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SYNTHESIS OF SUBSTITUTED 1,2,4-TRIAZINES BASED ON 1,2-BIS(2,5-DIMETHYL-3-THIENYL)ETHANEDIONE

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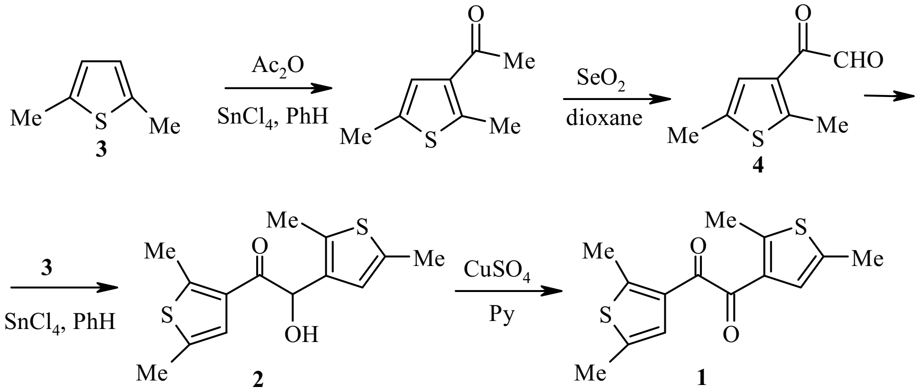
A novel, convenient method has been developed for the synthesis of 1,2-bis(2,5-dimethyl-3-thienyl)ethanedione, from which were prepared 5,6-bis(2,5-dimethyl-3-thienyl)-1,2,4-triazines (analogs of the photochromic 1,2-diarylethenes). The principial possibility of using 1,2,4-triazines obtained as photochromic agents was investigated.

Keywords: 1,2-diarylethenes, α-diketone, 1,2-dithienylethenes, 1,2,4-triazines, photochromes.

1,2,4-Triazines have been relatively little studied but, none the less, they are extremely promising in the search for novel biologically active compounds. Amongst these derivatives there are known highly efficient pesticides (metribuzin, metamitron etc.) and pharmaceutical compounds [1].

One of the classical methods for the synthesis of 1,2,4-triazines is based on the use of α-diketones [1] and allows one to prepare 1,2,4-triazines containing different substituents in positions 5 and 6 (previously introduced at the stage of synthesis of α-diketone). The aim of our work was to synthesize some previously unreported 3-substituted 5,6-di(2,5-dimethyl-3-thienyl)-1,2,4-triazines based on 1,2-bis(2,5-dimethyl-3-thienyl)ethanedione (**1**) [2]. The latter was prepared according to:

Scheme 1



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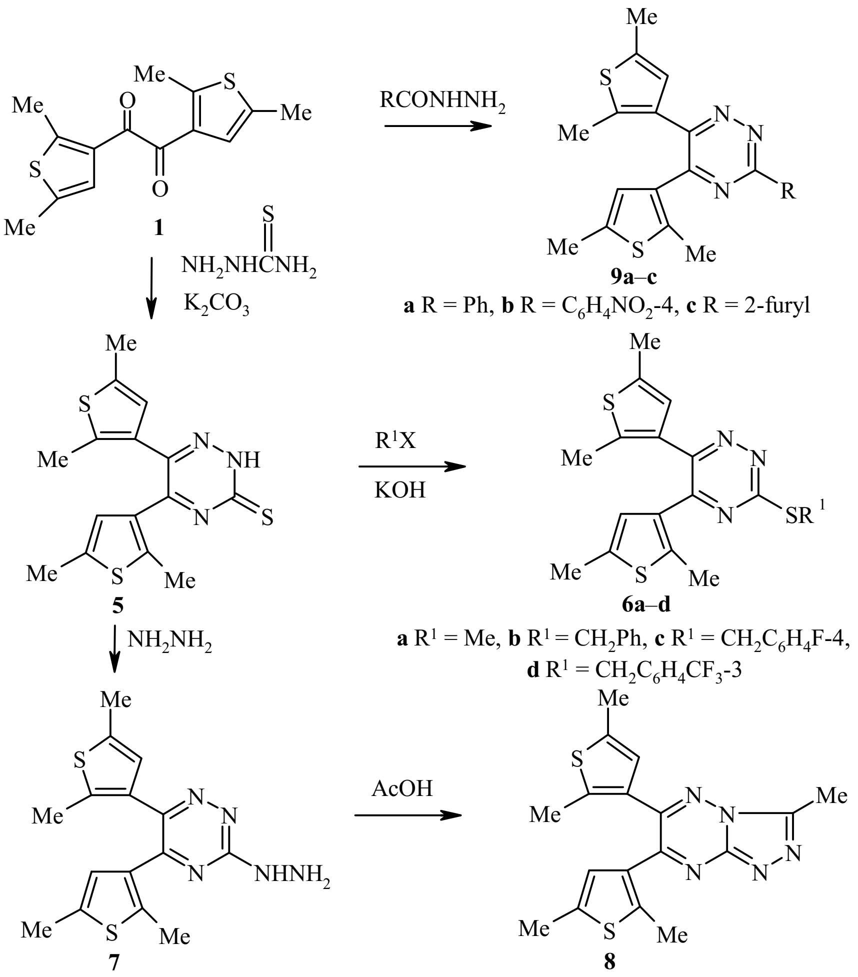
The synthesis of the intermediate acyloin **2** was achieved according to the basic scheme reported in the literature [3]. We have developed a new method to prepare the starting 2,5-dimethylthiophene (**3**). In contrast to the method for preparation of 2,5-dimethylthiophene well known in the literature *via* treatment of hexane-2,5-dione with phosphorus pentasulfide under quite severe conditions and without solvent [4], we have carried out the reaction of these components in carbon tetrachloride. This significantly eases the separation of the target material. Compound **4** was obtained as a hydrate and was used for further reactions without additional purification. The formation of acyloin **2** and its oxidation using $CuSO_4$ to the target diketone occurs in quantitative yield.

Compound **1** was used in the synthesis of various 5,6-dithienyl-1,2,4-triazines according to Scheme 2.

Scheme 2



Hence condensation of α-diketone **1** with semicarbazide in the presence of potassium carbonate without separation of the intermediate thiosemicarbazone formed gave 1,2,4-triazine-3-thione (**5**) in high yield. The action of various alkylating reagents on the latter in basic medium gives the corresponding 3-alkylthio-1,2,4-triazines **6a-d**. The conditions for carrying out the reaction depend significantly on the nature of the alkylating agent (see also [5]). Alkylation using methyl iodide occurs in water but for benzyl bromide and its 4-F and 3-CF_3 substituted derivatives it is performed in DMF. The thioxo group in position 3 of the triazine ring is readily substituted by the hydrazine function upon refluxing a solution of thione **5** in alcohol with excess

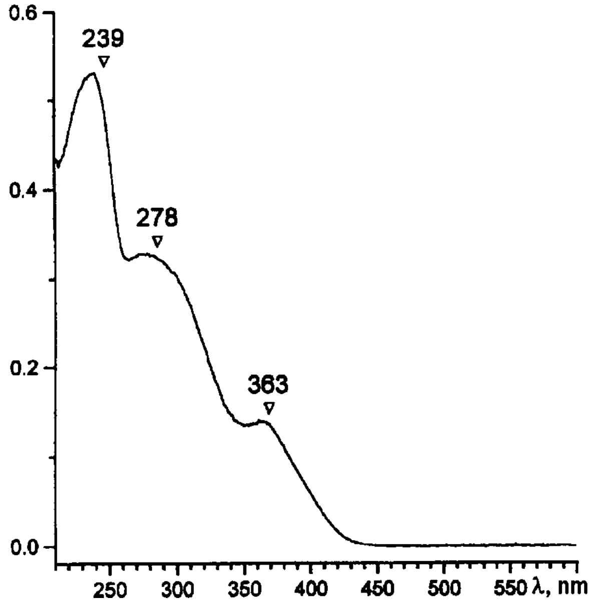


Fig. 1. Absorption spectrum of
5,6-bis(2,5,-dimethyl-3-thienyl)-2,3-dihydro-1,2,4-triazine-3-thione (**5**) in acetonitrile.

