The Synthesis of Pyrimido[4,5-*c*]pyridazines and Pyrido[2,3-*d*]pyrimidines Related to Toxoflavin and Fervenulin

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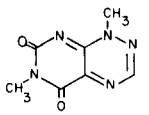
4-Deazatoxoflavin (1,6-dimethyl-1,5,6,7-tetrahydropyrimido[4,5-*c*]-5,7-pyridazinedione) (**7**) and several other 4-deazatoxoflavin and 4-deazafervenulin analogs have been prepared with the required intermediates. 3,5,7-Trimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione (**19**) and 8-phenyl-3,5,7-trimethyl-2,3,4,8-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione (**20**) were also prepared.

Toxoflavin (**1**), a toxic compound with antibiotic properties, was isolated from natural sources (3,4) and the toxicity and antibacterial activity have been disclosed (4,5). The structure elucidation (6-8) and the total synthesis (9) have been reported for toxoflavin. Fervenulin (**2**) was isolated (10) and the antibiotic properties were revealed (11). The structure proof and synthesis of fervenulin has been published (12,13). Thus it appeared of interest to us to prepare 4-deaza and 2,4-dideazatoxoflavin and fervenulin analogs.



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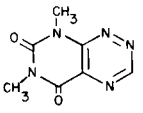

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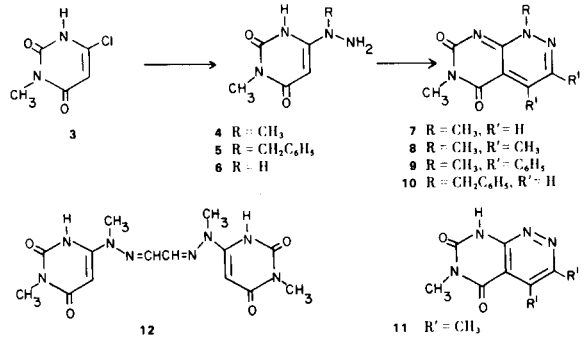
The first report of a pyrimido[4,5-*c*]pyridazine was that of Pfleiderer and Ferch (14) who synthesized 4-deazafervenulin among other compounds in this ring system by ring closure of the pyridazine ring on appropriately substituted pyrimidines, while Jones (15) cyclized the pyrimidine ring *via* the Hofmann reaction of pyridazinediamides. This latter reaction was studied by Nakagome, Castle and Murakami (16) who confirmed the structure of the pyrimido[4,5-*c*]pyridazine proposed by Jones (14) as well as isolated and characterized the alternate ring system, namely the pyrimido[5,4-*c*]pyridazine. Yanai, *et al.*, (17) have also reported on pyrimido[4,5-*c*]-pyridazines.

For the synthesis of the compounds in this paper, 6-chloro-3-methyluracil (**3**) (9) served as the starting material. Compound **3** reacted smoothly with methylhydrazine, benzylhydrazine and hydrazine to give **4**, **5** and **6**, respectively. When **4** was allowed to react with glyoxal (14) (Method A), 4-deazatoxoflavin (**7**) was obtained in 71% yield as well as a 20% yield of glyoxal-*bis*-(3-methyluracil-6-methylhydrazone) (**12**). By a modified procedure (Method B), the yield of **7** was improved to 92% without formation of byproduct **12**. Compound **4** when allowed to react with either 2,3-butanedione or benzil gave **8** and **9**, respectively. Furthermore, **5** with glyoxal gave **10**. Compound **11**, which can be considered to be 2,4-dimethyl-8-desmethyl-4-deazafervenulin, was obtained from **6** and 2,3-butanedione. These transformations are shown in Flow Sheet I.

