Rearrangement of 1,3-Thiazolidine Sulfoxides

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Oxidation of 1,3-thiazolidines **3** gave a mixture of *cis*- and *trans*-sulfoxides **4** and **5**, major and minor, respectively. In the presence of an acid catalyst both the *cis* and *trans* sulfoxides underwent ring expansion reaction to produce dihydro-1,4-thiazines **2** in good yields. Under neutral conditions (100°/DMF) the *cis*-sulfoxides afforded a sigmatropic rearrangement with the 2-methylene group to generate probable sulfenic acids **6** followed by dehydration to **2**, while the *trans* isomer rearranged more slowly involving the 2-methyl group to form isomeric dihydrothiazines **18** possibly *via* sulfenic acids **7**. Structures and isomerization of the *cis*- and *trans*-sulfoxides are also discussed.

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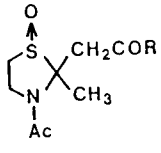
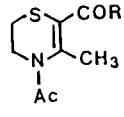
Introduction.

The rearrangement of appropriately substituted cyclic sulfoxides to a ring expansion product is of considerable mechanistic interest as well as synthetic utility. Recently we have reported the rearrangements of some 1,3-oxathiolane sulfoxides to dihydro-1,4-oxathiins [1]. This paper describes thermal and acid catalyzed rearrangements of 1,3-thiazolidine sulfoxides **1** to dihydro-1,4-thiazines **2**. Although the ring expansion of benzothiazolidine sulfoxides [2,3] and simple tetrahydrothiazole 1-oxides [2] to the corresponding 1,4-thiazines have been reported, 1,3-thiazolidine sulfoxides derived from acetoacetanilide or acetoacetic ester had not been previously prepared or studied.

Chart I



1



2

R = a NHC_6H_5 ; b OCH_3

It seemed to be interesting to investigate the rearrangements of these new sulfoxides and to compare these results with those obtained with 1,3-oxithiolanesulfoxides.

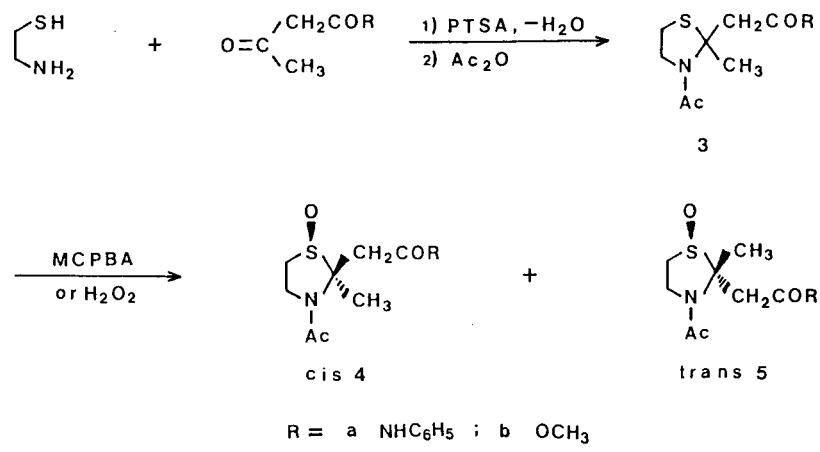
Results and Discussion.

1,3-Thiazolidine Sulfoxides.

The parent 1,3-thiazolidines **3** were prepared by the acid-catalyzed condensation of 2-aminoethanethiol with the appropriate β-keto amide or ester, and subsequent acetylation [4] of the resulting 1,3-thiazolidines. Oxidation of the sulfide **3** with various oxidizing agents gave a mixture of *cis*- and *trans*-sulfoxides **4** and **5** as major and minor products, respectively (see Scheme I). We have arbitrarily named the isomer as *cis* when the sulfoxide oxygen and the CH_2COR group are on the same face of the thiazolidine ring and *trans* when they are on the opposite faces. The pairs of diastereomers were separated from each other by fractional crystallization or preparative tlc.

