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Article

A Novel and Simple Synthetic Route for a Piperazine Derivative

Maria A. S. da Silva,[a] Solange de O. Pinheiro,[a] Thiago dos S. Francisco,[a] Francisco O. N. da Silva,[a] Alzir A. Batista,[b] Javier Ellena,[c] Idalina M. M. Carvalho,[a] Jackson R. de Sousa,[a] Francisco A. Dias-Filho,[a] Elisane Longhinotti[d] and Izaura C. N. Diógenes*[,a]

[a]*Departamento de Química Orgânica e Inorgânica, Universidade Federal do Ceará, CP 6021, 60455-970 Fortaleza-CE, Brazil*

[b]*Departamento de Química, Universidade Federal de São Carlos, 13565-905 São Carlos- SP, Brasil*

[c]*Instituto de Física, Universidade de São Paulo, 13656-905 São Carlos-São Paulo, Brasil*

[d]*Departamento de Química Analítica e Físico-Química, Universidade Federal do Ceará, CP 6035, 60455-970 Fortaleza-CE, Brasil*

Um novo derivado da piperazina, 5-oxopiperazinio-3-sulfonato monohidratado, foi produzido a partir de uma rota sintética simples como resultado da adição do íon bisulfito, HSO_3^-, ao anel e do ataque nucleofílico de moléculas de água a moléculas de pirazina. O material isolado foi caracterizado por RMN, espectrometria de massa, infravermelho e difração de raios-X.

A new derivative of piperazine, 5-oxopiperazinium-3-sulfonate monohydrate, was produced from a simple synthetic route as a result of the nucleophilic addition to HSO_3^- bisulphite ion and of the nucleophilic attack of water molecules on pyrazine molecules. The isolated material was characterized by means of NMR, mass spectrometry, infrared, and X-ray diffraction.

Keywords: piperazine, nucleophilic addition, mass spectrometry, NMR

Introduction

Synthetic methods and strategies have been extensively investigated to enable access to piperazine derivatives, particularly the oxo species, due to the importance of this class of compounds in a wide range of biological activities.[1-11] Also some of these species have been recently probed to be versatile as a probe for crystal structure. For instance, the propensity to form macromolecular arrays in the solid state enables the formation of planar or non-planar type structures.[12,13]

We report herein the synthesis of a novel piperazine derivative obtained from the direct reaction of pyrazine and SO_2 in aqueous solution.

Results and Discussion

5-Oxopiperazinium-3-sulfonate monohydrate was prepared by the direct reaction of pyrazine with SO_2 gas in water. The isolated material crystallizes as pale yellow monoclinic prisms in the space group P1. Figure 1 and Table 1 present, respectively, the ORTEP[14] view of the compound and selected bond lengths and angles. In addition, an illustration of the hydrogen bonds involved in the packing of the water molecule in the crystal is also presented in Figure 1. Bond lengths (Å) and angles (°) of the intermolecular hydrogen bonds are presented in Table 1. The elemental analysis data are consistent with the chemical formulation $C_4H_8N_2O_4S{\cdot}H_2O$.

The distances observed between the carbon atoms are far shorter than those reported for piperazine (1.614 Å), morpholine (1.599 Å), thiomorpholine (1.588 Å), and thioxane (1.575 Å). However, the C(1)-C(2) and C(3)-C(4) bond lengths are higher than those observed for benzene ring (1.40 Å).[16] This result suggests a non-aromatic ring as evidenced by the ORTEP view illustrated in Figure 1. In addition, the conformation of the ring is that of a distorted chair as suggested by the C(4)-N(1)-C(1) and C(3)-N(2)-C(2) angles. This is probably due to the strain induced by the attachment of SO_3 and carbonyl groups. This suggestion

