Tetrahedron Letters No.43, pp. 5285-5290, 1966. Pergamon Press Ltd.
Printed in Great Britain.

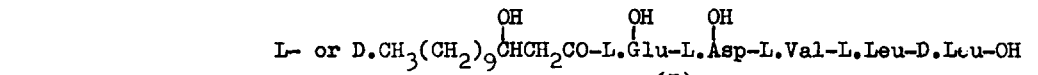
ON THE STRUCTURE OF ESPERIN. 1. ESPERINIC ACID

Yu.A.Ovchinnikov, V.T.Ivanov, P.V.Kostetsky, M.M.Shemyakin
Institute for Chemistry of Natural Products,
USSR Academy of Sciences, Moscow, USSR

(Received 19 August 1966)

In the beginning of the 1950^{ies} Japanese chemists isolated a new highly potent antibiotic, esperin, from the cultural fluid of certain strains of Bacillus mesentericus (1,2).

On mild alkaline hydrolysis this antibiotic forms a tribasic acid (m.p. 195°, $[\alpha]_D^{15}$ +12.5°, c 1.6, CH_3OH) called esperinic acid. Esperinic acid displays less antibiotic activity than esperin and is also less toxic. Based on the results of its complete and partial acid hydrolysis, hydrazinolysis and terminal amino acid determination in conjunction with molecular weight and IR data, esperinic acid was ascribed the formula of the hydroxyacylpeptide (I) (3-5).



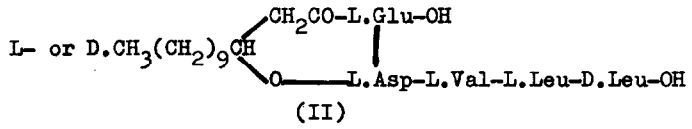
L- or D.$CH_3(CH_2)_9$CHOHCH$_2$CO-L.Glu-L.Asp-L.Val-L.Leu-D.Leu-OH

(I)

The configuration of the β-hydroxytridecanoic acid remained unelucidated, becouse in the acid hydrolysis of esperin and esperinic acid dehydration takes place, leading only to trans-2-tridecenoic acid.

On the basis of the above facts esperin was formulated as an eleven-membered cyclodepsipeptide with a tripeptidic side

chain (II). Compounds of such cyclotridepsipeptide structure had not been encoutered earlier in nature.



(II)

In view of the fact that certain data of the Japanese authors appeared not very convincing we undertook a synthetic study of the structure of this antibiotic. Becouse the synthesis of compound (II) with its trifunctional amino acids and the strained 11-membered ring is of considerable difficulty, we decided to attack the structural problem, by first synthesizing esperinic acid rather than esperin. In order to select the correct structure for esperinic acid (and esperin) it was necessary to synthesize both forms of esperinic acid (with L- and D-hydroxyacid residues).

The two forms of the acid were synthesized by stepwise building up of the peptide chain beginning with the N-terminus, according to Scheme 1. The yields and constants of the compounds synthesized are given in Table 1*.

* DL-β-hydroxytridecanoic acid (6) was prepared by hydrogenation or ethyl 3-ketotridec-12-enoate (7) in presence or Raney Ni, followed by saponification of the hydrogenation product. Its resolution was achieved by means of (+) and (-)-phenylethylamines, the less soluble (++) salt (XVI) being precipitated from Et_2O-$CHCl_3$ mixture with (+)-phenylethylamine and the corresponding (- -) salt (XVII) with (-)-phenylethylamine. A comparison of the ORD curves for (+)-β-hydroxytridecanoic (XVIII), (-)-β-hydroxytridecanoic (XIX) and D-β-hydroxydecanoic (8) acids showed that (XVIII) has the L-configuration and (XIX) the D-configuration.

