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# SYNTHESIS AND STRUCTURE OF DIHYDRAZONES OBTAINED FROM THE DIHYDRAZIDE OF S,S′-(1,3,4-THIADIAZOLE-2,5-DIYL)BIS(2-MERCAPTOPROPIONIC ACID)

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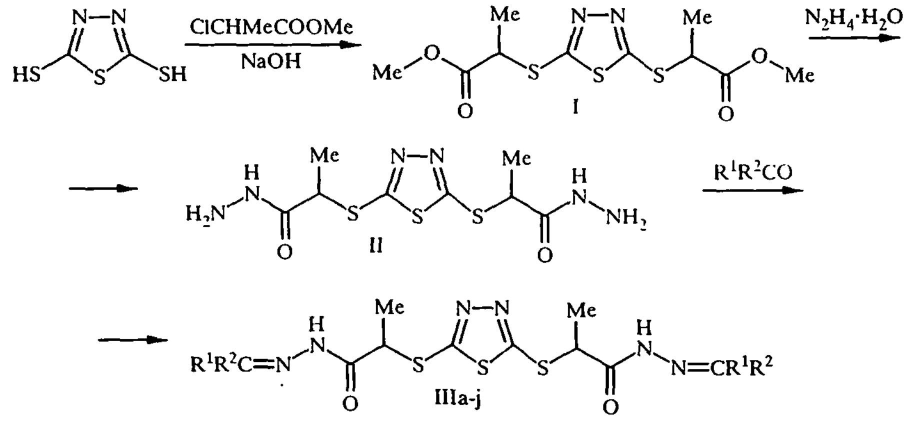
It has been established by PMR spectroscopy that dihydrazones obtained by the condensation of the dihydrazide of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid) with aldehydes, ketones, and ß-dicarbonyl compounds exist in solution as a mixture of stereoisomeric forms, the ratio of which depends on the structure of the carbonyl compound used in the condensation.

*E′,Z′*-conformational (twisting) isomerism due to hindered rotation about an N—CO amide bond and *E,Z*-geometric syn- and anti-isomerism relative to a C=N bond in bisacyl hydrazone derivatives of 2-mercaptoacetic acid have already been studied by us [1, 2]. However, there are no data in the literature on hydrazones of α-substituted 2-mercaptoacetic acid. With the aim of filling the gap existing in this area we have synthesized and studied the structure of dihydrazones from the dihydrazide of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid).

In the present work the dihydrazide (II) was isolated from the condensation of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid) dimethyl ester (I) with hydrazine hydrate in 2-propanol. Compound (II) reacts with aldehydes or ketones to form bisacyl hydrazones (IIIa-l), (IV), and (V) (Scheme 1).

Scheme 1



IIIa-j $R^1 = H$, *l* $R^1 = CH_3$; a $R^2 = 2,3\text{-}(MeO)_2C_6H_3$; b $R^2 = 2,4\text{-}(HO)_2C_6H_3$;
c $R^2 = 2\text{-}HO\text{-}3\text{-}MeOC_6H_3$; d $R^2 = 4\text{-}(Me)_2NC_6H_4$; e $R^2 = 4\text{-}ClC_6H_4$; f $R^2 = 3\text{-}NO_2C_6H_4$;
g $R^2 = 2\text{-}BrC_6H_4$; h $R^2 = 3,4\text{-}(OCH_2O)C_6H_3$; i $R^2 = C_4H_3O$; j $R^2 = 5\text{-}(Me)_2NC_4H_2O$;
k $R^1 = R^2 = C_3H_7$; *l* $R^2 = 3,4\text{-}(OCH_2O)C_6H_3CH_2$