*e-mail: izaura@dqoi.ufc.br

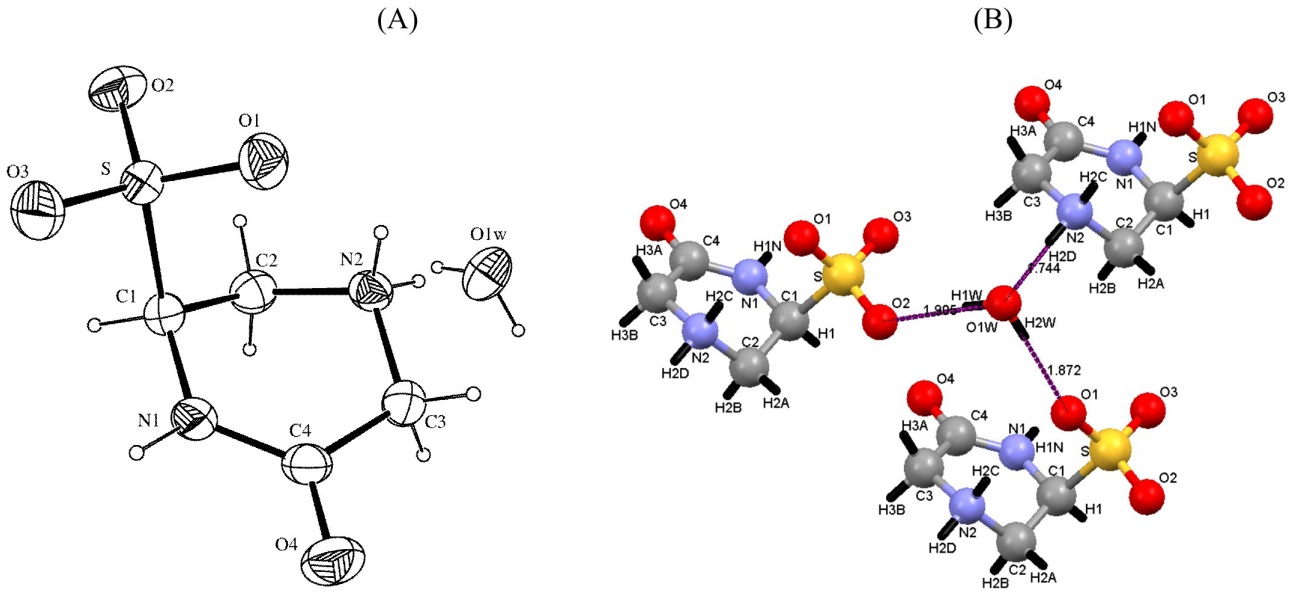

Figure 1. (A) *ORTEP*[14] view showing the atoms labelling and the 50% probability ellipsoids and (B) illustration of the hydrogen bonds involved in the packing of the solvated water molecule of the 5-oxopiperazinium-3-sulfonate monohydrate.

Table 1. Selected bond lengths (Å) and angles (°)

N(1)-C(4)	1.342(2)	C(4)-N(1)-C(1)	125.46(12)
N(1)-C(1)	1.4478(19)	C(3)-N(2)-C(2)	112.24(11)
N(2)-C(3)	1.4869(18)	N(1)-C(1)-C(2)	111.33(12)
N(2)-C(2)	1.4882(18)	N(2)-C(3)-C(4)	115.07(12)
C(1)-C(2)	1.511(2)	N(2)-C(2)-C(1)	110.07(12)
C(3)-C(4)	1.507(2)	N(1)-C(4)-C(3)	118.89(13)
S-C(1)	1.8157(15)	C(2)-C(1)-S	111.77(10)
O(4)-C(4)	1.342(2)	O(4)-C(4)-C(3)	118.06(13)

is reinforced by the different bond lengths N(1)-C(4) (1.342 Å) and N(1)-C(1) (1.4478 Å) which reflect different withdrawing capability of the SO_3 and CO fragments.

The infrared spectrum of the isolated compound presents signals typically assigned to substituted piperazine. Two absorptions characteristic of the piperazine ring, assigned to the CN stretching vibrational modes,[17,18] are observed at 1130 and 1168 cm^{-1}. A very sharp and intense band is observed at 1037 cm^{-1} and is assigned to the ring CH_2 rocking motions. According to Spell,[17] this is one of the most useful band for detecting the presence of di-substituted piperazines. The band observed at 1680 cm^{-1} is assigned[17,18] to the carbonyl stretching frequency thus indicating the presence of this group in the molecule. Two sharp absorptions assigned,[17,18] to SO stretching modes of the SO_3 fragment are observed at 1005 and 957 cm^{-1}.

