Tetrahedron Letters No.2, pp. 159-162, 1971. Pergamon Press. Printed in Great Britain.

THE SYNTHESIS AND SOME PROPERTIES OF BEAUVERICIN

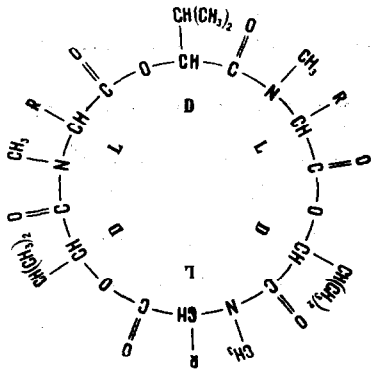
Yu.A.Ovchinnikov, V.T.Ivanov, I.I.Mikhaleva

Institute for Chemistry of Natural Products, USSR

Academy of Sciences, Moscow, USSR

(Received in USA 19 November 1970; received in UK for publication 21 December 1970)

Recently Hamill et al. (1) established the structure of a new depsipeptide antibiotic beauvericin the antimicrobial and mitochondrial activity of which had been reported somewhat earlier (2,3). The structure of beauvericin (I) was found to be very similar to that of the membrane active cyclodepsipeptide antibiotics enniatins A, B and C (II)-(IV) (4), differing from them only in the nature of the N-methylamino acid (Fig. 1).



	R
I Beauvericin	$-CH_2C_6H_5$
II Enniatin A	$-CH(CH_3)C_2H_5$
III Enniatin B	$-CH(CH_3)_2$
IV Enniatin C	$-CH_2CH(CH_3)_2$

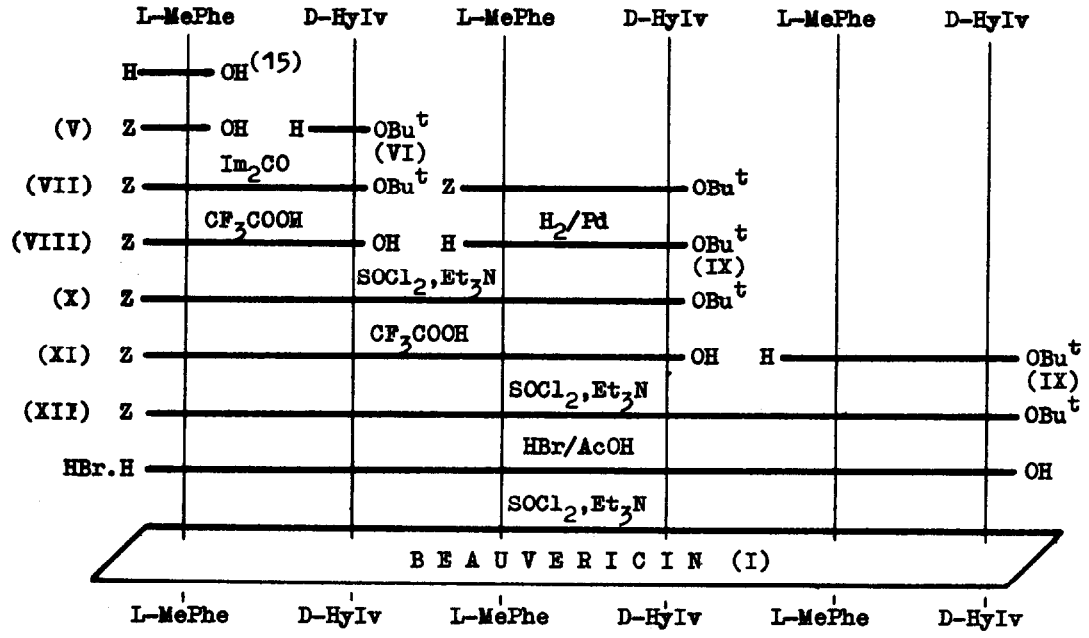
Fig. 1

Beauvericin's chemical similarity to the enniatins and its wide spectrum of biological activity indicated that it should complex with alkaline cations and induce cation permeability of artificial and biological membranes. However Dorshner et al. (3) found that this antibiotic peculiarly had a relatively weaker effect on mitochondria in the presence of Na^+ than in the presence of Li^+ or K^+ ions.

As part of our studies on the chemistry of membrane active cyclodepsipeptides (4-8) we undertook investigation of the conformational and membrane properties of beauvericin and their comparison with those of enniatins A, B and C. The present report describes the synthesis of beauvericin and results of its preliminary physico-chemical study.