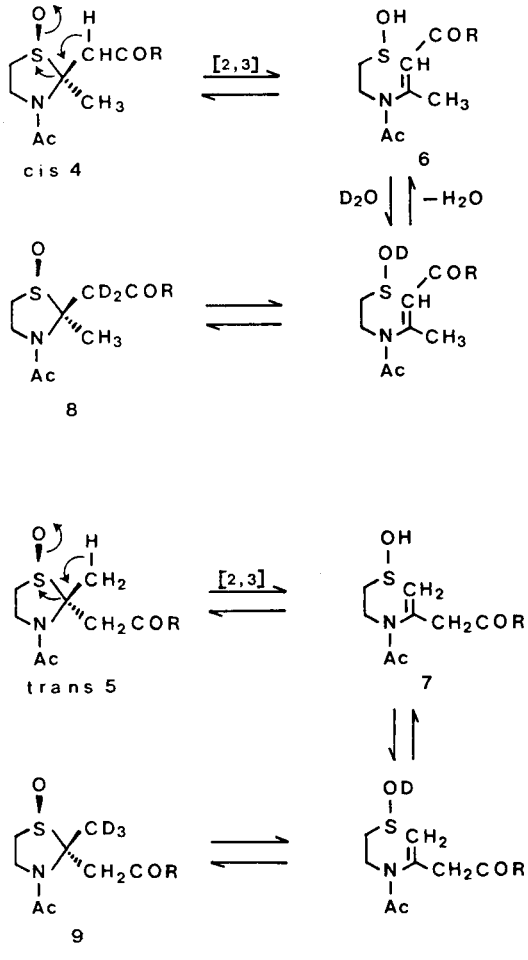
Assignment of stereochemistry to the *cis* and *trans* isomers was based on the ^1H nmr data and deuterium incorporation in the 2-methylene and 2-methyl groups. In the ^1H nmr spectra the amide proton in the *cis*-sulfoxide appeared at considerably lower field than in the *trans* isomer indicating that a hydrogen bonding exists between the NH

Scheme I



R = a NHC_6H_5 ; b OCH_3

Scheme II



proton and the oxygen of the sulfoxide.

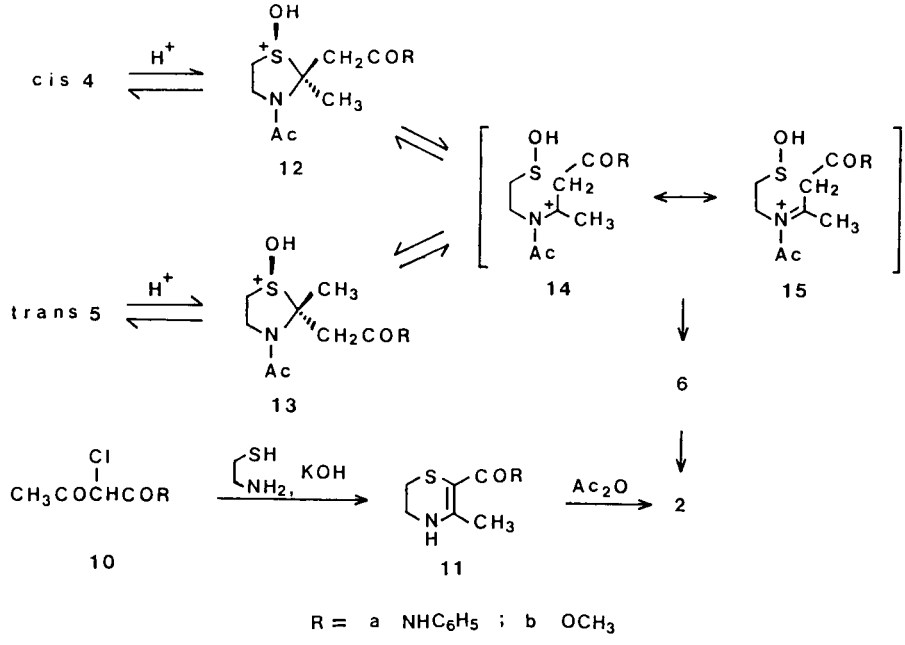
Strong evidence for the stereochemistry of the *cis*- and *trans*-sulfoxides was found in the deuteration reactions of the two isomers (see Scheme II). When the major isomer was heated in refluxing toluene in the presence of a large excess of deuterium oxide the 2-methylene group was deuterated. This reaction would proceed *via* sulfenic acid intermediate **6** formed by a sigmagropic ring opening involving the methylene hydrogens of the side chain, resulting in **8**. Under the same conditions the minor isomer incorporated deuterium in the 2-methyl group to give **9**, possibly by way of sulfenic acid **7** formed by a sigmatropic rearrangement with 2-methyl hydrogens. Thus, it was concluded that the major sulfoxides had the sulfoxide oxygen *cis* to the amide or ester side chain and that the minor isomers had the corresponding *trans* relationship.

