Syntheses with Nitriles. 62 (1). 3,5-Dicyanopyridine Derivatives by Vilsmeier Formylation of Malononitrile and Tetracyanopropenides (2)

Martin Mittelbach and Hans Junek*

Institute of Organic Chemistry, Karl-Franzens-University of Graz, A-8010 Graz, Austria

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Reaction of malononitrile with dimethylformamide and phosphorus oxychloride gave (dimethylaminomethylene)malononitrile (**1**), 4-chloro-7-methyl-5,7-diaza-1,3,5-octatriene-1,1,3-tricarbonitrile (**3a**) and the pyridine **2**. Compounds **3a** and **3b** as well as the triaza-derivative **3c** may also be obtained by treatment of tetracyanopropenides **4a-c** with dimethylformamide and phosphorus oxychloride. Ring closures were achieved by heating **3** under alkaline or acidic conditions. Substitution of chlorine in **3a** with aromatic amines provided 1-aryl-1,2-dihydro-2-imino-3,5-pyridinedicarbonitriles **7**. Hydrolysis of **7** gave the 2-oxo-derivatives **8**.

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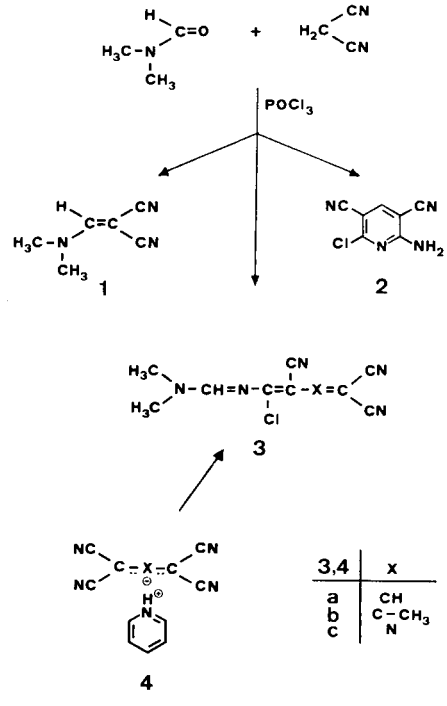
As we have shown in a previous paper (3) the reaction of (aminomethylene)malononitrile with *N,N*-dimethylformamide dimethylacetal leads to (dimethylaminomethylene)-malononitrile (**1**), which can also be prepared by simple condensation of malononitrile with dimethylformamide in the presence of acid chlorides (4,5).

Carrying out this reaction by using phosphorus oxychloride as the reagent, two other compounds in a ratio dependent on the reaction conditions were obtained in addition to the expected product. The colorless product was identified as 2-amino-6-chloro-3,5-pyridinedicarbonitrile (**2**) by comparing it with an authentic sample (6). The deep yellow product separated in a 17% yield. Analytical and spectroscopic data indicate two isomeric structures **3a** and **5b** are possible. In 1974 Kukhar and Pavlenko (7) obtained a compound of the same elemental composition as our yellow product by reaction of the potassium salt of 1,1,3,3-tetracyanopropene with dimethylformamide chloride, the so-called Vilsmeier reagent (8).

Kukhar favoured the structure of the noncyclised tricarbonitrile **3a** because of its physical properties, but did not give any further chemical evidence. However, **5b** can be excluded by an unambigous synthesis from **2**, dimethylformamide and phosphorus oxychloride. Compound **5b** is completely colorless and has different spectroscopic properties. Consequently, the only possible structure for the yellow product is that of 4-chloro-7-methyl-5,7-diaza-1,3,5-octatriene-1,1,3-tricarbonitrile (**3a**).