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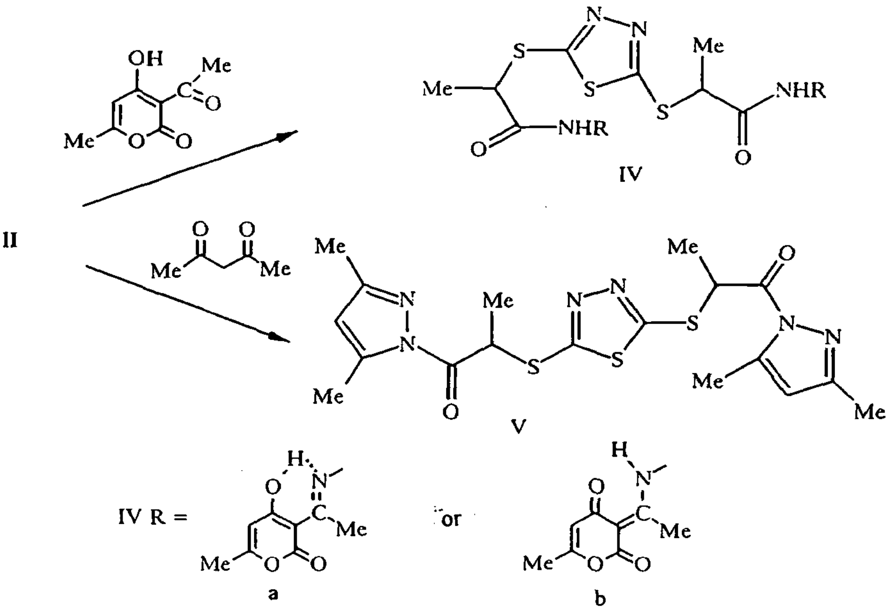
We have established analogously to [2] that the dihydrazones (IIIa-*l*) exist in DMSO or DMF solution as a mixture of only two isomeric forms (*E'*, *Z'*). This follows from the doubling in the PMR spectra of the proton signals of the CHCO, =CH, and NH groups, which coalesce on heating the solutions to 120°C. According to the data of [2] the proton signals of CHCO and NH groups of the *Z'* conformer of dihydrazones (IIIa-*l*) are found at higher field and the proton signal of the =CH group at lower field compared to the signals of the *E'* isomer.

It is known that acylhydrazones of both the *E'* and *Z'* forms are capable of forming intermolecular hydrogen bonds and only the *E'* form is able to form cyclic dimers [3]. It follows from the data of Table 2 that the *Z'* isomer predominates in the dihydrazones (IIIb,c) obtained from 2-hydroxybenzaldehydes. Possibly in these dihydrazones, which possess weak luminescence arising from an intramolecular hydrogen bond [2], a chelate ring is formed linking the electron pair of the imine nitrogen atom with the hydroxyl group proton [4]. Ring formation clearly assists the predominating *Z'* conformation.

The *E'* conformer predominates in dihydrazone (IIIi) obtained from 2-furaldehyde. In the case also of dihydrazone (IIIj) the effect of the strong electron-donating dimethylamino group in the position of the furan ring increases the electron density on the furan oxygen atom which enables the latter to form an intramolecular hydrogen bond with the -NH—N= group proton. The predominating *Z'* conformer also assists this in the present case.

Scheme 2



It was shown previously [2] that the dipyrazole obtained by the condensation of 1,3,4-thiadiazole-2,5-dithioglycolic acid dihydrazide with acetylacetone exists as a nonequilibrium mixture of two *E'*, *Z'* isomeric forms due to the presence in the molecule of a conjugated system of double bonds hindering rotation about the N—CO bond. In our case the analogous dipyrazole (V) exists only in the *E'* form. This follows from its PMR spectrum in which the signal for the $C\underline{H}(CH_3)_2$ proton is detected as only one quartet at 5.49 ppm. It is evident on spatially modeling dipyrazole (V) that it may exist only in the *E'* form since the formation of the *Z'* form is prevented by the close distance between the methyl group of the α-propionic acid fragment and the 2-methyl group of the pyrazole ring.

The existence of dihydrazone (IV) also in only one *E'* form is probably explained by the formation of a stable six-membered chelate ring stabilized by a strong intramolecular hydrogen bond. The low field signal for the NH group proton is at 15.93 ppm in the PMR spectrum of compound (IV) which points in favor of such a ring. Compounds formed

TABLE 1. Characteristics of Compounds (I)-(V)