hydrazine hydrate, as has been observed previously in other examples [6]. By analogy with the previous work [7], hydrazine **7** formed is, in its turn, cyclized using excess acetic acid to form the substituted triazolotriazine **8**. Condensation of α-diketone **1** with aromatic carboxylic acid hydrazides in acetic acid in the presence of ammonium acetate gives 3-aryl-1,2,4-triazines **9** in 51-60% yields.

Because of the structural similarity of the synthesized 5,6-bis(2,5-dimethyl-3-thienyl)-1,2,4-triazines with photochromic dihetarylethenes [8] we carried out a photochemical study of solutions of compounds **5-9** in acetonitrile. The characteristic spectrum of compound **5** is given in Figure 1.

In the absorption spectrum described in the literature for 3,5,6-triphenyl-1,2,4-triazine there are present three absorption bands at 227, 261, and 386 nm. The first two bands are evidently due to π-π^* transitions and the less intense third band to n-π^* transitions [1]. In the absorption spectra of triazines **5-9** synthesized by us there are also three groups of bands at 220-250, 260-290, and 340-380 nm (Table 1).

TABLE 1. Absorption Spectra Bands for Substituted 5,6-Bis(2,5-dimethyl-3-thienyl)-1,2,4-triazines (**5-9**)

Compound	Absorption spectra bands, nm		
	first group	second group	third group
5	239	278	363
6	225, 250	270	365
7	238	272	359
8	229	270	370
9a	219, 250	270	345 sh
9b	227	284	350 sh
9c	230	300	

It is noted overall that the differences in the structure of 1,2,4-triazines **5-9** markedly influences the position of the bands in the absorption spectra but this does not distort these spectra and, obviously, points to the uniform nature of the conjugation between the triazine and thiophene rings.

A change in structure of 1,2,4-triazines **5-9** does not occur under the influence of UV irradiation, i.e. they are not photochromes while the bisthienylazoles (photochromic analogs of diarylethenes [9]) exhibit photochromic properties [10].

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker AM-300 and WM-250 instruments using DMSO-d$_6$ or CDCl$_3$ solvent. The melting points were measured on a Boetius heating stage and are not corrected. Analysis of the reaction mixtures and control of the purity of the products were carried out using TLC on Silufol UV-254 plates with ethyl acetate-hexane as eluent. Irradiation of the samples was carried out with a DRS-500 mercury lamp using light filters to separate the mercury lines in the spectrum (313 and 365 nm). The irradiation intensity of the mercury lamp was determined using a F$_4$ filter photocell which was calibrated using a ferrioxalate actinometer [11]. Absorption spectra were recorded on a Shimadzu UV-2101PC spectrophotometer. For determining the quantum yield, a solution of the material was irradiated with λ = 313 and 365 nm light.

2,5-Dimethylthiophene (3). Phosphorus pentasulfide (36.25 g, 0.16 mol) was added to a solution of acetonylacetone (47.08 g, 0.41 mol) in CCl$_4$ (70 ml) and the mixture obtained was refluxed for 4 h with vigorous stirring. The reaction product was cooled, the precipitate filtered off, and the filtrate distilled collecting the fraction with bp 133-135°C. Product **3** was obtained (35.21 g, 76%); n_D^{20} = 1.5127, lit. n_D^{20} = 1.5120 [4].

2-(2,5-Dimethyl-3-thienyl)-2-oxoacetaldehyde (4). 2,5-Dimethyl-3-acetylthiophene (8.18 g, 0.053 mol) (sythesized as reported in method [12]) was added to a solution of selenium dioxide (5.89 g, 0.053 mol) in dioxane (45 ml) and water (2 ml) at 60°C. The obtained mixture was refluxed with stirring for 3 h, filtered and the filtrate was evaporated in vacuo. The residue was crystallized from water to give **4** as the crystallohydrate (6.11 g, 62%); mp 135-137°C.

