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SMILES REARRANGEMENT—XV[1]

THE S→N TYPE REARRANGEMENT IN URACIL DERIVATIVES

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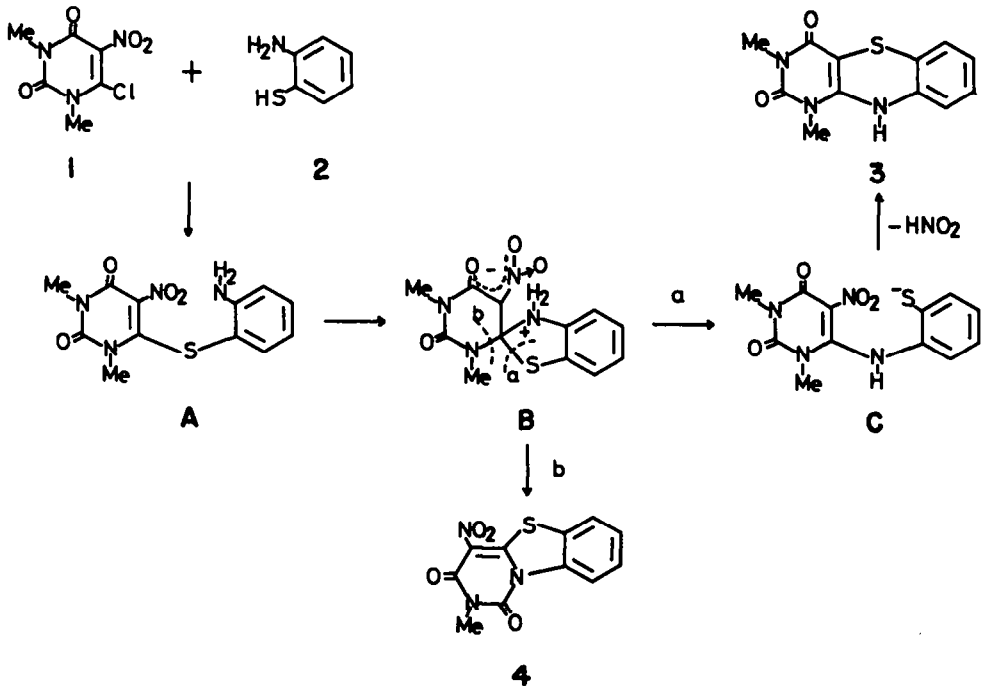
Abstract—The reaction of 1,3-dimethyl-6-(2-acetamidophenylthio)uracil **6** with caustic alkali followed by methylation gave 1,3-dimethyl-6-(2-methylthioanilino)uracil **7** accompanied with 1,3-dimethyl-5-acetyl-6-(2-methythioanilino)uracil **8**. Pyrimido[1,5]benzothiazepine **10** was obtained in high yield by the Smiles rearrangement of **6**, trapping of the resulting thiolate ion with formalin and subsequent acid-catalysed cyclization. Treatment of 1,3-dimethyl-6-(2-aminophenylthio)uracil **5** with hot acetic acid gave 1,3-bis[(2-benzothiazolyl)acetyl]-1,3-dimethylurea **12**. Upon heating **5** or N-acetyl derivative **6** in dimethylsulfoxide, 5-thiaisoalloxazine **3** was obtained in moderate yield. Mechanisms of the observed reactions were discussed.