S C H E M E 1

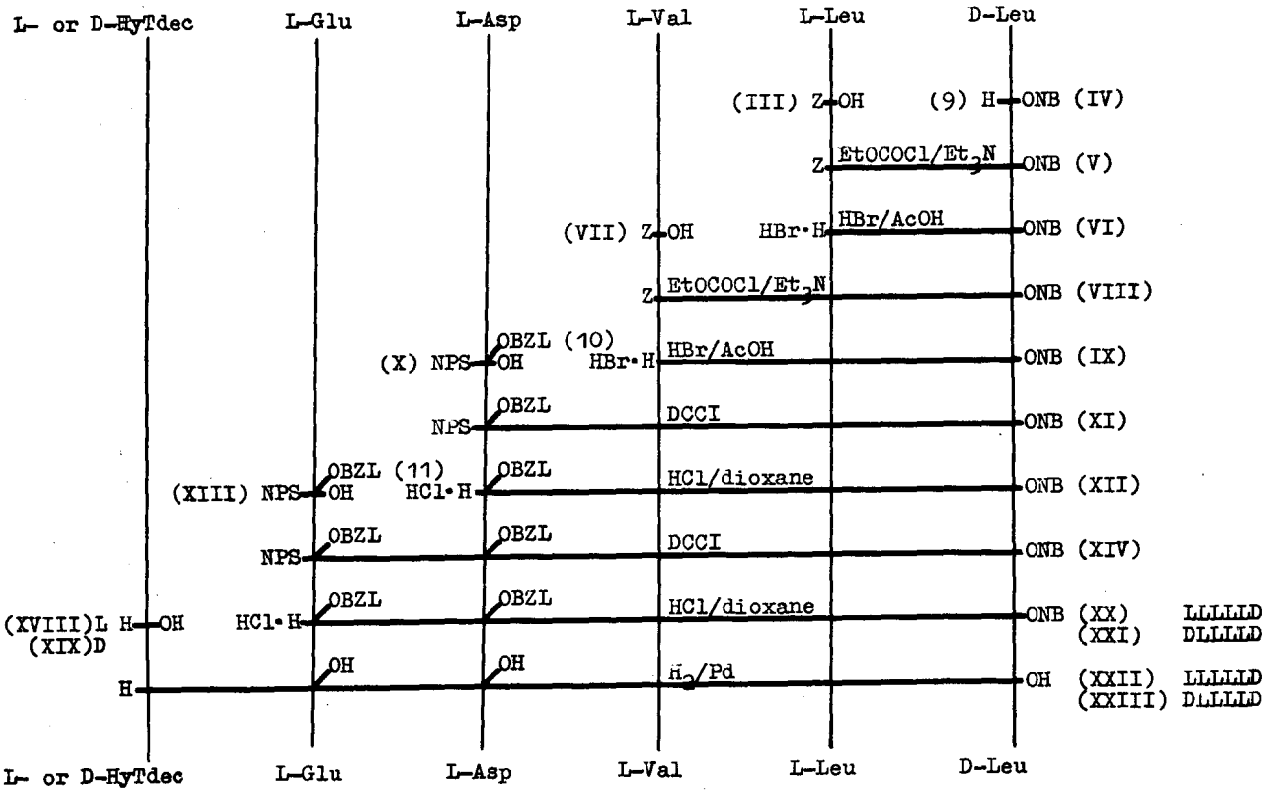

L- or D-HyTdec
L-Glu
L-Asp
L-Val
L-Leu
D-Leu
(III) Z-OH
(9) H-ONB (IV)
Z EtOCOCl/Et3N ONB (V)
(VII) Z-OH
HBr·H HBr/AcOH ONB (VI)
Z EtOCOCl/Et3N ONB (VIII)
(X) NPS-OBZL (10) OH
HBr·H HBr/AcOH ONB (IX)
NPS-OBZL DCCI ONB (XI)
(XIII) NPS-OBZL (11) OH
HCl·H HCl/dioxane ONB (XII)
NPS-OBZL OBZL DCCI ONB (XIV)
(XVIII)L H-OH
(XIX)D
HCl·H OBZL OBZL HCl/dioxane ONB (XX) LLLLLD
(XXI) DLLLLD
H OH OH H2/Pd OH (XXII) LLLLLD
(XXIII) DLLLLD
L- or D-HyTdec
L-Glu
L-Asp
L-Val
L-Leu
D-Leu