Beauvericin was prepared according to the scheme starting with carbobenzoxy-N-methyl-L- phenylalanine (V) and tert.-butyl-D-α-hydroxyisovalerate (VI) (9,10) by the methods used previously for preparation of enniatins A, B, C and their analogs (11-14). Cyclization of the free hexadepsipeptide in benzene under

highly dilute conditions by the chloride method gave the cyclodepsipeptide (I) which was isolated chromatographically on neutral alumina (grade III activity in a benzene-ethyl acetate system, the ethyl acetate concentration being increased from 0 to 60%).



The yields and constants of the products are summarized in the table 1. Synthetic beauvericin has the same specific rotation, IR-, UV-, NMR- and mass-spectra as the natural product, the differences in the melting point are apparently due to the different conditions of crystallization (in our case it was heptane while American authors used aqueous MeOH).

TABLE 1

Constants of the Prepared Compounds

Compound:	I	V	VII	VIII	IX	X	XI	XII
Yield (%)	25	85	75	90	70	85	87	85
M.P. (°C)	147-148*	66-67	73-74	92-93	oil	105-106	amorph.	118-120
$[\alpha]_D^{20}$ (c 0.7 C_6H_6)	+69.0°**	-21.8°	-23.4°	-44.5°	+22.6°	-38.5°	-29.5°	-41.8°

*In (1) m.p. 93-94° is reported. **c 0.1 CH_3OH

The synthetic beauvericin exhibited a high antimicrobial activity [table 2, cf.(2,4,16)] in a good agreement with its ability we discovered to form 1:1 complexes with alkaline cations. The conductometrically determined stability constants in ethanol of the complexes (4,17) are 100 for Li^+, 300 for Na^+, 3100 for K^+ and 3500 liter/ mole for Rb^+ and Cs^+. In general beauvericin is very similar to enniatins A and B [see (4,5,13)] in its complexating and antimicrobial activity.

TABLE 2

Antimicrobial Activity of Beauvericin (γ/ml)

Microorganism	Minimal Growth Inhibiting Concentration
St. aureus 209 P	2-4.5
St. aureus UV 3	2-4
St. faecalis	2-4
Sar. lutea	1
Bac. subtilis	2-3
Mycob. phlei	1-2
Cand. albicans	9-12
E. coli	25

Recently on the basis of ORD (5,7) and CD (18) we showed that enniatins A, B and C exist as equilibrium mixture of the conformers (a non-polar form N and polar form P), the composition of the mixture depending on the polarity of the medium and presence of cations. The ORD curves of beauvericin (Fig. 2) also show the existence of an N ⇄ P equilibrium, the conformation of the complex resembling P conformation, which exists in polar media (trifluoroethanol). A study of the N ⇄ P transition in the system dioxan-trifluoroethanol for enniatins A, B, C and beauvericin indicated that beauvericin (Fig.3) is intermediate between enniatins A

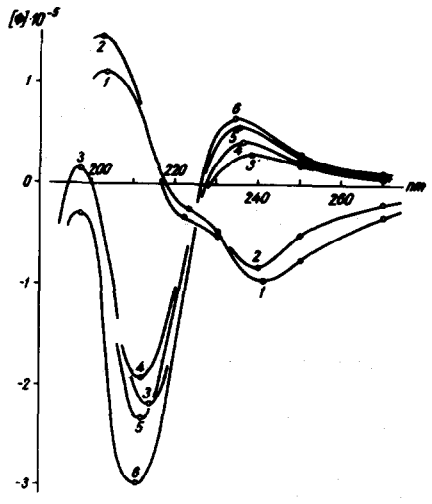


Fig.2. ORD curves of beauvericin in different media. 1 Heptane; 2 Dioxan; 3 Acetonitril; 4 Ethanol; 5 0.02 M KCl in ethanol; 6 Trifluoroethanol.