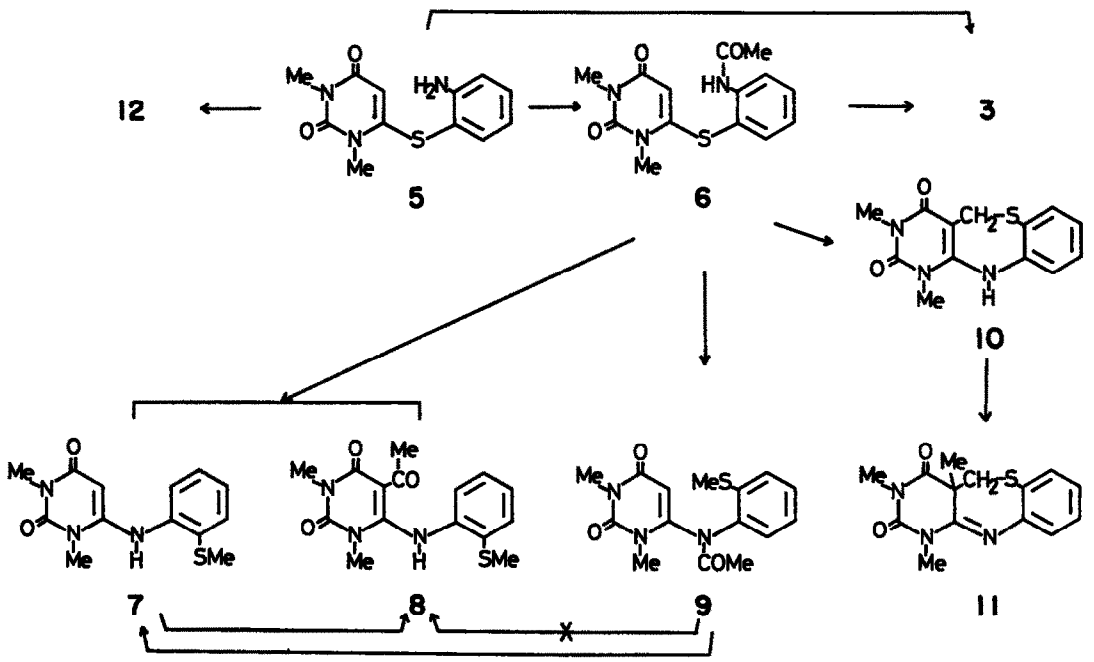
In the course of our studies on the Smiles rearrangement of azaheterocycles, we have observed an unusual rearrangement in the reaction of 1,3 - dimethyl - 5 - nitro - 6 - chlorouracil **1** with 2-aminothiophenol **2**.[1] While the reaction in benzene containing excess triethylamine gave 1,3 - dimethyl - 2,4 - dioxo - 1,2,3,4 - tetrahydro - 10H - pyrimido[5,4-*b*][1,4]benzothiazine (5-thiaisoalloxazines) **3**, the reaction in acetic acid results in the formation of 2 - methyl - 4 - nitro - 1,3 - dioxo - 2,10 - dihydropyrimido[4,3 - *b*]benzothiazoline **4**. The formation of **3** apparently involves the base-catalysed Smiles rearrangement and the latter reaction appeared to proceed via the novel uracil ring cleavage of a spiro-Meisenheimer intermediate **B** in the acid-catalysed Smiles rearrangement (see Scheme 1).

This paper described some observations related to the Smiles rearrangement of 1,3-dimethyl-6-(2-aminophenylthio)uracil **5** and N-acetyl derivative **6**, involving the novel type of double acyl migration and the formation of 1,3-bis[(2-benzothiazolyl)acetyl]-1,3-dimethylurea **12** resulting from a spiro-Meisenheimer intermediate of the Smiles rearrangement. We also report new synthetic methods of 5-thiaisoalloxazine **3** and 1,3 - dimethyl - 2,4 - dioxo - 1,2,3,4,5,11 - hexahydropyrimido[5,4 - *c*][1,5]benzothiazepine **10** via the Smiles rearrangement.

Contrary to 1,3-dimethyl-6-(2-aminophenylthio)uracil **5**, N-acetyl derivative **6** rearranged with ease to give 1,3-dimethyl-6-(2-methylthioanilino)uracil **7** upon treatment with an equimolar amount of methanolic sodium hydroxide followed by methylation with methyl iodide. Tlc analysis showed the presence of another product which was isolated by silica gel chromatography. The structure of the product thus obtained was confirmed to be 1,3-dimethyl-5-acetyl-6-(2-methylthioanilino)uracil **8**



Scheme 1.



