The Synthesis of Several Imidazo[4,5-*d*]isothiazoles. Derivatives of a New Ring System

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Dedicated to the memory of Dr. Roland K. Robins

Several derivatives of the new imidazo[4,5-*d*]isothiazole ring system have been synthesized from the appropriately substituted isothiazolediamines. The reaction of 3-methyl-4,5-diaminoisothiazole (**4a**) with diethoxymethyl acetate gave a low yield of 3-methylimidazo[4,5-*d*]isothiazole (**5a**). However, the analogous reaction of 4,5-diaminoisothiazole (**4b**) with diethoxymethyl acetate failed to yield the parent imidazo[4,5-*d*]isothiazole ring system. The diamines **4a** and **4b** were readily cyclized with thiocarbonyldiimidazole to give the unstable thiones **6a** and **6b**, which were alkylated *in situ* to afford good yields of the corresponding 5-methylthioimidazo[4,5-*d*]isothiazoles **7a** and **7b**, respectively. Neither of these compounds could be reduced to the corresponding 5-unsubstituted derivatives *via* treatment with Raney nickel. To the best of our knowledge, this is the first report of the imidazo[4,5-*d*]isothiazole ring system.

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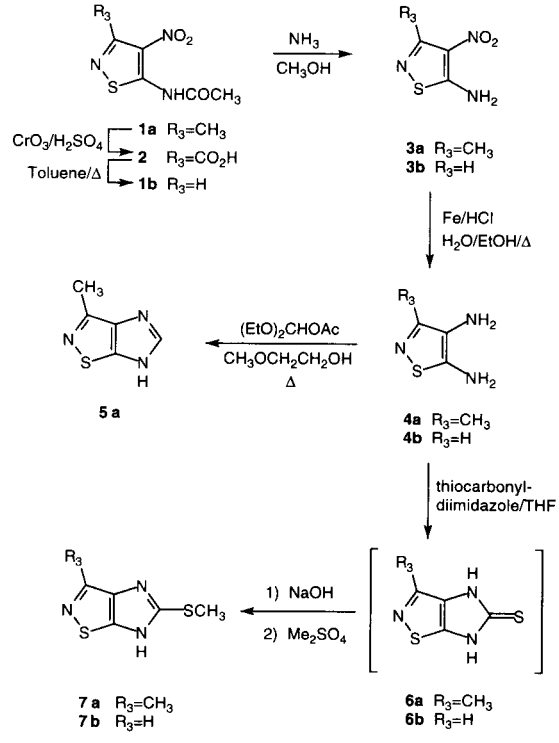
The purine ring system has been one of the most extensively investigated heterocyclic systems since its discovery as a key component of DNA and RNA, and a plethora of analogs and derivatives of the purine system have been reported. While many of these modifications have merely exchanged natural substituents for unnatural ones, such as in 6-mercaptopurine [1], which possesses antitumor and immunosuppressive properties, there are an equal number of compounds with modifications of the purine skeleton itself. Some examples having significant biological activity include 8-azaguanine [2,3], 2-azaadenine [4], several pyrazolopyrimidines [5-8], a series of pyrrolopyrimidines [9-12], and the nucleoside antibiotic oxanosine [13], which has an oxygen atom substituted for the N-1 of guanosine.

While modifications of purine have been extensive, they have for the most part conserved the 6:5 fused heterocyclic system of the purine ring. As part of our program to prepare a series of novel purine analogs, we were interested in a substitution of the C2-N3 linkage of the purine ring with a single atom, leading to a 5:5 fused ring system. A bivalent sulfur atom has often been compared to a -(CH = CH)- group in aromatic systems [14,15]. We have extended this analogy, and envisioned the imidazo[4,5-*d*]isothiazole ring system as an analog of purine, having the -(N = CH)- group in the pyrimidine ring of purine replaced with a sulfur atom. The resulting imidazo[4,5-*d*]isothiazole ring system should retain similar spatial characteristics relative to purine, but would be expected to have very different electronic characteristics, possibly leading to interesting biological properties.

