116. Preparation and Antimicrobial Activity of *enantio*-[1-Valine]malformin

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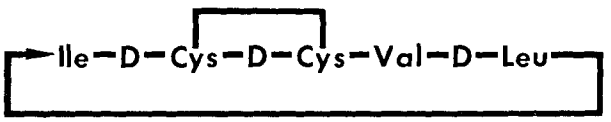
Zusammenfassung. Die stufenweise Synthese der im Titel genannten Verbindung, *Cyclo*-(D-Val)-Cys-Cys-(D-Val)-Leu, wird beschrieben. Die mikrobiologische Untersuchung dieser Verbindung zeigt, dass sie das Wachstum von *Gram*-negativen Mikroorganismen nicht beeinflusst.

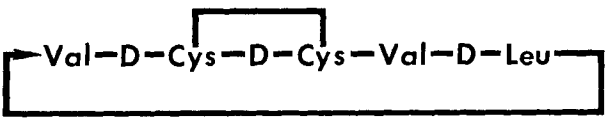
The malformins, a group of cyclic pentapeptides isolated from the culture filtrates of *Aspergillus niger* [1] [2], were reported to influence the growth of plants [3], exhibit antibiotic properties [4], inhibit mitosis in plants [5], and to be cytostatic *in vitro* to P-815 mastocytoma cells [6]. Recently *Bodanszky* & *Stahl* [7] [8] reported the cyclic pentapeptide structure I[1]) for one of the malformins formed by *Aspergillus niger*[2]).

A second natural product isolated from the same culture filtrates may be formulated as II by analogy with I [7] [8] by re-examining the data reported by *Curtis et al.* [2].

The antibiotic properties of the malformins, particularly against *Gram*-negative microorganisms [4], were of interest. However, the high toxicity exhibited by these



I



II

[1]) The prefix D denotes D-amino acids, no prefix is used for L-amino acids.

[2]) The synthetic approaches pursued in connection with the structure determination of these substances in the laboratory of Prof. *R. W. Curtis* (Purdue University) and similar efforts in the laboratory of Prof. *A. Schöberl* (Tierärztliche Hochschule Hannover) were reviewed by *Bodanszky & Stahl* [7] [8].

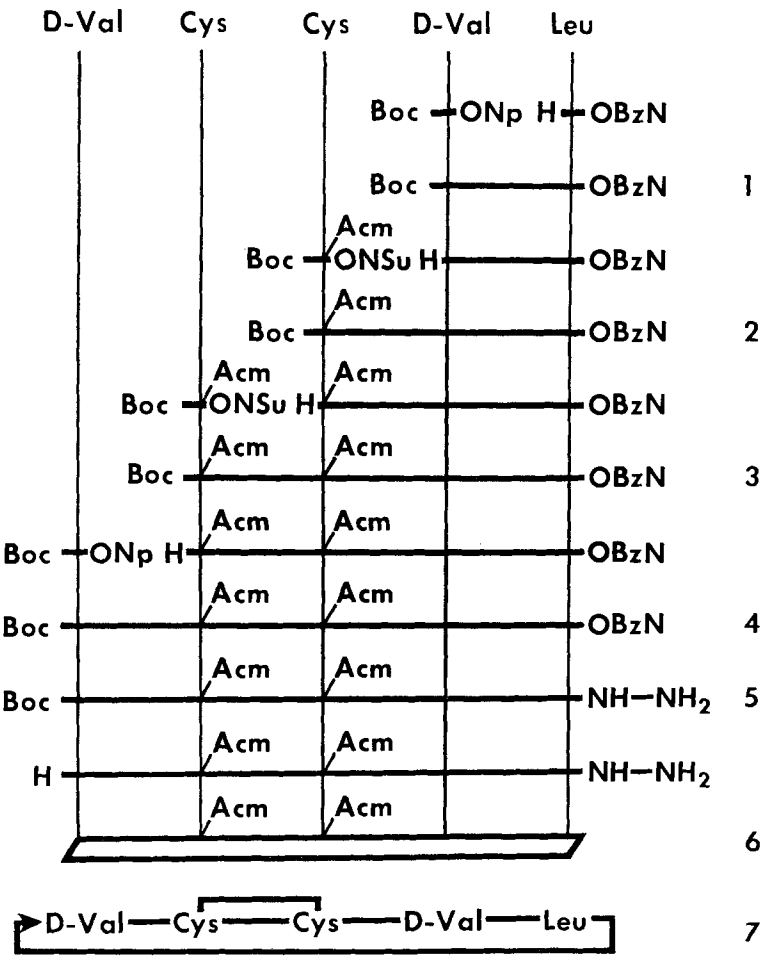
substances [6] shed serious doubt on their practical utility as antibacterial agents for the treatment of infectious disease in man or animal.