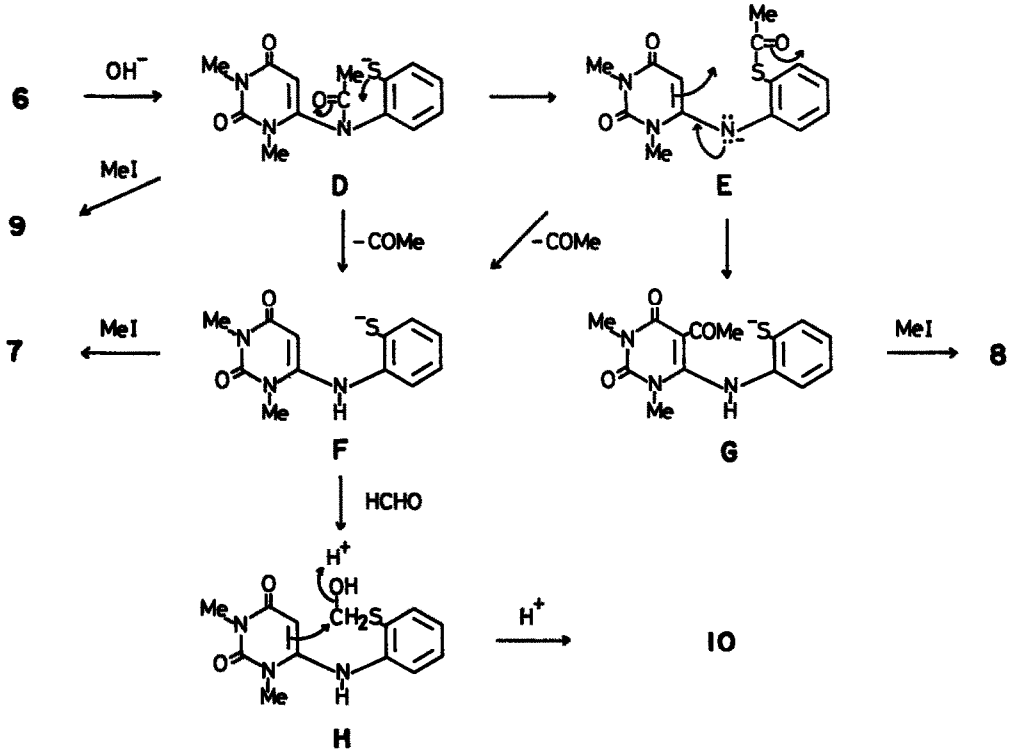
Scheme 2.

on the basis of spectral and microanalytical data. The C_5-acetyl derivative **8** was prepared independently by acetylation of the rearranged product **7** with pyridine-acetic anhydride.

Alkaline treatment of **6** in the presence of excess methyl iodide gave 1,3-dimethyl-6-(N-acetyl-2-methylthioanilino)uracil **9** rather than **7** and **8** in excellent yield, suggesting that instant trapping of the initially formed thiolate ion **D** with methyl iodide prevents cleavage of the amide bond in **D**.[2] The acyl group migration from nitrogen to oxygen has been demonstrated in the Smiles rearrangement of 2-acetamidodiphenyl ethers[3] and β-(N-acylamino)ethyl phenyl ethers.[4]

Thus, the formation of the C_5-acetyl derivative **8** can be considered to involve both the N→S acetyl transfer in **D** and the S→C acetyl transfer in the thiolester **E**. (see Scheme 3)

Direct migration of the acetyl group from N to C (C_5)



Scheme 3.

was not realised; The N-acetyl derivative **9** did not give the C_5-acetyl derivative **8** either under photolytic(300 nm UV light) or thermolytic(at 180° in dimethylsulfoxide) condition.

The yield of **8** was variable (1 ~ 15%), probably due to competitive occurrence of simple hydrolysis of the amide bond in **D** or the thiol ester bond in **E** leading to the thiolate intermediate **F**. In fact, the N-acetyl derivative **9** was smoothly hydrolysed to give **7** by the action of caustic alkali.

Our previous work has shown that UV irradiation of the methylsulfonium ylide of the 5-thiaisoalloxazine **3** causes a facile ring-expansion leading to the pyrimido[1,5]benzothiazepines **10**.[5] A more convenient preparative method of **10** was achieved by the combination of the Smiles rearrangement of **6** and a subsequent Mannich-type cyclization.[6] When the N-acetyl derivative **6** was treated with methanolic caustic alkali in the presence of formaldehyde and, without isolation of the intermediate, the reaction mixture was acidified, the thiazepine **10** was obtained in high yield.