A literature search revealed that very little was known about fully aromatic 5:5 fused heterocycles containing the isothiazole nucleus, and that the imidazo[4,5-*d*]isothiazole system was unknown. Toward our goal of studying the chemical and biological properties of these novel purine analogs, we investigated some strategies to prepare the imidazo[4,5-*d*]isothiazole ring system. There are two simple disconnections to the ring system, the first being the formation of the N-S bond of the isothiazole ring from an existing imidazole. The second route involves the ring closure of a 4,5-diaminoisothiazole derivative to give the

Scheme I. Synthesis of the imidazo[4,5-*d*]isothiazole ring system.



desired fused imidazole. The ring closure of *ortho* diamines is a strategy that has been well exploited in the synthesis of many fused imidazole containing systems, including purine analogs, and is the focus of this investigation.

A review of the literature established that 3-methyl-4,5-diaminoisothiazole [16] (**4a**, Scheme I) would be a suitable isothiazolediamine for initial studies, as it can be readily prepared from the commercially available 5-amino-3-methylisothiazole hydrochloride *via* 5-acetamido-3-methyl-4-nitroisothiazole [17] (**1a**). Furthermore, **1a** has been oxidized to the 3-carboxylic acid derivative **2** [16]. We found that **2** was readily decarboxylated in toluene at reflux to give 5-acetamido-4-nitroisothiazole (**1b**), which provided a route to 3-unsubstituted imidazo[4,5-*d*]isothiazole derivatives. The literature preparation of the diamine **4a** involved a catalytic reduction of compound **1a**, followed by deprotection with strong acid to give the dihydrochloride of **4a** in 54% yield from **1a**, and an unspecified yield of the free diamine. We found that the initial treatment of **1a** with methanolic ammonia, followed by a chemical reduction of the resulting 5-amino-4-nitroisothiazole **3a** gave the desired diamine **4a** in 95% overall yield. Similarly, deprotection of **1b** to afford 5-amino-4-nitroisothiazole (**3b**), was followed by a chemical reduction to yield 4,5-diaminoisothiazole (**4b**).

This procedure provided quantities of **4a** and **4b** sufficient to fully investigate their suitability for use in ring closing reactions. Initially, we attempted to obtain the desired imidazo[4,5-*d*]isothiazoles *via* a reaction with formate derivatives, which would provide a simple route to 5-unsubstituted derivatives. It was previously reported that the reaction of **4a** with diethoxymethyl acetate gave only 5-(4)amino-4(5)-(acetoxymethylene)aminoisothiazoles [16]. We were also unable to obtain any ring closed products at various temperatures with these conditions. The reaction of **4a** with triethylorthoformate, formamidine acetate, formic acid, as well as certain dimethylformamide derivatives gave similar unsuccessful results, even at high temperatures.

We next attempted to annulate the diamines **4a** and **4b** with a thiocarbonyl electrophile, assuming that the resulting 5-mercaptoimidazo[4,5-*d*]isothiazoles **6a** and **6b** could be desulfurized with Raney nickel. The reaction of **4a** with thiocarbonyldiimidazole in anhydrous THF gave a major product (by tlc) which decomposed upon attempts at isolation. On a small scale, this product was subjected immediately to column chromatography, and the eluant concentrated at 0° to yield a mixture of what appeared to be **6a** and an isothiocyanate, resulting from ring opening. This was inferred from the proton nmr spectrum (dimethyl sulfoxide-d_6) of the mixture, which contained singlets at δ 2.20 and 2.38 corresponding to the 3-methyl groups, broad singlets at δ 13.08 and 12.87 corresponding to the NH protons of **6a**, and another broad singlet at 7.30, assumed to be an amino peak of the decomposition product.

Since **6a** appeared to be stable in solution, we assumed that alkylation *in situ* would lead to a more stable compound, **7a**. This indeed proved to be the case, and a direct addition of methyl iodide to the reaction mixture gave low yields of **7a**. We subsequently found that it was far more efficient to make the sodium salt of **6a** by treatment with 1*M* sodium hydroxide, followed by alkylation with dimethylsulfate. This procedure has now provided multigram quantities of 3-methyl-5-methylthioimidazo[4,5-*d*]isothiazole (**7a**) in 60-70% yields. To the best of our knowledge, this is the first example of the imidazoisothiazole ring system. Similarly, reaction of **4b** under the same conditions afforded 5-methylthioimidazo[4,5-*d*]isothiazole (**7b**).

