

A SYNTHETIC APPROACH TO CYCLIC PEPTIDE MODELS

BY REGIOSELECTIVE REMOTE PHOTOCYCLIZATION OF SULFIDE-CONTAINING PHTHALIMIDES^{1,2}

Yasuhiko Sato, Hideo Nakai and Tomishige Mizoguchi

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda, Saitama, 335

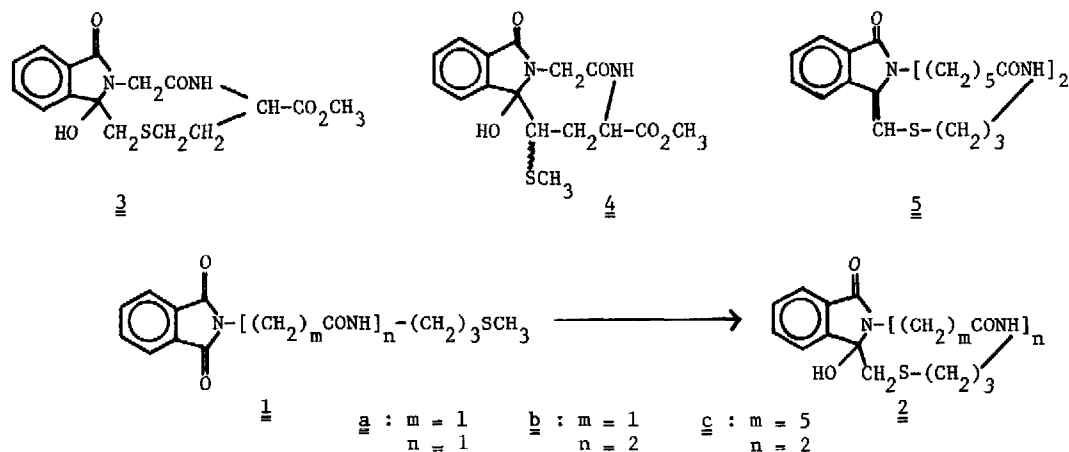
Yuichi Kanaoka*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060 Japan

(Received in Japan 24 March 1976; received in UK for publication 16 April 1976)

Syntheses of cyclic peptides have received much attention because a number of biologically active derivatives including antibiotics and peptide hormones³ have been found. For synthesizing cyclic peptides it is generally essential to effect cyclization of linear peptide substrates with a selected activating group such as azide at high dilutions^{3a}. Our recent finding that certain sulfide-containing phthalimides undergo unusually facile and regioselective remote photocyclization leading to macrocycles⁴ prompted us to test the possibility of employing this technique for the synthesis of cyclic peptide analogs. In a preliminary experiment, irradiation of N-phthaloylglycinemethiamide 1a has produced a mixture of the expected eight- and ten-membered 2a cyclic compounds⁴.

Irradiation of N-phthaloylglycyl-L-methionine methyl ester with a 400 W high-pressure mercury lamp in 10 mM acetone solution for 0.5 hr afforded a mixture of the cyclized products, 3 (46%) and 4 (5%)⁵. In support of the assigned structure, the cyclol 3 was readily converted into the dehydrated product (mp 255-6°) on treatment with acid. Homologous N-substituted phthalimides 1b-c containing amide bonds together with a ω -methylthio group were prepared and the photolysis was performed as above. The expected heteromeric cyclic peptide analogs, 2b (mp 270°, 16%)⁵ and 2c (mp 115-7°, 64%)⁵, respectively, were readily obtained as a result of the C-C bond formation between the imide carbonyl and the sulfide methyl through this extensive Norrish type II process^{4,6}. For a typical example, the nmr spectrum of 2c had a methylene peak (3.57 δ , s, pyridine) instead of methyl in 1c, and the molecular weight values determined by a vapor-pressure method and mass spectrometry were 478 and 461, respectively, in agreement with the monomeric value (461), thus excluding the alternative possibility of the intermolecular



reaction. On treatment with *p*-toluenesulfonic acid, $\underline{2c}$ similarly afforded the dehydrated compound $\underline{5}$ (mp 199–201°; nmr, vinyl H, 6.54 δ , s, DMSO).

Number of amino acid residues in linear peptide substrates is important in determining the efficiency to give cyclic peptides^{3a}. The phthalimides with long side chains containing at least two amide bonds $\underline{1}$ are now cyclized in moderate yields to demonstrate versatility of this synthetic photoreaction affording macrocycles up to a twenty-one membered ring $\underline{2c}$, which is nearly equivalent in size to that of cyclic heptapeptide. Further possible utilities of this approach for cyclic peptide studies including cylindrical models⁷ and for more general synthetic application⁸ are currently under investigation.

Acknowledgments We are grateful to Dr. B. Witkop, N.I.H., for valuable advice on cylindrical peptides. Y.S., H.N., and T.M. are grateful to Mr. M. Yamazaki, Director, for encouragement and to Mr. H. Ogiwara for technical assistance.

References and Notes

- 1) Photochemistry of the Phthalimide System. XIII. Part XII: Y. Kanaoka, K. Sakai, R. Murata and Y. Hatanaka, *Heterocycles*, **3**, 719 (1975).
- 2) Photoinduced Reactions. XXV: Part XXIV: Y. Kanaoka and Y. Hatanaka, *J.Org.Chem.*, **41**, 400 (1976).
- 3) a) E. Schröder and K. Lübke, "The Peptides" (translated by E. Gross) vol.1, p271 (1965), Academic Press, New York; (b) M. Bodansky and D. Perlman, *Science*, **163**, 352 (1969).
- 4) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka and Y. Kanaoka, *J.Am.Chem.Soc.*, **98**, in press.
- 5) All new compounds gave satisfactory analyses and their structures were supported by the spectral (uv, ir, nmr, mass) properties.
- 6) a) Y. Kanaoka, H. Migita, Y. Sato and H. Nakai, *Tetrahedron Letters*, 51 (1973); (b) Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi and Y. Kanaoka, *ibid.*, 4565 (1973); (c) Y. Kanaoka and Y. Migita, *ibid.*, 3693 (1974).
- 7) Recent studies of the conformation of cyclic and "cylindrical" peptides have been particularly useful in understanding of the general physicochemical behavior of polypeptides and proteins; cf. C.H. Hassall and W.S. Thomas, *Chem. in Britain*, **7**, 145 (1971).
- 8) A "photolysis of donor-acceptor pair system" method has been proposed as an attractive general synthetic approach on the basis of the photoreactions of certain phthalimides^{4,6}.