Synthesis, hydrolysis reactions and conformational study of 2-substituted 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine 1,1-dioxides

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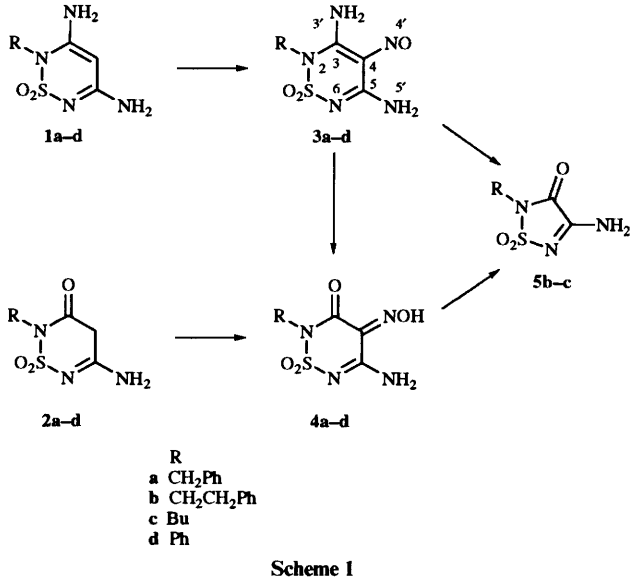
The 2-substituted 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine 1,1-dioxides are present in solution as a mixture of two rotational conformers of the nitroso group that are stabilized by hydrogen bonds with the amino groups in positions 3 and 5. The stability of these conformations has been studied using ^{1}H, ^{13}C and ^{15}N NMR spectroscopy, as well as molecular orbital *ab initio* calculations. In addition, hydrolysis reactions of these compounds have been carried out affording 5-amino-4-hydroxyimino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides and 4-amino-3-oxo-2,3-dihydro-1,2,5-thiadiazole 1,1-dioxides.

In continuation of our research into the chemistry of 1,2,6-thiadiazine 1,1-dioxides, we report the synthesis, conformational study and reactivity of 2-substituted 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine 1,1-dioxides. These compounds, in analogy with the 3,5-diamino-4-hydroxyimino-4*H*-1,2,6-thiadiazine 1,1-dioxide, could be used as intermediates in the synthesis of fused heterocycles, some of which have shown interesting biological activities.[1,2]

Results and discussion

Synthesis and reactivity

Nitrosation of the 3,5-diamino-2*H*-1,2,6-thiadiazine **1** and 5-amino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides **2** provides in the first case, the corresponding 4-nitroso derivatives **3** and in the second, the corresponding 4-hydroxyimino compounds **4** with moderate yield (Scheme 1).

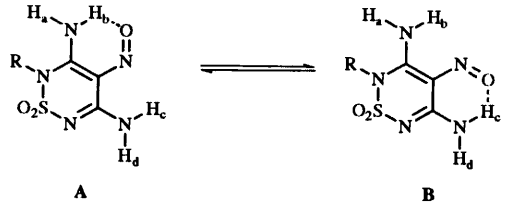


Scheme 1

The mild acid hydrolysis of the 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazines **3** affords the previously mentioned 5-amino-3-oxo derivatives **4**. A similar reaction of the 3-amino groups of some 3,5-diamino-2*H*-1,2,6-thiadiazines **1** has been previously reported by us.[3] However, when the hydrolytic conditions are stronger, 3,5-diamino-4-nitroso derivatives **3** yield the corresponding 4-amino-3-oxo-2,3-dihydro-1,2,5-thiadiazole 1,1-dioxides **5**. The mechanism proposed for this reaction involves the hydrolysis of the amino groups and ring contraction.[4] The poor yield of this reaction could be due to the strong reaction conditions needed for the hydrolysis of the amino group in position 5, which has not been previously reported in the literature for this kind of heterocyclic compound, that could destroy part of the final product obtained. Supporting this hypothesis, the hydrolysis of the 5-amino-3-oxothiadiazines **4** provides the thiadiazoles **5** with similar poor yields. These results indicate that even though this reaction could be interesting from a mechanistic point of view, the synthesis of the final compounds could be achieved with better yield using other synthetic methods already described.[4,5]