The possibility of preparing biologically active analogs of cyclic peptide and depsipeptide antibiotics by synthesizing their *enantio*-derivatives (reversal of the optical configuration of the individual building blocks) or their *retro-enantio*-structures (reversal of the optical configuration of the individual building blocks as well as their sequence) was demonstrated in *Shemyakin*'s laboratory [9] While the substances studied by the Russian workers contained repeating structural units and thus elements of symmetry [9], it was recently shown that a *retro-enantio* antamanid analog which contained no such repeating structural features exhibited biological properties comparable to that of the natural product [10]. It appeared that it might be possible to employ the topochemical principles referred to above for the synthesis of malformin analogs which might retain the antibacterial activity [4] of the natural product while its toxic effect [6] would possibly be lower. The preparation of the title compound (**7**) appeared particularly attractive since the substance represents the *enantio* as well as the *retro-enantio* analog of II. A paper in which the same palindrome peptide (**7**) was chosen for synthesis [11] appeared after completion of this work. Since the synthetic approach followed in this report is different from that employed in [11], it appears worthwhile to describe the present synthesis.

The stepwise synthesis of *enantio*-[1-valine]malformin (**7**) is illustrated in the accompanying scheme. The carbonyl *termini* in the linear intermediates **1**–**4** were protected by the *p*-nitrobenzyl ester group (OBzN); the *t*-butoxycarbonyl group (Boc) served to block the amino *termini* in **1**–**5**, while the acetamidomethyl group (Acm) was used to protect the cysteine thiol groups [12]. Active ester[3]) couplings were employed in the preparations of **1**–**4**. The pentapeptide ester **4** was allowed to react with hydrazine hydrate in a methanol solution to afford the hydrazide **5** which was deblocked, converted to the azide, and cyclized to yield **6**. The reaction of the latter (**6**) with iodine resulted in the removal of the Acm groups and formation of the S-S bridge to give the bicyclic substance **7**.

In the course of the last two steps of the above synthesis the possibility of formation of di- (or poly-)meric cyclization products existed. In the mass spectrum of the monocyclic substance **6** no signals for the molecular ion or ions with masses greater than that of the latter were observed. The stepwise loss of the two acetamidomethyl protecting groups with back transfer of two hydrogen atoms during the electron impact fragmentation of **6** gave rise to ions at $m/e = 588$ and $m/e = 517$, respectively. The ion at $m/e = 517$ could be identified by peak-matching as the expected $C_{22}H_{39}N_5O_5S_2$-fragment resulting from the above described loss of the two S-protecting groups from **6**. This finding, together with NMR.- and IR.- spectral evidence, as well as the correct microanalysis, established the monomeric nature of **6**. The mass spectrum of **7** revealed, as expected for a bicyclic compound, relatively intense signals for the molecular ion at $m/e = 515$ ($C_{22}H_{37}N_5O_5S_2$) and for the $M + 1$ ion at $m/e = 516$, both of which could be confirmed in the high resolution mass spectrum of **7**. The low mass signals in the spectrum were characteristic of the amino acid

[3]) The abbreviations ONp for the *p*-nitrophenyl ester group and ONSu for the N-hydroxysuccinimide ester group were used.



residues contained in the pentapeptide **7** (*cf.* [2]). The absence of signals of masses greater than that of the molecular ion in the above spectrum, together with the IR.- and *Raman*-spectral findings and the microanalytical result, established the nature of the endproduct of the synthesis as the desired monomeric bicyclic substance **7**.

The *Gram*-negative antimicrobial properties of *enantio*-[1-valine]-malformin (**7**) were evaluated against *Escherichia coli* JUHL, *Pseudomonas aeruginosa* BMH # 10, *Salmonella typhimurium* ED. # 9, *Proteus vulgaris* ABBOTT JJ, and *Proteus mirabilis* FIN. # 9. It was found that the minimum inhibitory concentration of the substance was greater than 200 γ/ml and thus the malformin analog **7** does not show good activity against these *Gram*-negative microorganisms.

