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SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, AND MASS SPECTROMETRIC STUDY OF SOME 8-METHYL-6H-THIAZOLO[3,2-f]XANTHINES

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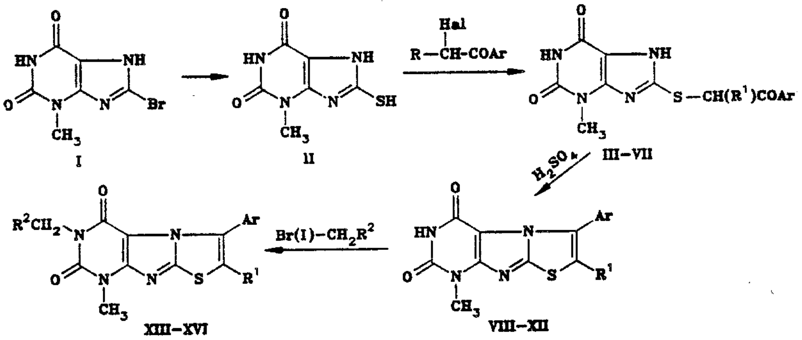
Alkylation of 8-mercapto-3-methylxanthine with α-haloketones has given the corresponding aroylmethylthio-3-methylxanthines, from which have been obtained some novel 3-aryl-8-methyl-6H-thiazolo[3,2-f]xanthines.

Reports have appeared in the literature on the preparation [1-3] and chemical properties [4] of derivatives of 6,8-dimethylthiazolo[3,2-f]xanthine. 8-Methyl-6H-thiazolo[3,2-f]-xanthines have not been described, and are of interest in terms of extending the synthetic possibilities by modifying the uracil fragment, by alkylation and conversion from the tricyclic thiazoloxanthine system into thiazolopurines, which are in the final analysis of special importance in the search for biologically active compounds and potential drugs.

Treatment of 8-bromo-3-methylxanthine (I) [5] with an excess of potassium hydrosulfide at 170-175°C in a sealed ampul results in the formation of 8-mercapto-3-methylxanthine (II), alkylation of which with α-haloketones in DMF affords the 8-aroylmethylthio-3-methylxanthines (III-VII).



III—VI, VIII—X, XIII, XIV $R^1=H$, VII, XI $R^1=C_2H_5$; XII, XIV, XVI $R^1—Ar=—(CH_2)_4—$;
III, VII, VIII, XI, XIII, XV $Ar=C_6H_5$, IV $Ar=C_6H_4CH_3$-*p*, V, IX $Ar=C_6H_4Cl$-*p*, VI, X
$Ar=C_6H_4NO_2$-*p*; XIII, XIV $R^2=COC_6H_4Cl$-*p*, XV, XVI $R^2=H$

It should be noted that on reaction of 2-bromocyclohexanone with the xanthine (II), the reaction does not stop at the formation of 8-(2-oxocyclohexylthio)-3-methylxanthine, but affords the tetracyclic compound (XII). 8-Methyl-6H-thiazolo[3,2-f]xanthine may be further alkylated at the unsubstituted nitrogen $N_{(6)}$ of the uracil moiety. For example, reaction of α-bromo-p-chloroacetophenone with (VIII) or (XII) in DMF in the presence of anhydrous potassium carbonate gives the 6-p-chlorobenzoylmethylated (XIII) and (XIV). Alkylation of these compounds with methyl iodide under similar conditions affords the known thiazoloxanthines (XV) and (XVI) [1].