TABLE 1

Compound	Yield (%)	M.p. (°C)	$[\alpha]_D$
V	72	113-114, C_2H_5OH	+5.3° c 1.0, C_2H_5OH
VI	99	103-105, $CHCl_3$-n.C_6H_{14}	+40° c 3.0, $CHCl_3$
VIII	90	162-163, C_2H_5OH	-33° c 1.7, $CHCl_3$
IX	90	132-134, $CHCl_3$-n.C_6H_{14}	-17.5° c 2.0, $CHCl_3$
XI	80	172-173, CH_3OH	-22° c 1.0, $CHCl_3$
XII	90	185-189, $CHCl_3$-n.C_6H_{14}	-13° c 1.0, CH_3OH
XIV	93	197-198, CH_3OH	-50° c 2.0, $CHCl_3$
XV	90	197-202, $CHCl_3$-n.C_6H_{14}	-20° c 1.7, $CHCl_3$
XVI	46	66, $CHCl_3$-Et_2O	+18° c 3.0, $CHCl_3$
XVII	51	66, $CHCl_3$-Et_2O	-17° c 3.0, $CHCl_3$
XVIII	95	79, n.C_6H_{14}	+16° c 2.0, $CHCl_3$
XIX	99	79, n.C_6H_{14}	-15° c 2.0, $CHCl_3$
XX	75	212-213, CH_3OH	-14° c 3.6, $CHCl_3$
XXI	74	213-214, CH_3OH	-23° c 5.0, $CHCl_3$
XXII	75	181-182, CH_3OH-H_2O	-30° c 1.6, CH_3OH
XXIII	75	181-182, CH_3OH-H_2O	-46° c 1.6, CH_3OH
XXIV	85	234-235, $CHCl_3$-n.C_6H_{14}	-20° c 4.0, $CHCl_3$

[a] In all cases the analytical data correspond to the required values.

The hydroxyacylpeptides (XXII) and (XXIII) are individual compounds, as was shown by their thin layer chromatography in different solvent systems. For greater assurance of the correctness of the assigned structures one of the compounds synthesized, namely, (XXII), was subjected to a variety of reactions, the behavior of this compound being in accord with the proposed structure: Its complete acid hydrolysis showed

it to be composed of valine, leucine, aspartic and glutamic acid residues. Methylation of (XXII) with diazomethane gave a cristalline triester (XXIV) which on hydrazinolysis was converted to the corresponding trihydrazide. Curtius reaction of the latter and complete hydrolysis of the reaction product gave α,β-diaminopropionic acid and α,γ-diaminobutyric acid. This indicated the presence in (XXII) of free ω-carboxyl groups in the aspartic and glutamic acid residues. Finally the structure of (XXII) and of its diastereoisomer (XXIII) was confirmed by their IR and NMR spectra.

At the same time both compounds had constants differing from attributed to esperinic acid by Japanese investigators and moreover, in contrast to esperinic acid they were totally devoid of antimicrobial activity against all the microorganisms investigated. Hence one must arrive at the conclusion that the esperinic acid formed in the alkaline hydrolysis of esperin possesses another structure than that of (I), which raises grave doubts as to the correctness of formula (II) for esperin, itself.

REFERENCES

1. Jap. pat., 1145 (151); C. A. 46, 11596 (1952).
2. Jap. pat., 2497 (151); C. A. 47, 690 (1953).
3. H. Ogawa, T. Ito, J. Agr. Chem. Soc. Japan, 24, 191 (1951).
4. H. Ogawa, T. Ito, J. Agr. Chem. Soc. Japan, 26, 432 (1952).
5. T. Ito, H. Ogawa, Bull. Agr. Chem. Soc. Japan, 23, 536 (1959).
6. M. Skogh, Acta Chem. Scand., 6, 809 (1952).
7. R. E. Bowman, J. Chem. Soc., 1950, 322.

8. M. M. Shemyakin, Yu. A. Ovchinnikov, V. K. Antonov, A. A. Kiryushkin, V. T. Ivanov, V. I. Shchelokov, A. M. Shkrob, Tetrahedron Letters, 1964, 47.

9. M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryushkin, K. Kh. Khalilulina, Zhurn. Obshch. Khimii, 35, 1399 (1965).

10. L. Zervas, C. Hamalidis, J. Am. Chem. Soc., 87, 99 (1965).

11. L. Zervas, D. Borovas, E. Gazis, J. Am. Chem. Soc., 85, 3660 (1963).