portion of this process. Since dependence of the transport velocity on energy-yielding metabolism is one of the theoretical requirements for active transport[5], this strongly suggests that xylose is indeed actively transported. Similar evidence was adduced by BIHLER, HAWKINS and CRANE[10] to classify 6-deoxy-1,5-anhydro-D-glucitol as active; although this compound was not found to be accumulated, its transport was inhibited by 4,6-dinitro-*o*-cresol and by anaerobiosis[10].

Evidence for a two-stage mechanism in xylose transport. An appraisal of the above findings suggests that, like the active sugars[10,12,14], xylose transport occurs in two stages: (1) a phlorizin-sensitive, Na^+-dependent, energy-independent *entry* into the epithelial cell and (2) an oxygen-dependent, DNP-sensitive step, probably equivalent to the energy-dependent *accumulation* step, typical of active compounds.

Concluding remarks. It seems clear that xylose, a sugar hitherto considered as non-active, is transported, in the hamster small intestine, through the same pathway as the active sugars. The evidence includes demonstration of Na^+ requirement, competitive inhibition by phlorizin, sugar active transport inhibition by xylose and reciprocal inhibition of active compounds on xylose transport. Although no xylose accumulation was observed, participation of an energy-dependent component in xylose transport in the hamster is evinced by the inhibitory action of anaerobiosis and dinitrophenol. Investigations now in progress[15] seem to indicate that the apparent lack of xylose accumulation against the gradient is due to the small affinity of this pentose for an accumulation process different from entry. This contention is supported by the lack of significant change in apparent Km values for xylose, as determined in aerobiosis or in anaerobiosis. In significant contrast, typical active compounds such as arbutin show a drastic decrease in apparent affinity for the (overall) system when nitrogen instead of oxygen is used while determining these constants. These observations, in agreement with an earlier suggestion by WIDDAS[16], suggest that sugar active transport involves two different processes, the first of which seems to be a typical facilitated diffusion process identical to the carrier-mediated xylose transport mechanism of SALOMON et al.[6]. It seems warranted to conclude that the properties of the overall sugar active transport process are indeed a composite of partial features of at least two distinct stereospecific processes. Evidence in favour of this hypothesis will be presented in a forthcoming series of papers[20].

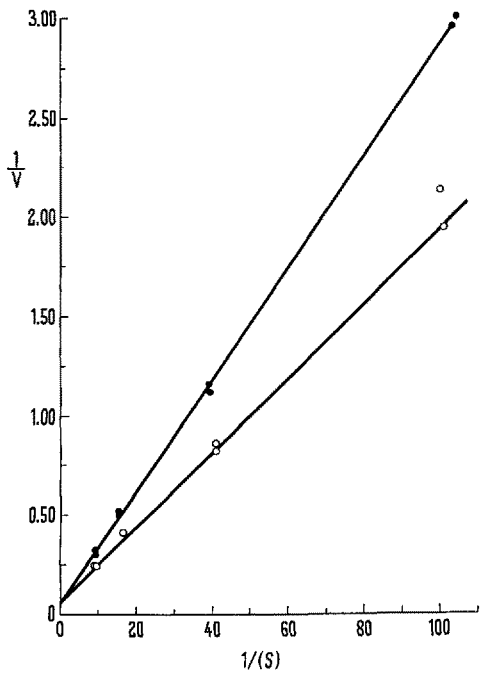

Fig. 2. Phlorizin competitive inhibition on xylose transport. Incubations in oxygen atmosphere were for 10 min in 4 ml Krebs-Henseleit[17] phosphate buffer containing 2 ml of a mixture in varying proportions of isotonic (0.3 *M*) xylose and mannitol. o, xylose; •, xylose plus 3.33×10^{-5} *M* phlorizin. Velocities[8,9,12] and mean substrate concentrations are plotted as reciprocals[13]. Other experimental details as in Figure 1.

Résumé. Dans les cellules épithéliales de l'intestin grêle du Hamster, l'absorption de xylose comprend deux étapes: (1) une *entrée* sensible à la phlorizine, et (2) une étape sensible au dinitrophénol, probablement équivalente à l'étape d'*accumulation* dépendant de l'énergie et typique des sucres actifs.

F. ALVARADO

Department of Enzymology, Instituto G. Marañón, Centro de Investigaciones Biológicas, C.S.I.C., Madrid (Spain), December 6, 1963.