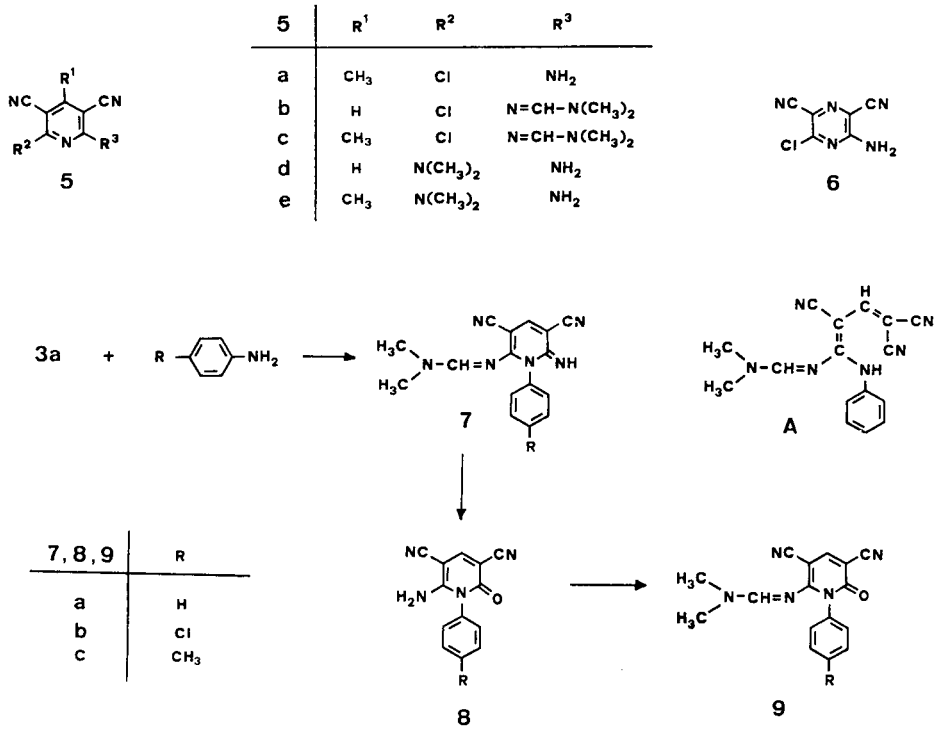
In 1966 Jutz and Müller (9) investigated the Vilsmeier formylation of malononitrile. By treating the latter with the Vilsmeier reagent they isolated (3-chloro-2-cyano-5-dimethylamino-4-aza-2,4-pentadiene-1-ylidene)dimethylammonium chloride. The structure of this compound differs from that of **3a** by exchange of the dicyanomethylene group for a dimethylammonium group.

Compound **3a** can also be prepared in a simple way by treating pyridinium-(1,1,3,3-tetracyanopropenide) (**4a**) (10) with dimethylformamide and phosphorus oxychloride. In the same way the C-methyl and the aza-analogue pyridinium salts **4b** and **4c** (10,11) led to compounds **3b** and **3c**. The advantage of this synthesis is to avoid the use of the hygroscopic Vilsmeier reagent in an additional step.



Moreover, the yield was very high. Compounds **3a-c** should be conveniant starting materials for the synthesis of heterocyclic compounds. Treating **3a-c** with concentrated hydrochloric acid led to the known pyridines **2** and **5a** as well as the pyrazine **6**. Heating **3a** and **3b** in alkaline solution gave 6-dimethylaminopyridines **5d** and **5e**, which may also be obtained from **2** and **5a** by reaction with dimethylamine. By heating **3a** and **3b** in acetic acid, the isomeric pyridines **5b** and **5c** were formed. This reaction involves a ring closure in combination with a subsequent reaction of the dimethylaminomethylene group.

Kukhar and Pavlenko (7) tried to substitute chlorine in **3a** for aniline at room temperature and obtained a reaction product with the assumed structure A. In opposition to that we found that reaction with anilines only takes place at higher temperature to produce 1-aryl-1,2-dihydro-2-imino-3,5-pyridinecarbonitriles **7a-c**. The ring-closed structure can be confirmed by ^{13}C-nmr data (see experimental). Hydrolysis of **7** in hydrochloric acid leads to



5	R^1	R^2	R^3
a	CH_3	Cl	NH_2
b	H	Cl	$N{=}CH{-}N(CH_3)_2$
c	CH_3	Cl	$N{=}CH{-}N(CH_3)_2$
d	H	$N(CH_3)_2$	NH_2
e	CH_3	$N(CH_3)_2$	NH_2

7,8,9	R
a	H
b	Cl
c	CH_3

the corresponding pyridones **8a-c**. This reaction involves hydrolysis of the amidine and the conversion of the imino group to a carbonyl group. By heating **8a** with *N,N*-dimethylformamide dimethylacetal dimethylformamide can be introduced again (**9a**).