Conformational characterization of the 3,5-diaminothiadiazines 3

The 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazines **3** in solution present a duplication of their NMR signals (Tables 1–3). In the ^{15}N NMR spectra, the presence of two signals corresponding to nitroso nitrogen (*ca.* 267 and 256 ppm) indicates that the equilibrium observed corresponds to two conformations of the 4-nitroso groups (Scheme 2), allowing us to discard the



Scheme 2

existence of the respective 4-hydroxyimino tautomers, whose signals appear in the range −25 to −45 ppm in these kind of heterocycles.[6] The four additional signals at *ca.* −280 ppm indicate the presence of four NH_2 groups which eliminates a possible amino–imino tautomerism in these compounds. Finally, the signals corresponding to the endocyclic nitrogen can be observed (*ca.* −239 and −232 ppm for N-2 and −216 and −202 ppm for N-6).

Table 1 ^{15}N NMR spectral data of compounds **3b** and **c**

Comp.	N-2	N-4′	$NH_2(3')$ and $NH_2(5')$	N-6
3b	−232.4, −239.3	266.9, 256.0	−282.6, −284.6, −287.7, −288.5	−202.2, −216.0
3c	−231.0, −237.9	266.5, 256.0	−282.6, −284.5, −287.7, −288.4	

Table 2 ^1H NMR spectral data of compounds **3a–d**

	A					**B**					**A + B**
Comp.	H_a	H_b	H_c	H_d	Side chain	H_a	H_b	H_c	H_d	Side chain	Side chain
3a	8.70 (br)	12.70	8.89	8.39	5.05	8.70 (br)	9.93	10.40 (d)	8.70 (d)	5.24	7.26–7.41 (m)
3b	9.22 (br)	12.77	8.80	8.30	3.93 (t), 2.93 (t)	9.04 (br)	9.87	10.46 (d)	8.63 (d)	4.14 (t), 3.04 (t)	7.19–7.34 (m)
3c	8.98 (br)	12.76	8.76	8.26	3.70 (t), 1.57 (t), 1.32 (t)	9.98 (br)	9.83 (br)	10.45 (d)	8.58 (d)	3.89 (t), 1.67 (t), 1.35 (t)	0.88 (q)
3d	8.25 (br)	12.55	8.91	8.41		8.25 (br)	9.80 (br)	10.40 (d)	8.69		7.42–7.59 (m)

Table 3 ^{13}C NMR spectral data of compounds **3a–d**

	A				**B**				**A + B**
Comp.	C-3	C-4	C-5	Side chain	C-3	C-4	C-5	Side chain	Side chain
3a	147.5	134.2	161.7	44.8	160.0	136.5	150.3	46.8	127.1, 127.9, 128.7, 134.2, 134.5
3b	147.0	133.7	161.4	32.8, 42.6	160.2	136.0	149.9	33.2, 44.9	126.6, 128.3, 128.8, 128.9, 137.4
3c	147.2	133.6	161.4	42.7, 29.1	160.2	135.9	150.0	43.9, 29.6	29.1, 13.6
3d	147.6	133.6	161.3		160.0	135.7	149.7		129.2, 129.4, 130.2, 130.5, 131.8

The assignment of the signals corresponding to each conformer in ^1H and ^{13}C NMR spectra, using $[^2H_6]$DMSO as solvent, has been made using first freshly prepared solutions, in which the conformer adopted in the solid state is more abundant, and then equilibrated solutions, where the populations of both conformers are similar.

The analysis of the ^1H NMR spectra of **3** shows some similarities with those of the corresponding 5-nitrosopyrimidines. In both cases, the signals corresponding to one of the NH_2 groups hydrogen bonded to the nitroso group appear at *ca.* 10.5 and 8.0 ppm with a constant coupling of 4.5 Hz.†,[7] The absence of substituents close to the hydrogen bonded NH_2 in the ring of these nitrosopyrimidines indicates that these signals, in the case of **3**, should correspond to H_c and H_d of conformer **B** (Scheme 2). The remaining two NH signals of conformer **B**, have been assigned based on the larger variability of H_a due to the effects of substituents attached to position 2 and the electrostatic interaction of H_b with the nitroso nitrogen that lead, in general, to larger δ shifts (Table 2). The assignment of the protons of conformer **A** has been carried out using the knowledge of the hydrogen bond effects on the δ shifts.