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Synthetic Peptides Related to Eledoisin[1]

After the structure of eledoisin, a powerful vasodilating and hypotensive peptide isolated from the salivary glands of a mollusc[2], had been elucidated[2] and confirmed by synthesis[3], we prepared a large number of analogues of this substance in order to investigate the influence of structural modifications on its biological properties. In a previous communication[4] we listed in a Table those analogues and partial sequences which have been found to be devoid or almost devoid of biological activity.

[1] Part II. See [4] for part I.
[2] V. ERSPAMER and A. ANASTASI, Exper. *18*, 58 (1962).
[3] ED. SANDRIN and R. A. BOISSONNAS, Exper. *18*, 59 (1962).
[4] B. CAMERINO, G. DE CARO, R. A. BOISSONNAS, ED. SANDRIN, and E. STÜRMER, Exper. *19*, 339 (1963).

No.	Chemical formula	Relative biological activities: Contraction of guinea-pig ileum	Hypotensive effect in cat	Hypotensive effect in rabbit
1	H– Pyr-Pro-Ser-Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2 Eledoisin	100	100	100
2	*Bz*-Pyr-Pro-Ser-Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	100	100	–
3	*Bz-Pyr-Glu*(NH_2)-Pro-Ser-Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	100	100 ± 20	–
4	H-Glu(OH)-Pro-Ser-Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	150	–	80
5	*Bz*-Pyr——Ser-Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	100	–	100
6	*Bz*-Pyr————Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	100	–	> 100
7	*Bz*-Pyr-Pro(*Bz-Pyr*)——Lys-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	50	–	100
8	*Bz*-Pyr-Pro-Ser-*Nle*-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	200 ± 14	50 ± 10	–
9	*Bz*-Pyr-Pro-Ser-*Nva*-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	165	< 100	80
10	H——Pro-Ser-*Nle*-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	100	–	> 100
11	H——Pro-Ser-*Nva*-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	130	> 100	> 100
12	H——*Ala-Phe-Ala*-Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	75	–	200
13	H——Pro-Ser——Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	60	60	–
14	*Bz*-Pyr————Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	30	–	< 50
15	H————Asp(OH)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	20	50	–
16	H-Pyr-Pro-Ser-Lys-Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	90 ± 10	300 ± 80	–
17	*Bz*-Pyr-Pro-Ser-Lys-Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	175 ± 40	470 ± 90	–
18	H—— Pro-Ser-Lys-Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	75	–	200
19	H-*Ala*——Ser-Lys-Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	75	–	200
20	*Bz*-Pyr-Pro-Ser-*Nle*-Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	5	–	< 10
21	H—— Pro-Ser-*Nle*-Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	50	–	100
22	H————Asp(NH_2)-Ala-Phe-Ile-Gly-Leu-Met-NH_2	20	50	–
23	H—— Pro-Ser-Lys-*But*-Ala-Phe-Ile-Gly-Leu-Met-NH_2	100	–	250
24	*Bz*-Pyr-Pro-Ser-*Asp*(NH_2)-*Lys*-Ala-Phe-Ile-Gly-Leu-Met-NH_2	150	–	250
25	H——Pro-Ser–Asp(NH_2)-Lys-Ala-Phe-Ile-Gly-Leu-Met-NH_2	105	> 100	> 100
26	H——Pro-Ser-Lys——Ala-Phe-Ile-Gly-Leu-Met-NH_2	60 ± 10	230 ± 20	–
27	*Bz*-Pyr-Pro-Ser-Lys——Ala-Phe-Ile-Gly-Leu-Met-NH_2	20	–	100
28	H——Pro-Ser(*H-Pro-Ser*)-Lys——Ala-Phe-Ile-Gly-Leu-Met-NH_2	50	–	100
29	H—— Pro-Ser-*Nle*——Ala-Phe-Ile-Gly-Leu-Met-NH_2	50	–	80
30	H—— Pro-Ser-*Nva*——Ala-Phe-Ile-Gly-Leu-Met-NH_2	75	–	250
31	H—— Pro-Ser————Ala-Phe-Ile-Gly-Leu-Met-NH_2	90	> 100	> 100