The author is indebted to the late Prof. Dr. *J. Rudinger* of the Eidgenössische Technische Hochschule in Zürich for stimulating discussions during the course of this investigation. I likewise wish to thank my colleagues Drs. *W. Cole*, *J. H. Seely* and *A. M. Thomas* for much valued advice. Thanks are due to Mr. *W. H. Washburn* and his staff for IR. and *Raman* spectra, to Mr. *M. Cirovic* for NMR. spectra, to Mrs. *Sandra L. Mueller* for mass spectra, to Mrs. *Julie Hood* for microanalyses, and to Dr. *R. L. Girolami* and Mrs. *C. M. Vojtko* for the microbiological assays.

Experimental part

General Remarks. The m.p.'s were determined on a *Fisher-Johns* melting point apparatus. Optical rotations were measured with a *Hilger & Watts* polarimeter using solutions of CH_3OH unless stated otherwise, the IR. spectra were obtained with a *Perkin-Elmer* Model 521 grating spectrophotometer and KBr pellets unless stated otherwise (ν_{max} in cm^{-1}), and the *Raman* spectrum was obtained on a *Carey* Model 83 *Raman* spectrophotometer using an argon laser. The NMR. spectra were determined at 100 MHz with a *Varian* HA-100 spectrometer employing deuterioacetic acid (AcOH-d_4) solutions unless stated otherwise. Chemical shifts (δ) were reported in ppm from internal tetramethylsilane ($\delta = 0$); δ-values for multiplets refer to the center of the observed peaks. Mass spectra (MS.) were recorded with an *AEI.* MS-902 mass spectrometer with an ionizing energy of 70 eV; samples were introduced into the source by a direct inlet system. Silica gel 60 made by *E. Merck*, Darmstadt, was used for the column chromatography; individual fractions obtained were assayed by thin layer chromatography (TLC.) on silica gel G plates which were developed with $CHCl_3/CH_3OH$ 95:5; the spots were detected with the chlorine/*o*-toluidine system.

Boc-(D-Val)-Leu-OBzN (**1**). To an ice-cold suspension of 7.50 g (21.6 mmol) of Leu-OBzN·HBr [13] and 4.40 g (43.5 mmol) of $N(C_2H_5)_3$ in 12 ml of $CHCl_3$ there was added, with stirring, 7.50 g (22.2 mmol) of Boc-(D-Val)-ONp [14] and 13 ml of $CHCl_3$. The resulting reaction mixture was stirred in the cold for 2 h and then for 24 h at room temperature. The solution was diluted with 400 ml of $CHCl_3$ and the organic solution was washed with two 400-ml portions of ice-cold H_2O, nine 400-ml portions of an ice-cold 5% $NaHCO_3$-solution, three 400-ml portions of a 5% citric acid solution, and finally with two 200-ml portions of a saturated NaCl-solution. The aqueous phases were extracted in series with four 400-ml portions of $CHCl_3$. The organic extracts were dried over anhydrous $MgSO_4$, filtered, combined, and evaporated to leave 8.90 g of crystalline substance which was recrystallized from ethyl acetate/heptane to afford 6.76 g of **1**, m.p. 99–101°. A part of this sample was recrystallized twice from ethyl acetate/heptane: m.p. 99–101°; $[\alpha]_D^{22} = +7°$ ($c = 0.99$, $CHCl_3$). – IR. ($CHCl_3$): 3438, 1742, 1705, 1678, 1609, 1525, 1346. – NMR. ($CDCl_3$): 7.85 (*q*, $J_{AB} = 9$ Hz, Ar), 5.23 (*s*, CH_2-benzyl), 4,65 and 3.95 (*m*, α-CH), 2.2 (*m*), 1.65 (*m*), 1.43 (*s*, Boc), 1.2 and 0.93 ppm (*m*, CH_3).