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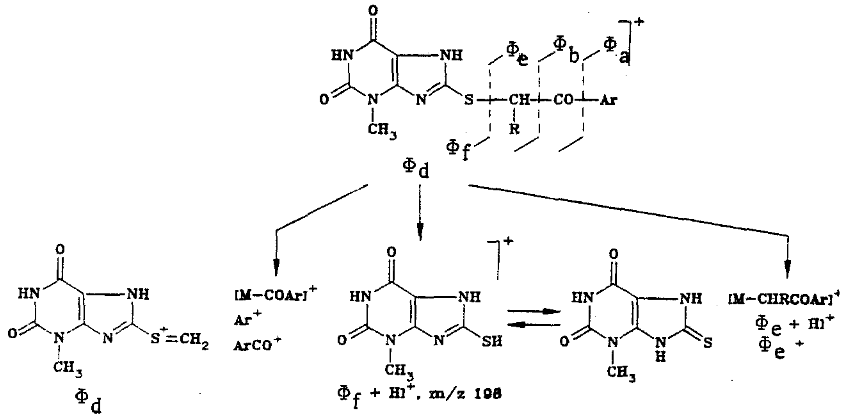
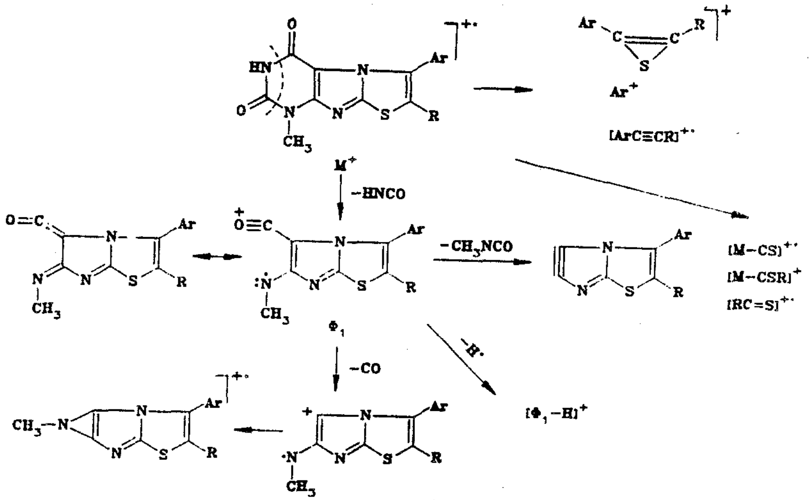
The IR spectra of (III-VII) show absorption for the stretching vibrations of the free NH in the imidazole moiety at 3490-3450 cm^{-1}. The absorption at 3135-3160 cm^{-1} is attributed to ν_s of the uracil NH [6]. The ν_{CO} absorption is seen at 1705-1690 cm^{-1}. The IR spectra of (III-VII) also show clear absorption for ν_{C-H} of the aromatic ring at 3040-3090 cm^{-1}. The uracil carbonyl absorption is shifted to lower frequencies (1690-1665 cm^{-1}). The IR spectra of (VIII-XI) display ν_{NH} absorption at 3190-3100 cm^{-1}. C–H stretching vibrations are seen at 3080-3050 cm^{-1}, and the absorption at 710-695 cm^{-1} is attributed to extraplanar deformational vibrations of this group. The uracil ν_{CO} absorption appears as two intense bands at 1725-1705 cm^{-1}. The IR spectra also contain series of bands at 1650-1505 cm^{-1} ($\nu_{C=N}$ and $\nu_{C=C}$), and bands at 1300, 1290, 1280, 1170, 1030-1015, 930, and 835-830 cm^{-1}, assigned to stretching vibrations of the rings of the heterosystem (skeletal bands) [6, 7].

Molecular ion peaks (M^+) are located in the mass spectra of (III) and (V-XII) corresponding to their empirical composition. In the case of the noncyclic compounds (III) and (V-VII), the intensities of the M^+ peaks are between 18 and 43% of I_{max}, while for the cyclic compounds (VIII-XII) the M^+ peaks are of maximum intensity [8]. The stabilities to electron impact (W_M) therefore lie in the range 0.8-3.0 for (III) and (V-VII), and between 9.4 and 12.4 for (VIII-XII).

The mode of fragmentation of $M^{+\cdot}$ in (III) and (V-VII) is in accordance with their structure. Breakdown occurs with rupture of the bond α to the carbonyl broup (as in the breakdown of ketones [9]), and by β-decomposition relative to the purine ring with and without migration of hydrogen. The structure of the substituent at $C_{(8)}$ is thus clearly established. Breakdown of the hetaryl moiety of the molecule in these compounds is represented by a small number of fragment ions. Ions specific for xanthines are present (43 and 54*) [4, 10, 11].