1,2-Bis(2,5-dimethyl-3-thienyl)-2-hydroxy-1-ethanone (2). A solution of SnCl$_4$ (2.61 g, 0.01 mol) in benzene (20 ml) was added dropwise with stirring to a solution of glyoxal hydrate **4** (1.89 g, 0.01 mol) and 2,5-dimethylthiophene **3** (1.23 g, 0.011 mol) in benzene (50 ml). The mixture obtained was held at room temperature for 3 h and then carefully poured into water (50-60 ml) and extracted with ether (3 × 20 ml). The extract was washed with water, sodium carbonate solution, and water, dried with MgSO$_4$ and evaporated. The residue was crystallized from acetic acid to give acyloin **2** (2.5 g, 95%); mp 135-137°C. ^{1}H NMR spectrum (CDCl$_3$), δ, ppm, J (Hz): 2.31 (3H, s, CH$_3$); 2.32 (3H, s, CH$_3$); 2.50 (3H, s, CH$_3$); 2.73 (3H, s, CH$_3$); 4.43 (1H, d, J = 5.9, OH); 5.52 (1H, d, J = 5.9, OCH); 6.32 (1H, s, H$_{\text{Het}}$); 6.68 (1H, s, H$_{\text{Het}}$). Found, %: C 59.81; H 5.70; S 22.69. $C_{14}H_{16}O_2S_2$. Calculated, %: C 59.97; H 5.75; S 22.87.

1,2-Bis(2,5-dimethyl-3-thienyl)ethanedione (1). A solution of benzoin **2** (3.41 g, 0.012 mol) in pyridine (10 ml) was added to a solution of copper (II) sulfate pentahydrate (26 g, 0.104 mol) in pyridine (26 ml) and water (20 ml). The mixture was heated with stirring at 70-80°C on a water bath for 2 h. The product was extracted with ether (3 × 15 ml) and the extract was washed with HCl solution (10%), water, dried over MgSO$_4$, and evaporated. The residue was crystallized from acetic acid to give diketone **1** (3.14 g, 93%); mp 64-65°C (lit. mp 64.5-65.5°C [2]).

5,6-Bis(2,5-dimethyl-3-thienyl)-2,3-dihydro-1,2,4-triazine-3-thione (5). A mixture of diketone **1** (0.56 g, 0.002 mol) in ethanol (5 ml) and thiosemicarbazide (0.18 g, 0.002 mol) was refluxed for 30 min. K$_2$CO$_3$ (0.55 g, 4 mmol) was added to the reaction mixture which was then cooled, diluted with water, and acidified with acetic acid. The precipitate was filtered off and washed on the filter with a small amount of ethanol to give triazinethione **5** (0.62 g, 93%); mp 175-177°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.00 (3H, s, CH$_3$); 2.12 (3H, s, CH$_3$); 2.20 (3H, s, CH$_3$); 2.35(3H, s, CH$_3$); 6.20 (1H, s, H$_{\text{Het}}$); 6.62 (1H, s, H$_{\text{Het}}$). Found, %: C 54.02; H 4.53; N 12.60; S 28.55. $C_{15}H_{15}N_3S_3$. Calculated, %: C 54.02; H 4.53; N 12.60; S 28.84.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-methylthio-1,2,4-triazine (6a). Methyl iodide (0.10 g, 0.65 mmol) was added to a solution of thione **5** (0.20 g, 0.61 mmol) and NaOH (0.08 g, 0.002 mol) in water (3 ml) and the reaction mixture was stirred at room temperature for 3 h. The precipitate was filtered off and washed on the filter with a small amount of ethanol to give the product **6a** (0.195 g, 92%); mp 110-112°C. ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 2.15 (3H, s, CH$_3$); 2.31 (3H, s, CH$_3$); 2.32 (3H, s, CH$_3$); 2.40 (3H, s, CH$_3$); 2.70 (3H, s, SCH$_3$); 6.42 (1H, s, H$_{\text{Het}}$); 6.55 (1H, s, H$_{\text{Het}}$). Found, %: C 55.05; H 4.89; N 12.27; S 27.55. $C_{16}H_{17}N_3S_3$. Calculated, %: C 55.30; H 4.93; N 12.09; S 27.68.