$C_{23}H_{35}N_3O_7$ (465.534) Calc. C 59.33 H 7.58 N 9.03% Found C 59.72 H 7.76 N 9.05%

Boc-Cys(Acm)-(D-Val)-Leu-OBzN (**2**). A solution of 5.33 g (11.5 mmol) of Boc-(D-Val)-Leu-OBzN (**1**) in 35 ml of 4 N HCl in dioxane was allowed to stand at room temp. for 20 min. The solution was then added dropwise to 1200 ml of ether with stirring in the cold; the dropping funnel was rinsed with 5 ml of 4 N HCl in dioxane and then with 100 ml of ether. The substance in the resulting suspension was allowed to collect at the bottom of the flask and the supernatant was decanted. The dipeptide · HCl salt was resuspended in 150 ml of ether, allowed to collect, and the ether was decanted; the last procedure was repeated six times. The (D-Val)-Leu-OBzN ·HCl was collected on a filter, washed with several small portions of ether, and dried in a dessicator over KOH-pellets and P_2O_5 under high vacuum for 4 h.

A solution of the dipeptide ·HCl salt (3.90 g, 9.7 mmol) in 12 ml of $CHCl_3$ was cooled by immersion into an ice bath, 2.21 g (21.9 mmol) of $N(C_2H_5)_3$ was added with stirring, and then 4.12 g (10.6 mmol) of Boc-Cys(Acm)-ONSu [12] was added together with 4 ml of $CHCl_3$. The resulting reaction mixture was stirred in the cold for 2 h and then at room temp. overnight. Evaporation of the solvent left a residue of 10.95 g which was purified by chromatography on 160 g of silica gel using $CHCl_3/CH_3OH$ 95:5 as the eluting solvent mixture. A total of 7.39 g of coupling product was isolated, the substance was recrystallized from acetone/heptane to yield 6.79 g of **2**, m.p. 112–113°.

An analytical sample of the above protected tripeptide **2** had the following physical constants: m.p. 111–112°; $[\alpha]_D^{23} = -12°$ ($c = 1.03$). – IR.: 3300, 1745, 1652, 1606, 1520, 1342. – NMR.: 7.89 (*q*, $J_{AB} = 9$ Hz, Ar), 5.3 (*s*, br., CH_2-benzyl), 4.8–4.2 (complex *m*, 3 α-CH, NH–CH_2–S), 2.94 (*s*, CH_2), 2.5 (*s*, CH_3CO) 1.7 (*m*), 1.41 (*s*, Boc), 0.97 ppm (*m*, CH_3).

$C_{29}H_{45}N_5O_9S$ (639.756) Calc. C 54.44 H 7.09 N 10.95% Found C 54.54 H 7.15 N 10.95%

Boc-Cys(Acm)-Cys(Acm)-(D-Val)-Leu-OBzN (**3**). A solution of 6.68 g (10.4 mmol) of Boc-Cys(Acm)-(D-Val)-Leu-OBzN (**2**) in 80 ml of 4 N HCl in dioxane was deblocked in the same manner as described above for the dipeptide **1** to yield 5.58 g (9.7 mmol) of Cys(Acm)-(D-Val)-Leu-OBzN

·HCl which was converted to the free base by adding 2.16 g (21.3 mmol) of $N(C_2H_5)_3$ to the ice-cold solution of the HCl salt in 25 ml of DMF. Then 4.20 g (10.8 mmol) of Boc-Cys(Acm)-ONSu [12] and 5 ml of cold DMF were added to the above stirred mixture. The reaction was allowed to proceed in the cold for 2 h and then at room temp. overnight. Evaporation of the solvent left a residue of 15.48 g of crude coupling mixture which was purified by chromatography on 225 g of silica gel using $CHCl_3/CH_3OH$ 95:5 as the eluent. The partially purified product amounted to 7.67 g of substance which was recrystallized from acetone/heptane to yield 6.50 g of product which melted at 125–127°. The substance was again subjected to chromatography on 220 g of silica gel to yield, after recrystallization from acetone/heptane, 5.84 g of pure **3**, m.p. 163–164°. Samples of different m.p. were found to be identical by TLC., NMR. and IR. spectra.

A sample free of solvent melted at 152–153° and showed $[\alpha]_D^{24} = -14°$ ($c = 1.04$). – IR.: 3400, 3300, 1742, 1652, 1520, 1342. – NMR.: 7.89 (*q*, $J_{AB} = 9$ Hz, Ar), 5.3 (*s*, CH_2-benzyl), 5.0–4.2 (complex *m*, 4 α-CH, 2 NH–CH_2–S), 2.95 (*m*, 2 S–CH_2), 2.05 (*s*, 2 CH_3CO), 1.7 (*m*), 1.44 (*s*, Boc), 0.96 ppm (*m*, CH_3).