| Compound | Empirical formula | Found, % / Calculated, % |  |  | Mp, °C | Yield, % |
|---|---|---|---|---|---|---|
|  |  | C | H | S |  |  |
| I | $C_{10}H_{14}N_2O_4S_3$ | 37,40<br>37,26 | 4,22<br>4,34 | 29,55<br>29,85 | — | 61 |
| II | $C_8H_{14}N_6O_2S_3$ | 29,69<br>29,81 | 4,25<br>4,37 | 29,61<br>29,84 | 156...158 | 74 |
| IIIa | $C_{26}H_{30}N_6O_6S_3$ | 50,62<br>50,47 | 4,81<br>4,89 | 15,78<br>15,55 | 96...98 | 95 |
| III b | $C_{22}H_{22}N_6O_6S_3$ | 46,75<br>46,96 | 3,80<br>3,95 | 17,35<br>17,10 | 147...150 | 92 |
| III c | $C_{24}H_{26}N_6O_6S_3$ | 48,97<br>48,80 | 4,28<br>4,47 | 16,02<br>16,29 | 104...106 | 85 |
| III d | $C_{26}H_{32}N_8O_2S_3$ | 53,19<br>53,41 | 5,40<br>5,52 | 16,66<br>16,45 | 106...109 | 87 |
| III e | $C_{22}H_{20}Cl_2N_6O_2S_3$ | 46,69<br>46,56 | 3,70<br>3,55 | 16,72<br>16,95 | 175...177 | 83 |
| III f | $C_{22}H_{20}N_8O_6S_3$ | 45,11<br>44,90 | 3,31<br>3,42 | 16,16<br>16,35 | 105...107 | 93 |
| III g | $C_{22}H_{20}Br_2N_6O_2S_3$ | 40,42<br>40,25 | 2,95<br>3,08 | 14,41<br>14,65 | 90...93 | 78 |
| III h | $C_{24}H_{22}N_6O_6S_3$ | 49,05<br>49,14 | 3,89<br>3,78 | 16,61<br>16,40 | 189...191 | 75 |
| III i | $C_{18}H_{18}N_6O_4S_3$ | 45,35<br>45,18 | 3,84<br>3,78 | 20,26<br>20,10 | 125...127 | 82 |
| III j | $C_{22}H_{28}N_8O_4S_3$ | 49,02<br>49,23 | 5,35<br>5,26 | 17,71<br>17,92 | ≥135<br>(decomp.) | 65 |
| III k | $C_{22}H_{38}N_6O_2S_3$ | 51,45<br>51,35 | 7,36<br>7,44 | 18,88<br>18,70 | 97...99 | 24 |
| III *l* | $C_{28}H_{30}N_6O_6S_3$ | 52,17<br>52,33 | 4,55<br>4,71 | 15,81<br>15,56 | 99...101 | 78 |
| IV | $C_{24}H_{26}N_6O_8S_3$ | 46,12<br>46,29 | 4,15<br>4,21 | 15,74<br>15,45 | 125...127 | 58 |
| V | $C_{18}H_{22}N_6O_2S_3$ | 47,88<br>47,98 | 4,99<br>4,92 | 21,22<br>21,35 | 197...198 | 31 |

by reacting 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one with amines [5, 6] may exist in two tautomeric forms (a and b). Based on certain PMR and IR spectra the authors of [6] expressed a preference for form b. We are also of this opinion, however we do not consider it possible to confirm that compound (IV) exists in form b (Scheme 2).

## EXPERIMENTAL

The PMR spectra were obtained on a Hitachi R 22 (90 MHz) spectrometer, internal standard was HMDS. Solvents: for (I) $(CD_3)_2CO$; for (II), (IIIa,h,j) DMF-$D_7$; DMSO-$D_6$ for the remaining compounds. Quantitative determinations were carried out on the basis of PMR spectra by fivefold integration of the signal of the $CH_3\underline{CH}$ methine proton, but for compound (IIIj) the signal of the NH group proton was used. The characteristics of the compounds synthesized are given in Table 1, and the PMR spectral data are given in Table 2.

**Dimethyl S,S′-(1,3,4-Thiadiazole-2,5-diyl)bis(2-mercaptopropionate) (I).** 2,5-Dimercapto-1,3,4-thia-diazole (30 g: 0.2 mole) was added to a solution of NaOH (16.8 g: 0.42 mole) in a mixture of methanol (200 ml) and 2-propanol (100 ml). Methyl 2-chloropropionate (50.2 g: 0.4 mole) was added dropwise with stirring at 35°C, after which the reaction mixture was stirred at 60°C for 1 h, then diluted with water. The precipitated oil was separated, and passed through a column of aluminum oxide (eluent 2-propanol). Diester (I) was obtained as an oil. PMR spectrum (acetone-$D_6$): 1.49 (3H, d, $CH_3$); 4.33 ppm (1H, q, CH).