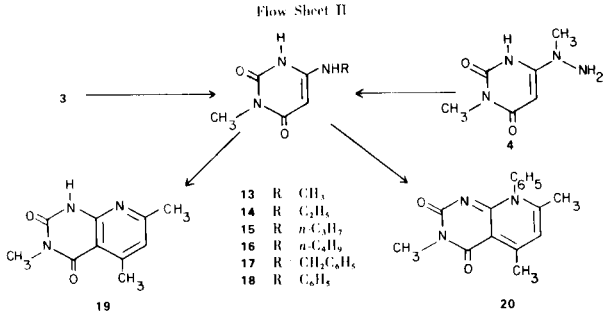
Flow Sheet I



The pyrido[2,3-*d*]pyrimidines have been reported by a number of investigators (18-25). We allowed 6-chloro-3-methyluracil (**3**) to react under pressure with a series of amines producing 6-alkylamino-3-methyluracils (**13**, **14**, **15**, **16** and **17**). 6-Methylamino-3-methyluracil (**13**) (26) was also prepared by the Raney nickel cleavage of 6-(α-methylhydrazino)-3-methyluracil (**4**) establishing unequivocally the α-hydrazino structure of **4**. When **3** was allowed to react with aniline, **18** was obtained. Using the method of Ridi, Checchi and Papini (22) **18** was condensed with 2,4-pentanedione to give 8-phenyl-3,5,7-trimethyl-2,3,4,8-teteahydropyrido[2,3-*d*]-2,4-pyrimidinedione (**20**). An attempt to prepare 8-benzyl-3,5,7-tri-

methyl-2,3,4,8-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione by reaction of **17** with 2,4-pentanedione resulted in loss of the benzyl group and gave the fervenulin analog, 3,5,7-trimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione (**19**). Compound **19** may be considered to be 2,4-dimethyl-8-desmethyl-2,4-dideazafervenulin. Similar attempts to condense the 6-alkylamino-3-methyluracils (**13**, **14**, **15** and **16**) with 2,4-pentanedione (22) or malonaldehyde tetramethyl acetal (25) failed. These transformations are shown in Flow Sheet II.

Flow Sheet II



4-Deazatoxoflavin (**7**) was inactive in broth dilution at 0.32 μmole/ml. or less against *E. coli* and *S. aureus*, but was active against *Pseudomonas* #586 at 0.08 μmole/ml. Compound **7** was inhibitory but not lethal (27). 4-Deazatoxoflavin (**7**) showed negative cytotoxicity at 10^{-4} *M* against mouse leukemia L-1210 (28), and was non-toxic at 50 mg./kg. in CF1 strain mice for seven days (29). Likewise compounds **8** and **11** were also non-toxic at 50 mg./kg. in CF1 strain mice for seven days (29). 4-Deazatoxoflavin (**7**) has been demonstrated to bind to herring sperm DNA (Cal Biochem. #2621) using the thermometric titration technique (30).

EXPERIMENTAL

Melting points were taken in capillary tubes in an electrically heated oil bath (Thomas-Hoover) and in a melting block for melting points above 300° and are uncorrected. The pmr spectra were obtained in trifluoroacetic acid and DMSO-d_6 on a Varian A-60 spectrometer and chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Infrared spectra were obtained in potassium bromide pellets on a Hilger-Watts Infragraph H1200 spectrometer. Ultraviolet spectra were recorded in 95% ethanol solutions except where noted on a Cary Model 14 recording spectrometer. Analytical samples were prepared by recrystallization from ethanol except where noted.

6-Chloro-3-methyluracil (**3**).

This compound was prepared from 2-thiobarbituric acid (Aldrich) by the method of Daves, Robins and Cheng (9).

6-(α-Methylhydrazino)-3-methyluracil (**4**).

This compound was prepared from 6-chloro-3-methyluracil by the method of Daves, Robins and Cheng (9).

6-(α-Benzylhydrazino)-3-methyluracil (**5**).