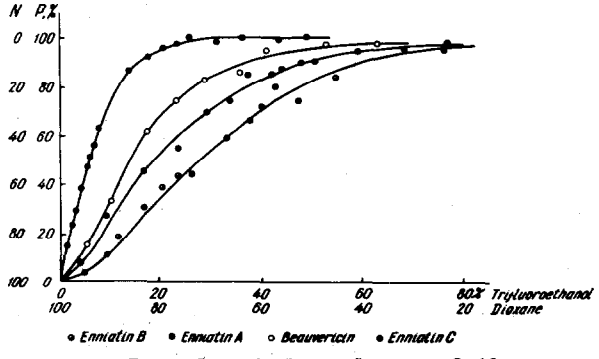


Fig. 3. Solvent dependence of the relative conformer composition of beauvericin and enniatins A, B and C.

and C in its tendency to assume the P conformation, being closer, however, to enniatin A. This similarity of the conformational characteristics apparently can serve as explanation of the above mentioned parallelism of the complex formation and antimicrobial properties of these antibiotics. The effect of beauvericin on model and biological membranes is at present being investigated.

REFERENCES

1. R.L.Hamill, C.E.Higgens, N.E.Boaz and M.Gorman, Tetrahedron Letters, 4255 (1969).
2. R.L.Hamill, C.E.Higgens and M.Gorman, Abstr. Eighth Intersci. Conf. on Antimicrob. Agents & Chemother.,October 1968, New York, p. 18.
3. E.Dorshner, H.Lardy, Abstr. Eight Intersci. Conf. on Antimicrob. Agents & Chemother., October 1968, p. 11.
4. M.M.Shemyakin, Yu.A.Ovchinnikov, V.T.Ivanov, V.K.Antonov, A.M.Shkrob, I.I.Mikhaleva, A.V.Evstratov, G.G.Malenkov, Biochem. Biophys. Res. Commun., 29, 834 (1967).
5. M.M.Shemyakin, Yu.A.Ovchinnikov, V.T.Ivanov, V.K.Antonov, E.I.Vinogradova, A.M.Shkrob, G.G.Malenkov, A.V.Evstratov, I.A.Laine, E.I.Melnik and I.D.Ryabova, J. Membrane Biol., 1, 402 (1969).
6. V.T.Ivanov, I.A.Laine, N.D.Abdullaev, L.B.Senyavina, E.M.Popov, Yu.A.Ovchinnikov, M.M.Shemyakin, Biochem. Biophys. Res. Commun., 34, 803 (1969).
7. Yu.A.Ovchinnikov, V.T.Ivanov, A.V.Evstratov, V.F.Bystrov, N.D.Abdullaev, E.M.Popov, G.M.Lipkind, S.F.Arkhipova, E.S.Efremov and M.M.Shemyakin, Biochem. Biophys. Res. Commun., 37, 669 (1969).
8. E.M.Popov, V.Z.Pletnev, A.V.Evstratov, V.T.Ivanov, Yu.A.Ovchinnikov, Khim. Prir. Soed., (USSR), in press (1971).
9. M.M.Shemyakin, Yu.A.Ovchinnikov, V.T.Ivanov, A.A.Kiryushkin, Tetrahedron, 19, 518 (1963).
10. Pl.A.Plattner, K.Vogler, R.O.Studer, P.Quitt, W.Keller-Schierlein, Helv. Chim. Acta, 46,927 (1963).
11. M.M.Shemyakin, Yu.A.Ovchinnikov, A.A.Kiryushkin, V.T.Ivanov, Tetrahedron Letters,885 (1963).
12. M.M.Shemyakin, Yu.A.Ovchinnikov, A.A.Kiryushkin, V.T.Ivanov, Izv. Academ. Nauk, ser. khim., (USSR), 579 (1963).
13. Yu.A.Ovchinnikov, V.T.Ivanov, I.I.Mikhaleva, M.M.Shemyakin, Izv. Academ. Nauk, ser. khim., (USSR), 1912 (1964).
14. I.I.Mikhaleva, I.D.Ryabova, T.A.Romanova, T.I.Tarasova, V.T.Ivanov, Yu.A.Ovchinnikov, M.M.Shemyakin, Zh. Obsch. Khim., (USSR), 38, 1228 (1968).
15. E.Fisher, W.Lipschitz, Ber., 48, 360 (1915).
16. E.Gaumann, S.Roth, L.Ettlinger, Pl.A.Plattner, U.Nager, Experientia, 3 , 202 (1947).
17. I.M.Andreev, G.G.Malenkov, A.M.Shkrob, M.M.Shemyakin, Molek. Biol., 5, in press (1971).
18. V.K.Antonov, L.D.Bergelson, V.T.Ivanov, G.G.Malenkov, Yu.A.Ovchinnikov, A.M.Shkrob, Proc. Symp. on Molecular Basis of Membrane Function, D.C.Tosteson, Ed., Prentice Hall, New York, p. 173 (1969).