iminium ion, as shown below.



In this pilot study of cyclic β-cyanoenamines, the structural features of this function

have been shown to be sufficiently amide-like to warrant further study of this novel class of analogs of the peptide bond. Although the demonstrated compatibility of the ß-cyanoenamines with many of the operations of conventional peptide synthesis is gratifying, and novel structural analogies remain to be explored (e.g. the potential for oxidatively converting conformationally constrained Mcc derivatives to less constrained glutamic acid derivatives), the ease of acid-induced epimerization of the Mcc group has caused us to examine bicyclic ß-cyanoenamines that cannot epimerize and that have greater conformational constraint. The first of these is described in the accompanying communication.

Acknowledgements

Financial support from the National Science Foundation (Grant 8116986) is gratefully acknowledged. We thank Dr. C. Costello for high resolution mass spectra and Dr. J. Dewan for determination of the x-ray structure of 7. Funds to purchase x-ray diffraction equipment were obrtained through NIH Grant S10RR02243-01.

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3. 4, mp 195-201°C(dec), as K^+ salt; 7, mp 105-107°C, high resolution MS, (m/e) Calcd. 371.1845; Found, 371.1873.
4. Schulz, G.; Schirmer, R., "Principles of Protein Structure," Springer-Verlag, New York, 1979, pp 19,25.
5. 6, mp 141-142°C; high resolution MS, (m/e) Calcd; 251.1628; Found: 251, 1626.
6. Separation of 11A and 11B, HPLC on Vydac C_{18} #22A column, eluent 12:88 CH_3CN-H_2O (no buffer); 1st diastereomer, high resolution MS (m/e) Calcd: 414.2016; Found: 414.202; 2nd diastereomer, (m/e) Calcd: 414.2016; Found: 414.202.

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