$[\alpha]_D^{22}$ in 95% acetic acid (c = 1)	Mp. (with dec.)	Electrophoretic mobility in 80% formic acid		Elemental formula		Elemental analysis C	H	O	N	S	F
				$C_{54}H_{85}O_{15}N_{13}S$	C	53.8	7.2	21.2	15.0	2.7	–
−44°	230°	0.48	Try	$+H_2O$	F	53.2	7.9	21.4	14.6	2.8	–
				$C_{61}H_{91}O_{15}N_{13}S$	C	54.3	6.7	–	–	2.3	4.1
−48°	200°	0.56	Try	$+CF_3COOH$	F	54.0	7.0	–	–	2.4	3.9
				$C_{66}H_{103}O_{17}N_{15}S$	C	53.6	6.7	–	–	2.1	3.8
−52°	200°	0.53	Try	$+CF_3COOH$	F	53.2	6.9	–	–	2.1	4.2
				$C_{54}H_{87}O_{16}N_{13}S$	C	48.6	6.3	–	–	2.2	7.9
−43°	200°	0.81	Try	$+2CF_3COOH$	F	48.4	6.4	–	–	2.4	6.7
				$C_{56}H_{84}O_{14}N_{12}S$	C	53.8	6.6	–	–	2.5	4.4
−35.5°	200°	0.5	Try	$+CF_3COOH$	F	53.6	6.9	–	–	2.5	4.5
				$C_{53}H_{79}O_{12}N_{11}S$	C	54.7	6.7	–	–	2.7	4.7
−30°	210°	0.53	Try	$+CF_3COOH$	F	54.5	6.8	–	–	2.7	4.2
					C	60.3	7.0	17.2	13.1	2.3	–
−48°	240°	0.21	Try	$C_{70}H_{97}O_{15}N_{13}S$	F	59.8	7.3	17.0	13.3	2.6	–
					C	58.0	7.3	19.0	13.3	2.5	–
−41°	250°	0.32	Try	$C_{61}H_{91}O_{15}N_{12}S$	F	57.8	7.6	18.6	13.6	2.4	–
					C	57.7	7.1	19.2	13.5	2.6	–
−60°	240°	0.18	Try	$C_{60}H_{88}O_{15}N_{12}S$	F	57.5	7.4	19.2	13.4	2.5	–
				$C_{49}H_{79}O_{13}N_{11}S$	C	52.1	6.9	–	–	2.7	4.9
−49°	230°	0.45	Try	$+CF_3COOH$	F	51.7	6.7	–	–	2.7	5.5
				$C_{48}H_{77}O_{13}N_{11}S$	C	51.7	6.8	–	–	2.8	4.9
−49°	200°	0.57	Try	$+CF_3COOH$	F	51.4	6.8	–	–	2.8	4.8
				$C_{50}H_{75}O_{12}N_{11}S$	C	53.5	6.6	–	–	2.7	4.9
−27°	250°	0.54	Try	$+CF_3COOH$	F	53.1	6.7	–	–	2.8	4.5
				$C_{43}H_{68}O_{12}N_{10}S$	C	50.8	6.6	–	13.2	3.0	5.4
−46°	250°	0.53	Try	$+CF_3COOH$	F	50.2	6.7	–	13.3	3.0	5.8
					C	58.4	7.0	18.2	13.0	3.3	–
−36.5°	260°	0.2	Try	$C_{47}H_{67}O_{11}N_9S$	F	58.0	7.4	18.4	13.3	3.4	–
				$C_{35}H_{56}O_9N_8S$	C	50.4	6.6	–	12.8	3.6	6.5
−32°	250°	0.62	Try	$+CF_3COOH$	F	50.2	6.8	–	12.9	3.6	7.0
				$C_{54}H_{86}O_{14}N_{14}S$	C	51.7	6.7	–	15.1	2.5	4.4
–	195°	0.58	Try	$+CF_3COOH$	F	51.4	6.8	–	15.5	2.5	4.6
				$C_{61}H_{92}O_{14}N_{14}S$	C	54.4	6.7	–	14.1	2.3	4.1
−53.5°	220°	0.64	Try	$+CF_3COOH$	F	54.4	7.0	–	14.0	2.3	4.6
				$C_{49}H_{81}O_{12}N_{13}S$	C	48.8	6.4	–	–	2.5	8.8
−37.5°	220°	0.88	Try	$+2CF_3COOH$	F	48.2	6.4	–	–	2.6	9.0
				$C_{47}H_{79}O_{12}N_{13}S$	C	47.9	6.4	–	–	2.5	8.9
−30°	240°	0.86	Try	$+2CF_3COOH$	F	47.3	6.4	–	–	2.5	8.3
					C	58.0	7.3	17.7	14.4	2.5	–
−62°	270°	0.16	Try	$C_{61}H_{91}O_{14}N_{13}S$	F	57.5	7.5	17.4	14.1	2.4	–
				$C_{49}H_{80}O_{12}N_{12}S$	C	52.1	7.0	–	–	2.7	4.9
−47°	240°	0.55	Try	$+CF_3COOH$	F	51.5	7.0	–	–	2.6	5.0
					C	55.0	7.5	16.8	16.5	4.2	–
−38°	230°	0.62	Try	$C_{35}H_{57}O_8N_9S$	F	55.1	7.8	17.3	16.3	4.2	–
				$C_{49}H_{82}O_{11}N_{12}S$	C	49.9	6.7	–	–	2.5	8.9
−45°	200°	0.84	Try	$+2CF_3COOH$	F	49.5	6.7	–	–	2.7	8.7
				$C_{61}H_{92}O_{14}N_{14}S$	C	54.4	6.7	–	–	2.3	4.1
−52.5°	200°	0.54	Try	$+CF_3COOH$	F	54.0	7.1	–	–	2.4	4.0
				$C_{49}H_{81}O_{12}N_{13}S$	C	48.8	6.4	–	–	2.5	8.7
−39°	200°	0.82	Try	$+2CF_3COOH$	F	48.3	6.6	–	–	2.7	8.6
				$C_{45}H_{75}O_{10}N_{11}S$	C	49.4	6.5	–	–	2.7	9.6
−41°	215°	0.88	Try	$+2CF_3COOH$	F	49.0	6.3	–	–	3.0	9.6
				$C_{57}H_{86}O_{12}N_{12}S$	C	55.5	6.9	–	–	2.5	4.5
−52°	220°	0.5	Try	$+CF_3COOH$	F	54.9	7.3	–	–	2.5	4.6
				$C_{53}H_{87}O_{13}N_{13}S$	C	49.7	6.5	–	–	2.3	8.3
−43.5°	250°	0.85	Try	$+2CF_3COOH$	F	49.2	6.3	–	–	2.6	8.6
				$C_{45}H_{74}O_{10}N_{10}S$	C	53.1	7.1	–	–	3.0	5.4
−46°	220°	0.64	Try	$+CF_3COOH$	F	52.5	7.0	–	–	3.1	6.1
				$C_{44}H_{72}O_{10}N_{10}S$	C	52.8	7.0	–	–	3.1	5.4
−47°	230°	0.66	Try	$+CF_3COOH$	F	52.5	7.0	–	–	3.1	6.0
				$C_{39}H_{63}O_9N_9S$	C	52.0	6.8	–	–	3.4	6.0
−49°	240°	0.58	Try	CF_3COOH	F	51.8	6.7	–	–	3.4	6.3