TABLE 2. PMR Spectra of Dihydrazones (III)-(V)

| Compound | Chemical shifts, δ, ppm | | | | | E′ isomer, % |
|---|---|---|---|---|---|---|
| | $\underline{\mathrm{CH}}_3\mathrm{CH}$, d | $\mathrm{CH_3}\underline{\mathrm{CH}}$, q | =CH, s | NH, s | other signals | |
| IIIa | 1,62 | 4,49 (Z′)<br>5,53 (E′) | 8,38 (E′)<br>8,53 (Z′) | 11,37 (Z′)<br>11,77 (E′) | 3.78 (6H, d, $CH_3O$) | 62 |
| IIIb | 1,56 | 4,38 (Z′)<br>5,09 (E′) | 8,07 (E′)<br>8,13 (Z′) | 11,16 (Z′)<br>11,62 (E′) | 9.76 (1H, d, OH); 10.89 (1H, s, OH) | 28 |
| IIIc | 1,51 | 4,41 (Z′)<br>5,16 (E′) | 8,30 (E′)<br>8,41 (Z′) | 11,54 (Z′)<br>11,96 (E′) | 3.71 (3H, s, $CH_3O$); 9.25 d and 10.51 (1H, OH) | 42 |
| IIId | 1,49 | 4,12 (Z′)<br>4,78 (E′) | 7,42 (E′)<br>7,60 (Z′) | 10,86 (Z′)<br>11,04 (E′) | 1.95 (6H, s, $CH_3$) | 54 |
| IIIe | 1,51 | 4,44 (Z′)<br>5,19 (E′) | 7,91 (E′)<br>8,13 (Z′) | 11,09 (Z′)<br>11,75 (E′) | 7.44 (4H, m, Ph) | 53 |
| IIIf | 1,55 | 4,37 (Z′)<br>5,13 (E′) | 8,56 (E′)<br>8,73 (Z′) | 11,62 (Z′)<br>11,82 (E′) | 7.78 (4H, m, Ph) | 56 |
| IIIg | 1,51 | 4,36 (Z′)<br>5,13 (E′) | 8,22 (E′)<br>8,42 (Z′) | 11,62 (Z′)<br>11,87 (E′) | 7.45 (4H, m, Ph) | 55 |
| IIIh | 1,60 | 4,51 (Z′)<br>5,29 (E′) | 7,89 (E′)<br>8,09 (Z′) | 11,22 (Z′)<br>11,62 (E′) | 5.93 (2H, s, $OCH_2O$); 6.71 (3H, m, Ph) | 55 |
| IIIi | 1,51 | 4,38 (Z′)<br>5,11 (E′) | 7,93 (E′)<br>8,33 (Z′) | 11,36 (Z′)<br>11,50 (E′) | 6.44 (1H, m, $\mathrm{OCH{=}\underline{CH}}$); 6.73 (1H, t, $\mathrm{C{=}\underline{CH}{-}CH{=}CH}$); 7.71 (1H, d, $\mathrm{O\underline{CH}{=}CH}$) | 58 |
| IIIj[*] | 1,49 | 4,42 (Z′)<br>5,11 (E′) | 7,67 (E′)<br>7,84 (Z′) | 10,89 (Z′)<br>11,44 (E′) | 6.60 (1H, t, 3-H-furyl) | 42 |
| IIIk | 1,52 | 4,67 (Z′)<br>5,13 (E′) | — | — | 10.29 (*Z′*) 10,49 (*E′*) 0.84 (6H, t, $CH_3$) | 53 |
| III*l* | 1,67 | 4,80 (Z′)<br>5,29 (E′) | — | — | 10.53 (*Z′*) 10.60 (*E′*) 2.02 (3H. d. $CH_3C{=}$); 6.11 (2H, s, $OCH_2O$) | 51 |
| IV | 1,59 | 4,71 (E′) | — | — | 2.38 (3H, s, $CH_3$); 2.69 (3H, s, $CH_3$); 5.96 (2H, s, CH=); 11.3 (1H, br, NH); 15.93 (1H, br, OH) | 100 |
| V | 1,56 | 5,49 | — | — | 2.09 (3H, s, $CH_3C{=}O$); 2.38 (3H, s, $CH_3C{=}N$); 6.11 (1H, s, CH=) | 100 |

[*] The signal of the $\mathrm{C\underline{H}(CH_3)}$ proton overlaps the signal of the $\mathrm{\underline{C}{=}C{-}N(CH_3)_2}$ proton of the furan substituent.

