Tetrahedron Letters No.45, pp. 4433–4436, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE CONFIGURATION OF ECHINULIN [o, 1]

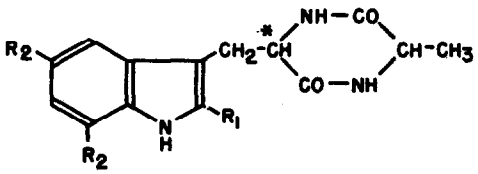
R. Nakashima [oo] and G.P. Slater

Prairie Regional Laboratory, National Research Council of Canada,

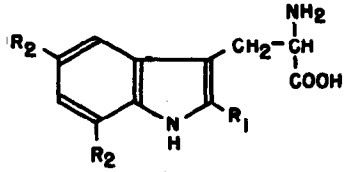
Saskatoon, Saskatchewan.

(Received in U.S.A. 10 July 1967)

The structure of echinulin (Ia) has been established by Quilico and co-workers (1) except for the configuration of the optically active centre (*) of the tryptophan moiety. The Italian workers (2) found that hydrolysis



I



II

a, $R_1 = -C(CH_3)_2CH=CH_2$; $R_2 = -CH_2-CH=C(CH_3)_2$

b, $R_1 = -C(CH_3)_2CH_2CH_3$; $R_2 = -CH_2CH_2CH(CH_3)_2$

of echinulin (Ia) with HBr gave L(+)-alanine but they could not isolate the amino acid echinin (IIa). However, hydrolysis of hydroechinulin (Ib) gave L(+)-alanine and hydroechinin (IIb). Using their procedure (2) in a previous investigation (3) pure hydroechinin (IIb) could not be obtained. Thus it was not possible to establish the configuration of this amino acid (IIb) using the optical rotatory dispersion method of Craig and Roy (4).

A recent study (5) has shown the feasibility of determining the configuration of piperazinediones by O.R.D. Accordingly, we investigated

---

[o] Presented to the 50th Annual Conference of the Chemical Institute of Canada, June 6, 1967, Toronto.

[oo] N.R.C. Postdoctorate fellow 1966 -

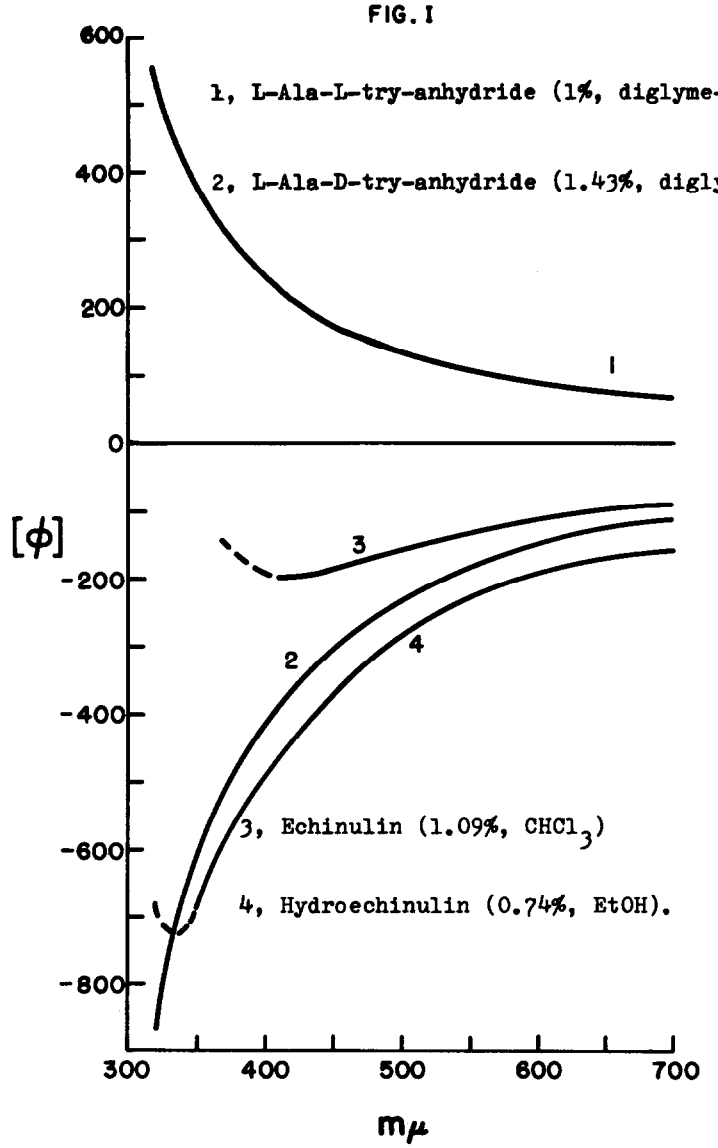
[1] Issued as N.R.C. No. 9685.

