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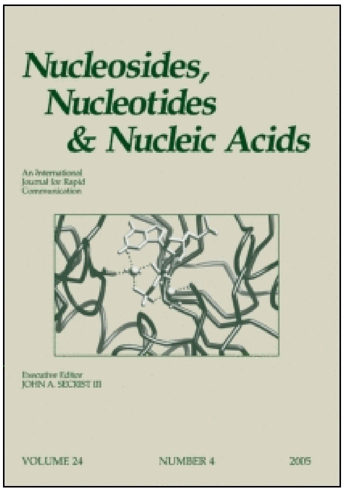

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Crystal Structure and Molecular Conformation of 4-Thiouracil-2'-Trifluorothioacetamide -3', 5'-Diacetyl-β-D-Riboside

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CRYSTAL STRUCTURE AND MOLECULAR CONFORMATION OF 4- THIOURACIL-2'-TRIFLUOROTHIOACETAMIDE -3', 5'- DIACETYL - β -D-RIBOSIDE

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ABSTRACT

4-thiouracil-2'-trifluorothioacetamide-3', 5'-diacetyl-β-D-riboside is one of the modified thiouracil analogs synthesized in our institute. The determination of the crystal and molecular structure of this compound was carried out with a view to study the conformation of the molecule in the solid state as well as to investigate the conformations of the trifluoroacetamide and the acetyl substituents of the ribose and their effects on the conformation of the ribose ring. Crystals of 4-thiouracil-2'-trifluorothioacetamide-3',5'- diacetyl-β- D-riboside are orthorhombic, space group $P2_1 2_1 2_1$, with cell dimensions a= 15.351 (2), b= 15.535 (1), c= 8.307 (1) Å , V=1981.0 (7) $Å^3$, Z=4, D_m= 1.53, D_c=1.527 g/c.c. and μ=30.1cm $^{-1}$. The structure was determined using CuKα (λ =1.5418 Å) at a temperature T of 297K, with 2333 reflections, which were collected on a Enraf-Nonius CAD-4 diffractometer, out of which 2249 (I $\geq 2\sigma$) were considered observed. The structure was determined by direct methods using MULTAN and refined by full matrix least squares method to a final reliability factor of 0.054 and a weighted R factor of 0.079. The nucleoside is in the *anti* conformation [χ_{CN} =51.4 (5)°], the ribose has the unusual C (2') *endo*- C(1') *exo* ($^2T_1$) , and a g+ conformation [ψ=47.5 (4)] across C(4')-C(5') bond. The pseudorotation angle P is 152.8 (4) ° and the amplitude of pucker τ_m of 42.7 (3)°. The average C-F bond distance is 1.308 Å . There is no base pairing and the typical base-base hydrogen bonded interactions are not present in this structure. On the other hand, a hydrogen bonded dimer is formed involving C(3') - H(3')... O (2) and N(3) -H (N3) ... O (A1) hydrogen bonds joining the base, ribose ring and the acetyl group. The trend towards longer exocyclic bonds at the acetyl centers in compounds with strongly electronegative aglycones, is also exhibited in this compound, with C(3')-O(3') and C(5')-O(5') being much longer than C(1')-O(4'). The acetyl groups also take part in C-H...O hydrogen bonding with the acetyl oxygen atom OA2.

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INTRODUCTION

In the course of preparing 2'-amino analogs of nucleosides, the title compound 4-thiouracil-2'-trifluorothioacetamide-3',5'-diacetyl-β-D-ribose (TTDR) was synthesized in our institute. The crystal structural study of TTDR was undertaken with a view to study the conformation of the trifluoroacetamide and the acetyl groups, evaluate their effects on the conformation of the ribose ring and compare these with the effects observed in crystalline pyranosides (1).