EXPERIMENTAL

All melting points were taken on a Büchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 421 Spectrometer (potassium bromide). The pmr spectra were measured on a Varian A-60A instrument. A Varian HA-100 D spectrometer modified by Digilab Inc., was used to determine carbon -13 nmr spectra. The uv spectra were measured using a Hitachi 200 spectrophotometer. Mass spectra were obtained with a Varian MAT 111.

4-Chloro-7-methyl-5,7-diaza-1,3,5-octatriene-1,1,3-tricarbonitrile (**3a**).

a) From Malononitrile.

To a stirred and ice cooled solution of malononitrile (13.2 g 0.20 mole) in dimethylformamide (DMF) (43.8 g, 0.60 mole) phosphorus oxychloride (18.3 ml, 0.20 mole) was added dropwise. The ice bath was removed until the temperature rose to 50-60°. This temperature was maintained for 4 hours. The solution was poured on 100 g of crushed ice and neutralized by sodium hydrogen carbonate. The precipitate which resulted was filtered and recrystallized from DMF to give yellow needles of **3a** (4.0 g, 17%) mp 200° dec; ir: 2210 (CN) 1635 (C=N) cm^{-1}; uv (ethanol): λ max (log ε) 260 (3.8), 411 nm (4.6); ms: (80 ev) m/e 235 (35%), 233 (100%), 199 (12%), 198 (98%), 171 (18%), 157 (8%); no pmr due to decomposition in DMSO.

Anal. Calcd. for $C_{10}H_8ClN_5$ (233.7): C, 51.40; H, 3.45; Cl, 15.17; N, 29.97. Found: C, 51.22; H, 3.47; Cl, 15.19; N, 29.63.

b) From Pyridinium-(1,1,3,3-tetracyano-2-propene-1-ide) (**4a**).

To a stirred and ice cooled solution of **4a** (5.0 g, 22.6 mmoles) in 10 ml of DMF, phosphorus oxychloride (2.0 ml, 21.8 mmoles) was added dropwise. The solution was stirred at 20°, until a yellow precipitate was formed, then 20 ml of ice cooled water was added and the precipitate was filtered and dried to give **3a** (4.6 g, 87%).

4-Chloro-2,7-dimethyl-5,7-diaza-1,3,5-octatriene-1,1,3-tricarbonitrile (**3b**).

To a stirred and ice cooled solution of pyridinium-(1,1,3,3-tetracyano-2-methyl-2-propene-1-ide) (**4b**) (10) (2.35 g, 10.0 mmoles) in 10 ml of DMF-phosphorus oxychloride (1.53 g, 10.0 mmoles) was added dropwise. The solution was heated to 40° until a yellow precipitate was formed (5 minutes). After adding 20 ml of ice water the precipitate was collected and recrystallized from acetic acid to give **3b** (2.35 g, 95%), mp 220° dec; ir: 2220, 2200 and 2180 (CN), 1630 (C=N) cm^{-1}; pmr (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 3.11 (s, 3H, NCH_3), 3.31 (s, 3H, NCH_3), 7.97 (s, 1H, CH); uv (methanol); λ max (log ε) 265 (4.3), 410 nm (4.3).

Anal. Calcd. for $C_{11}H_{10}ClN_5$ (247.7): C, 53.34; H, 4.07; Cl, 14.31; N, 28.28. Found: C, 53.65; H, 4.10; Cl, 14.18; N, 28.32.

4-Chloro-7-methyl-2,5,7-triaza-1,3,5-octatriene-1,1,3-tricarbonitrile (**3c**).

Compound **3c** can be prepared by an analogous method to that for **3b** from pyridinium [dicyano(dicyanomethyleneamino)methanide] (**4c**) (11). Orange needles were obtained from acetone (71%), mp 205° dec; ir: 2220 (CN), 1640 (C=N) cm^{-1}; uv (methanol); λ max (log ε) (3.6), 392 nm (4.4).