Breakdown of the thiazoloxanthines (VIII-XII) commences with degradation of the thiazole ring, resulting in the appearance of the ions [M − CS]$^+$, [M − CSR]$^+$, and [RC=S]$^+$. The presence of the uracil moiety is verified by the elimination of HNCO followed by CH_3NCO [10-12].



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*The numbers representing the ions are their m/z values.

TABLE 1. Properties of Compounds Obtained

Compound	T_{mp}, °C	R_f*		Found, %				Empirical formula	Calculated, %				Yield, %
		4:1:1	3:2:1	C	H	N	S		C	H	N	S	
III	241—243	0,55	0,61	53,4	3,9	10,4	9,7	$C_{14}H_{12}N_4O_3S$	53,2	3,8	17,7	10,1	63
IV	267—269			54,0	4,3	16,4	9,6	$C_{15}H_{14}N_4O_3S$	54,3	4,5	16,9	9,7	33
V	259—261	0,53	0,64	47,8	3,4	15,9	9,1	$C_{14}H_{11}ClN_4O_3S$	47,9	3,2	15,9	9,4	70
VI	246—248	0,56	0,62	46,5	3,2	19,5	8,9	$C_{14}H_{11}N_5O_5S$	46,5	3,1	19,4	8,8	83
VII	212—214			—	—	16,6	9,6	$C_{16}H_{16}N_4O_3S$	55,8	4,7	16,3	9,3	85
VIII	305—307	0,49	0,56	56,5	3,6	18,9	10,6	$C_{14}H_{10}N_4O_2S$	56,4	3,4	18,8	10,7	100
IX	321—322	0,54	0,62	50,5	3,1	16,9	9,7	$C_{14}H_9ClN_4O_2S$	50,5	2,7	16,8	9,6	80
X	>330	0,57	0,63	49,2	2,8	20,7	9,0	$C_{14}H_9N_5O_4S$	49,0	2,6	20,4	9,3	98
XI	273—275			58,7	4,1	16,8	9,6	$C_{16}H_{14}N_4O_2S$	59,0	4,3	17,2	9,8	80
XII	314—316			—	—	20,3	11,6	$C_{12}H_{12}N_4O_2S$	52,2	4,4	20,3	11,6	52
XIII	219—221			58,5	3,4	12,8	7,1	$C_{22}H_{15}ClN_4O_3S$	58,6	3,4	12,4	7,4	74
XIV	210—212			—	—	13,1	7,5	$C_{20}H_{17}ClN_4O_3S$	56,0	4,0	13,0	7,5	72

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*System butanol—acetic acid—water.

The structures of (XIII) and (XIV) are also reliably confirmed by their mass spectra. The mass spectrum of (XIII) shows peaks for M^+ corresponding to the calculated molecular mass with m/z 450/452, in a ratio of 3:1. The presence of a substituent at $N_{(6)}$ is confirmed by the fragment ions $[M - COC_6H_4Cl]^+$ (breakdown α to the carbonyl group) and $[M - ClC_6H_4CO{-}CH{=}NCO]^+$ (retrodiene breakdown). The appearance of a fragment ion 276 results from cleavage of the purine moiety of the molecule. The presence of the thiazole ring is established by ions 134 $[\overline{S{-}CH{=}C}{-}C_6H_5]^+$ and 102 $[HC{\equiv}C{-}C_6H_5]^+$. Similarly, in (XIV) the presence of the $CH_2COC_6H_4{-}Cl$-p substituent is shown by the occurrence in its mass spectrum of the ion doublets 111/113 ($[C_6H_4{-}Cl]^+$) and 139/141 ($Cl{-}C_6H_4CO]^+$) and the loss of $CH{-}COC_6H_4Cl$ from M^+, resulting finally in the pseudomolecular ion of (XII).

The mass spectra of these compounds therefore show that a characteristic feature of 6H- and 6-substituted thiazolo[3,2-f]xanthines is breakdown involving bonds in the thiazole ring of the tricyclic system, together with elimination of the 6-substituent with α- or β-fission of the bond relative to the heterosystem.

