D-Isoleucine, an Exceptional Amino-acid Residue of the Antibiotic, Monamycin

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Summary D-Isoleucine has been isolated from a natural peptide, the antibiotic monamycin, for the first time.

INVESTIGATIONS on the biosynthesis of valinomycin,[1] triostin,[2] bacitracin,[3] tyrocidin,[4] and other cyclic peptides[5] have established that the constituent D-amino-acids are not incorporated directly into these antibiotics. It has been suggested that these D-residues arise from C-2 epimerisation of the corresponding members of the L-series, although the stage at which this occurs in the sequence of biosynthesis of the cyclic peptides has not been defined. A survey of amino-acids produced by micro-organisms was in accord with this suggestion.[6] For example, it was remarked that, as a consequence, "while there are many compounds which contain L-isoleucine or D-alloisoleucine, the two other isomers D-isoleucine and L-alloisoleucine did not occur in the peptides described so far."

The constituents of the monamycin family of antibiotics are cyclohexadepsipeptides[7] with one α-hydroxy-acid residue —either L-2-hydroxy-3-methylpentanoic acid, or L-2-hydroxy-3-methylbutyric acid. Each compound contains one residue of either D-isoleucine or D-valine. The assignment of configuration to the D-isoleucine is based on a detailed study of its properties. A comparison of the optical rotations of the pure amino-acid and its 2,4-dinitrophenyl derivative with those of the isoleucine isomers[7,9] established that our compound was either D-alloisoleucine or D-isoleucine (Table).

TABLE

Characteristics of isomers of isoleucine

	From monamycin	L-Isoleucine	D-Isoleucine	L-Alloisoleucine	D-Alloisoleucine
$[\alpha]_D^{25}$	−31·7[a]	+36·7[a]	−36·6[a]	+34·9[a]	−34·8[a]
		+40·7[b]	−40·7[b]	+38·5[b]	−38·4[b]
DNP-$[\alpha]_D^{25}$	−87·0[c]	+84·8[c]		+87·5[c]	

[solvents: a, 1N-HCl; b, 6N-HCl; c, 1N-NaOH].

The compound was identified as D-isoleucine through oxidation with chloramine-T to the corresponding enantiomer of α-methylbutyraldehyde [2,4-dinitrophenylhydrazone, $C_{11}H_{14}N_4O_4$, m.p. 134—136°, $[\alpha]_D^{26}$ −29·8° (*c*, 1 in AcOH)]. The related product from D-alloisoleucine has $[\alpha]_D$ + 29·9°.[10] Moreover, there was evidence from amino-acid analyses (Beckman Model 120C) for the assignment of our compound to the isoleucine series; authentic isoleucine, alloisoleucine, and leucine were clearly differentiated.[11]

According to the "α-epimerisation rule",[6] D-isoleucine would be derived from L-alloisoleucine, an isomer which has not, itself, been observed in Nature. However, there is one example of a natural amino-acid with this configuration. *N*-Methyl-γ-methyl-L-alloisoleucine has been obtained from both etamycin[12] and triostin C.[13]

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[1] J. C. MacDonald, *Canad. J. Microbiol.*, 1960, **6**, 27.
[2] T. Yoshida and K. Katagiri, *Biochemistry*, 1969, **8**, 2645.
[3] N. Cornell and J. E. Snoke, *Biochim. Biophys. Acta*, 1964, **91**, 533.
[4] M. A. Ruttenberg and B. Mach, *Biochemistry*, 1966, **5**, 2864.
[5] E. Katz, *Lloydia*, 1968, **31**, 364.
[6] M. Bodanszky and D. Perlman, *Science*, 1969, **163**, 352.
[7] C. H. Hassall, R. B. Morton, Y. Ogihara, and W. A. Thomas, *Chem. Comm.*, 1969, 1079; K. Bevan, J. S. Davies, M. J. Hall, C. H. Hassall, R. B. Morton, Y. Ogihara, D. A. S. Phillips, and W. A. Thomas, unpublished results.
[8] W. A. H. Huffman and A. W. Ingersoll, *J. Amer. Chem. Soc.*, 1951, **73**, 3366.
[9] K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, 1954, **76**, 1328.
[10] W. S. Fones, *J. Amer. Chem. Soc.*, 1954, **76**, 1377.
[11] K. A. Piez, *J. Biol. Chem.*, 1954, **207**, 77.
[12] J. C. Sheehan, H. G. Zachan, and W. B. Lawson, *J. Amer. Chem. Soc.*, 1958, **80**, 3349.
[13] J. Shoji, K. Tori, and H. Otsuka, *J. Org. Chem.*, 1965, **30**, 2772.