Anal. Calcd. for $C_9H_7ClN_6$ (234.7): C, 46.07; H, 3.01; Cl, 15.11; N, 35.82. Found: C, 46.01; H, 3.03; Cl, 15.06; N, 35.88.

2-Amino-6-chloro-3,5-pyridinedicarbonitrile (**2**), 2-Amino-6-chloro-4-methyl-3,5-pyridinedicarbonitrile (**5a**), and 3-Amino-5-chloro-2,5-pyrazinedicarbonitrile (**6**).

A suspension of 10.0 mmoles each of **3a,b,c** in 20 ml of concentrated hydrochloric aicd was heated to 80° for 30 minutes. After cooling 30 ml of water was added and the precipitate was collected.

Compound **2**.

The residue was recrystallized from DMF giving 1.4 g (78%) of colorless needles, mp 200° sublimes (reported (6), mp 200° sublimes).

Compound **5a**.

The residue was recrystallized from DMF-water giving 1.7 g (90%) of colorless needles, mp 210° (reported (10), mp 210°).

Compound **6**.

The residue was recrystallized from ethanol-water giving 1.3 g (75%) of colorless crystals, mp 234° dec (reported (11), mp 234-236° dec).

2-Chloro-6-[(dimethylamino)methyleneamino]-3,5-pyridinedicarbonitrile (**5b**) and 2-chloro-6-[(dimethylamino)methyleneamino]-4-methyl-3,5-pyridinedicarbonitrile (**5c**).

a) From **2** and **5a**, respectively.

To a stirred and ice cooled solution of 10.0 mmoles of **2** and **5a**. respectively in 10 ml of DMF, phosphorus oxychloride (1.53 g, 10.0 mmoles) was added dropwise. The solution was heated to 70° for 1 hour. After cooling, 20 ml of ice cooled water was added slowly and the precipitate was filtered.

Compound **5b**.

The precipitate was recrystallized from DMF-water giving 1.4 g (69%) of colorless crystals, mp 206°; ir: 2240 (CN) cm^{-1}; pmr (DMSO-d_6): δ 3.13 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 8.41 (s, 1H, CH), 8.50 (s, 1H, N = CH-N).

Anal. Calcd. for $C_{10}H_8ClN_5$ (233.7): C, 51.40; H, 3.45; Cl, 15.17; N, 29.97. Found: C, 51.31; H, 3.43; Cl. 14.93; N, 29.88.

Compound **5c**.

The precipitate was recrystallized from DMF-water giving 1.7 g (67%) of colorless crystals, mp 280°; ir: 2220 (CN) cm^{-1}; pmr (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 3.05 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 8.47 (s, 1H, N = CH-N).

Anal. Calcd. for $C_{11}H_{10}ClN_5$ (247.7): C, 53.34; H, 4.07; Cl, 14.31; N, 28.28. Found: C, 53.27; H, 4.06; Cl, 14.51; N, 28.08.

b) From **3a** and **3b**, respectively.

Compound **5b**.

A solution of 10.0 mmoles of **3a** in 50 ml of acetic acid was heated under reflux for 4 hours. The solvent was destilled off and the residue was treated with 50 ml of water. The precipitate is collected to give 0.58 g (27%) of **5b**, mp 205°.

Compound **5c**.

A solution of 10.0 mmoles of **3b** in 50 ml of acetic acid was heated under reflux for 1 hour. On cooling a colorless precipitate separates, which was collected, yield 1.8 g (75%), mp 278°.

2-Amino-6-dimethylamino-3,5-pyridinedicarbonitrile (**5d**).

A solution of **3a** (2.33 g 10.0 mmoles) in 20 ml of 2*N* sodium hydroxide was heated under reflux for 20 minutes. The precipitate which formed on cooling was collected and recrystallized from DMF/water to give 1.3 g (54%) of **5d**, mp 169°.

Anal. Calcd. for $C_9H_9N_5$ (187.2): C, 57.74; H, 4.85; N, 37.41. Found: C, 57.42; H, 4.83; N, 37.04.