Methylation of **10** with methyl iodide in DMF in the presence of potassium carbonate gave the C-Me derivative **11**, whose structure was confirmed on the basis of microanalytical result and spectral data. The NMR spectrum (δ) showed a C-Me signal (1.50) in addition to methylene proton signals (2.78 and 3.92, AB-type, J = 15 Hz).

The formation of the thiazepine **10** can be outlined as shown in Scheme 3. The thiolate ion **F** could be trapped by formaldehyde to give the hydroxymethylthio derivative **H**, which undergoes an acid-catalysed cyclization leading to **10**.

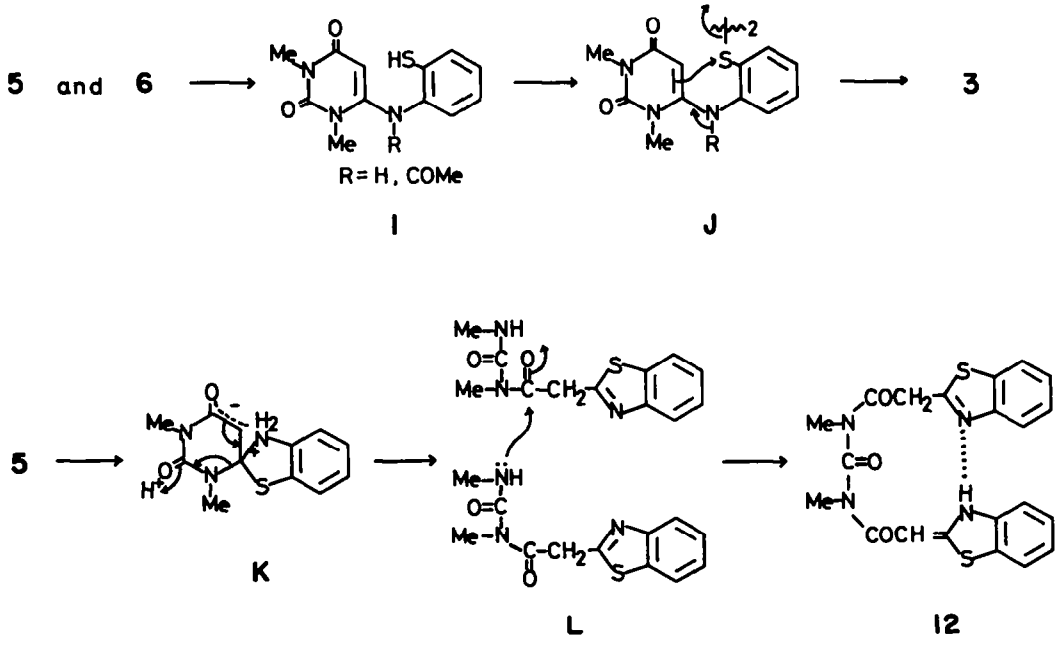
Previously, thermal and photochemical Smiles rearrangements have been observed in some instances.[7,8] Although the uracil derivatives **5** and **6** were unchanged upon irradiation (250 nm UV light), they underwent the thermal rearrangement to give the 5-thiaisoalloxazines **3** in DMSO. Monitoring of the reaction by taking NMR spectra showed that the conversion of **5** to **3** is faster than that of the N-acetyl derivative **6** and the concurrent formation of unidentified products. Silica gel chromatography of the reaction mixture, however, allowed to isolate only **3**.

In view of chemical and biochemical interests, current attentions have been directed toward the preparation of the 5-thiaisoalloxazines **3**.[1,9-11] The present result also provides a new preparative method of **3**.

The reaction sequence for the formation of **3** can be outlined as shown in Scheme 4. The sulfide **5** or **6** rearranges thermally to the thiol intermediate **I** which could undergo oxidation to give the disulfide **J**. Subsequent cyclisation of **I**→**3** can be explained in terms of scission of the disulfide bond by the attack of the nucleophilic enaminone β-carbon. This type of fused[1,4]thiazine formation has been reported in other enaminone systems.[12,13] At present, however, we cannot rule out an alternative path to **3**, involving radical addition of the thiol group to the uracil ring in **I** followed by oxidation.