6-Chloro-3-methyluracil (**3**) (4.5 g.) was suspended in 40 ml. of 95% ethanol and 9.0 g. of benzylhydrazine (excess) was added. The mixture was allowed to reflux with stirring for 3 1/2 hours, evaporated to dryness and the remaining oily residue was dissolved in absolute ethanol followed by addition of absolute ether. The yield of the white precipitate was 2.6 g. (38%), m.p. 183-185°; ir cm^{-1}: 3190 and 3300 (-NH_2), 1685 (C=O), 1625 (C=O); pmr (DMSO-d_6): 3.13 δ (-NCH_3, singlet), 4.9 δ (C_5H, singlet), 6.64 δ (-NH_2 and -NH, broad singlet), 7.43 δ (phenyl, singlet).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.5; H, 5.7; N, 22.8. Found: C, 58.7; H, 5.5; N, 22.9.

6-Hydrazino-3-methyluracil (**6**).

This compound was prepared by the method of Zee-Cheng and Cheng (31).

1,6-Dimethyl-1,5,6,7-tetrahydropyrimido[4,5-*c*]-5,7-pyridazinedione (4-Deazatoxoflavin) (**7**). Method A.

The method of Pfleiderer and Ferch (14) was used with slight modification. To a boiling solution of 0.5 g. (2.9 mmoles) of 6-(α-methylhydrazino)-3-methyluracil (**4**) in 15 ml. of water was added dropwise 2.0 ml. (3.4 mmoles) of 40% aqueous glyoxal solution. There was an immediate precipitation of a red-brown solid. The precipitate was filtered and the filtrate was evaporated to dryness under reduced pressure, yield 0.4 g. (71%), m.p. 235-237° dec.; uv λ max (nm) (water, *p*H 1.7): 365 (ε, 4,360), 257 (ε, 15,100); pmr (TFA): 3.67 δ (N_1-CH_3, singlet), 4.73 δ (N_6-CH_3, singlet), 9.05 δ (C_4H, distorted doublet), 9.34 δ (C_3H, distorted doublet), $J_{3,4}$ = 4 Hz.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.0; H, 4.2; N, 29.2. Found: C, 50.4; H, 4.5; N, 28.9.

Glyoxal-*bis*-(3-methyluracil-6-methylhydrazone) (**12**).

The reddish-brown precipitate from the above reaction was washed with dimethylformamide, acetic acid, water and ethanol, respectively. This method was used because of the difficulty encountered in attempting recrystallization, yield, 0.2 g. (20%), m.p. 341-343°.

Anal. Calcd. for $C_{14}H_{20}N_8O_4$: C, 46.1; H, 5.5; N, 30.8. Found: C, 45.7; H, 5.6; N, 30.6.

1,6-Dimethyl-1,5,6,7-tetrahydropyrimido[4,5-*c*]-5,7-pyridazinedione (4-Deazatoxoflavin) (**7**). Method B.

This superior method of preparation of 4-deazatoxoflavin (**7**) was carried out by bringing 3 g. (17.6 mmoles) of 6-(α-methylhydrazino)-3-methyluracil (**4**) in 200 ml. of water to the boiling point followed by the addition all at once of 2.82 g. (19.4 mmoles) of 40% aqueous glyoxal. After three minutes at reflux temperature, a yellow precipitate began to form and the mixture was heated to reflux for an additional twenty minutes, then allowed to stand at 0° for about three hours. Upon filtration, 1.3 g. of light yellow solid solid was collected, m.p. 239-241° dec. The filtrate was continuously extracted with chloroform in a liquid-liquid extraction apparatus, the chloroform solution dried (anhydrous sodium sulfate) and the solvent removed under reduced pressure providing 1.9 g. of light yellow material, m.p. 239-240° dec. Tlc indicated both fractions were pure, total yield 3.2 g. (95%). Upon recrystallization from 95% ethanol, 3.1 g. (92%) of **7**, m.p. 239-241° dec., was obtained in two crops. This product was identical (uv and nmr) to that prepared by Method A.

1,3,4,6-Tetramethyl-1,5,6,7-tetrahydropyrimido[4,5-*c*]-5,7-pyridazinedione (**8**).