The ir spectroscopic data were identical with those of product obtained from **2** and dimethylamine (6).

2-Amino-6-dimethylamino-4-methyl-3,5-pyridinedicarbonitrile (**5e**).

A solution of **3b** (2.0 g, 8.1 mmoles) in 20 ml of 2*N* sodium hydroxide was heated under reflux for 20 minutes. The precipitate which formed on cooling was collected and recrystallized from DMF/water to give 1.0 g (61%) of **5e**, mp 198°.

Anal. Calcd. for $C_{10}H_{11}N_5$ (201.2): C, 59.69; H, 5.51; N, 34.80. Found: C, 59.25; H, 5.51; N, 34.37.

An authentic sample was isolated by reaction of **5a** and dimethylamine.

1-Aryl-1,2-dihydro-3,5-pyridinedicarbonitriles **7a-c**.

General Procedure.

A suspension of 10.0 mmoles of **3a** and 20.0 mmoles of the coresponding aniline in 70 ml of chloroform was heated under reflux for 1 hour. The product was obtained as a yellow precipitate which was collected after cooling and washed with 50 ml of water.

6-[(Dimethylamino)methyleneamino]-1,2-dihydro-2-imino-1-phenyl-3,-5-pyridinedicarbonitrile (**7a**).

Recrystallization from ethanol gave 2.0 g (69%) of **7a**, mp 200°; ir: 3340 (NH), 2230 and 2220 (CN) cm^{-1}; uv (ethanol): λ max (log ε) 394 (4.2), 287 (4.4), 238 nm (4.2); pmr (DMSO-d_6): δ 2.58 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3) 6.31 (broad, 1H, NH), 7.13-7.62 (m, 5H, phenyl), 7.98 (s, 1H, CH), 8.17 (s, 1H, N = CH-N).

Anal. Calcd. for $C_{16}H_{14}N_6$ (290.3): C, 66.19; H, 4.86; N, 28.95. Found: C, 66.02; H, 4.85; N, 29.10.

1-(4-Chlorophenyl)-6-[(dimethylamino)methyleneamino]-1,2-dihydro-2-imino-3,5-pyridinedicarbonitrile (**7b**).

Recrystallization from DMF/water gave 1.0 g (31%) of **7b**, mp 230° dec; ir: 3360 (NH), 2230 and 2210 (CN) cm^{-1}; uv (ethanol): λ max (log ε) 396 (4.2), 287 (4.6), 243 (4.3) nm; pmr (DMSO-d_6); δ 2.61 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 6.50 (broad, 1H, NH), 7.25 (d, 2H, phenyl), 7.58 (d, 2H, phenyl), 7.96 (s, 1H, CH), 8.13 (s, 1H, N = CH-N).

Anal. Calcd. for $C_{16}H_{13}ClN_6$ (324.8): C, 59.17; H, 4.03; Cl, 10.92; N, 25.87. Found: C, 58.99; H, 4.03; Cl, 11.17; N, 25.80.

6-[(Dimethylamino)methyleneamino]1,2-dihydro-1-imino-1-(4-methylphenyl)-3,5-pyridinedicarbonitrile (**7c**).

Recrystallization from ethanol gave 1.8 g (59%) of **7c**, mp 200°; ir: 3360 (NH), 2225 and 2220 (CN) cm^{-1}; uv (ethanol): λ max (log ε) 393 (4.2), 2.87 (4.4), 238 (4.2) nm; pmr (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.62 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 6.22 (broad, 1H, NH), 7.10 (d, 2H, phenyl), 7.38 (d, 2H, phenyl), 7.98 (s, 1H, CH), 8.17 (s, 1H, N = CH-N); ms: (80 eV) m/e 304 (43%), 303 (100%), 260 (40%), 149 (70%); ^{13}C-nmr (DMSO-d_6): δ 19.04 (s, toluene-CH_3), 32.68 (s, NCH_3), 38.18 (s, NCH_3), 78.52 (s, pyridine-C-3), 91.43 (s, pyridine-C-5), 114.59 (s, CN), 115.79 (s, CN), 126.46 (s, toluene-C-2), 127.90 (s, toluene-C-3), 132.34 (s, toluene-C-4), 136.17 (s; toluene-C-1), 147.66 (s, pyridine-C-4), 154.14 (s, N = CH-N), 158.32 (s, pyridine-C-2), 161.20 (s, pyridine-C-6).