In order to compare the reaction of **1** with **2** in acetic acid, behavior of the sulfide **5** toward acid was examined. Upon heating **5** in acetic acid, 1,3-bis[(2-benzothiazolyl)acetyl]-1,3-dimethylurea **12** was obtained in 40% yield together with the N-acetyl derivative **6** in 10% yield. The expected dihydropyrimido[4,3-*b*]benzothiazoline(**4**: H in place of NO_2) was not isolated from the reaction mixture. The structure of **12** was confirmed by microanalytical and spectral data; The NMR spectrum (δ, in DMSO-d_6) showed the presence of imino, methine and methylene groups (10.05 (1H, br.), 4.55 (1H, s), 4.37 (2H, s): These signals were deuterium exchangeable). Thus, the structure of **12** was proposed to involve both of benzothiazole and benzothiazoline tautomeric forms which are bridged by an H-bond.

The formation of **12** can be outlined as depicted in Scheme 4. A benzothiazole intermediate **L** could be formed by acid-catalysed cleavage of the uracil ring in the spiro-Meisenheimer intermediate **K**. The important feature of the reaction is an intermolecular reaction of **L**



Scheme 4.

accompanied with loss of dimethylurea, which occurs instead of an intramolecular cyclisation leading to dihydropyrimido[4,3-*b*]benzothiazoline observed in the reaction of **1** with **2** in acetic acid. Some examples of the collapse of the spiro-Meisenheimer intermediate in the Smiles rearrangement to form new heterocyclic rings have been reported.[1,14] In this point of view, the formation of **12** is noticeable.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were recorded with a Hitachi 215 spectrometer for KBr discs and H^1NMR spectra with a Hitachi R-20B 60 MHz spectrometer in $CDCl_3$ or DMSO-d_6 containing tetramethylsilane as internal standard. Mass spectra were measured at 75 eV with a JOEL JM-OISG spectrometer and UV spectra with a Shimazu MPS-50L spectrometer in EtOH. Column chromatography was performed on silica gel (Mallinckrodt: 100 mesh) using chloroform as eluent.

1,3-Dimethyl-6-(2-acetamidophenylthio)uracil **6**. Compound **5**[6] (1 g) was dissolved in a mixture of pyridine (20 ml) and Ac_2O (5 ml). The mixture was allowed to stand at room temp. overnight and was poured into ice-water. The crystals thus obtained were recrystallised from EtOH to give **6**, m.p. 205–206°, (1 g) as colorless prisms. (Found: C, 55.01; H, 4.98; N, 13.75. Calc. for $C_{14}H_{15}O_3N_3S$: C, 55.08; H, 4.95; N, 13.77%). NMR: δ2.15 (3H, s, COMe), 3.25 (3H, s, NMe), 3.60 (3H, s, NMe), 4.80 (1H, s, C_5–H) and 7.10–8.50 (4H, m, ArH).

Rearrangement of 1,3-dimethyl-6-(2-acetamidophenylthio)uracil **6** *with caustic alkali*. A suspension of **6** (1 g) in MeOH containing NaOH (0.13 g) was stirred at room temp. until a clear soln was obtained. Addition of excess MeI to the mixture deposited **7** (0.6 g), which was separated by filtration and recrystallised from EtOH to give colorless prisms, m.p. 226°. (Found; C, 56.35; H, 5.45; N, 15.05. Calc. for $C_{13}H_{15}O_2N_3S$: C, 56.30; H, 5.45; N, 15.15%). IR: 3275 (NH), 1680 and 1615 cm^{-1} (CO), NMR: δ2.43 (3H, s, SMe), 3.32 (3H, s, NMe), 3.60 (3H, s, NMe), 5.00 (1H, s, vinyl H), 6.57 (1H, br, NH) and 7.20–7.50 (4H, m, ArH). After concentration of the mother liquor under reduced pressure, the residue was dissolved in $CHCl_3$, washed with water and dried ($MgSO_4$). The $CHCl_3$ soln was chromatographed on the silica gel to separate **8** (0.1 g) and **7** (0.1 g). The first eluate **8** was recrystallised from EtOH to give colorless prisms, m.p. 191°. (Found: C, 56.50; H, 5.40; N, 13.25. Calc. for $C_{15}H_{17}O_3N_3S$: C, 56.42; H, 5.37; N, 13.16). IR: 1700 and 1650 cm^{-1} (CO), NMR: δ2.50 (3H, s, SMe), 2.70 (3H, s, COMe), 2.95 (3H, s, NMe), 3.38 (3H, s, NMe), 6.70–7.30 (4H, m, ArH), 13.35 (1H, br, NH). The C_5-acetyluracil **8** was identical in every respect with a sample prepared by acetylation of **7** with pyridine–Ac_2O at room temp.