The structures of the 8-methyl-6H-thiazolo[3,2-f]xanthines have been confirmed by direct synthesis. Alkylation of (VIII) and (XII) with methyl iodide in DMF gives the 6,8-dimethylthiazolo[3,2-f]xanthines (XV) and (XVI) [1].

EXPERIMENTAL

IR spectra were recorded on a Perkin—Elmer 580B spectrophotometer, in KBr disks and Vaseline oil. Mass spectra were obtained on a Varian MAT-311A instrument with direct introduction of the sample into the ion source, evaporation temperature 100-150°C, accelerating voltage 3 kV, cathode emission current 1 mA, ionizing electron energy 70 eV.

The properties of the compounds obtained are given in Tables 1-3.

<u>8-Mercapto-3-methylxanthine (II)</u>. A mixture of 9.8 g (40 mmole) of 8-bromo-3-methylxanthine [5] and 4.32 g (60 mmole) of potassium hydrosulfide in 50 ml of methanol was heated for 8 h in a sealed ampul at 170-175°C. It was then cooled, the solid which separated diluted with 200 ml of water, and just acidified with concentrated HCl. The solid was filtered

TABLE 2. Characteristics of Absorption Bands of Functional Groups in the Compounds Obtained

Compound	$\nu_{C=O}$	ν_{NO_2}	$\nu_{C=C,\ C=N}$	ν_{NH}	$\nu_{CH(ar)}$
III	1665, 1695, 1705		1555, 1580, 1600	3160, 3490	3050
IV	1695, 1700		1550, 1580, 1610	3165, 3450	3045
V	1695, 1700		1555, 1595	3155, 3450	3040
VI	1675, 1690, 1700	1345, 1525	1505, 1595	3140	3065
VII	1665, 1690, 1700		1550, 1580, 1600, 1625	3135, 3450	3080, 3090
VIII	1700, 1715		1520, 1575, 1650	3180	3060
IX	1700, 1720		1518, 1575, 1650	3190	3060
X	1690, 1725	1300, 1555	1525, 1575, 1605	3130	3050
XI	1685, 1705		1525, 1575, 1600	3160	3070

TABLE 3. Mass Spectra of Compounds Obtained

Ions, with arbitrary designations	III	V	VI	VII	VIII	IX	X	XI	XII
M^+	316 (24)*	352 (15), 350 (43)	361 (28)	344 (26)	298 (100)	334 (34), 332 (100)	343 (100)	326 (100)	276 (100)
$[M-\mathrm{COAr}]^+$	211 (44)	211 (100)	211 (77)	239 (60)					
$[M-\mathrm{CRCOAr}]^+$	198 (15)	198 (23)	198 (15)	198 (19)					
$[M-\mathrm{CHRCOAr}]^+$	197 (19)	197 (29)	197 (13)	197 (15)					
$[\mathrm{CH_2RCOAr}]^+$	120 (20)	156 (10), 154 (30)	165 (16)	148 (30)					
$[\mathrm{CHRCOAr}]^+$	119 (10)	155—153 (10)	164 (10)	147 (45)					
$[\mathrm{Ar}]^+$	77 (42)	113 (30), 111 (90)	122 (15)	77 (65)	77 (10)	113—111 (10)	122 (15)	77 (35)	77 (18)
$[\mathrm{COAr}]^+$	105 (100)	141 (30), 139 (90)	150 (100)	105 (100)					
$[\mathrm{CH_3NCO}]^+$	57 (10)	57 (16)	57 (15)	57 (13)					
$[\mathrm{HNCO}]^+$	43 (30)	43 (38)	43 (24)	43 (50)	43 (25)	43 (40)	43 (36)	43 (20)	43 (38)
$\Phi_1[M-\mathrm{NHCO}]^+$					255 (10)	291—289 (12)	300 (9)	273 (10)	233 (12)
$[M-\mathrm{CS}]^+$					254 (36)	290 (10), 288 (32)	299 (19)	282 (55)	
$[M-\mathrm{CSR}]^+$					253 (18)	289—287 (10)	298 (10)	241 (14)	
$[M-\mathrm{HNCO},\ -\mathrm{CH_3NCO}]^+$					198 (23)	234 (11), 232 (27)	243 (34)		176 (11)
$[\underset{\diagdown\,\mathrm{S}\,\diagup}{\mathrm{ArC{=}CR}}]^+$					134 (15)	170—168 (10)	179 (10)	162 (16)	
$[\mathrm{ArC{=}CR}]^+$					102 (21)	138 (10), 136 (30)	147 (10)	130 (11)	
$[\mathrm{RC{=}S}]^+$					45 (36)	45 (36)	45 (18)	73 (13)	
$[M-\mathrm{C_2H_4}]^+$									248 (10)
$[M-\mathrm{H}]^+$									275 (17)
$[M+\mathrm{H}]^+$									277 (13)
$[\Phi_1-\mathrm{C_2H_4}]^+$								155 (11)	
$[\Phi_1-\mathrm{C_2H_5}]^+$								154 (13)	
$[\Phi_1-\mathrm{CO}]^+$									205 (11)
$[\Phi_1-\mathrm{H_2CNH}]^+$									204 (10)

