Tetrahedron Letters No. 48, pp 4665 - 4668, 1971. Pergamon Press. Printed in Great Britain.

SYNTHETIC STUDY ON ECHINULIN AND RELATED COMPOUNDS. PART II.[1]
A STEREOSELECTIVE TOTAL SYNTHESIS OF OPTICALLY ACTIVE ECHINULIN[2]

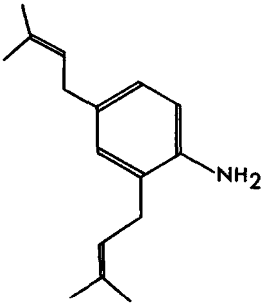
Noboru Takamatsu, Shoji Inoue, and Yoshito Kishi*
Faculty of Pharmacy, Meijo University, Showa, Nagoya 468, Japan
* Department of Agricultural Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

(Received in Japan 7 October 1971; received in UK for publication 29 October 1971)

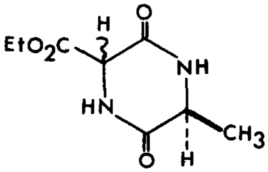
In connection with investigations directed towards the total synthesis of echinulin (10), we have reported a synthesis of 2,4-di(3,3-dimethylallyl)aniline (1) from N,N-di(3,3-dimethylallyl)aniline by an acid-catalyzed amino Claisen rearrangement.[1] In this communication, we would like to describe a stereoselective total synthesis of optically active echinulin (10).

According to Saxtons' method,[3] the aniline (1) was condensed with purified ethyl 4-bromo-2,2-dimethylacetoacetate to yield the isobutyrate (2).[4,5] After the isobutyrate (2) was reduced to the primary alcohol (3)[4] by the reduction with lithium aluminum hydride, it was oxidized to the aldehyde (4)[4] with Ac_2O-DMSO. The aldedhye (4) was converted to the indole (5)[4,7] by Wittig reactoin, which was then transformed to the corresponding gramine (6)[4,8] by Mannich reaction.

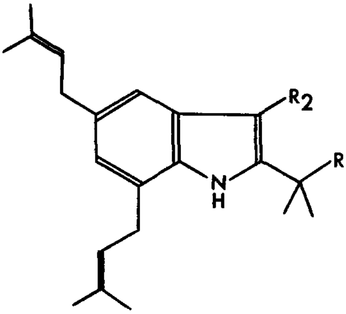
For the stereoselective conversion of the gramine (6) into optically active echinulin (10), the method developed recently by Kishi et al[9] was adopted. Namely, the gramine (6) was condensed with the diketopiperazine (7)[9] synthesized from L-alanine, to afford the ester (8) in a mixture of cis and trans isomers (ca. 1:2 ratio).[4,10] After the carboethoxy group in the compound (8) was hydrolyzed with 0.1N sodium hydroxide in aqueous dioxane, the acid (9)[11] thus obtained was heated under reflux to yield a mixture of cis and trans diketopiperazine, which was separated by silica gel column chromatography to give a major diketopiperazine (10)[4,12](2 parts) and a minor diketopiperazine (11)[4,13](1 part). The major product was identical with natural



(1)



(7)



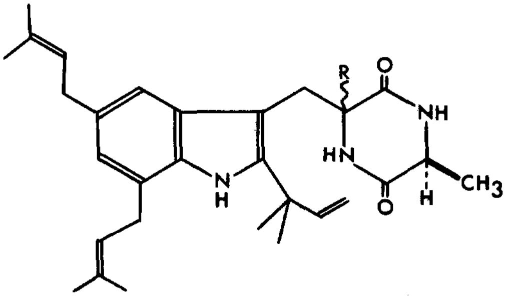
(2) $R_1=COOC_2H_5$, $R_2=H$

(3) $R_1=CH_2OH$, $R_2=H$

(4) $R_1=CHO$, $R_2=H$

(5) $R_1=CH{=}CH_2$, $R_2=H$

(6) $R_1=CH{=}CH_2$, $R_2=CH_2N(CH_3)_2$



(8) $R=COOC_2H_5$: a mixture of cis and trans isomers

(9) R=COOH: a mixture of cis and trans isomers

(10) R=H: cis isomer≡ECHINULIN

(11) R=H: trans isomer≡EPI-ECHINULIN

echinulin[14] in all respects (mp, mixed mp, nmr, ir in KBr disc, uv, $[\alpha]_D$, tlc on silica gel) and therefore the minor product corresponds to epi-echinulin on the echinin part.[15]