$C_{35}H_{55}N_7O_{11}S_2$ (813.978) Calc. C 51.64 H 6.81 N 12.05% Found C 51.49 H 6.94 N 11.92%

Boc-(D-*Val*)-*Cys*(*Acm*)-*Cys*(*Acm*)-(D-*Val*)-*Leu-OBzN* (**4**). A solution of 3.08 g (3.8 mmol) of the protected tetrapeptide **3** in 90 ml of 4 N HCl in dioxane was deblocked as described for **1** and **2** above to yield 2.66 g (3.5 mmol) of Cys(Acm)-Cys(Acm)-(D-Val)-Leu-OBzN ·HCl. The latter was dissolved in 12 ml of DMF, the solution was cooled and treated first with 0.81 g (8 mmol) of $N(C_2H_5)_3$ and then with 1.33 g (3.9 mmol) of Boc-(D-Val)-ONp [14] and 3 ml of cold DMF. The mixture was stirred in the cold for 2 h and then overnight at room temperature. Evaporation of the solvent left a residue of 4.62 g of crude reaction mixture which after chromatography on 220 g of silica gel yielded 2.52 g of coupling product from the eluates with $CHCl_3/CH_3OH$ 95:5; recrystallization of the substance from acetone afforded 2.03 g of **4**, m.p. 208–210°.

A sample of **4** was recrystallized for analysis, m.p. 211–212°; $[\alpha]_D^{24} = -14°$ ($c = 1.06$). – IR.: (3315, 1740, 1652, 1520, 1342. – NMR.: 7.9 (*q*, $J_{AB} = 9$ Hz, Ar), 5.32 (*s*, CH_2-benzyl), 5.05–4.0 (complex *m*, 5 α–CH, 2 NH–CH_2–S), 2.95 (*m*, S–CH_2), 2.05 (2 CH_3CO), 1.7 (complex *m*), 1.43 (*s*, Boc), 0.95 ppm (*m*, CH_3).

$C_{40}H_{64}N_8O_{12}S_2$ (913.108) Calc. C 52.61 H 7.06 N 12.27% Found C 52.43 H 7.23 N 12.21%

Boc-(D-*Val*)-*Cys*(*Acm*)-*Cys*(*Acm*)-(D-*Val*)-*Leu-NH-NH*$_2$ (**5**). A solution of 1.95 g (2.1 mmol) of the protected ester **4** in 220 ml of CH_3OH was cooled by immersion into an ice bath and 3 ml of 85% hydrazine hydrate was added with stirring. The reaction was allowed to proceed in the cold for 18 h and then at room temp. for 3 days. The crystalline hydrazide **5** was collected on a filter and washed with several small amounts of CH_3OH: 1.45 g m.p. 231–233°; $[\alpha]_D^{25} = -20°$ ($c = 0.96$, DMF). – IR.: 3310, 1685 (shoulder), 1655, 1637 (shoulder), 1520. – NMR.: 5.0–3.95 (complex *m*, 5 α–CH, 2 NH–CH_2–S), 3.0 (*m*, 2 S–CH_2), 2.06 (2 CH_3CO), 1.65 (complex *m*), 1.44 (*s*, Boc), 0.96 ppm (*m*, CH_3).

$C_{33}H_{61}N_9O_9S_2$ (792.022) Calc. C 50.04 H 7.76 N 15.92% Found C 50.18 H 7.84 N 15.80%

Cyclo-(D-*Val*)-*Cys*(*Acm*)-*Cys*(*Acm*)-(D-*Val*)-*Leu* (**6**). A solution of 1.45 g (1.83 mmol) of the hydrazide **5** in 8 ml of CH_2Cl_2 and 8 ml of CF_3COOH was stirred at room temp. for 20 min. The solvent was evaporated under reduced pressure and the residue was redissolved six times in 20 ml of CH_2Cl_2 which was likewise evaporated. The residue amounted to 2.27 g after drying over KOH-pellets and P_2O_5 under vacuum for 2 h. The substance was dissolved in 80 ml of CH_3OH and treated with 50 g of freshly washed (CH_3OH) Rexyn® 201 (OH). The resin was collected on a filter and washed with six 50-ml portions of CH_3OH; evaporation of the filtrate left a residue of 1.19 g (1.72 mmol) of (D-Val)-Cys(Acm)-Cys(Acm)-(D-Val)-Leu-NH-NH_2.