the O.R.D. of echinulin (Ia), hydroechinulin (Ib) and the two piperazinediones (I, R_1=R_2=H) prepared from L(+)-alanine and L(+)-tryptophan, and from L(+)-alanine and D(-)-tryptophan.

The O.R.D. spectra over the range 300-700 mμ were determined with a Jasco O.R.D./UV-5 spectrometer (Japan Spectroscopic Co. Ltd.) and are reproduced in Fig. 1. It is immediately evident that the piperazinedione (I, R_1=R_2=H) containing L(+)-tryptophan gives a plain, positive, (6) curve whereas the compound synthesized from D(-)-tryptophan gives a plain, negative curve. It was not possible to measure the O.R.D. spectra of echinulin (Ia) and hexahydroechinulin (Ib) in the same solvent used for the piperazinediones. However, the plain, negative curves are similar in shape despite differences in solvent. In particular, the curves for hydroechinulin and L-alanyl-D-tryptophan anhydride are essentially parallel, and there is no change in the signs of the curves for echinulin and hydroechinulin although these were determined in solvents of appreciably different polarity. The results indicate that echinulin and L-alanyl-D-tryptophan anhydride are structurally related. Echinulin may therefore be regarded as a piperazinedione in which the tryptophan residue has the D-amino acid configuration and the alanine has the L-configuration.

The dispersion curves of echinulin and hydroechinulin indicate troughs at 410 mμ and 340 mμ, respectively. The difference in the positions may be a solvent effect. However, using the concentrations shown in Fig. 1, instrument noise became significant for these two compounds in the region of the broken lines. Thus, the occurrence and precise location of the troughs are not unequivocably established. Some difficulties have been encountered in extending the measurements below 300 mμ which appear to be related to the ultraviolet absorption of the indole nucleus. These aspects of the work are being considered and a full report will be made at a future date.

FIG. I


600
400
200
0
-200
-400
-600
-800
[φ]
300
400
500
600
700
mμ
1, L-Ala-L-try-anhydride (1%, diglyme-H2O,4:1)
2, L-Ala-D-try-anhydride (1.43%, diglyme-H2O)
1
2
3
4
3, Echinulin (1.09%, CHCl3)
4, Hydroechinulin (0.74%, EtOH).

References

1. C. Cardani, G. Casnati, F. Piozzi, and A. Quilico, Tetrahedron Letters, No. 16, 1 (1959), and references therein.
2. A. Quilico, C. Cardani, and F. Piozzi, Gazz. Chim. Ital., 86, 211 (1956).
3. J.C. MacDonald and G.P. Slater, Can. J. Microbiol., 12, 455 (1966).
4. J. Cymerman Craig and S.K. Roy, Tetrahedron, 21, 1847 (1965).
5. D. Balasubramanian and D.B. Wetlaufer, J.Am. Chem. Soc., 88, 3449 (1966).
6. C. Djerassi, Optical Rotatory Dispersion, p 12. McGraw Hill Inc., New York (1960).