The configuration of the echinin moiety of echinulin (10) was determined by several methods[16] as it is belonging to L-series of amino acids. This assignment is also supported by the results obtained in the synthesis, because it has been shown that on decarboxylation of the system of the acid (9) the cis diketopiperazine predominates over the trans isomer.[9]

REFERENCES AND FOOTNOTES

1. Part I.; N. Takamatsu, S. Inoue, and Y. Kishi, Tetrahedron Letters,
2. Presented to the 91th Annual Meeting of Pharmaceutical Society of Japan, April 8, 1971, Fukuoka
3. E. Houghton and J. E. Saxton, Tetrahedron Letters, 5475 (1968); J. Chem. Soc., 595 and 1003 (1969)
4. Satisfactory analytical and spectroscopic data were obtained for the compound.
5. viscous liquid; ms 367(M^+), 312, 294; $\delta_{ppm}^{CDCl_3}$ 1.23 (3H, t, J=7), 1.65 (6H, s), 1.77-1.88 (12H), 3.40 (2H, broad d, J=8), 3.53 (2H, broad d, J=8), 4.16 (2H, q, J=7), 5.43 (2H, broad), 6.31 (1H, d, J=2), 6.72 (1H, broad s), 7.23 (1H, broad s)
6. viscous liquid; ms 321(M^+), 306, 293, 277, 266; $\delta_{ppm}^{CDCl_3}$ 1.45 (6H, s), 1.72-1.83 (12H), 3.39 (2H, broad d, J=8), 3.50 (2H, broad d, J=8), 5.07 (2H, AB part of ABX system, J=18, 10, 2), 5.4 (2H, broad), 6.03 (1H, X part of ABX system, J=18, 10), 6.20 (1H, d, J=2), 6.76 (1H, broad s), 7.20 (1H, broad s), 7.84 (1H, broad)
7. The same indole was recently synthesized in a different way by H. Plieninger and H. Sirowej, Chem. Ber., <u>104</u>, 1869 and 2027 (1971)
8. viscous liquid; ms 333(M^+-45), 328, 264, 262, 249; $\delta_{ppm}^{CDCl_3}$ 1.57 (6H, s), 1.73-1.85 (12H), 2.25 (6H, s), 3.42 (2H, broad d, J=7), 3.52 (2H, broad d, J=7), 3.58 (2H, s), 5.15 (2H, AB part of ABX system, J=18, 10, 1.5), 5.4 (2H, broad), 6.18 (1H, X part of ABX system, J=18, 10), 6.77 (1H, broad s), 7.48 (1H, broad s), 7.9 (1H, broad)
9. Y. Kishi, S. Nakatsuka, T. Fukuyama, and T. Goto, Tetrahedron Letters,
10. The ratio was estimated from tlc, but no attempts to separate the mixture were made.
11. No attempts to isolate the product were made.

12. mp 241-4°; $[\alpha]_D^{20}$ -25.5° (c, 1.00 in chloroform)

13. mp 205-6°

14. We are indebted to Professor R. Nakashima, Kyoto University, for the generous gift of a sample of natural echinulin (mp 241-4°; $[\alpha]_D^{20}$ -26.0 (c, 1.00 in chloroform).

15a. About echinin, an amino acid corresponding to the tryptophan moiety of echinulin, see A. Quilico, Res. Prog. Org. Biol. Med. Chem., 1, 225 (1964).

b. Epimerization of echinulin (10) with triethylamine in ethanol gives epi-echinulin: J. W. Westley, V. A. Close, D. N. Nitecki, and B. Halpern, Anal. Chem., 40, 1888 (1968).

16a. See the reference of 15b.

b. E. Houghton, and J. E. Saxton, Tetrahedron Letters, 5475 (1968); J. Chem. Soc. (C), 1003 (1969)

c. R. Nakashima, and G. P. Slater, Tetrahedron Letters, 4433 (1967); Cand. J. Chem., 47, 2069 (1969)

d. R. Nakashima, and G. P. Slater, Tetrahedron Letters, 2649 (1971)