To a boiling solution (0.5 g., 0.003 mole) of 6-(α-methyl-

hydrazino)-3-methyluracil (**4**) in 15 ml. of water was added dropwise 0.6 g. (6 mmoles) of 2,3-butanedione. Upon cooling, yellow needles precipitated, yield 0.56 g. (84%), m.p. 235-237° dec.; uv λ max (nm) (95% ethanol): 325 (ε, 3,380), 277 (ε, 2,470); pmr (TFA): 2.84 δ (C_4, methyl singlet), 3.16 δ (C_3, methyl singlet), 3.58 δ (N_6, methyl singlet), 4.57 δ (N_1, methyl singlet); ir ν (cm^{-1}): 2950 (C-H), 1700 (C=O), 1650 (C=O), 1380 (C-H).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.5; H, 5.5; N, 25.4. Found: C, 54.4; H, 5.5; N, 25.6.

1,6-Dimethyl-3,4-diphenyl-1,5,6,7-tetrahydropyrimido[4,5-*c*]-5,7-pyridazinedione (**9**).

6-(α-Methylhydrazino)-3-methyluracil (**4**) (0.36 g., 2 mmoles) and 0.42 g. (2 mmoles) of benzil in 25 ml. of 2-methoxyethanol was refluxed overnight. Upon cooling, the yellow product which formed was filtered and dried, yield 0.17 g. (25%), m.p. 308-310°. The analytical sample was purified by recrystallization from 2-methoxyethanol; uv λ max (nm) (95% ethanol): 348 (ε, 5,030), 261 (ε, 16,290), 217 (ε, 15,590); pmr (TFA): 3.55 δ (N_6, ethyl singlet), 4.78 δ (N_1, methyl singlet), 7.02-7.64 δ (multiplet, phenyl); ir ν (cm^{-1}): 1700 (C=O), 1660 (C=O), 740 and 700 (mono-substituted benzene ring).

Anal. Calcd. for $C_{20}H_{16}N_4O_2 \cdot 1/2\ H_2O$: C, 68.0; H, 4.9; N, 15.9; Found: C, 67.7; H, 5.1; N, 15.6.

1-Benzyl-6-methyl-1,5,6,7-tetrahydropyrimiod[4,5-*c*]-5,7-pyridazinedione (**10**).

6-(α-Benzylhydrazino)-3-methyluracil (**5**) (0.5 g.) was dissolved in 25 ml. of warm absolute ethanol. Aqueous glyoxal (40%) (2.0 ml., 3.4 mmoles) was added dropwise until a white precipitate began to form. The solution was heated and then cooled and the precipitate filtered. The filtrate was evaporated to dryness leaving an oily residue which solidified when washed with acetone, combined yield, 0.29 g. (50%), m.p. 302-304°; ir ν (cm^{-1}): 1705 (C=O), 1625 (C=O); pmr (TFA): 3.6 δ (methyl, singlet), 5.33 δ (methylene, singlet), 6.9-7.66 δ (C_3H, C_4H, and phenyl, complex multiplet).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.7; H, 4.5; N, 20.9. Found: C, 62.2; H, 4.2; N, 20.9.

3,4,6-Trimethyl-5,6,7,8-tetrahydropyrimido[4,5-*c*]-5,7-pyridazinedione (**11**).

6-Hydrazino-3-methyluracil (**6**) (0.55 g., 3.5 mmoles) was dissolved in 60 ml. of hot ethanol. **2,3-Butanedione** (1 g., 11.6 mmoles) was added dropwise. The solution was brought to the boiling point. A white precipitate appeared immediately and the solution was allowed to cool. The precipitate was filtered, washed with cold ethanol and dried. Additional product was obtained upon concentration of the filtrate, yield 0.70 g. (97%), m.p. 261-263°; uv λ max (nm) (95% ethanol): 323 (ε, 13,540), 268 (ε, 10,980), 238 (ε, 13,950); pmr (TFA): 2.27 δ (C_4, methyl singlet), 2.79 δ (C_3, methyl singlet), 3.54 δ (N_6, methyl singlet), 6.37 δ (broad, NH); ir ν (cm^{-1}): 3200 (N-H), 1710 (C=O), 1680 (C=O), 1365 (C-H in CH_3).