It is known that 2-mercaptoimidazoles, as well as the corresponding 2-alkylthioimidazoles are readily desulfurized by Raney nickel [18]. However, the application of this reaction to the imidazo[4,5-*d*]isothiazoles **7a** and **7b** failed under a variety of conditions, apparently opening the isothiazole ring to give monocyclic imidazoles as the only isolable products. The reaction of **7a** with Raney nickel (W-2 grade, Aldrich) resulted in the rapid formation of a major product (by tlc). This product had a dark green color, even after column chromatography, probably due to complexation with nickel cations generated by oxidation of the catalyst. Proton nmr spectra (dimethyl sulfoxide-d_6) of the crude material showed that the initial product formed retains two methyl groups (δ 2.33 and 2.50 ppm), indicating that the methylthio group had not been removed. An aromatic proton resonance is also evident at δ 7.57 ppm, presumably due to a reduction of the isothiazole sulfur atom. This implies that Raney nickel preferentially reduces the imidazo[4,5-*d*]isothiazole ring to afford imidazole products, and precludes the use of Raney nickel to obtain 5-unsubstituted compounds from the corresponding 5-alkylthio derivatives. Numerous attempts were made to purify this compound (chelex resin, treatment with acid or base, crystallization, and saturation with hydrogen sulfide), but all attempts failed.

The inability to desulfurize **7a** to afford the 5-unsubstituted imidazo[4,5-*d*]isothiazoles prompted us to re-investigate the ring closure of **4a** with formate derivatives. After many unsuccessful attempts, it was found that the reaction of **4a** and diethoxymethyl acetate in 2-methoxyethanol at 150° in a steel reaction vessel led to a mixture of products. A 27% yield of 3-methylimidazo[4,5-*d*]isothiazole (**5a**) was isolated from this mixture by chromatography. Unfortunately, the reaction of **4b** under similar conditions resulted in a complex reaction mixture, from which the parent imidazo[4,5-*d*]isothiazole ring system could not be isolated. An increase in the reaction temperature beyond

150° gave only intractable mixtures of decomposition products. The 3-methyl diamine **4a** would be expected to have a greater electron density than the corresponding 3-unsubstituted compound, due to the electron donating effects of the 3-methyl group. Apparently, this small difference is responsible for the unsuccessful preparation of imidazo[4,5-*d*]isothiazole from 4,5-diaminoisothiazole (**4b**).

In summary, the first members of the hitherto unknown imidazo[4,5-*d*]isothiazole ring system have been synthesized from substituted isothiazole diamines. This approach gave good yields of both the 3-methyl and 3-unsubstituted derivatives when thiocarbonyldiimidazole was utilized in the preparation of the 5-alkylthio derivatives **7a** and **7b**. However, the use of diethoxymethyl acetate gave only a low yield of 3-methylimidazo[4,5-*d*]isothiazole (**5a**), and did not effect formation of any imidazo[4,5-*d*]isothiazole. Derivatives bearing a 5-methylthio substituent cannot be desulfurized with Raney nickel due to the destruction of the isothiazole portion of the ring system. Investigations are continuing toward developing synthetic methods which will allow us to prepare imidazo[4,5-*d*]isothiazoles with more variability at the 3 and 5-positions of the ring, and we are exploring further the chemical and biological properties of this new ring system.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used as provided. Tetrahydrofuran (sodium/benzophenone), toluene (sodium/benzophenone), and methoxyethanol (calcium oxide) were distilled from the indicated drying agent, and stored over activated 4Å molecular sieves under positive pressure of argon prior to use. Methanolic ammonia was prepared by saturating methanol with anhydrous ammonia at 0°, and was stored at −15°. All reactions involving air sensitive material were conducted under an argon atmosphere. Evaporations were carried out under reduced pressure (water aspirator) on a rotary evaporator with a bath temperature of 35-40°, unless otherwise specified. All products were dried under reduced pressure (water aspirator) at 30-35° over phosphorous pentoxide to constant mass unless otherwise specified. Thin-layer chromatography (tlc) was run on Analtech 60F-254 silica gel plates, and detection of components on tlc was made by uv light absorption at 254 nm. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). Silica gel (32-63 mesh) was used for chromatography, which was carried out using the flash technique [19]. Melting points were taken on an Electrothermal IA9100 capillary melting point apparatus and are uncorrected. Samples which decomposed upon melting are denoted with (dec) following the decomposition temperature. Ultraviolet spectra were recorded on a Kontron 860 spectrophotometer. Infrared spectra were measured on a Perkin-Elmer infrared spectrometer. The ^{1}H nmr spectra (300 or 360 MHz) were obtained on Bruker instruments. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Elemental analyses were performed by University of Michigan Chemistry Department analyses laboratory.