Sulfoxide to Dihydro-1,4-thiazine Conversion.

In the presence of an acid catalyst both the *cis*- and *trans*-sulfoxides readily underwent ring expansion reactions in refluxing benzene to produce dihydro-1,4-thiazines **2** in good yields (see Scheme III). The structure of this compound was confirmed by ^{1}H nmr spectroscopy as well as independent synthesis by way of α-chloroacetoacetanilide or ester **10**.

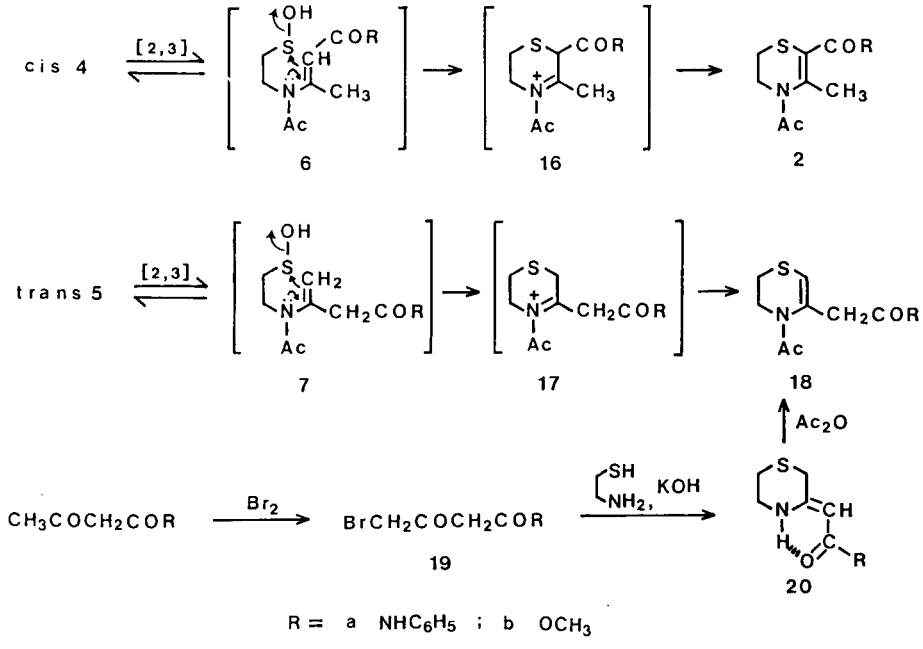
In DMF at 100° under neutral conditions the *cis*-sulfoxides were rearranged smoothly to **2**, while the *trans* isomers reacted more slowly to form the isomeric dihydro-1,4-thiazines **18** (see Scheme IV). The structure of **18** was identified by ^{1}H nmr spectroscopy and independent synthesis involving γ-bromo-β-ketoamide or ester **19**.

Scheme III



R = a NHC_6H_5 ; b OCH_3

Scheme IV



Interestingly, when the *trans*-sulfoxides were heated in refluxing toluene instead of DMF in the absence of catalyst the starting materials were recovered unchanged, showing a remarkable solvent effect.

Mechanism of the Sulfoxide Rearrangements.

The ring expansion reaction of the *cis*- and *trans*-sulfoxide **4** and **5** under neutral conditions (DMF, 100°) may proceed *via* sulfenic acids **6** and **7**, respectively, as generated by a sigmatropic rearrangement involving the 2-methylene or 2-methyl group. The sulfenic acid intermediacy was demonstrated by the deuterium incorporation reaction as described earlier.

