Tetrahedron Letters No.52, pp. 5475-5478, 1968. Pergamon Press. Printed in Great Britain.

# STUDIES IN THE ECHINULIN SERIES: PRELIMINARY SYNTHETICAL STUDIES, AND THE ABSOLUTE CONFIGURATION OF ECHINULIN

E. Houghton and J.E. Saxton

Department of Organic Chemistry, University of Leeds

(Received in UK 11 September 1968; accepted for publication 25 September 1968)

In connection with investigations directed towards the total synthesis of echinulin (I), we report the synthesis of the two model diastereoisomers (II), both derived from L-alanine.

Ethyl α-2-indoleisobutyrate (III), m.p. 120-122°, prepared by an improved version of the method reported by Jönsson[1], was reduced ($LiAlH_4$) to the corresponding primary alcohol (IV), m.p. 90-92°, which was then oxidised ($Ac_2O$-DMSO)[2] to the aldehyde (V), m.p. 68-70°. Wittig reaction of (V) with methylene triphenylphosphorane afforded 3-(2-indolyl)-3-methylbut-1-ene (VI) as a colourless oil, which was then converted by Mannich condensation with formaldehyde and dimethylamine into the oily base (VII). This Mannich base was then condensed with diethyl N-carbobenzyloxy-L-alanylaminomalonate (VIII), m.p. 119-121°, by means of powdered sodium hydroxide in refluxing xylene to give the ester (IX) as a colourless glass, $[\alpha]_D^{20°}$ + 15·4° (EtOAc). Saponification of (IX) (2N NaOH), followed by acidification and decarboxylation of the product, afforded the non-crystalline mono-ester (X), which was further saponified to the corresponding acid (XI). Removal of the protecting carbobenzyloxy group from XI was achieved by means of 2N HBr/AcOH at room temperature for two hours, conditions which had previously been shown not to destroy

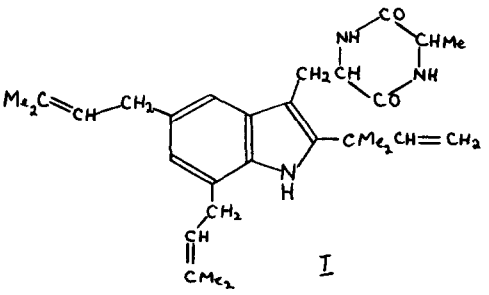
the $-CMe_2CH=CH_2$ grouping. The resulting amino-acid was cyclised without purification by boiling its solution in toluene and removing the water formed by azeotropic distillation. Chromatography of the product on Kieselgel G afforded the two pure diastereoisomers (II). (-)-Alanyl-2-(1,1-dimethylallyl) tryptophan anhydride (II) forms colourless needles, m.p. 228-235°, $[\alpha]_D^{20°}$ -68° (AcOH); its diastereoisomer, (+)-alanyl-2-(1,1-dimethylallyl) tryptophan anhydride (II), forms colourless needles, m.p. 264-272°, $[\alpha]_D^{20°}$ + 22·3° (AcOH).

A consideration of the O.R.D. spectra of the two diastereoisomers (II) and that of echinulin (I) allows the absolute configuration of these compounds to be elucidated; the data are tabulated briefly below:

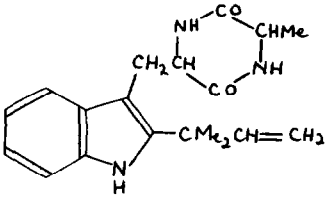
| Compound | [Ø] | $\lambda_{m\mu}$ |
|---|---|---|
| Echinulin (I) | - 15,500 tr | 238 |
| | + 19,950 | 216 |
| (+) Isomer of (II) [m.p. 264-272°; $[\alpha]_D^{20°}$ + 22·3°] | - 27,200 tr | 230 |
| | + 46,250 | 214 |
| (-) Isomer of (II) [m.p. 228-235°; $[\alpha]_D^{20°}$ -68°] | + 34,000 pk | 230 |
| | - 39,500 | 213 |