5-Acetamido-4-nitroisothiazole (**1b**).

A suspension of 5-acetamido-4-nitroisothiazole-3-carboxylic acid [16] (4.83 g, 21 mmoles, **2**) in dry toluene (210 ml) was heated at reflux for 2 hours, at which point all the solid had dissolved, and gas evolution had ceased. The solvent was removed, and the residue dried to yield 3.92 g (100%) of crude **1b**, mp 141-143°. This material was of sufficient purity for use in further reactions. A 1.64 g portion of the crude product was recrystallized from ethanol to yield 1.39 g (85%) of **1b** as plates, mp 144-145.5°; tlc (2% methanol/chloroform): R_f = 0.67; ir (potassium bromide): ν 3300 (NH), 1703 (C=O), 1540 (NO_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.92 (broad s, 1H), 8.89 (s, 1H), 2.46 (s, 3H).

Anal. Calcd. for $C_5H_5N_3O_3S$: C, 32.09; H, 2.69; N, 22.45. Found: C, 32.25; H, 2.61; N, 22.45.

5-Amino-3-methyl-4-nitroisothiazole (**3a**).

In one portion, 5-acetamido-3-methyl-4-nitroisothiazole [17] (28 g, 0.14 mole, **1a**) was added to 500 ml of methanolic ammonia at 0° in a 1000 ml plastic bottle with a screw cap. The bottle was sealed tightly, and the solution was allowed to warm to room temperature over 18 hours. The solvent was removed *in vacuo*, and the residue recrystallized from absolute ethanol then dried *in vacuo* to yield 20 g (90%) of **3a**, mp 180-182°. A second crop gave an additional 2 g (9%), mp 177-179°, lit [17] mp 185-186°; tlc (30% ethyl acetate/hexane): R_f = 0.37; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.76 (broad s, 2H), 2.46 (s, 3H).

5-Amino-4-nitroisothiazole (**3b**).

Crude 5-acetamido-4-nitroisothiazole (1.64 g, 8.7 mmoles, **1b**) was added to 80 ml of methanolic ammonia cooled with an ice bath. The solution was sealed in a pressure bottle, and allowed to stir at room temperature for 24 hours. The solution was cooled to 0°, and the solid collected by filtration, and dried to yield 1.02 g (80%) of **3b** as a light orange powder, mp 248-249°. The filtrate was concentrated, and the residue recrystallized from ethanol to yield an additonal 0.24 g (19%) of **3b** as plates, mp 249-250°; tlc (5% methanol/chloroform): R_f = 0.50; ir (potassium bromide): ν 3280-3190 (NH_2), 1612 (NO_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.80 (broad s, 2H), 8.58 (s, 1H).

Anal. Calcd. for $C_3H_3N_3O_2S$: C, 24.83; H, 2.08; N, 28.95. Found: C, 24.70; H, 2.24; N, 29.12.

4,5-Diamino-3-methylisothiazole (**4a**).