In addition, the ^1H NMR spectrum at different temperatures of **3b** shows four signals corresponding to the amino groups which coalesce to two signals at 363 (conformer **B**) and 373 K (conformer **A**) (Fig. 1). These signals should correspond to the amino groups that are not forming a hydrogen bond with the nitroso group in either conformation (8.80 and 8.30 ppm in conformer **A** and 9.87 and 9.04 ppm in conformer **B**). Using these values, the rotation barriers of these amino groups have been calculated to be 17.7 and 16.8 kcal mol^{-1},‡ respectively. These energy barriers are similar to the one observed for formamide[8] (17.8 kcal mol^{-1}) which could be associated with the double bond character of these C–N bonds.

† The ^1H NMR spectrum of the commercial 5-nitroso-2,4,6-triaminopyrimidine shows the following signals: 10.21 (1 H, d, J = 4.5 Hz), 8.11 (1 H, s), 7.71 (1 H, d, J = 4.5 Hz), 7.30 (1 H, s), 7.14 (2 H, s).
‡ 1 cal = 4.184 J.

Table 4 Equilibrium constant K, and ΔG for **3a** at 303 K in different solvents (A⇄B). (The population of each conformation was estimated according to the relative integral of the CH_2 signal of the benzyl group in the ^1H NMR spectra.)

Solvent	K	ΔG/kcal mol^{-1}
$[^2H_6]$Acetone	0.61	0.3
$[^2H_6]$DMSO	0.96	0.02
$[^2H_4]$Acetic acid	0.70	0.2
$[^2H_5]$Pyridine	0.71	0.2
$[^2H_7]$DMF	0.75	0.2

The ^{13}C NMR spectra of these compounds show a big influence in the chemical shift of the C-3 and C-5 carbons depending on the conformation of the NO group (Table 3). In both cases, the carbon in the Z position to the NO group shows the smaller chemical shift. The same situation has been found for nitrosamines, amides, thioamides and oximes.[9]

The conformational equilibria of these compounds **3** is achieved in less than 30 min. The conformational barrier should be between 20 and 40 kcal mol^{-1} in order to observe separately the signals of both conformers by NMR spectroscopy, the equilibrium reached in minutes and the absence of coalescence at the temperature studied.[10] The relationship of the signals is maintained unaltered even when the $[^2H_6]$DMSO solutions are heated to 90 °C, showing that the entropic differences of these conformations are very small. A study of the equilibrium constant in different solvents (Table 4) shows that the stability of both conformers is very similar irrespective of the solvent.

The molecular orbital calculations performed in the model compound (**3**, R = Me) indicates that in the gas phase, conformer **A** is 0.54 kcal mol^{-1} (MP2/6-31G*//RHF/6-31G* level of calculation) more stable than conformer **B**, in good agreement with the small experimental energetic differences observed in solution (Table 4).

The theoretical calculations predict non-planar thiadiazine rings, with the SO_2 group out of the plane defined by the rest of the atoms. Similar results have been found in X-ray structures of this kind of heterocycle.[11] The calculated C–NH_2 bond