Alkylation of 5,6-Bis(2,5-dimethyl-3-thienyl)-2,3-dihydro-1,2,4-triazine-3-one (5) (General Method). A solution of KOH (0.07 g) in water (1 ml) and the alkylating agent (0.6 mmol) were added to a solution of triazinethione **5** (0.6 mmol). The reaction product was stirred for 6 h, water was added and the precipitated product was filtered off.

3-Benzylthio-5,6-bis(2,5-dimethyl-3-thienyl)-1,2,4-triazine (6b). Obtained from thione **5** and benzyl bromide. Yield 72%; mp 101-103°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm, *J* (Hz): 2.08 (3H, s, CH$_3$); 2.22 (3H, s, CH$_3$); 2.30 (3H, s, CH$_3$); 2.38 (3H, s, CH$_3$); 4.55 (2H, s, SCH$_2$); 6.42 (1H, s, H$_{\text{Het}}$); 6.60 (1H, s, H$_{\text{Het}}$); 7.35 (3H, m, H$_{\text{Ar}}$); 7.50 (2H, d, J = 6.7, H$_{\text{Ar}}$). Found, %: C 62.25; H 5.05; N 9.54; S 22.52. $C_{22}H_{21}N_3S_3$. Calculated, %: C 62.38; H 5.00; N 9.25; S 22.71.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-(4-fluorobenzylthio)-1,2,4-triazine (6c). Obtained from thione **5** and 4-fluorobenzyl bromide. Yield 78%; mp 105-107°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.08 (3H, s, CH$_3$); 2.22 (3H, s, CH$_3$); 2.30 (3H, s, CH$_3$); 2.36 (3H, s, CH$_3$); 4.56 (2H, s, SCH$_2$); 6.42 (1H,, s, H$_{\text{Het}}$); 6.60 (1H, s, H$_{\text{Het}}$); 7.17 (2H, m, H$_{\text{Ar}}$); 7.55 (2H, m, H$_{\text{Ar}}$). Found, %: C 59.66; H 4.49; N 9.19; S 21.55. $C_{22}H_{20}FN_3S_3$. Calculated, %: C 59.84; H 4.56; N 9.52; S 21.78.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-[3-(trifluoromethyl)benzylthio]-1,2,4-triazine (6d). Obtained from thione **5** and 3-(trifluoromethyl)benzyl bromide. Yield 67%; mp 75-77°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.05 (3H, s, CH$_3$); 2.18 (3H, s, CH$_3$); 2.28 (3H, s, CH$_3$); 2.33 (3H, s, CH$_3$); 4.65 (2H, s, SCH$_2$); 6.45 (1H, s, H$_{\text{Het}}$); 6.60 (1H, s, H$_{\text{Het}}$); 7.60 (2H, m, H$_{\text{Ar}}$); 7.82 (2H, m, H$_{\text{Ar}}$). Found, %: C 56.02; H 4.14; N 8.22; S 19.33. $C_{23}H_{20}F_3N_3S_3$. Calculated, %: C 56.19; H 4.10; N 8.55; S 19.57.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-hydrazino-1,2,4-triazine (7). A solution of triazinethione **5** (0.46 g, 1.3 mmol) in ethanol (4 ml) and an 80% aqueous solution of hydrazine hydrate (0.5 ml, 8.2 mmol) was refluxed for 3 h. After cooling, the precipitated product was filtered off to give 0.431 g (98%) of hydrazine **7**; mp 157-159°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.00 (3H, s, CH$_3$); 2.25 (3H, s, CH$_3$); 2.30 (3H, s, CH$_3$); 2.35 (3H, s, CH$_3$); 6.40 (1H, s, H$_{\text{Het}}$); 6.58 (1H, s, H$_{\text{Het}}$); 8.80 (1H, s, NH). Found, %: C 54.19; H 5.12; N 21.35. S 19.21. $C_{15}H_{17}N_5S_2$. Calculated, %: C 54.35; H 5.17; N 21.13; S 19.35.