In the present paper we are reporting on some of the analogues or partial sequences which have been found to be highly active, in some cases even more so than eledoisin itself. The Table indicates the level of activity on guinea-pig ileum, and, where comparisons have been made, on rabbits' and cats' blood pressure; all data referred to eledoisin taken as 100. (Where no standard deviation is given, data may be regarded as good approximations only.) In addition, the physical properties and elemental analysis of these peptides are given. The methods used for the synthesis of these peptides are described elsewhere in detail[5].

The data given in [4] have furnished evidence that any alteration to the six amino acids of the C-terminal moiety of the eledoisin molecule (i.e. -Ala-Phe-Ile-Gly-Leu-Met-NH_2) is likely to yield biologically inactive peptides. This was recently confirmed by another group of workers[6]. From the present data it will be evident that alterations to the five amino acids of the N-terminal moiety of eledoisin (i.e. H-Pyr-Pro-Ser-Lys-Asp(OH)-), even changes affecting the acid or basic groups, do not interfere to any great extent with biological activity. It thus appears that almost one-half of the peptide chain can be modified or even left out without substantial loss of biological activity. Nevertheless, such modifications do affect the relation between the biological activities, as measured in the different tests, in an unpredictable manner[7].

Zusammenfassung. Die Eigenschaften einer Serie von synthetischen Peptiden, die mit Eledoisin strukturell und wirkungsmässig verwandt sind, werden beschrieben.

E. STÜRMER, ED. SANDRIN, and R. A. BOISSONNAS

Medizinisch-biologische und Pharmazeutisch-chemische Forschungslaboratorien der Sandoz AG., Basel (Switzerland), March 13, 1964.