EXPERIMENTAL METHODS

Crystals were obtained by a slow evaporation of an aqueous ethanol/ water solution of TTDR at room temperature. Rectangular shaped single crystals were obtained. The crystal data, diffraction data collection parameters and refinement information are summarized in Table. 1. The data was collected on a CAD-4 diffractometer at room temperature (22±3° C) using CuKα radiation ($\lambda = 1.5418$Å) by the ω/2θ scan method. Accurate lattice parameters were determined by least-squares refinement of 25 medium angle reflections with $10 < \theta < 28°$. The ω scan angle ranges used for data collection was $(0.75 + 0.15 \tan\theta)°$ and the scan was extended on each side by 25% for background determination. The width of the horizontal variable aperture was ($4.0 + 1.2 \tan\theta$)mm. The vertical size of the slit used was 4mm. One hundred seconds was set as the maximum time limit for the slowest scan; faster scan rates were used for stronger reflections. Crystallographic computations were carried out on a PDP 11/34 computer with the Structure Determination Package program (2) of Enraf-Nonius. The intensities of three reflections at $\chi \sim 90°$ were measured for different values of φ from 0 to 360° in steps of 10° and the resultant curve of transmission as a function of φ was used to calculate absorption corrections for all reflections. Maximum and minimum transmission factors were 0.99 and 0.90 with an average value of 0.94. The structure was solved by an application of the multi solution methods using the program MULTAN (3). 360 E-values ($|E| \geq 1.3$) were used in the multi solution method. The structure was obtained using the RANTAN provision in MULTAN. The best E-map with a combined figure of merit of 3.00 and a residual of 0.217 gave the positions of all the non-hydrogen atoms in the molecule. The crystal structure was refined by full-matrix least-squares method using the SDP programs on a microvax II computer. The R factor at the end of isotropic refinement was 0.15. Further refinement was carried out with anisotropic thermal parameters for all the non-hydrogen atoms. The R factor at the end of anisotropic refinement was 0.074. A difference Fourier synthesis computed at this stage revealed all the hydrogen atoms in the molecule. The final round of refinements were carried out with anisotropic

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Table 1. Crystal data, data collection parameters, refinement details and final structural parameters.

Formula	$C_{15}H_{16}N_3O_6F_3S_2$	No. of independent reflections	2333
Formula weight	455.4	No. of independent reflections ≥2σ	2249
Space group	$P2_12_12_1$		
a(Å)	15.351(2)	Function minimized	$\Sigma w[\lvert Fo\rvert^2-(1/k)\lvert Fc\rvert^2]$
b(Å)	15.535(1)	No. of variables refined	337
c(Å)	8.307(1)	R-factor	0.054
V(Å^3)	1981.0(7)	Weighted R-factor	0.079
F(000)	1248	Goodness of fit	2.61
Z	4	Max electron density on final ΔF syntheses (eÅ^{-3})	±0.12
D_{obs}(g·cm^{-3})	1.53	Crystal size (mm)	0.46x0.21x0.12
D_{calc}(g·cm^{-3})	1.527	Scan method	ω-2θ
μ(cm^{-1})	30.1	2θ range (°)	0-154°
Scan range (°)	0.90	Final extinction coefficient	2.41 x 10^{-7}
Scan speed (deg min^{-1})	2.0		

Average standard deviations:

I) in bond lengths	0.004Å	ii) in bond angles	0.3°
involving hydrogens	0.02Å	involving nonhydrogens	2°
iii) in torsion angles	1°		

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thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms. The final R factor was 0.054 for 2249 reflections ($I \geq 2\sigma$). The weighted R factor was 0.079 and the goodness of fit (S) was 2.61. In the final full-matrix least-squares refinement cycle, each non-hydrogen shift was < 0.2% of the estimated standard deviations. The function minimized in least squares was $\sum w (|F_o|-1/k|F_c|)^2$ where $w = 1/\sigma (|F_o|^2 = 4|F_o|^2 / \sigma (|F_o|^2)^2$ and $\sigma^2 (|F_o|^2) = [\sigma^2 (I) + p^2 I^2 I^2] / LP$, where $p = 0.05$, $\sigma (I)$, is the standard deviation of intensity I based on counting statistics; k is the scale factor and $|F_o|$ is the observed structure amplitude, L is the Lorentz factor and P is the polarization factor. The maximum and average values of Δ/σ are 0.1 and 0.02 respectively and the final $|\Delta\rho|$ was 0.1e/Å^3. The programs and scattering factors are taken from Enraf-Nonius (1979) and ORTEP program of C. K. Johnson were used (4).