**S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid) Dihydrazide (II).** Hydrazine hydrate (60 ml) was added dropwise to a solution of diester (I) (32.2 g: 0.1 mole) in 2-propanol (200 ml) at 30-40°C. The 2-propanol was partially evaporated, the precipitated crystals of dihydrazide (II) were filtered off, and washed with a little water. PMR spectrum (DMF-$D_7$): 1.44 (3H, d, $CH_3$); 4.24 ppm (1H, q, CH).

**Bis(2,3-dimethoxybenzylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIa).** A mixture of dihydrazide (II) (3.22 g: 10 mmole), dioxan (50 ml), water (5 ml), and 2,3-dimethoxybenzaldehyde (3.32 g: 20 mmole) was stirred at 70°C for 1.5 h. The dioxan was partially evaporated, the residue diluted with water, the amorphous substance (IIIa) was filtered off, and washed with ether.

**Bis(2,4-dihydroxybenzylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIb).** A mixture of dihydrazide (II) (3.22 g: 10 mmole), dioxan (50 ml), water (5 ml), and 2,4-dihydroxybenzaldehyde (2.8 g: 20 mmole) was stirred at 70°C for 1.5 h. The dioxan was partially distilled off, and the residue diluted with water. The oily reaction product was rubbed in water, the separated crystals of dihydrazone (IIIb) were filtered off, and washed with 2-propanol.

**Bis(2-hydroxy-3-methoxybenzylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIc)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (50 ml), and 2-hydroxy-3-methoxybenzaldehyde (3.04 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIb).

**Bis(4-dimethylaminobenzylidenehydrazide of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIId)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), and 4-dimethylaminobenzaldehyde (2.98 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIa).

**Bis(4-chlorobenzylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid) (IIIe)** was obtained from dihydrazone (II) (3.22 g: 10 mmole), dioxan (40 ml), and 4-chlorobenzaldehyde (2.8 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIa) with the difference that hexane was used for dilution.

**Bis(3-nitrobenzylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid) (IIIf)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), and 3-nitrobenzaldehyde (3.02 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIb).

**Bis(2-bromobenzylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic acid) (IIIg)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), and 2-bromobenzaldehyde (3.7 g: 20 mmole) by stirring the mixture at 75°C for 2.5 h. Subsequent treatment was according to the procedure for obtaining dihydrazone (IIIb).

**Bis(piperonylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIh)** was obtained from dihydrazone (II) (3.22 g: 10 mmole), dioxan (50 ml), water (5 ml), and 3,4-methylenedioxy-benzaldehyde (3 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIa). The dihydrazone (IIIh) obtained was recrystallized from a mixture of 2-propanol—dioxan—water, 5:1:3.

**Bis(furfurylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIi)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), and 2-furaldehyde (1.92 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIb).

**Bis(5-dimethylaminofurfurylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIj)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (50 ml), water (5 ml), and 5-dimethylamino-2-furaldehyde (2.79 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIa).

**Bis(4-heptylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIk).** A mixture of dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), water (3 ml), and 4-heptanone (2.28 g: 20 mmole) was heated to 60°C and stirred for 1 h at room temperature. The dioxan was partially distilled off, the residue diluted with hexane, and the precipitated oil evaporated until the appearance of crystals. These were then treated with ether, and the precipitated crystals of dihydrazone (IIIk) were filtered off, and washed with hexane.

**Bis(1-piperonylethylidenehydrazide) of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IIIl)** was obtained from dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), and methyl piperonyl ketone (3.56 g: 20 mmole) by the procedure for obtaining dihydrazone (IIIa).

**Bis[1-(6-methyl-2,4-dioxo-3,4-dihydro-2H-pyran-3-yl)ethylidenehydrazide] of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptopropionic Acid) (IV).** A mixture of dihydrazide (II) (3.22 g: 10 mmole), dioxan (40 ml), methanol (20 ml), water (3 ml), and 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (3.36 g: 20 mmole) was heated to 50°C and stirred for 1 h at room temperature, then partially evaporated, and diluted with water. The precipitated crystals of dihydrazone (IV) were recrystallized from ethanol.

**2,5-Bis[2-(3,5-dimethyl-1-pyrazolyl)-1-methyl-2-oxoethylthio]-1,3,4-thiadiazole (V).** A mixture of dihydrazide (II) (3.22 g: 10 mmole) and acetylacetone (50 ml) was heated at 105°C for 2 h. The acetylacetone was then partially evaporated, and the precipitated crystals of dihydrazone (V) were filtered off, and washed with hexane.

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