^1H and ^{13}C NMR data of the 5-oxopiperazinium-3-sulfonate monohydrate are reported in the experimental

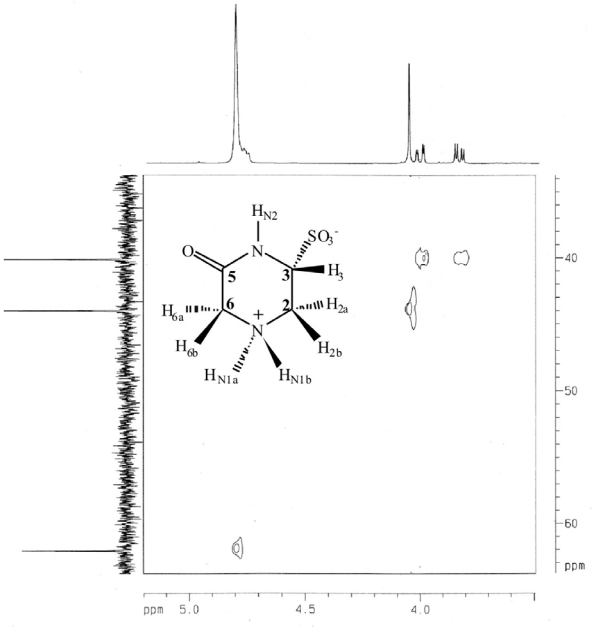

Figure 2. 500 MHz 2D HMQC spectrum of the 5-oxopiperazinium-3-sulfonate monohydrate in D_2O.

section. HMQC spectrum, illustrated in Figure 2, was acquired to undoubtedly assign the protons.

The singlet at 4.06 ppm in the ^1H NMR spectrum is assigned to the H_{6a} and H_{6b} protons based on the correlation with the C_6 carbon in the HMQC spectrum. The doublet of doublet at 3.82 ppm is assigned to the geminal (^2J 12 Hz), and vicinal (^3J = 5 Hz) coupling of the H_{2a} proton with the H_{2b} and H_3 protons, respectively. According to the HMQC spectrum, the signals at 3.82 and 4.01 ppm are correlated to the same carbon atom. This assignment is reinforced by the

data obtained from COSY spectrum in which a correlation between the H_{2a} and H_{2b} protons and between these protons and the H_3 proton is observed. The signal at 4.77 ppm is assigned to the H_3 proton. Although the COSY spectrum indicates a correlation between this proton and the H_{2a} and H_{2b} protons, it is not possible to assign the multiplicity due to the solvent signal. In fact, for piperazine compounds, the exchange between the protons of the amine fragment and deuterium atoms is frequently observed resulting in a single signal in the water region (4.8 ppm).[19]

The mass spectrum of the 5-oxopiperazinium-3-sulfonate monohydrate, illustrated in Figure 3, presents two metastable ions at *m/z* 197 and 99.

The fact that the peak at *m/z* 99 is more intense than that at *m/z* 197 is consistent with the current observation that in heteroatom-containing molecules, the amino fragment presents lower abundance. This effect is indeed observed for some diketopiperazine species.[20,21] Figure 4 presents a suggestion of a mechanism for the formation of these major ions.

Attempts were made in order to apply the same synthetic approach starting with pyridine, pyrazinamide, and imidazole. However, none of these molecules was reduced as pyrazine, meaning not only that two nitrogen atoms in the ring are required, but also that these atoms should be located *trans* to each other in order for the