Iron powder (16.8 g, 300 mmoles) was added to a solution of 5-amino-3-methyl-4-nitroisothiazole (**3a**, 7.96 g, 50 mmoles) in 500 ml of 50% aqueous ethanol (v/v %). To the rapidly stirred suspension was added 1*M* hydrochloric acid (12.5 ml), and the suspension was heated at reflux for 1 hour in the dark under an inert atmosphere. Heating was discontinued, the reaction was allowed to cool 5 minutes, and 50 ml of Dowex-2($^-$OH) was added. The mixture was stirred for 0.5 hour, filtered through Celite, and the filter cake was washed with warm ethanol (500 ml). The combined filtrates were concentrated in the dark to a small volume (not to dryness), and the resulting solution was lyophilized in the dark to yield 6.19 g (96%) of **4a**. This solid decomposes to colored products upon exposure to light, but can be stored indefinitely in the freezer (−15°), mp 121.5-123°, lit [16] mp 123°; tlc (10% methanol/chloroform): R_f = 0.41; ^{1}H nmr (dimethyl sulfoxide-d_6): δ

5.54 (s, 2H), 3.65 (s, 2H), 2.08 (s, 3H).

Anal. Calcd. for $C_4H_7N_3S$: C, 37.19; H, 5.46. Found: C, 37.19; H, 5.30.

4,5-Diaminoisothiazole (**4b**).

Iron powder (3.90 g, 70 mmoles) was added to a solution of 5-amino-4-nitroisothiazole (**3b**, 1.69 g, 11.6 mmoles) in 100 ml of 50% aqueous ethanol (v/v %). To the rapidly stirred suspension was added 1 *M* hydrochloric acid (2.5 ml), and the suspension was heated at reflux for 1 hour in the dark under an inert atmosphere. Heating was discontinued, the reaction was allowed to cool 5 minutes, and 12 ml of Dowex-2 ($^-$OH) was added. The mixture was stirred for 0.5 hour, filtered through Celite, and the filter cake was washed with warm ethanol (100 ml). The combined filtrates were concentrated in the dark to a small volume (not to dryness), and the resulting solution was lyophilized in the dark to yield 1.12 g (84%) of **4b**. This solid decomposes to colored products upon exposure to light, but can be stored indefinitely in the freezer (−15°), mp 128-128.5°; tlc (5% methanol/chloroform): R_f = 0.29; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.66 (s, 1H), 5.60 (bs, 2H), 3.85 (bs, 2H).

Anal. Calcd. for $C_3H_5N_3S$: C, 31.29; H, 4.38; N, 36.49. Found: C, 31.60; H, 4.36; N, 36.84.

3-Methylimidazo[4,5-*d*]isothiazole (**5a**).

To 4,5-diamino-3-methylisothiazole (**4a**, 1 mmole, 129 mg) in methoxyethanol (10 ml) at 80° was added diethoxymethyl acetate (0.17 ml, 1.05 mmoles) dropwise over 2 minutes. The resulting solution was stirred 2 hours at 80°, then heated 2 hours at 150° in a sealed vessel. After cooling to room temperature, the solution was poured into water (20 ml) containing 85 mg (1 mmole) of sodium bicarbonate, and the suspension was allowed to stand at 5° overnight. The solid residue was removed by filtration, and the precipitate washed with water (2 x 5 ml). The combined filtrates were concentrated *in vacuo*, taken up in 1:1 methanol/chloroform, then adsorbed onto 1.5 g sodium sulfate. This residue was applied to a column and chromatographed (2 x 20 cm, 5% methanol/chloroform). Fractions containing only **5a** by tlc analysis were combined, 5 ml water was added, and the resulting mixture was concentrated *in vacuo* until a homogeneous solution was obtained. The resulting aqueous solution of **5a** was lyophilized to obtain 37 mg (27%) of a yellow powder, mp 135-136°; tlc (10% methanol/chloroform): R_f = 0.46; uv (ethanol): λ max 250 nm (ε 9,500); (*p*H 1): λ max 247 nm (ε 8,200); (*p*H 11): λ max 259 nm (ε 10,100); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.98 (broad s, 1H), 8.12 (s, 1H), 2.50 (s, 3H); ms (electron impact) m/z 139 (M^+); hrms (electron impact) Calcd. for $C_5H_5N_3S$: 139.0204. Found: 139.0209.