Anal. Calcd. for $C_9H_{10}N_4O_2 \cdot H_2O$: C, 48.2; H, 5.4; N, 25.0. Found: C, 48.4; H, 5.3; N, 24.9.

6-Methylamino-3-methyluracil (**13**) (26).

6-(α-Methylhydrazino)-3-methyluracil (**4**) (1.0 g., 6.5 mmoles) was suspended in 100 ml. of absolute ethanol to which about 1.5 g. of Raney nickel catalyst was added and the mixture was hydrogenated at atmospheric pressure overnight. Removal of the catalyst and evaporation of the filtrate gave yellow crystals, yield, 0.6 g. (66%), m.p. 295-297° (Lit. (26), m.p. 290°). The analytical sample was recrystallized from ethanol and water (50% solution); ir ν (cm^{-1}): 3380 (-NH), 1700 (C_4 C=O), 1690 (C_2 C=O).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.9; N, 27.1. Found: C, 46.4; H, 5.8; N, 26.9.

General Procedure for the Preparation of 6-Substituted Amino-3-methyluracils.

6-Chloro-3-methyluracil (**3**) was allowed to react with a 10-15 molar excess of the requisite amine in a pressure bottle for three hours at about 30° above the boiling point of the corresponding amine. The sealed reaction mixture was allowed to cool overnight and the excess amine was evaporated leaving a solid residue which was recrystallized from 95% ethanol.

6-Methylamino-3-methyluracil (**13**) (26).

From 1 g. (6 mmoles) of **3** and 15 ml. of 40% aqueous methylamine, 0.41 g., (44%) of **13**, m.p. 295-297° (Lit. (26) m.p. 290°), was obtained; ir ν (cm^{-1}): 3380 (N-H), 1720 (C=O), 1690 (C=O).

6-Ethylamino-3-methyluracil (**14**).

From 2 g. (12 mmoles) of **3** and 7 g. of ethylamine, 1.9 g. (92%) of **14**, m.p. 276-278°, was obtained; ir ν (cm^{-1}): 3350 (-NH), 1705 (C_4 C=O), 1625 (C_2C=O).

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.7; H, 6.6; N, 24.8. Found: C, 49.5; H, 6.6; N, 24.7.

3-Methyl-6-*n*-propylaminouracil (**15**).

From 1 g. (6 mmoles) of **3** and 4.5 g. of *n*-propylamine, 0.25 g. (23%), m.p. 241-242.5°, of **15** was obtained; pmr (DMSO-d_6): [0.9 δ (triplet), 1.45 δ (multiplet), 3.04 δ (triplet) *n*-propyl], 3.11 δ (N_3 methyl singlet), 4.58 δ (C_5H, singlet), 5.87 δ (OH, singlet), 6.08 (broad NH); ir ν (cm^{-1}): 3310 (N-H), 3050 (=C-H, 1720 (C=O), 1640 (C=O), 1380 (C-H, in CH_3).

Anal. Calcd. for $C_8H_{13}N_3O_2 \cdot 1/2\ H_2O$: C, 50.0; H, 7.3; N, 21.9. Found: C, 50.0; H, 7.3; N, 22.0.

6-*n*-Butylamino-3-methyluracil (**16**).

From 1 g. (6 mmoles) of **3** and 7.95 g. of *n*-butylamine, 0.57 g. (48%), m.p. 232-233.5°, was obtained; pmr (DMSO-d_6): [0.9 δ (triplet), 1.44 δ (multiplet), 3.04 δ (triplet *n*-butyl], 3.32 δ (N_3, methyl, singlet), 4.6 δ (C_5, H, singlet), 6.02 δ (broad NH), 10.1 δ (broad OH); ir ν (cm^{-1}): 3250 (N-H), 3100 (=C-H), 1720 (C=O), 1640 (C=O).

Anal. Calcd. for $C_9H_{15}N_3O_2 \cdot 1/2\ H_2O$: C, 52.4; H, 7.8; N, 20.4. Found: C, 52.5; H, 8.0; N, 20.4.