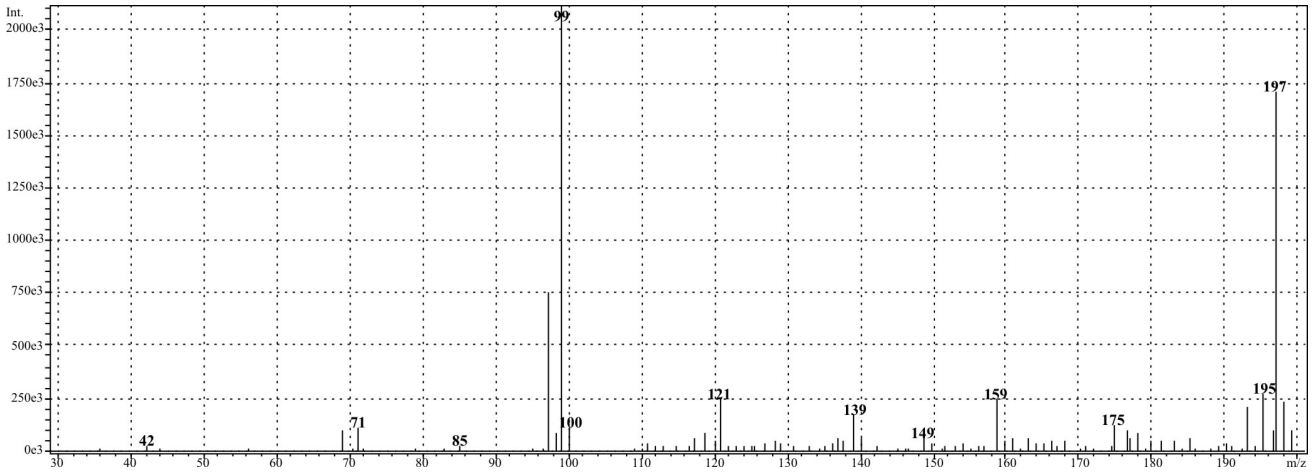

Figure 3. Mass spectrum of the 5-oxopiperazinium-3-sulfonate monohydrate in water/methanol solution.

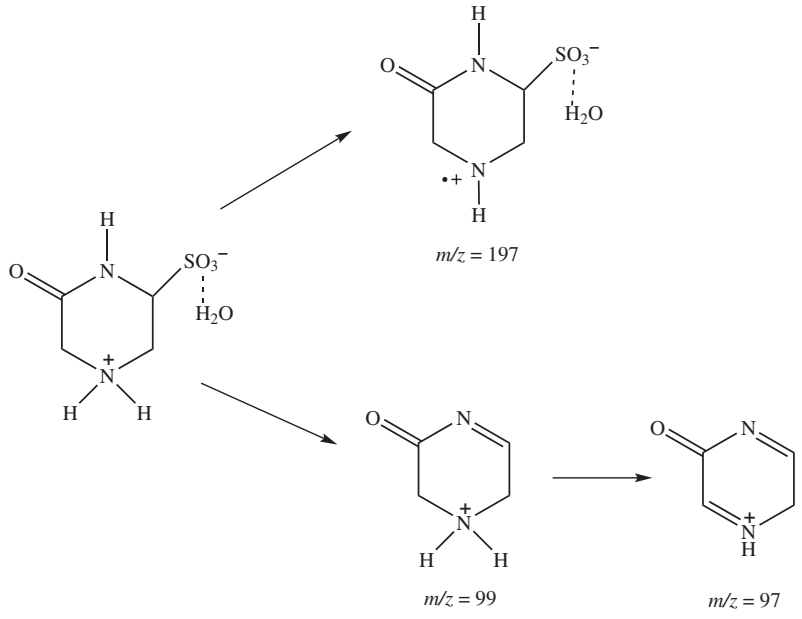

Figure 4. Suggested mechanism for the formation of the major ions from the fragmentation of the 5-oxopiperazinium-3-sulfonate monohydrate in water/methanol solution.