[5] ED. SANDRIN and R. A. BOISSONNAS, Helv. chim. acta *46*, 1637 (1963); *47*, 417 and in press (1964).
[6] E. SCHRÖDER and K. LÜBKE, Exper. *20*, 19 (1964).
[7] Further analogues of eledoisin are described and discussed in the following paper (Part III), by L. BERNARDI, G. BOSISIO, F. CHILLEMI, G. DE CARO, R. DE CASTIGLIONE, V. ERSPARMER, A. GLAESSER, and O. GOFFREDO (Exper. *20*, 306 (1964)). The results reported by these authors are in line with our own findings.

Synthetic Peptides Related to Eledoisin[1]

In a previous paper[2] a first group of synthetic peptides related to eledoisin was presented. We wish now to report briefly some chemical data and biological actions of a new group of peptides similarly related to eledoisin or to its fragments[3]. While the problem of the relationship between the chemical structure and the biological activity of eledoisin-like polypeptides will be discussed in detail elsewhere, we wish, on the grounds of the former[2] and present data, to call attention here to a few essential points:

(1) It is possible to reduce consistently the size of the eledoisin molecule, without any drastic reduction in its biological activity, by means of a progressive elimination of the N-terminal amino acid residue. A minimum of five amino acid residues is needed in order to have an appreciable activity (No. 8). This increases sharply in the C-terminal hexapeptide (No. 7) and reaches a high level in the octapeptide (No. 5). Maximum activity is attained in the nonapeptide (No. 4), which is approximately twice as active as eledoisin, even if assayed in the dog blood pressure.

(2) The structure of the highly active hexapeptide Ala-Phe-Ile-Gly-Leu-Met-NH_2 (No. 7) has been altered stepwise by changing amino acid residues; from the data reported in the Table it may be seen that substitution of the phenylalanine residue produces a tremendous decay in the specific biological activity. The same is true for any substitution of the leucine and methioninamide residues. The only striking exceptions are so far represented by compounds Nos. 39 and 40, where the substitution of the methioninamide with ethioninamide has caused a 5- to 6-fold increase in activity[4].

Changes in biological activity produced by substitution of one of the three remaining amino acids are more irregular and apparently unpredictable. A high degree of activity is present in compounds Nos. 26, 27 and 29, where isoleucine has been replaced by valine and phenylalanine. However, compounds Nos. 25 and 28, where isoleucine has been replaced by leucine and alanine, are practically devoid of activity. Likewise substitution of glycine furnishes in some cases active compounds (Nos. 30 and 32), in other cases inactive compounds (No. 31). Finally, alanine can be replaced, often with advantage, by a number of amino acids, the most interesting being lysine (No. 14), which considerably enhances the biological activity. It may be further seen from the Table that through suitable substitution of two amino acid residues (Nos. 29 and 40) it is possible to obtain hexapeptides which are more active, even on molar basis, than eledoisin itself.

(3) The introduction of a D. amino acid residue into the molecule does not necessarily destroy the biological activity. In the case of No. 20 as compared with No. 16 this activity is rather enhanced.

(4) Compounds Nos. 41 to 47 show that a free terminal amino group is not necessary for the biological activity.

(5) The activity ratio between eledoisin and a given eledoisin-like polypeptide may vary conspicuously according to the different preparation of test-objects used in the bioassay.

Riassunto. Vengono descritte le proprietà di una serie di peptidi sintetici affini all'Eledoisina sia per la struttura che per l'attività.

L. BERNARDI*, G. BOSISIO*, F. CHILLEMI*, G. DE CARO**, R. DE CASTIGLIONE*, V. ERSPAMER**, A. GLAESSER*, and O. GOFFREDO*

Laboratori ricerche, Farmitalia, Milano, and Istituto di Farmacologia dell'Università di Parma** (Italy), March 13, 1964.*

[1] Part III. For part II see [3]; for part I see [2].
[2] B. CAMERINO, G. DE CARO, R. A. BOISSONNAS, ED. SANDRIN, and E. STÜRMER, Exper. *19*, 339 (1963).
[3] In the paper by E. STÜRMER, ED. SANDRIN, and R. A. BOISSONNAS (Part II) in this same issue (Exper. *20*, 303 (1964)) another large group of peptides related to eledoisin is presented and discussed.
[4] The biological activities of various polypeptides having as C-terminal amino acid S-alkyl-homocysteinamides and their homologues will be the subject of a later report.