The echinulin spectrum exhibits a negative Cotton effect and provides a clear indication that echinulin is stereochemically related to L-tryptophan and L-alanine, since the spectrum is closely similar to that reported by Balasubramanian and Wetlaufer[3] for L-alanyl-L-seryldiketopiperazine. The differences that might be expected for diastereoisomers in this series are indicated by the fact that the dextrorotatory isomer of (II) exhibits an O.R.D. spectrum almost identical with that of echinulin and must therefore have the same absolute configuration at both asymmetric centres; in contrast, its diastereoisomer, which must have the L-alanyl-D-'tryptophanyl' configuration, shows a markedly different spectrum with a positive Cotton effect.

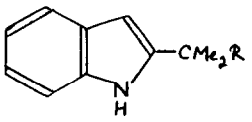
This conclusion is at variance with the tentative conclusion reported recently by Nakashima and Slater[4] on the basis of a comparison of the incomplete O.R.D. spectra (above 290 mμ) of echinulin, hexahydroechinulin, and the two diastereoisomers (XII), derived from L-alanine. Inspection of



I



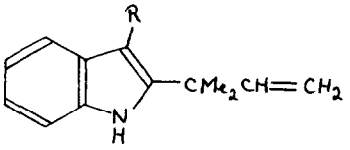
II



III ; R = COOEt

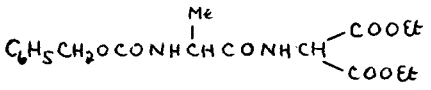
IV ; R = $CH_2OH$

V ; R = CHO

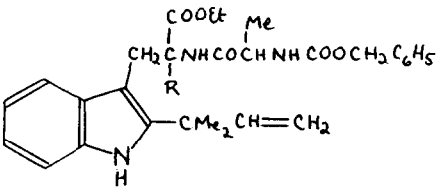


VI ; R = H

VII ; R = $CH_2NMe_2$

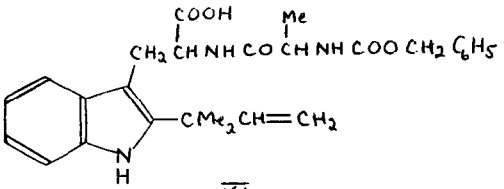


VIII

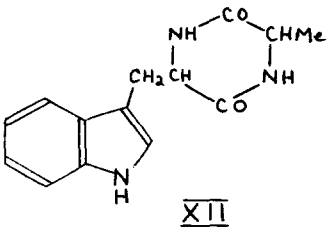


IX ; R = COOEt

X ; R = H



XI



XII

the complete O.R.D. spectra of echinulin and the two model diastereoisomers (II) reveals the significant Cotton effect, and thus leads to the conclusion that echinulin is derived from L-tryptophan, a result which is more easily reconciled with MacDonald and Slater's radioactive tracer experiments in which L-tryptophan was shown to be a more effective precursor of echinulin than D-tryptophan in Aspergillus amstelodami[5].

Satisfactory analytical and spectrographic data have been obtained for all the compounds described.

We are indebted to Professor A. Quilico for the gift of a generous sample of echinulin, and to Professor W. Klyne and Dr. P.M. Scopes for the O.R.D. spectra.

## References

1. A. Jönsson, Svensk. Kem. Tidskr., 67, 188 (1955).
2. J.D. Albright and L. Goldman, J. Am. Chem. Soc., 87, 4214 (1965).
3. D. Balasubramanian and D.B. Wetlaufer, J. Am. Chem. Soc., 88, 3449 (1966)
4. R. Nakashima and G.P. Slater, Tetrahedron Letters No. 45, 4433 (1967).
5. J.C. MacDonald and G.P. Slater, Can. J. Microbiol, 12, 455 (1966).