6,7-Bis(2,5-dimethyl-3-thienyl)-3-methyl[1,2,4]triazolo[4,3-*b*][1,2,4]triazine (8). A solution of hydrazine **7** (0.25 g, 0.75 mmol) and acetic acid (3 ml) was refluxed for 4 h, then cooled and the precipitated product filtered off to give triazolotriazine **8** (0.23 g, 87%); mp 202-204°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.20 (3H, s, CH$_3$); 2.29 (3H, s, CH$_3$); 2.30 (3H, s, CH$_3$); 2.33 (3H, s, CH$_3$); 2.72 (3H, s, CH$_3$); 6.38 (1H, s, H$_{\text{Het}}$); 6.49 (1H, s, H$_{\text{Het}}$). Found, %: C 57.25; H 4.75; N 19.55; S 18.23. $C_{17}H_{17}N_5S_2$. Calculated, %: C 57.44; H 4.82; N 19.70; S 18.04.

3-Aryl-5,6-bis(2,5-dimethyl-3-thienyl)-1,2,4-triazine (9a-c) (General Method). A mixture of diketone **1** (2.4 mmol), hydrazide of the corresponding aromatic carboxylic acid (5 mmol), and ammonium acetate (3 g) in acetic acid (5 ml) and water (0.5 ml) was refluxed with a reflux condenser for 6 h. After cooling, the precipitated product was filtered off and crystallized from acetic acid.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-phenyl-1,2,4-triazine (9a). Obtained from diketone **1** and benzoic acid hydrazide. Yield 60%; mp 113-114°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.12 (3H, s, CH_3); 2.32 (3H, s, CH_3); 2.39 (3H, s, CH_3); 2.41 (3H, s, CH_3); 6.52 (1H, s, H_{Het}); 6.72 (1H, s, H_{Het}); 7.62 (3H, m, H_{Ar}); 8.50 (2H, m, H_{Ar}). Found, %: C 66.65; H 5.00; N 11.25; S 16.82. $C_{21}H_{19}N_3S_2$. Calculated, %: C 66.81; H 5.07; N 11.13; S 16.99.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-(4-nitrophenyl)-1,2,4-triazine (9b). Obtained from diketone **1** and 4-nitrobenzoic acid hydrazide. Yield 56%; mp 170-172°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm, *J* (Hz): 2.15 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.39 (3H, s, CH_3); 2.41 (3H, s, CH_3); 6.55 (1H, s, H_{Het}); 6.75 (1H, s, H_{Het}); 8.45 (2H, d, J = 8.8, H_{Ar}); 8.72 (2H, d, J = 8.8, H_{Ar}). Found, %: C 59.51; H 4.20; N 13.09; S 15.29. $C_{21}H_{18}N_4O_2S_2$. Calculated, %: C 58.70; H 4.29; H 13.26; S 15.18.

5,6-Bis(2,5-dimethyl-3-thienyl)-3-(2-furyl)-1,2,4-triazine (9c). Obtained from diketone **1** and 2-furancarboxylic acid hydrazide. Yield 51%; mp 105-106°C. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 2.10 (3H, s, CH_3); 2.30 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.38 (3H, s, CH_3); 6.48 (1H, s, H_{Het}); 6.65 (1H, s, H_{Het}); 6.80 (1H, m, H_{Fur}); 7.50 (1H, m, H_{Fur}); 8.08 (1H, m, H_{Fur}). Found, %: C 62.28; H 4.70; N 11.09; S 17.26. $C_{19}H_{17}N_3OS_2$. Calculated, %: C 62.10; H 4.66; N 11.43; S 17.45.

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