Anal. Calcd. for $C_{17}H_{16}N_6$ (304.4): C, 67.09; H, 5.30; N, 27.61. Found: C, 67.52; H, 5.50; N, 27.86.

1-Aryl-1,2-dihydro-2-oxo-3,5-pyridinedicarbonitriles **8a-c**.

General Procedure.

Compounds **8a-c** were obtained by heating a solution of 10.0 mmoles of **7a-c** in 10 ml of 2N hydrochloric acid for 1 hour. The colorless precipitates formed in hot solution were collected.

6-Amino-1,2-dihydro-2-oxo-1-phenyl-3,5-pyridinedicarbonitrile (**8a**).

The residue was recrystallized from DMF-water giving 1.5 g (64%) of colorless crystals, mp 320°; ir: 3350 and 3260 (broad, NH_2), 2240 and 2230 (CN), 1705 (C = O) cm^{-1}; pmr (DMSO-d_6): δ 7.10-7.68 (m, 5H, phenyl), 7.80 (s, 2H, NH_2), 8.30 (s, 1H, CH).

Anal. Calcd. for $C_{13}H_8N_4O$ (236.2): C, 66.10; H, 3.41; N, 23.72. Found: C, 66.38; H, 3.39; N, 23.53.

6-Amino-1-(4-chlorophenyl)-1,2-dihydro-2-oxo-3,5-pyridine dicarbonitrile (**8b**).

The residue was recrystallized from acetic acid giving 1.0 g (37%) of colorless crystals, mp 295° dec; ir: 3360 and 3250 (broad, NH_2), 2250 and 2240 (CN), 1690 (C = O) cm^{-1}; ms: (80 eV) m/e 271 (24%), 270 (80%), 269 (56%), 244 (8%), 242 (24%), 207 (52%), 180 (24%), 111 (100%); too sparingly soluble for pmr.

Anal. Calcd. for $C_{13}H_7ClN_4O$ (270.7): C, 57.68; H, 2.61; N, 20.70. Found: C, 57.24; H, 2.46; N, 20.28.

6-Amino-1,2-dihydro-1-(4-methylphenyl)-2-oxo-3,5-pyridinedicarbonitrile (**8c**).

The residue was recrystallized from DMF-water giving 0.7 g (28%) of

colorless crystals, mp 290°; ir: 3370 and 3260 (broad, NH_2), 2250 and 2220 (CN), 1690 (C=O) cm^{-1}; pmr (DMSO-d_6): δ 2.49 (s, 3H, CH_3), 7.23 (d, 2H, phenyl), 7.43 (d, 2H, phenyl), 7.80 (s, 2H, NH_2),

Anal. Calcd. for $C_{14}H_{10}N_4O$ (250.3): C, 67.19; H, 4.03; N, 22.39. Found: C, 66.97; H, 4.00; N, 22.42.

6-[(Dimethylamino)methyleneamino]-1,2-dihydro-1-(4-methylphenyl)-2-oxo-3,5-pyridinedicarbonitrile (**9c**).

A suspension of **8c** (0.5 g, 2.0 mmoles) in dimethylformamide dimethylacetal (5.0 g, 42.0 mmoles) was heated under reflux for 2 hours. After addition of crushed ice the precipitate was filtered and recrystallized from ethanol to produce colorless needles (0.4 g 66%), mp 192°; ir: 2250 and 2240 (CN), 1680 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 2.40 (s, 3H, CH_3), 2.75 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 6.97 (d, 2H, phenyl), 7.28 (d, 2H, phenyl), 7.81 (s, 1H, CH), 8.00 (s, 1H, N=CH-N).

Anal. Calcd. for $C_{17}H_{15}N_5O$ (305.3): C, 66.87; H, 4.95; N, 22.94. Found: C, 66.49; H, 4.82; N, 22.72.

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