At an elevated temperature (100°) the sulfenic acids **6** and **7** in DMF now undergo a nucleophilic attack at the sulfur atom by the π-electrons of the internal double bond to form, most likely, the imminium ions **16** and **17** respectively, and then produce **2** and **18** with loss of the acidic protons (see Scheme IV). Unlike in the rearrangement of 1,3-oxathiolane sulfoxides, thiolsulfinates [1] which would possibly be formed by dimerization of the sulfenic acids **6** were not observed.

On the other hand, in the presence of acid catalyst the ring expansion reactions may also proceed *via* sulfenic acids, but the ring opening of the sulfoxides may occur by a stepwise mechanism involving protonated sulfoxides or sulfonium ions **12** and **13**. From these a common sulfenic acid **6** would be generated by direct β-elimination involving only the carbonyl activated methylene protons. It is more likely, however, that the sulfenic acid was formed *via* carbocation **14** or iminium ion **15** (see Scheme III), based on the observed *cis-trans* isomerization of the sulfoxides **4** and **5** as discussed later. The cyclization of **6** to **2** with loss of water is facilitated under acid catalysis.

cis-trans Isomerization of the Sulfoxides.

The results of the deuteration reaction provide evidence of the sulfoxide-sulfenic acid equilibrium and show that no isomerization between the *cis*- and *trans*-sulfoxides takes place under neutral conditions. The stereospecific recyclization of sulfenic acids **6** and **7** to their parent sulfoxides **4** and **5**, respectively, may arise from the geometrical requirements of the reacting bond and atom in the reverse sigmatropic rearrangement [5,6]. In the presence of an acid catalyst, however, it was found that *cis-trans* isomerization of the sulfoxides indeed occurred. Thus, when either *cis*- or *trans*-sulfoxide was heated with *p*-toluenesulfonic acid as the catalyst in refluxing benzene the reaction mixture contained in addition to the ring expansion product **2** both the *cis* and *trans* isomers, suggesting that the ring closure of the sulfenic acid to the sulfoxide was nonstereospecific [7]. Such nonstereospecificity is probably due to the carbocation intermediate **14** formed from the protonated sulfoxides **12** and **13**. This carbocation may, in competition with forming the sulfenic acid **6** which leads to **2**, recyclize nonsterospecifically to give a mixture of the two isomeric sulfoxides **4** and **5**.

EXPERIMENTAL

All melting points were obtained with an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 735B or Analect Model

FX-6160 FT-IR spectrophotometer. All ^{1}H nmr spectra were recorded on a Varian Model EM360 spectrometer with TMS as an internal standard and are reported in δ units. Mass spectra were recorded on VG 12-250 spectrometer. Elemental analyses of new compounds are within 0.4% of the theoretical values, unless otherwise noted. Chromatographic isolations were accomplished either by preparative thin-layer chromatography, using Kieselgel GF 254 silica gel.

Synthesis of 3-Acetyl-2-methyl-2-(*N*-phenylcarbamoylmetyl)-1,3-thiazolidine (**3a**).

A solution of acetoacetanilide (13 g, 0.073 mole), 2-aminoethanethiol (6.2 g, 0.08 mole), and *p*-toluenesulfonic acid monohydrate (PTSA) (0.7 g) in benzene (75 mℓ) was refluxed for 16 hours with a Dean-Stark water separator and then cooled to room temperature. The reaction mixture was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* to give a yellow oily liquid (16.8 g, 98%). This oily residue was dissolved in acetic anhydride and stirring was continued for 4 hours at room temperature. The white precipitate was filtered off to give 1,3-thiazolidine **3a** (18.1 g, 91%); mp 197-204° dec; ^{1}H nmr (DMSO-d_6): (60 MHz) δ 1.85 (s, 3, 2-CH_3), 2.08 (s, 3, CH_3CO), 2.95 (t, 2, 5-CH_2, J = 6 Hz), 3.87 (t, 2, 4-CH_2, J = 6 Hz), 3.25 (d, 2, 2-CH_2), 7.00-7.80 (m, 5, ArH), 9.99 (s, 1, NH); ir (potassium bromide): 1680 (C=O), 1630 (C=O), 1600 (C=C) cm^{-1}; ms: (70 eV) m/e 278 (M^+).

Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.22; H, 6.69; N, 10.05.

Synthesis of 3-Acetyl-2-methyl-2-(*N*-phenylcarbamoylmethyl)-1,3-thiazolidine 1-Oxides **4a** and **5a**.

To an ice-cooled solution of 1,3-thiazolidine **3a** (1.39 g, 5 mmoles) in methylene chloride (10 mℓ), and benzeneseleninic acid (9 mg) was added 35% hydrogen peroxide in water (0.8 ml, about 8 mmoles) dropwise while the vigorous stirring at room temperature for 18 hours. The reaction mixture was washed with sodium bicarbonate solution and with cold water. The organic solution was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain a white foamy solid (1.27 g, 86%) consisting of *cis*-sulfoxide **4a** as a racemate of (1*S*,2*R*) and (1*R*,2*S*) and *trans*-sulfoxide **5a** as a racemate of (1*R*,2*R*) and (1*S*,2*S*) (The *cis/trans* ratio was 3:2 by ^{1}H nmr spectroscopy), which were separated by preparative tlc using 50:1 (v/v) chloroform-methanol as eluent.

Compound *cis*-**4a** had mp 49-51°; ^{1}H nmr (deuteriochloroform): (60 MHz) δ 1.73 (s, 3, 2-CH_3), 2.15 (s, 3, CH_3CO), 2.88-3.22 (m, 2, 5-CH_2), 3.02 and 4.03 (2d, 2, 2-CH_2, J = 15 Hz, AB pattern), 3.90-4.49 (m, 2, 2-CH_2), 7.05-7.80 (m, 5, ArH), 9.27 (s, 1, NH); ir (potassium bromide): 1670 (C=O), 1625 (C=O), 1040 (S→O) cm^{-1}; ms: (70 eV) m/e 294$^+$ (M^+).

Anal. Calcd. for $C_{14}H_{18}N_2O_3S$: C, 57.52; H, 6.10; N, 9.27; S, 10.92. Found: C, 57.2; H, 6.26; N, 9.54; S, 10.8

Compound *trans*-**5a** had mp 149.5-150.5°; ^{1}H nmr (deuteriochloroform): (60 MHz) δ 1.72 (s, 3, 2-CH_3), 2.14 (s, 3, CH_3CO), 3.08 and 3.88 (2d, 2, 2-CH_2, J = 15 Hz, AB pattern), 7.70-7.63 (m, 5, ArH), 8.36 (s, 1, NH); ir (potassium bromide): 1675 (C=O), 1625 (C=O), 1060 (S→O) cm^{-1}; ms: (70 eV) m/e 194 (M^+).

Anal. Calcd. for $C_{14}H_{18}N_2O_3S$: C, 57.52; H, 6.10; N, 9.27; S, 10.92. Found: C, 57.12; H, 6.16; N, 9.52; S, 10.89.

Synthesis of 4-Acetyl-5,6-dihydro-3-methyl-*N*-phenyl-1,4-thiazine-2-carboxamide (**2a**).

A solution of *cis*-sulfoxide **4a** (0.319 g, 0.11 mmole) and PTSA (10 mg) in benzene (100 mℓ) was heated at reflux with a Dean-Stark water separator for 6 hours. After cooling, the reaction mixture was washed with saturated sodium bicarbonate solution, with water and dried (sodium sulfate). The solvent was removed to obtain a crystalline solid. Recrystallized from ethyl acetate-petroleum ether to yield **2a** (0.26 g, 80%), mp 138-139°; ^{1}H nmr (deuteriochloroform): (60 MHz) δ 2.20 (s, 3, CH_3CO), 3.20 (t, 2, 6-CH_2), 3.82 (t, 2, 5-CH_2), 7.13-7.86 (m, 5, ArH), 8.43 (s, 1, NH); ir (potassium bromide): 3300 (N-H), 1660 (C=O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}O_2N_2S$: C, 60.84; H, 5.83; N, 10.14. Found: C, 60.80; H, 5.80; N, 10.10.