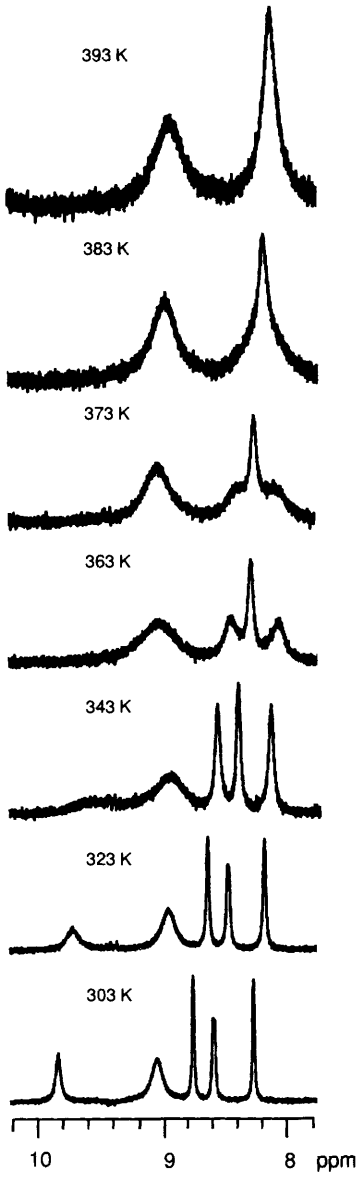


Fig. 1 ^{1}H NMR spectra of **3b** at different temperatures

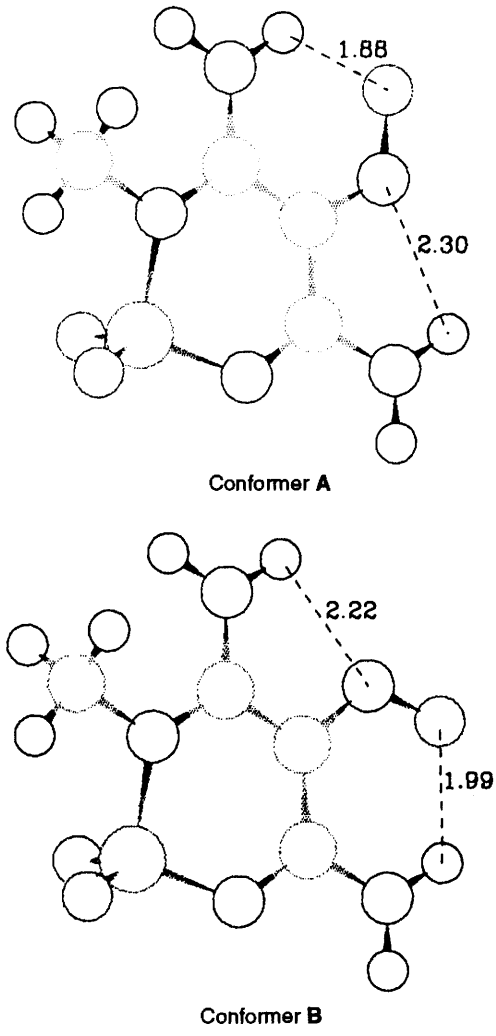


Fig. 2 Optimized geometries (RHF/6-31G*) of **3** (R = Me)

distances (1.33 Å) are similar to the experimental C=N bond distance of the pyridine (1.337 Å)[12] which indicates its partial double bond character and is in agreement with the observed high rotational barrier for the C–NH_2 bond as indicated by ^{1}H NMR spectroscopy. Regarding the hydrogen bond distances, the one calculated for conformer **A** is smaller than for conformer **B** (Fig. 2), which could explain the different displacement observed for the hydrogen atoms involved in the hydrogen bond in the ^{1}H NMR spectra.

Finally, the 5-amino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazines **4** present duplicated their signals in the NMR spectra due to an *E*/*Z* tautomerism of the hydroxyimino group (Table 5) as it has been shown previously for compound **4a**.[6]

Experimental

Molecular orbital *ab initio* calculations

The model compound **3** (R = Me) has been fully optimized in the two possible conformations, **A** and **B**, using the 6-31G* basis set[13] at the Hartree–Fock (HF) level of theory as is implemented in the GAUSSIAN-92 program.[14] The optimized geometries have been used to perform a single point calculation at the second-order Møller–Plesset perturbation (MP2) theory.[15]

Table 5 Equilibrium constant for **4a–d** at 303 K in [$^2H_6$]DMSO (*Z*⇄*E*). (The population of each conformation was estimated according to the relative intensity of the carbon signal attached to the N-2 in the ^{13}C NMR spectra)

Comp.	*K*
4a	0.67[a]
4b	1.35
4c	1.26
4d	1.20

[a] Identical to ref. 6.