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*Intensities given as % of strongest peak. Ion peaks with intensities greater than 10% shown.

off, and washed with water, alcohol, and acetone to give 7.65 g (96.5%) of the xanthine (II), R_f 0.57 (butanol—acetic acid—water, 4:1:2), mp > 330°C (decomp., DMF or conc. acetic acid). IR spectrum (KBr): 3125 (NH), 2970 (CH_3), 2600 (SH), 1700 (C=O), 1675 (C=N), 1588, 1537, 1450 (C=C), 695 cm^{-1} (C—S). PMR spectrum (CF_3COOH): 3.66 ppm (s, 3H, $-N_{(3)}-CH_3$). Found: C 36.7; H 3.3; N 28.6; S 16.1%. M 166. $C_6H_6N_4O_2$. Calculated: C 36.4; H 3.1; N 28.3; S 16.2%.

8-Aroylmethylthio-3-methylxanthines (III-VII). A mixture of 1.98 g (10 mmole) of the xanthine (I) and 10 mmole of the appropriate α-haloketone was boiled for 30-40 min in 30 ml of DMF. The mixture was cooled, diluted with 50-80 ml of water, and the solid which separated was washed with water, ethanol, and acetone, and dried to give (III)-(VII). Crystallization for analysis was carried out in ethanol or dioxane.

8-Methyl-6H-thiazolo[3,2-f]xanthines (VIII-XI). The 8-aroylmethylthio-3-methylxanthine (III-VII) was dissolved in 50-70 ml of conc. sulfuric acid (d 1.85), and kept for 16-24 h. The mixture was then diluted with 3-5 volumes of water, and the solid which separated was filtered off, washed with water, alcohol, and acetone, and dried to give (IX-XI). In the preparation of (VIII), the mixture was heated for a further 2 h on a boiling water bath. Compounds (VIII-XI) were purified for analysis by crystallization from dioxane.

2,3-Tetramethylene-8-methyl-6H-thiazolo[3,2-f]xanthine (XII). A mixture of 9.9 g (50 mmole) of the xanthine (I) and 9.74 g (55 mmole) of α-bromocyclohexanone in 100 ml of DMF was boiled for 1 h. The mixture was then cooled, diluted with three volumes of water, and the solid which separated was filtered off, washed with water and alcohol, and dried to give (XII), which was purified by recrystallization from dioxane.