Synthesis of Isomeric 1,4-Thiazine **18a**.

A solution of *trans*-sulfoxide **5a** (148.7 mg, 0.5 mmole) in DMF (2 mℓ) was heated at 100° while stirring for 17 hours. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in methylene chloride. The organic solution was washed with cold water and dried (sodium sulfate). After concentration a dark brown oily residue **18a**, which was separated through preparative tlc using 7:3 (v/v) benzene-ethyl acetate as eluent, was obtained.

Compound **9a** had mp 138-140°; ^{1}H nmr (deuteriochloroform): δ 2.20 (s, 3, CH_3), 3.0-3.18 (m, 2, 6-CH_2), 3.53 (s, 2, 2-CH_2), 3.75-3.95 (m, 2, 5-CH_2), 5.95 (s, 1, vinyl CH), 7.00-7.72 (m, 5, ArH), 9.17 (s, 1, NH); ir (potassium bromide): 1680 (C=O), 1620 (C=O), 1600 (C=C) cm^{-1}; ms: (30 eV) m/e (relative intensity) 276 (M^+, 7.0), 234 (28.2), 141 (base peak).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.84; N, 10.13; S, 11.60. Found: C, 60.7; H, 5.87; N, 10.1; S, 12.1.

Independent Synthesis of Isomeric 1,4-Thiazines **18** and **2** (Step 1).

Synthesis of Isomeric Tetrahydro-2*H*-1,4-thiazine **20a**.

To a suspended solution of γ-bromoacetoacetanilide **19a** (2.25 g, 9.3 mmoles) in benzene (100 mℓ) was added a solution of 2-aminoethanethiol (1.06 g, 9.3 mmoles) and sodium hydroxide (1.12 g) in methanol (2 mℓ) at 0-5° and stirring was continued at room temperature for 2 hours. The yellow precipitate was filtered off. The filtrate was evaporated and the residue was taken up in methylene chloride. The organic solution was washed with water and dried (sodium sulfate). The solvent was removed to give a yellow solid, which was crystallized from ethanol to give the compound **20a** (1.0 g, 43%) as white needles, mp 137.5-138.5°; ^{1}H nmr (deuteriochloroform): (60 MHz) δ 2.90 (t, 2, 6-CH_2), 3.20 (s, 2, 2-CH_2), 3.42 (t, 2, 5-CH_2), 4.58 (s, 1, vinyl CH), 6.90-7.70 (m, 5, ArH and 4-NH), 9.30 (s, 1, CONH); ir (potassium bromide): 3250 (N-H), 1630 (C=O) cm^{-1}; ms: (30 eV) m/e (relative intensity) 234 (M^+, 15.8), 142 (base peak), 93 (81.9).

Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.3; H, 6.06; N, 11.7; S, 13.3.

(Step 2).

Acetylation of Isomeric Thiazine **18a**.

A solution of thiazine **20a** (232 mg, 1 mmole) in acetic anhydride (3 mℓ) was heated at 100° while stirring for 2 hours. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in methylene chloride. The organic solution was washed with cold water, and dried (sodium sulfate). Evaporation of the solvent gave a dark brown oily residue which was separated by preparative tlc (benzene:ethyl acetate = 7:3). The first

band (Rf = 0.6) was extracted with ethanol to give **18a** (25 mg, 9.1%). This was identical in ^{1}H nmr and ir spectra to those obtained in the preceding experiment.

The dihydro-1,4-thiazine **2a** was obtained by essentially the same procedure with α-chloroacetoacetanilide **10a** *via* **11a** as described above.

Deuterium Incorporation Reaction. General Procedure.

To a solution of sulfoxide **4a** (100 mg) in benzene (10 mℓ) was added a deuterium oxide (1 mℓ). The solution was refluxed for 5 hours. After removing water by a Dean-Stark water trap, the solvent was removed under reduced pressure to obtain a colorless oily residue **9a**, in which carbonyl-activated hydrogens in 40% by ^{1}H nmr spectra were substituted with deuterium.

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