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ON THE STRUCTURE OF AMIDOMYCIN AND VALINOMYCIN

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IT has recently been shown[1], on the basis of synthetic methods for linear and cyclic depsipeptides developed in our laboratory[2], that the antibiotics enniatin A and enniatin B do not possess the cyclotetradepsipeptide structure proposed for them by Pl.A. Plattner et al.[3] and that the cyclohexadepsipeptide structure ascribed by D.W. Russell[4] to

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[1] M.M. Shemyakin, Yu.A. Ovchinnikov, A.A. Kiryushkin and V.T. Ivanov, Tetrahedron Letters №.7, 301 (1962); M.M. Shemyakin, Yu.A. Ovchinnikov, A.A. Kiryushkin and V.T. Ivanov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk in press (1962); Yu.A. Ovchinnikov, V.T. Ivanov, A.A. Kiryushkin and M.M. Shemyakin, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk 1497 (1962).

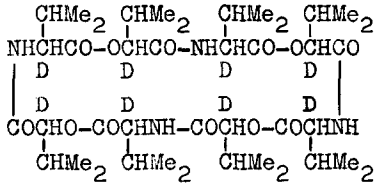
[2] M.M. Shemyakin, Angew. Chem. 71, 741 (1959); 72, 342 (1960); M.M. Shemyakin, E.I. Vinogradova, M.Yu. Feigina, N.A. Aldanova, V.A. Oladkina and L.A. Shchukina, Dokl. Akad. Nauk SSSR 140, 387 (1961).

[3] Pl.A. Plattner, U. Nager, Helv. Chim. Acta 31, 665 (1948); 31, 2192 (1948).

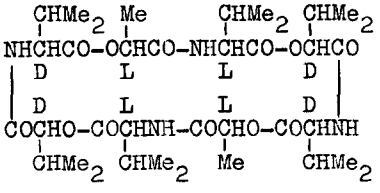
[4] D.W. Russell, Biochim. Biophys. Acta 45, 411 (1960); J. Chem. Soc. 753 (1962).

sporidesmolide I is indeed the actual structure of this compound[5].

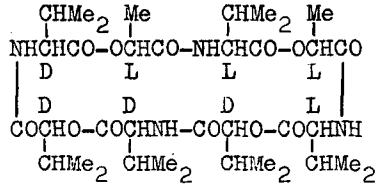
Being engaged in studying cyclization reactions of linear depsipeptides we were in a position to test the validity of the structures assigned to two other natural products, namely, the cyclooctadepsipeptide structures for the antibiotics amidomycin and valinomycin. L. Vining and W. Taber[6] proposed formula (I) for amidomycin ($C_{40}H_{68}O_{12}N_4$, m.p. 192°, $[\alpha]_D^{20}$ +19.2° in EtOH) and H. Brockmann and H. Geeren[7] suggested two formulas (II) and (III) for valinomycin



(I)



(II)



(III)

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[5] M.M. Shemyakin, Yu.A. Ovchinnikov, V.T. Ivanov, A.A. Kiryushkin, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk 1699 (1962).

[6] L. Vining, W. Taber, Canad. J. Chem. 35, 1109 (1957).

[7] H. Brockmann, H. Geeren, Ann. 603, 217 (1957).

($C_{36}H_{60}O_{12}N_4$, m.p. 190°, $[\alpha]_D^{20}$+31° in benzene); formula (II) they considered to be the most probable.

In the process of synthesis of the cyclooctadepsipeptides (I) and (II) from the corresponding linear depsipeptides we discovered that these cyclic compounds can be prepared not only from linear octadepsipeptides but also from tetradepsipeptides (IV, n = 1, X = X'= H, Y = OH) and (VIII), since the latter undergo partial doubling under the conditions of their cyclization by the acid chloride method. This was not observed with linear di-N-methyltetradepsipeptides, which under similar conditions are transformed only into the corresponding cyclotetradepsipeptides[1].

On cyclization of D-valyl-D-α-hydroxyisovaleryl-D-valyl-D-α-hydroxyisovaleric acid hydrobromide (IV, n = 1, X = X'= H, Y = OH)[2] by the chloride method ($SOCl_2$, Et_3N, 20°, 24 hrs in benzene, 0.001 mole/liter) the cyclotetradepsipeptide (V) (m.p. 291° from $CHCl_3$-EtOH, $[\alpha]_D^{20}$ +190° in $CHCl_3$; M.W. 402, 430*. Found: C, 60.30; H, 8.51; N, 6.86. $C_{20}H_{34}O_6N_2$ requires C, 60.28; H, 8.60; N, 7.03%) and the cyclooctadepsipeptide (I) (m.p. 234-236° from EtOH, $[\alpha]_D^{20}$ +131° in $CHCl_3$; M.W. 767, 795. Found: C, 60.04; H, 8.50; N, 7.23%. $C_{40}H_{68}O_{12}N_4$ requires C, 60.28; H, 8.60; N, 7.03%. Inactive against Candida albicans at concentrations up to 200 γ/ml.) were obtained.

* Here and elsewhere in this study the molecular weights were determined by isothermal distillation and by the thermoelectrical method in acetone, ethanol or chloroform.

The formation of compound (I) was established chromatographically (thin layer chromatography on Al_2O_3; benzene:ethyl acetate:ethanol 20:1:0.1) and by cyclization of D-valyl-(D-α-hydroxyisovaleryl-D-valyl)$_3$-D-α-hydroxyisovaleric acid (IV, n = 3, X = X'= H, Y = OH) ($[\alpha]_D^{20}$ + 73° in EtOH; M.W. (titration) 780. Found: C, 58.79; H, 8.58. $C_{40}H_{70}O_{13}N_4$ requires C, 58.92; H, 8.67%)*.