Chemistry

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 257 spectrophotometer. ^{1}H (200 or 300 MHz), ^{13}C (50 or 75 MHz) and ^{15}N (30 MHz) NMR spectra were recorded on a Varian Gemini-200 or Varian XL-300. $^{15}NH_4NO_3$ (^{15}N NMR) and TMS or the signals of the solvent (^{1}H and ^{13}C NMR) were used as reference. Mass spectra were obtained at 70 eV on a VG-12-250 spectrometer. Microanalyses were performed by the Departamento de Análisis, Centro Nacional de Química Orgánica, CSIC, Madrid, Spain.

Preparation of 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine 1,1-dioxides 3

A suspension of the corresponding 3,5-diaminothiadiazine **1**[3] (9 mmol) and sodium nitrite (11 mmol) in a mixture of dimethylformamide (10 cm^3) and water (5 cm^3) was cooled to 0 °C. Acetic acid (2 cm^3) was slowly added maintaining the

Table 6 Mp, yield and analytical data of compounds **3a–d** and **4a–d**

Compound	Molecular formula	Yield (%)	Mp/°C (solvent)	Found (%) (required) C	H	N	S
3a	$C_{10}H_{11}N_5O_3S$	56	212–214 (water)	42.39 (42.70)	4.20 (3.94)	24.83 (24.90)	11.38 (11.38)
3b	$C_{11}H_{13}N_5O_3S$	86	222–224 (water)	44.72 (44.74)	4.39 (4.44)	23.52 (23.71)	11.10 (10.86)
3c	$C_7H_{13}N_5O_3S$	63	176–178 (water)	33.74 (34.00)	5.21 (5.23)	28.10 (28.23)	13.14 (12.96)
3d	$C_9H_9N_5O_3S$	96	229–230 (water)	40.43 (40.45)	3.41 (3.39)	26.24 (26.20)	11.94 (12.00)
4a	$C_{11}H_{10}N_4O_4S$	62/70[a]	130–132 (water–ethanol)	42.67 (42.55)	3.67 (3.57)	19.60 (19.85)	11.75 (11.36)
4b	$C_{11}H_{12}N_4O_4S$	67/83[a]	180–181 (water–ethanol)	44.74 (44.59)	3.99 (4.08)	19.00 (18.91)	10.93 (10.82)
4c	$C_7H_{12}N_4O_4S$	50/88[a]	124–126 (toluene)	33.83 (33.87)	4.73 (4.87)	22.33 (22.57)	13.07 (12.91)
4d	$C_9H_8N_4O_4S$	94/94[a]	216–218 (water)	40.48 (40.30)	3.12 (3.01)	21.10 (20.89)	11.85 (11.95)

[a] Method A/Method B.

Table 7 IR and mass spectral data of compounds **3a–d** and **4a–d**

Compound	ν_{max}(Nujol)/cm^{-1}	*m/z* (%)
3a	2400, 3300 (NH_2), 1620 (C=N and C=C), 1550 (N=O)	281 (M^+, 17), 91 (100), 65 (9)
3b	3390, 3280 (NH_2), 1630 (C=N and C=C), 1540 (N=O)	295 (M^+, 47), 191 (45), 105 (100), 91 (17)
3c	3400, 3370, 3290 (NH_2), 1630 (C=C and C=N), 1560 (N=O)	247 (M^+, 53), 191 (100), 112 (5), 96 (13), 70 (15), 55 (17)
3d	3410, 3390 (NH_2), 1620 (C=N and C=C), 1560 (N=O)	267 (M^+, 100), 250 (4), 186 (8), 144 (52), 119 (38), 104 (11), 93 (21), 77 (67)
4a	3400, 3340 (NH_2 and OH), 1685 (C=O), 1655, 1630 (C=N)	282 (M^+, 2), 265 (6), 201 (1), 104 (5), 91 (100), 65 (14)
4b	3440, 3320 (NH_2 and OH), 1670 (C=O), 1650, 1620 (C=N)	296 (M^+, 2), 279 (7), 192 (27), 148 (19), 104 (100), 91 (42)
4c	3420, 3320 (NH_2 and OH), 1660 (C=O), 1640 (C=N)	248 (M^+, 36), 231 (2), 205 (6), 192 (100), 175 (16), 148 (26), 132 (11), 92 (52), 91 (90)
4d	3450, 3400, 3300 (NH_2 and OH), 1650 (C=O), 1580 (C=N)	268 (M^+, 100), 251 (4), 240 (87), 225 (78), 212 (6), 187 (51), 159 (14), 146 (11), 133 (7), 119 (55), 104 (7), 93 (37)