The cyclization of the above pentapeptide hydrazide was carried out under conditions very similar to those employed by *Bodanszky & Stahl* [8] in the preparation of the natural product. The pentapeptide hydrazide (1.19 g, 1.72 mmol) was dissolved in 20 ml of DMF and 0.5 ml of conc. hydrochloric acid and cooled in a Dry Ice/acetone bath to –20°, 1.75 ml of an aqueous solution of 1 N $NaNO_2$ was added and the mixture was stirred at –20° for 15 min. After the solution was diluted with 300 ml of DMF, which was precooled to –20°, 2.5 ml of $N(n\text{-}C_4H_9)_3$ was added and stirring of the solution at –20° was continued for 30 min, the acetone/Dry Ice bath was replaced by an ice bath and stirring was continued for 4 days. The precipitate which had formed was collected

on a filter and washed first with several small portions of DMF and then with water. The solid was dried over KOH-pellets under high vacuum to leave a residue of 0.50 g of pure cyclic pentapeptide **6**. The substance melted above 290°; $[\alpha]_D^{25} = -98°$ ($c = 1.10$, CF_3COOH). – IR.: 3275, 1660 (shoulder), 1638, 1540. – NMR. (CF_3COOH): 5.1–4.05 (complex *m*, 5 α–CH, 2 NH–CH_2–S), 3.2 (*m*, 2 S–CH_2), 2.39 and 2.45 (2 CH_3CO), 2.1 (complex *m*), 1.76 (*d*, br.), 1.09 (*m*, CH_3). – MS.: ions at *m/e* = 588, 517 (Calc. $C_{22}H_{39}N_5O_5S_2$: 517.2393, Found: 517.2396).

$C_{28}H_{49}N_7O_7S_2$ (659.86) Calc. C 50.96 H 7.48 N 14.86% Found C 51.04 H 7.70 N 14.82%

Cyclo-(D-*Val*)-*Cys*-*Cys*-(D-*Val*)-*Leu* (**7**). The experimental conditions of *Marbach & Rudinger* [15] were followed to remove the S-protecting groups of the cyclic pentapeptide **6** and form the desired S-S-bridge to complete the synthesis of *enantio*-[1-valine]malformin (**7**). To a stirred solution of 0.132 g of **6** in 860 ml of CH_3OH and 290 ml of H_2O a solution of 0.130 g of I_2 in 210 ml of CH_3OH was added dropwise at room temp. over a period of 90 min. The reaction was allowed to proceed for 16 h and the mixture was then concentrated under reduced pressure to about 250 ml. The resulting aqueous, somewhat turbid solution was first extracted with 450 ml of ethyl acetate and then with two 300-ml portions of the same solvent. The organic extracts were washed with two 150-ml portions of a 1% aqueous sodium thiosulfate solution and then with two 150-ml portions of H_2O. The ethyl acetate extracts were dried over anhydrous $MgSO_4$, filtered, combined and concentrated under reduced pressure to about 7 ml. After cooling, the precipitated solid was collected on a filter and washed with three 1-ml portions of ethyl acetate. A first crop of the desired bicyclic compound **7** amounted to 0.032 g; concentration of the mother liquors resulted in the isolation of an additional 0.010 g of **7**, both samples melted above 290°.

A sample of the first crop was dried for analysis. – IR.: 3340, 3295, 1665, 1635 (shoulder), 1523. – *Raman*: 493 (S-S bridge). – MS.: *m/e* 515 (20.4%, M^+, Calc. for $C_{22}H_{37}N_5O_5S_2$: 515.2236, Found: 515.2256), *m/e* = 516 (6.0%, $M + 1$, Calc. 516.2269, Found: 516.2278).

$C_{22}H_{37}N_5O_5S_2$ (515.688) Calc. C 51.24 H 7.23 N 13.58% Found C 51.24 H 7.42 N 13.28%

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