The structures of the cyclooctadepsipeptide (I) and the cyclotetradepsipeptide (V) were confirmed by their IR spectra and the results of alkaline hydrolysis. Alkaline hydrolysis of I and V (0.025 N 1:1 aqueous alcohol solution of NaOH, 48 hrs, 40°) yielded only D-α-hydroxyisovaleryl-D-valine (VI), characterized as the dicyclohexylamine salt (VII) (m.p. 197-198° from EtOH; $[\alpha]_D^{20}$ +24° in EtOH. Found: C, 66.40; H, 10.68; N, 7.20. $C_{22}H_{42}O_4N_2$ requires C, 66.29; H, 10.62; N, 7.02%). Compound (VI) was also prepared by counter synthesis from D-α-hydroxyisovaleric acid and D-valine by means of the azide method. Its dicyclohexylamine salt is identical with VII. Since the properties of compound (I) obtained synthetically

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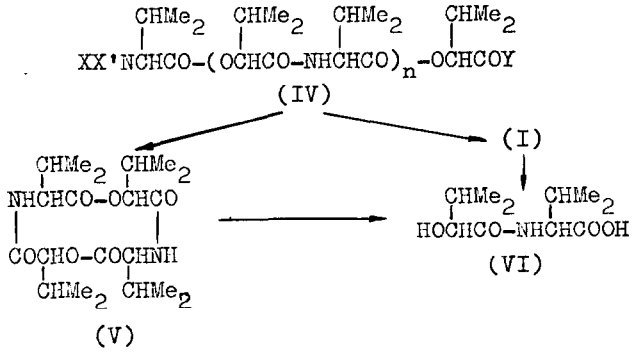
* This octadepsipeptide was prepared from the earlier described[2] protected octadepsipeptide (IV, X + X'= $C_6H_4(CO)_2$, Y = OCH_2Ph) by removal of the phthaloyl group with hydrazine hydrate and hydrogenolysis of the benzyl group under ordinary conditions.

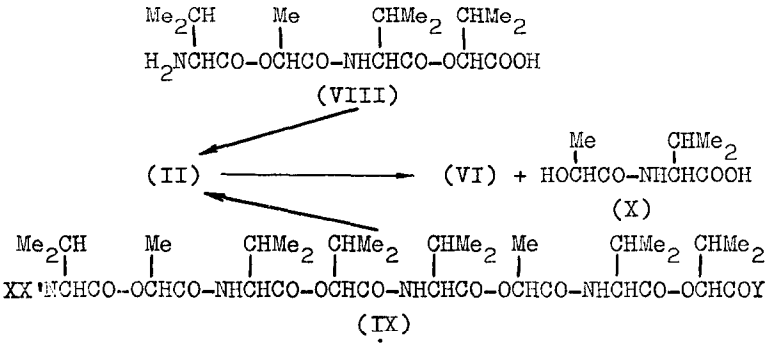
differ from those of amidomycin, it follows that the latter cannot possess structure (I).



Cyclization of D-valyl-L-lactyl-L-valyl-D-α-hydroxyisovaleric acid hydrochloride (VIII)[2] and D-valyl-L-lactyl--L-valyl-D-α-hydroxyisovaleryl-D-valyl-L-lactyl-L-valyl--D-α-hydroxyisovaleric acid (IX, X = X'= H, Y = OH) ($[\alpha]_D^{20}$ +6.5°; M.W. (titration) 782. Found: C, 56.70; H, 8.20; N, 7.18. $C_{36}H_{62}O_{13}N_4$ requires C, 56.97; H, 8.23; N, 7.38%)* by the acid chloride method under the above described conditions yielded the crystalline cyclooctadepsipeptide (II) (m.p. 218-219° from heptane, $[\alpha]_D^{20}$ -6° in benzene; M.W. 773, 748. Found: C, 58.46; H, 8.17; N, 7.44. $C_{36}H_{60}O_{12}N_4$ requires C, 58.36; H, 8.16; N, 7.56%. Inactive against Mycobacterium tuberculosis at concentrations up to 200 γ/ml.).

* This compound was obtained from the earlier described[2] protected octadepsipeptide (IX, X = X'= $C_6H_4(CO)_2$, Y = OCH_2Ph).

The structure of compound (II) was confirmed by the IR spectrum. On alkaline hydrolysis of the cyclooctadepsipeptide (II) under the conditions described for compound (I) only D-α-hydroxyisovaleryl-D-valine (VI) and L-lactyl-L-valine (X) were obtained. The latter was characterized as the dicyclohexylamine salt (XI) (m.p. 174–175°, $[\alpha]_D^{20}$ -13° in EtOH. Found: C, 64.58; H, 10.27; N, 7.30. $C_{20}H_{38}O_4N_2$ requires C, 64.82; H, 10.33; N. 7.56%). Compound (X) was also prepared by counter synthesis from L-lactic acid and L-valine by means of the azide method; its dicyclohexylamine salt is identical with XI.



The cyclooctadepsipeptide (II) synthesized by us differs greatly in properties from valinomycin, a direct comparison having been made with a specimen of valinomycin kindly placed at our disposal by Prof. H. Brockmann. It follows from the above said that formula (II) is not in conformity with the structure of valinomycin; as for formula (III), its validity is at present being investigated.