Tetrahedron Letters No. 16, pp 1395 - 1396, 1977. Pergamon Press. Printed in Great Britain.

ACID AND ALKALINE HYDROLYSIS OF THE ANTIBIOTIC NOSIHEPTIDE. THE STRUCTURE ELUCIDATION OF FIVE FRAGMENTS.

HENRI DEPAIRE, JEAN-PIERRE THOMAS* and ANDRE BRUN
(Rhône-Poulenc-Industries, Centre de Recherches Nicolas Grillet, Direction des Services Analytiques, 13 Quai J. Guesde, 94400 Vitry-sur-Seine, France)

and

GABOR LUKACS*
(Institut de Chimie des Substances Naturelles, CNRS., 91190 Gif-sur-Yvette, France)

(Received in UK 22 February 1977; accepted for publication 7 March 1977)

The antibiotic nosiheptide, isolated from Streptomyces actuosus N° 40037[1] is active against Gram positive bacteria. It is a yellow powder, mp 310-320°C, $\alpha_D^{20} = 38°$ (c=1 pyridine), soluble in DMSO , DMF , pyridine or a 80 : 20 mixture of chloroforme and methanol and insoluble in water. Microanalysis afforded an approximate and temporary molecular formula of $C_{54}H_{43}N_{13}O_{13}S_6$ reminiscent of micrococcin [2] and thiostrepton [3],[4].

Acid hydrolysis of the antibiotic permitted to isolate [5] four different fragments : A, B, C and D. Each of them proved to be stable under subsequent attempts of acidic cleavage yielding thus evidence for their independent origin.

Fragment A, isolated as a phenolic ketonic dimethyl ester, mp 241-243°C, analysed for $C_{20}H_{14}N_4O_6S_3$. On the basis of its spectral characteristics and in analogy with the structure of a fragment of the antibiotic micrococcin [2] and thiostrepton [3],[4] the structural hypothesis 1 is suggested for this fragment [5]. The ^{13}C N.M.R. (in $CDCl_3/CD_3OD$=80/20) chemical shift assignments for 1 are indicated in fig. 1.

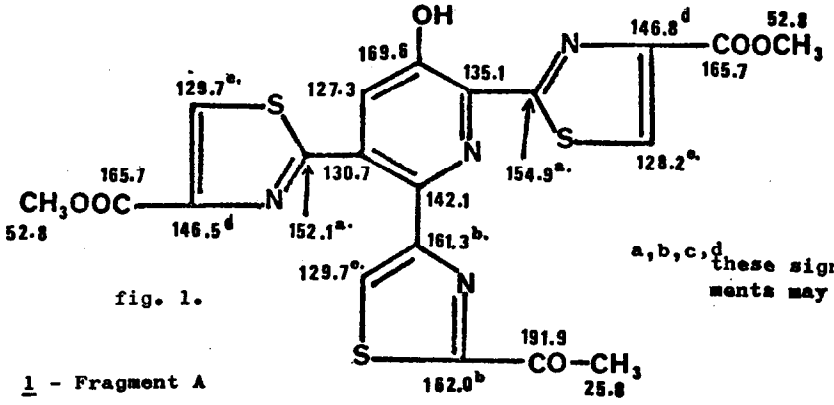


fig. 1.

a,b,c,d these signal assignments may be reversed.

1 - Fragment A

Fragment B is unambiguously identified to L-threonine by standard procedures.

Fragment C, isolated as a methyl ester, mp 99-101°C, analysed for $C_8H_9NO_3S$, was found identical with a constituent of micrococcin [2] to which the methyl-2-propionylthiazole-4-carboxylate structure 2 was attributed [6]. The ^{13}C N.M.R. chemical

shift assignments (in $CDCl_3/CD_3OD$=80/20) for 2 are given in fig. 2.

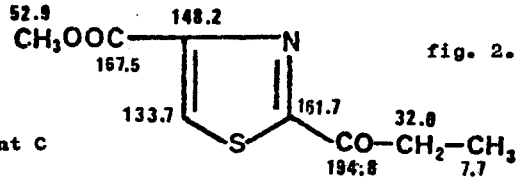


fig. 2.

2 - Fragment C

Fragment D, α_D^{20} = -2.6° (c=1.2 HCl 5 M), isolated as a diacid, analysed for $C_8H_{10}N_2O_5S$. On the basis of its spectral characteristics and in analogy with thiostreptine [3] the β-aminoacid structure 3 is proposed for this fragment. Its ^{13}C N.M.R. spectrum (in D_2O) indicates the presence of two diastereoisomers and the chemical shift assignments for 3 are indicated in fig. 3.

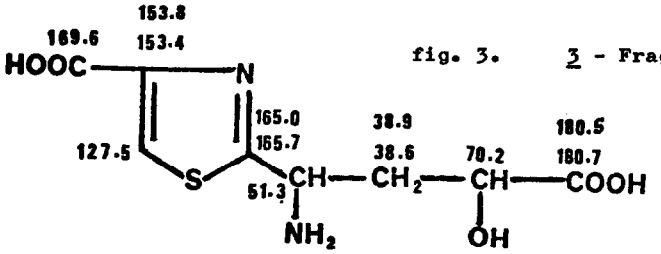
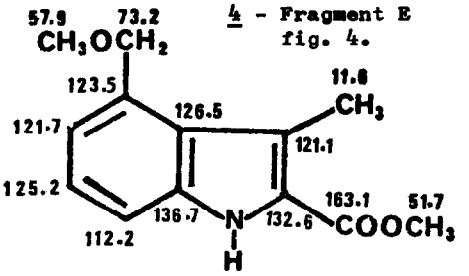


fig. 3. 3 - Fragment D

Alkaline hydrolysis of nosiheptide permitted to establish the liberation of four moles of ammonia and one equivalent of sulphide per mole of antibiotic and this result had important consequences in our speculations in connection with the constitution of nosiheptide. On the other hand, this experiment afforded an additional fragment that we called E.

Fragment E, isolated as a methyl ester methyl ether, mp 151-153°C, analysed for $C_{13}H_{15}NO_3$. The spectral characteristics of this fragment [7],[8] are in excellent agreement with structure 4 and the ^{13}C N.M.R. (in $CDCl_3$) chemical shift assignments are given in fig. 4.



4 - Fragment E
fig. 4.

REFERENCES

1. F. Benazet, M. Cartier, J. Florent, C. Godard, G. Jung, J. Lunel, D. Mancy, C. Pascal, J. Renaut, P. Tarridec, J. Theilleux, R. Tissier, M. Dubost and L. Ninet, to be published.
2. M.N. James and K.J. Watson, J.Chem.Soc., (C) 1361 (1966).
3. B.F. Anderson, D.C. Hodgkin and M.A. Viswamitra, Nature, 225, 233 (1970).
4. K. Tori, K. Tokura, K. Okabe, M. Ebata, H. Otsuka and G. Lukacs, Tetrahedron Letters, 185 (1976).
5. The isolation procedures of the antibiotic fragments will be reported in detail in the full paper ; the authors thank Mr. Jean-Claude Muller for his active participation in the isolation of all the fragments studied.
6. M.P.V. Mijovic and J. Walker, J.Chem.Soc., 3381 (1961).
7. Sadtler Standard Ultraviolet Spectra, n° 21754 UV (1974).
8. R.G. Parker and J.D. Roberts, J.Org.Chem., 35 , 996 (1970).