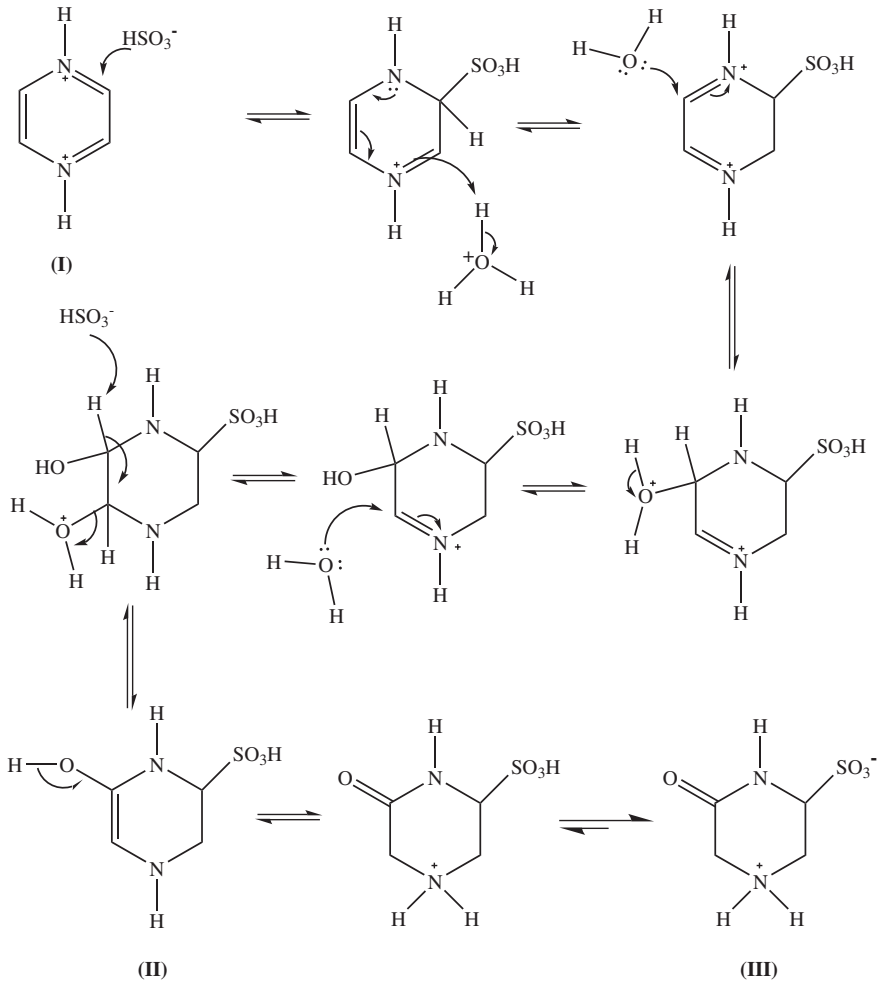

Figure 5. Mechanism suggested for the formation of the 5-oxopiperazinium-3-sulfonate monohydrate as consequence of the pyrazine reduction in acidic medium.

process to occur. In addition, the procedure was carried out in dried methanol instead of water. In such condition, no reaction was observed even after 24 h under vigorous stirring and SO_2 flow indicating that water molecules play a fundamental role in the mechanism. Based on these results and as conclusion, the mechanism presented in Figure 5 is suggested.

The reaction was carried out in acidic medium ($1.5 < pH < 4.0$) saturated with SO_2 gas. In such condition, it is well known that the most stable form of SO_2 molecules is the HSO_3^- bisulphite ion.[22] Therefore, a nucleophilic addition is suggested to occur with the attack initiated by HSO_3^- to one of the C=N bond of the ring (I). Then, a positively charged intermediate is formed and experiences successive attacks of water molecules, which act as nucleophiles like in a hydrolysis reaction. The hydrogen ions thus formed are pulled out of the ring by the HSO_3^- ion acting as a Bronsted base. Upon the elimination of water molecule, an enol (compound II) is formed and suffers tautomerism, furnishing compound III. The ORTEP view illustrated in Figure 1 is, indeed, the zwitterionic structure of the final product (III), which is the most stable form in acidic medium.

Experimental

The water used throughout was purified by a Milli-Q system (Millipore Co.).

Pyrazine, pyridine, pyrazinamide, and imidazole, from Aldrich, were used as received. Pure SO_2 (purity > 99.9%) delivered in a bottle as liquefied gas, was purchased from White Martins Praxair Inc.. All other chemicals and solvents were of analytical grade.

Elemental analyses were performed by on a FISIONS CHNS, mod. EA 1108 micro analyzer at the Microanalytical Laboratory at Universidade Federal de São Carlos in São Carlos, SP. LCMS (liquid chromatography mass spectrometry) analyses were conducted using isocratic elution (water/methanol, 90:10 v/v) with a Shimadzu C18 column (250×2.0 mm, 4.6 μm).