Anal. Calcd. for $C_5H_5N_3S$: C, 43.15; H, 3.62; N, 30.19. Found: C, 43.45; H, 3.67; N, 29.82.

3-Methyl-5-methylthioimidazo[4,5-*d*]isothiazole (**7a**).

To a solution of 4,5-diamino-3-methylisothiazole (**4a**, 3.00 g, 23.2 mmoles) in dry tetrahydrofuran (100 ml) under an argon atmosphere at room temperature was added thiocarbonyldiimidazole (4.35 g, 24.4 mmoles) in one portion, and the solution was stirred at room temperature for 0.5 hour. Water (200 ml) was added and the solution stirred for one minute, after which 1 *M* sodium hydroxide (26 ml) was added. After stirring for another minute, dimethyl sulfate (2.31 ml, 24.4 mmoles) was added dropwise, and the solution stirred for 0.5 hour at room temperature. The solution was then poured into ethyl acetate (300 ml), the layers were separated, and the aqueous layer extracted with ethyl acetate (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was chromatographed (chloroform to 2% methanol/chloroform, 5 x 35 cm) to yield an orange oil. This oil was taken up in ethanol (50 ml), diluted with 75 ml of water, concentrated to about 80 ml total volume, and then allowed to stand at 0°. The resulting solid was collected, washed with cold water and dried at room temperature in a desiccator at atmospheric pressure to yield 2.86 g (67%) of **7a**, mp 145-146°; tlc (10% methanol/chloroform): R_f = 0.46; uv (ethanol): λ max 254 nm (ε 14,500), 275 (18,600); (*p*H 1): λ max 239 nm (ε 9,400), 272 (13,400); (*p*H 11): λ max 249 nm (ε 8,900), 285 (13,000); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 13.12 (bs, 1H), 2.66 (s, 3H), 2.46 (s, 3H); ms (electron impact) m/z 185 (M^+), 170, 152, 102; hrms (electron impact) Calcd. for $C_6H_7N_3S_2$: 185.0081. Found: 185.0078.

Anal. Calcd. for $C_6H_7N_3S_2$: C, 38.89; H, 3.81; N, 22.69. Found: C, 38.55; H, 3.93; N, 22.49.

5-Methylthioimidazo[4,5-*d*]isothiazole (**7b**).

To a solution of 4,5-diaminoisothiazole (**4b**, 115 mg, 1 mmole) in dry tetrahydrofuran (5 ml) under an argon atmosphere at room temperature was added thiocarbonyldiimidazole (187 mg, 1.05 mmoles) in one portion, and the solution was stirred at room temperature for 1 hour. Water (10 ml) was added and the solution stirred for one minute, after which 1 *M* sodium hydroxide (1.05 ml) was added. After stirring for another minute, dimethyl sulfate (0.10 ml, 1.05 mmoles) was added dropwise, and the solution stirred for 1 hour at room temperature. The solution was diluted with 15 ml of water, then extracted with ethyl acetate (3 x 10 ml). The combined organics were washed with brine (10 ml), dried over magnesium sulfate, filtered, and concentrated *in vacuo* onto sodium sulfate (1.7 g), then chromatographed (chloroform to 2% methanol/chloroform, 2 x 20 cm). Fractions containing only **7b** (by tlc) were combined and concentrated to give 98 mg (57%) of crude **7b**, mp 153-153.5° dec, which contained no detectable impurities by tlc or nmr. A portion of this material was recrystallized from aqueous 1,4-dioxane to yield light yellow prisms, mp 155-155.5° dec; tlc (5% methanol/chloroform): R_f = 0.49; uv (ethanol): λ max 246 nm (ε 9,300), 278 (13,300); (*p*H 1): λ max 273 nm (ε 14,300); (*p*H 11): λ max 247 nm (ε 8,200), 288 (11,100); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 13.15 (bs, 1H), 8.48 (s, 1H), 2.67 (s, 3H).

Anal. Calcd. for $C_5H_5N_3S_2$: C, 35.07; H, 2.94; N, 24.54. Found: C, 35.13; H, 3.00; N, 24.67.

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