RESULTS AND DISCUSSION

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Figure 1 gives an ORTEP diagram of the molecule giving the atomic numbering scheme followed in the text. Table 2 gives the final fractional atomic coordinates of all the atoms in the molecule together with their standard deviations in parentheses and their equivalent thermal parameters (B_{eq}) . Figs. 2 (a) and (b) give the bond distances and bond angles involving the non-hydrogen atoms in the molecule.

The molecular dimensions of the uracil moiety agree very well (within 2σ) with the values compiled by Taylor and Kennard (5) from 28 accurate crystal structures containing 32 crystallographically independent uracil residues. Since the S-C single bond length is 1.81Å (6), the value of 1.646(3)Å obtained for the C(4)- S(4) bond length indicates its double bond character, as is expected from the major resonance form (the keto form) in the uracil moiety. Such double bond character in the C4-S4 bond is also observed in other similar molecules such as 2,4- dithiouracil (7), 4-thiouridine monohydrate (8), 1-methyl-4-thiouracil 9-methyl adenine (9), 1-β-D-arabinofuranosyl-4-thiouracil (10), 5,6-dihydro-1-methyl-4-thiouracil (11),1-methyl-4-thiouracil (12), 5,6-dihydro-2-thiouracil (13), 6-amino-2-thiouracil monohydrate (14).

For the ribose ring, the bond distances and angles for TTDR molecule generally agree with the values obtained for ribose with C2'-endo pucker. The P value for TTDR is 153° which is very near the range of 157 to 167° observed for C2'-endo puckered ribose. Most of the bond distances for the ribose moiety in TTDR fall in the ranges obtained for C2'-endo ribose, except for C(3')-O(3') and C(5')-O(5') bond lengths, which are longer than the expected range for C2'-endo ribose. This lengthening of the bond lengths could be due to the substitution of the acetyl groups on C(3') and C(5') atoms. The O(4')-C(1')-C(2') and C(4')-C(5')-O(5') bond angles for TTDR fall a little below

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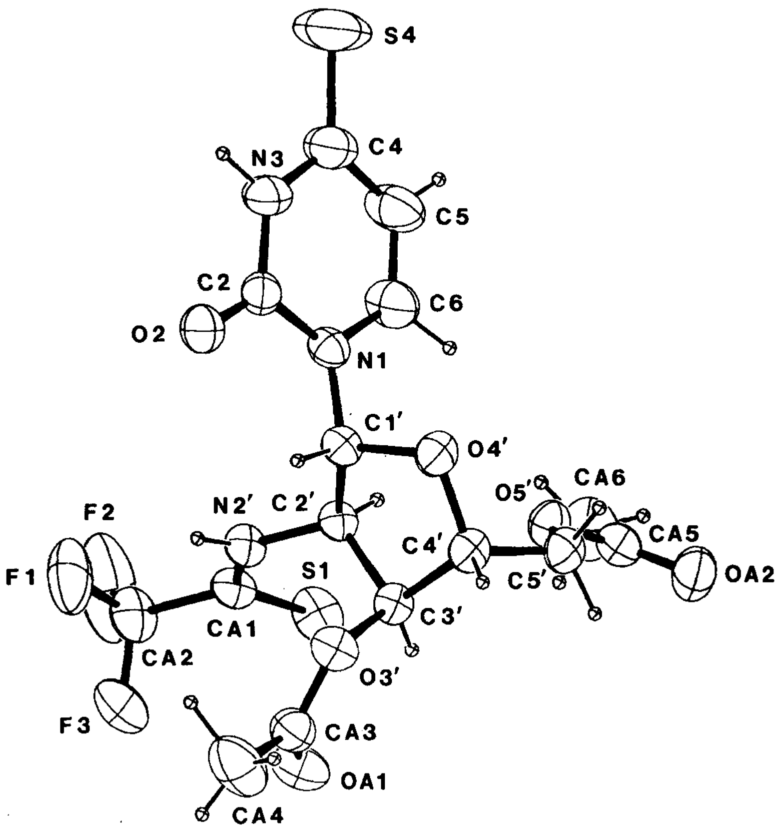