6-Benzylamino-3-methyluracil (**17**) (26).

From 2 g. (12 mmoles) of **3** and 9 g. of benzylamine, 2.4 g. (75%), m.p. 302-304° (Lit. (26) m.p. sinters at 260°, completely melted at 282°) was obtained; pmr (TFA): 3.53 δ (N_3, methyl singlet), 4.66 δ (benzyl CH_2, singlet), 5.83 δ (C_5H singlet), 7.38 (phenyl, singlet); ir ν (cm^{-1}): 3250 (N-H), 3100 (=C-H), 2900 (C-H aliphatic), 1720 (C=O), 1640 (C=O).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.7; N, 18.2. Found: C, 62.6; H, 5.6; N, 18.2.

6-Anilino-3-methyluracil (**18**).

6-Chloro-3-methyluracil (**3**) (5 g., 30 mmoles) was added to 4 g. of aniline in ethanol with hydrochloric acid added to *p*H 4. The mixture was refluxed for 15-20 hours at 100°, with stirring, allowed to cool and a yellow precipitate was formed, yield, 2.8 g. (42%), m.p. 325-327°; ir ν (cm^{-1}): 3250 (-NH), 1725 (C=O), 1625 (C=O); pmr (TFA): 3.6 δ (methyl, singlet), 7.23-7.83 δ

(C_5H and phenyl, complex multiplet).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.1; N, 19.3. Found: C, 60.8; H, 5,1; N, 19.4.

8-Phenyl-3,5,7-trimethyl-2,3,4,8-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione (**20**).

6-Anilino-3-methyluracil (**18**) (0.5 g., 2.5 mmoles) was mixed with 1.4 g. of phosphorus pentoxide to which 10 g. (10 mmoles) of 2,4-pentanedione was added. The reaction mixture was refluxed for 1.5 hours. The brown residue was recrystallized from ethanol, after being washed with boiling water. The yield was 0.3 g. (42%), m.p. 280° dec; uv λ max (nm) (95% ethanol): 367 (ε, 8,530), 278 (ε, 8,000), 255 (ε, 11,760), 218 (ε, 17,935); pmr (TFA): 2.44 δ (C_5, methyl singlet), 3.13 δ (C_7, methyl singlet), 3.53 δ (N_3, methyl singlet), 7.62 δ (C_6, H); 7.38-7.95 (complex multiplet phenyl); ir ν (cm^{-1}): 3050 (=C-H), 1680 (C=O), 1640 (C=O), 1380 (C-H in CH_3), 760 and 700 (monosubstituted benzene ring).

Anal. Calcd. for $C_{16}H_{14}N_3O_2 \cdot 1/2\ H_2O$: C, 66.4; H, 5.2; N, 14.5. Found: C, 66.7; H, 5.3; N, 14.3.

3,5,7-Trimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione (**19**).

The procedure of Ridi, Checchi and Papini (22) was used to attempt to prepare 8-benzyl-3,5,7-trimethyl-2,3,4,8-tetrahydropyrido[2,3-*d*]-2,4-pyrimidinedione, however, **19** was obtained. 6-Benzylamino-3-methyluracil (**17**) (0.5 g., 2.5 mmoles) was mixed with 1.4 g. of phosphorus pentoxide to which 10 g. (10 mmoles) of 2,4-pentanedione was added. The reaction mixture was refluxed for 1.5 hours. The residue was washed with boiling water and recrystallized from ethanol, yield 0.2 g., (40%), m.p. 242-244° dec.; uv λ max (nm): 293 (ε, 6,570), 257 (ε, 2,150), 231 (ε, 4,310); pmr (TFA): 2.87 δ (C_5, methyl singlet), 3.12 δ (C_7, methyl singlet), 3.58 δ (N_3, methyl singlet) 7.45 δ (C_6, H singlet); ir ν (cm^{-1}): 3200 (N-H), 1730 (C=O), 1670 (C=O), 1380 (C-H).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4; N, 20.5. Found: C, 58.6; H, 5.6; N, 20.1.

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