The experiments were carried out on a Shimadzu LCMS-2010 equipment and the flow rate was set at 0.2 mL min^{-1}. The measurements were performed in positive mode by scanning between *m/z* 30 and 300 using an APCI interface and SIM technique. The APCI parameters were set as follows: probe voltage (kV), 3.50; probe temperature, 250 °C; block temperature: 200 °C; CDL temperature: 230 °C; Q-array voltage: 0 and 20 V; gas flow: 2.5 L min^{-1}. The electronic spectrum was acquired with a Hitachi model U-2000 spectrophotometer. The transmission infrared spectrum of the compound dispersed in KBr was obtained by using a Perkin–Elmer instrument model Spectrum 1000. ^{1}H and ^{13}C NMR normal and two-dimension COSY ^{1}H-^{1}H and HMQC ^{1}H-^{13}C spectra were recorded on Bruker AVANCE 500 spectrometer.

The general synthetic procedure was followed using pyrazine (150 mg, 0.83 mmol) in water (2 mL), at room temperature, in a Schlenk flask. A flow of SO_2 was bubbled for 30 s at each 30 min of reaction. According to SO_2 equilibrium,[22] in the acidic condition (1.5 < pH < 7.0) in which the reaction was carried out, the HSO_3^- form is favored. Just after the beginning of SO_2 addition, a color change is observed. After 1 h of reaction, pale yellow crystals start to be produced. The mixture was kept under stirring and SO_2 addition for 3 h when it seems that the precipitate was no longer formed thus suggesting the complete consumption of the starting material. Calc. for $C_4H_8N_2O_4S.H_2O$: C, 24.24; H, 5.09; N, 14.13; S, 16.18%. Found: C, 24.12; H, 5.01; N, 14.09; S, 15.93%. Yield: 98%. Pale yellow crystals, mp > 250 ^{0}C. λ_{max} (H_2O): 238 nm.

^{1}H NMR (500 MHz, D_2O) δ 3.82 (dd, H_{2b}), 4.01 (dd, H_{2a}), 4.06 (s, H_{3a} e H_{3b}), 4.77 (s, H_1). $^{13}C\{^{1}H\}$ NMR (125 MHz, D_2O) δ 163.16 (s, C_4), 61.45 (s, C_1), 44.57 (s, C_3), 40.98 (s, C_2). Internal reference: DSS (sodium 4,4-dimethyl-4-silapentane-1-sulfonate). Crystallographic data and refinement parameters are reported in Table 2.

Supplementary Information

Crystallographic data for $C_4H_{10}N_2O_5S$ (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 746269. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).

Table 2. Crystal data and structure refinement parameters

Empirical formula	$C_4H_{10}N_2O_5S$	
Formula weight	198.03	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P-1	
Unit cell dimensions	a = 6.5211(2) Å	α= 100.405(2)°
	b = 6.6655(2) Å	β= 103.914(2)°
	c = 9.7323(3) Å	γ = 102.886(2)°
Volume	387.82(2) Å^3	
Z	2	
Density (calculated)	1.697 Mg m^{-3}	
Absorption coefficient	0.405 mm^{-1}	
F(000)	208	
Crystal size	0.24×0.18×0.15 mm^3	
Theta range for data collection	3.24 to 27.54°	
Index ranges	$-8 \le h \le 8$, $-8 \le k \le 8$, $-12 \le l \le 12$	
Reflections collected	3408	
Independent reflections	1770 (R(int) = 0.0130)	
Completeness to theta = 27.54°	98.4%	
Absorption correction[23]	Semi-empirical from equivalents	
Max. and min. transmission	0.904 and 0.880	
Refinement method	Full-matrix least-squares on F^2	
[a]Computing[24-26]	COLLECT, HKL Denzo and Scalepack SHELXS-97, SHELXL-97	
Data / restraints / parameters	1770 / 0 / 149	
Goodness-of-fit on F^2	1.092	
Final R indices [I>2σ(I)]	R1 = 0.0321, wR2 = 0.0830	
R indices (all data)	R1 = 0.0339, wR2 = 0.0840	
Largest diff. peak and hole	0.264 and –0.383 e.Å^{-3}	

[a] Data collection, data processing, structure solution and structure refinement respectively.

Acknowledgments

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