3-Phenyl-6-p-chlorobenzoylmethyl-8-methylthiazolo[3,2-f]- and 2,3-Tetramethylene-6-p-chlorobenzoylmethyl-8-methylthiazolo[3,2-f]xanthine (XIII) and (XIV). A mixture of 2.89 g (10 mmole) of (VIII) or 2.76 g (10 mmole) of xanthine (XII), 2.56 g (11 mmole) of α-bromo-p-chloroacetophenone, and 1.38 g (10 mmole) of anhydrous potassium carbonate in 50-70 ml of DMF was boiled for 4 h. The mixture was then cooled, diluted with an equal volume of water, and the solid which separated was filtered off, washed with water and acetone, and dried to given xanthines (XIII) and (XIV). Mass spectrum of (XIII) (sample evaporation temperature 137°C), m/z (%): 77 (8), 102 (10), 111 (13), 113 (4), 134 (6), 139 (31), 141 (10), 194 (5), 227 (10), 254 (13), 276 (11), 278 (3), 311 (100), 312 (28), 450 (46), 452 (17). Mass spectrum of (XIV) (sample evaporation temperature 100°C), m/z (%): 76 (12), 77 (18), 78 (14), 79 (20), 80 (16), 111 (10), 113 (3), 139 (11), 141 (40), 204 (19), 205 (21), 233 (13), 248 (18), 261 (10), 275 (31), 276 (100), 277 (15), 428 (6), 430 (2).

3-Phenyl- and 2,3-Tetramethylene-6,8-dimethylthiazolo[3,2-f]xanthines (XV, XVI). A mixture of 2.98 g (10 mmole) of (VIII) or 2.76 g (10 mmole) of (XII), 2 ml (10 mmole) of methyl iodide, and 1.38 g (10 mmole) of anhydrous potassium carbonate in 30 ml of DMF was boiled for 4 h. The mixture was then cooled, diluted with an equal volume of water, and the solid which separated filtered off and washed with water and acetone, giving (XV) and (XVI). Samples of these compounds gave no depression of melting point on admixture with samples obtained as described in [1].

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sym-TRIAZOLO[4,3-a][1,3]DIAZACYCLOALKANES. 4.* SYNTHESIS AND TRANSFORMATIONS OF 2-AMINOTHIOCARBONYL-sym-TRIAZOLO[4,3-a]PYRIMIDINE

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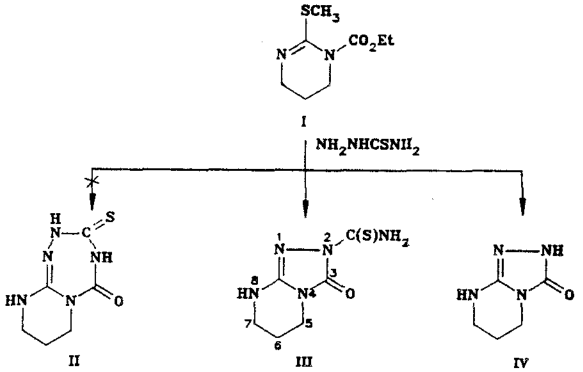
UDC 547.792.9'854.83'859.3.07

In the reaction of 1-ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidine with thiosemicarbazide, 2-aminothiocarbonyl-3-oxo-2,3,5,6,7,8-hexahydro-sym-triazolo[4,3-a]pyrimidine is formed, which as a result of the successive action of methyl iodide, K_2CO_3 solution, and cyclic amines, converts into 2,3,5,6,7,8-hexahydro-8-oxo-sym-triazolo[4,3-a]pyrimidine.

In continuation of the investigations carried out in [2] on the synthesis of new biologically active derivatives of guanidine, several transformations were carried out in order to obtain the derivatives of 2-guanidyl-3-oxo-sym-triazolo[4,3-a]pyrimidine.

As starting compounds, 2-methylthiol-ethoxycarbonyl-1,4,5,6-tetrahydropyrimidine (I) [3] and thiosemicarbazide were used. We might expect that as a result of the reaction, two isomeric compounds, derivatives of pyrimido[2,3-c][1,2,4,6]tetrazepine (II) or sym-triazolo-[4,3-a]pyrimidine (III), would be formed.



Among structures II and III the choice was made in favor of III according to the PMR spectrum, in which three one-proton signlets at 7.5, 8.9, and 9.27 ppm were observed in the low field. According to the data already obtained [1], the signal at 7.5 ppm can be assigned to the amidine grouping proton. The position of this proton in the pyrimidine ring is indicated by the presence of a signal of the 7-CH_2 methylene group protons in the spectrum, in the form of a multiplet, which converts into a triplet when heavy water is added (the amidine proton also disappears). The signals at 8.9 and 9.27 ppm may correspond to either

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*For Communication 3, see [1].

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