A soln of **6** (1 g) and excess MeI (0.5 g) in MeOH was allowed to react with NaOH (0.13 g) in aq MeOH. After evaporation of the solvent under reduced pressure, the residue was recrystallised from ether-n-hexane to give **9** (0.6 g), m.p. 138°. (Found; C, 56.44; H, 5.35; N, 13.21. Calc. for $C_{15}H_{17}O_3N_3S$: C, 56.41; H, 5.37; N, 13.16%). NMR: δ 2.10 (3H, s, COMe), 2.51 (3H, s, SMe), 3.35 (3H, s, NMe), 3.50 (3H, s, NMe), 5.50 (1H, s, vinyl H), 7.10–7.60 (4H, m, ArH). Upon treatment with methanolic alkali at room temp., **9** was smoothly hydrolyzed to give **7** quantitatively.

Formation of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-10H-pyrimido[5,4-b][1,4]benzothiazine **3** *via thermal rearrangement*. The derivative **6** (0.5 g) in DMSO (8 ml) was heated at 170–180° until disappearance of **6** was completed (monitored by tlc or NMR; *ca* 7 hr). The mixture was triturated with $CHCl_3$. Recrystallisation of the solid insoluble in $CHCl_3$ from EtOAc gave **3** as light yellow crystals (0.2 g), which was identified with an authentic sample by NMR and IR spectral comparisons.[1] Analogously, the amine **5** (0.5 g) gave **3** (0.15 g) after heating at 170° in DMSO for 5 hr.

Preparation of 1,3-dimethyl-2,4-dioxo-1,2,3,4,5,11-hexahydropyrimido[5,4-c][1,5]benzothiazepines **10**. A suspension of **6** (3 g) and 37% of H_2CO (10 ml) in a methanolic NaOH (5% NaOH 50 ml: MeOH 25 ml) was stirred at room temp. for 1 hr. After 37% H_2CO (10 ml) was further added, the mixture was acidified with HOAc and stirred for additional 1 hr to deposit **10**, m.p. 257°, (1.1 g), which was recrystallised from EtOH to give colorless needles. The thiazepine thus obtained was identical in every respect with a sample prepared by irradiation of methylsulfonium ylide of **3**.[5,9] Methylation of **10** with MeI in DMF in the presence of K_2CO_3 gave with ease **11**, m.p. 96°, quantitatively. (Found: C, 57.96; H, 5.20; N, 14.32. Calc. for $C_{14}H_{15}N_3O_2S$: C, 58.12; H, 5.23; N, 14.53%). NMR: δ 1.50 (3H, s, C-Me), 3.34 (3H, s, NMe), 3.50 (3H, s, NMe), 2.78 and 3.92 (each 1H, AB-type, quartet, J = 15 Hz), 6.80–7.55 (4H, m, ArH).

Reaction of 1,3-dimethyl-6-(2-aminophenylthio)uracil **5** *with acetic acid*. A soln of **5** (1 g) in AcOH (20 ml) was heated for 4 hr. The mixture was evaporated under reduced pressure to leave an oily mass, which was chromatographed on silica gel (solvent: $CHCl_3$) to isolate **12** and **6** in 40% and 10% yields, respectively. Recrystallisation of **12** from MeOH gave colorless crystals, m.p. 156°. (Found: C, 57.53; H, 4,14; N, 12.78. Calc. for $C_{12}H_{13}N_3O_2S$: C, 57.62; H, 4.11; N, 12.69%). NMR: δ 3.14 (3H, s, NMe), 3.38 (3H, s, NMe), 4.37 (2H, s, CH_2), 4.56 (1H, s, CH), 10.05 (1H, s, NH). Mass M^+ = 438. UV λ_{max}^{MeOH} nm (ε): 256 (*sh*)(17800), 285 (13300). IR: 3200 (NH), 1700, 1680, 1620 cm^{-1} (CO).

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