Table 8 ^{1}H NMR spectral data of compounds **4a–d**

Comp.	*Z* NH_2(5′)	*E* NH_2(5′)	*Z* + *E* OH	Side chain
4a[a]	9.00, 8.88	9.57, 8.95	14.48 (br)	7.36–7.20 (m), 4.88, 4.86
4b	8.97, 8.86	9.49, 9.00	14.50 (br)	7.33–7.19 (m), 3.87 (t), 3.85 (t), 2.90 (t), 2.87 (t)
4c	8.93, 8.82	9.50, 8.88	14.39 (br)	3.71 (t), 3.68 (t), 1.57 (m), 1.28 (m), 0.87 (t)
4d	9.03, 8.93	9.40, 9.32	14.08 (br)	7.53–7.26 (m)

[a] Identical to ref. 6, except for the OH signal.

Table 9 ^{13}C NMR spectral data of compounds **4a–d**

	Z				*E*				*Z* + *E*
Comp.	C-3	C-4	C-5	Side chain	C-3	C-4	C-5	Side chain	Side chain
4a[a]	158.0	136.3	153.3	45.8	153.4	135.2	159.5	45.2	127.4, 127.9, 128.5
4b	157.4	135.8	152.9	43.4	152.9	134.8	159.1	42.8	34.1, 126.5, 128.5, 128.6, 138.0
4c	157.5	135.0	153.1	42.2	153.3	134.7	159.1	41.6	13.5, 19.4, 30.2
4d	158.3	133.4	152.7		152.6	134.9	159.0		128.9, 129.1, 129.2

[a] Identical to ref. 6.

temperature between 0 and 5 °C. The mixture was stirred at the same temperature for 1 h, allowed to reach room temperature overnight and poured into water (100 cm^3). The resulting solid was filtered off and recrystallized. See Tables 1–3, 6 and 7 for yields, melting points, analytical data, IR, mass and NMR spectral data.

Preparation of 5-amino-4-hydroxyimino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides 4

Method A. These products were prepared as described above for **3** using as starting material the corresponding 5-amino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide **2**.[3]

Method B. A suspension of the corresponding 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine 1,1-dioxide **3** (3 mmol) in 1% hydrochloric acid (25 cm^3) was refluxed 30 min and then cooled. The solid was filtered off and recrystallized. Reaction yields, melting points, analytical data, IR, ^{1}H and ^{13}C NMR and mass spectral data of these compounds are gathered in Tables 6–9.

Preparation of 4-amino-3-oxo-2,3-dihydro-1,2,5-thiadiazole 1,1-dioxides 5

Method A. A suspension of the corresponding 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine **3** (1.2 mmol) in 1% hydrochloric

acid (25 cm^3) was refluxed for 6 h and then cooled. The solid was filtered off and chromatographed on preparative silica gel plates (silica gel 60 PF_{254}, Merck, 20 × 20 cm plates, layer thickness 2 mm), using chloroform–methanol (13 : 1) as eluent. Under these conditions the thiadiazole was the main spot with the largest R_f value.

Method B. As described above starting from the corresponding 5-amino-4-hydroxyimino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazine **2**.

5b: Yield 14% (Method A) and 16% (Method B), mp 158–160 °C (lit.,[4] 164–166 °C).

5c: Yield 13% (Method A), mp 74–76 °C (lit.,[5] 78–80 °C).

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