Tetrahedron Letters No. 17, pp. 1471-1472, 1970. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF TYROCIDINE C*

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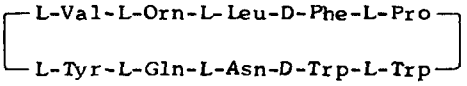
(Received in Japan 23 February 1970; received in UK for publication 13 March 1970)

In 1965 Craig et al. proposed the structure of tyrocidine C (TC) to be a cyclic decapeptide shown as VI in Figure, however, they did not describe a quantitative feature of its antibacterial activity and some physical properties (1).



VI or TC

We reported previously the syntheses of tyrocidine A (TA) (2), B (TB) (3) and E (4). We wish to report here synthesis of VI designated as TC, and chemical and biological properties of the synthetic VI.

Z(OMe)-Trp-D-Trp-OMe (I), mp 85-87°, $[\alpha]_D$ -7.2° (5), was prepared in 82% yield from Z(OMe)-Trp-OH·DCHA (3) and H-D-Trp-OMe·HCl by DCC method. Compound I was saponified to Z(OMe)-Trp-D-Trp-OH (II), 86%, mp 115-116°, $[\alpha]_D$ -21.6°. Z(OMe)-Asn-Gln-Tyr-Val-Orn(δ-Z)-Leu-D-Phe-Pro-OH (3) was treated with CF_3COOH, and excess CF_3COOH was removed by evaporation. Addition of NEt_3 into the residue until pH 6.5 yielded neutral octapeptide (III), 80%, mp 285-287° dec, $[\alpha]_D$ -19.7° (DMF). Acyldipeptide hydroxysuccinimide ester, which was derived from II by hydroxysuccinimide-DCC, was coupled with III to give Z(OMe)-Trp-D-Trp-Asn-Gln-

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* This work was presented at the 7th Symposium on Peptide Chemistry at Tokyo University, Japan, 21 November 1969.

Tyr-Val-Orn(δ-Z)-Leu-D-Phe-Pro-OH (IV) in 68% yield, mp 208-209° dec, $[\alpha]_D$ -23.6° (DMF). Cyclization reaction of IV by the usual way (2,3) gave cyclo-Trp-D-Trp-Asn-Gln-Tyr-Val-Orn(δ-Z)-Leu-D-Phe-Pro (V), 59% from IV, mp 225-228° dec, $[\alpha]_D$ -36.1° (Anal. Calcd for $C_{78}H_{95}O_{15}N_{15}\cdot 3H_2O$: C, 60.95; H, 6.62; N, 13.68%; mol wt, 1537. Found: C, 60.69; H, 6.63; N, 13.82; mol wt, 1550). Hydrogenation of V in the presence of an equiv of HCl in methanol yielded VI·HCl·$6H_2O$ as air-dried product; 82%, mp 218-220° dec, $[\alpha]_D$ -84.3° (Anal. Calcd for $C_{70}H_{89}O_{13}N_{15}\cdot HCl\cdot 6H_2O$: C, 56.30; H, 6.88; N, 14.07. Found: C, 56.35; H, 6.86; N, 13.83). Its homogeneity was also acertained by thin-layer and paper chromatographies, paper electrophoresis. Its amino acid ratios (3); Trp 1.80, Asp 0.97, Glu 1.05, Tyr 1.05, Val 1.00, Orn 1.04, Leu 1.07, Phe 0.99, Pro 1.06, NH_3 2.30.

Levels of antibacterial activity of VI were same as those of synthetic TA and TB for Gram positive microorganisms (Staph. aureus and B. subtilis) except Candida albicans; minimum concentration of growth-inhibition for C. albicans was 12.5 μg/ml with TA, 100 μg/ml with both TB and VI. Work on synthesis of a cyclic decapeptide corresponding to tyrocidine D is in progress in this laboratory.

REFERENCES AND FOOTNOTE

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5. Satisfactory elemental analyses and chromatographic data were obtained for all crystalline compounds. $[\alpha]_D$ refers to a solution in methanol at 25° otherwise noted. Z-, benzyloxycarbonyl; Z(OMe)-, p-methoxybenzyloxycarbonyl; DCC, dicyclohexylcarbodiimide; DCHA, dicyclohexylamine. Amino acid symbols except D-Phe and D-Trp denote the L-configuration.