Fig. 1. ORTEP drawing showing the conformation of the molecule and the atomic numbering scheme.

the expected range for C2'-endo ribose. The reason for this discrepancy could be the number of the different substituents on the ribose moiety of TTDR molecule as compared to the unsubstituted (free) C2'-endo ribose used in the tabulation of Taylor and Kennard. The bond shortening for N (2)-C(A1) is due both to a small contribution of the thioamidic resonance and mainly, to the different hybridizations of C(A1) and C(2') atoms. Analogously, the shortening of the O(3')-C(A3) and O(5')-C(A5) bonds as compared to the O(3')-C(3') and O(5')-C(5') ones is due to a small contribution of the esteric resonance and mainly, to the different hybridizations of the carbon atoms bonded to the O(3') and O(5') oxygens.

CONFORMATION OF THE MOLECULE (TTDR)

The uracil ring in TTDR molecule exhibits the anti conformation [χ_{CN} (C(6)-N(1)-C(1')-O(4') = 51.4 (5)}] across the glycosyl bond, typical of pyrimidine nucleoside. The ribose exhibits

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Table 2. Final fractional positional parameters and their estimated standard deviations.

Atom	X	Y	Z	B(A2)
S(1)	-0.03517(8)	0.25508(8)	0.5929(1)	3.91(2)
S(4)	0.2730(1)	-0.12047(9)	1.1309(4)	8.32(6)
F(1)	0.1951(2)	0.3566(3)	0.6128(4)	6.39(8)
F(2)	0.1299(3)	0.3050(3)	0.4149(4)	9.70(1)
F(3)	0.0850(3)	0.4185(2)	0.5231(7)	9.30(1)
O(4')	0.0163(2)	0.1865(2)	1.1903(3)	3.17(5)
O(3')	0.0050(2)	0.3740(2)	1.0663(4)	3.23(5)
O(2)	0.2607(2)	0.1935(2)	1.1334(6)	4.47(7)
O(5')	-0.1375(2)	0.1457(2)	1.0010(4)	3.13(5)
O(A1)	-0.0465(3)	0.4457(2)	0.8528(5)	4.83(7)
O(A2)	-0.2794(2)	0.1167(2)	1.0257(5)	4.32(7)
N(1)	0.1342(2)	0.1271(2)	1.0605(4)	2.74(5)
N(3)	0.2582(2)	0.0479(2)	1.1214(6)	4.00(8)
N(2')	0.0873(2)	0.2818(2)	0.8135(4)	2.62(5)
C(2)	0.2211(3)	0.1283(3)	1.1068(5)	3.03(7)
C(4)	0.2200(3)	-0.0304(3)	1.0946(8)	4.50(1)
C(5)	0.1317(4)	-0.0254(3)	1.0368(9)	5.20(1)
C(6)	0.0928(3)	0.0512(3)	1.0237(7)	4.26(9)
C(1')	0.0843(2)	0.2058(2)	1.0796(4)	2.48(6)
C(2')	0.0348(2)	0.2381(2)	0.9316(4)	2.31(5)
C(3')	-0.0348(2)	0.2947(2)	1.0113(4)	2.43(6)
C(4')	-0.0562(2)	0.2434(3)	1.1627(4)	2.77(6)
C(5')	-0.1392(3)	0.1916(3)	1.1522(5)	3.05(7)

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Table 2. Continued

C(A1)	0.0580(3)	0.2910(2)	0.6627(4)	2.67(5)
C(A2)	0.1170(3)	0.3426(3)	0.5536(5)	3.89(8)
C(A3)	-0.0063(3)	0.4450(3)	0.9781(6)	3.55(8)
C(A4)	0..0373(5)	0.5199(3)	1.0567(9)	5.7(1)
C(A5)	-0.2138(3)	0.1155(3)	0.9483(6)	3.23(7)
C(A6)	-0.2058(4)	0.0826(4)	0.7791(7)	5.0(1)
H(N3)	0.318(5)	0.043(4)	1.15(1)	7(2)*
H(C5)	0.103(4)	-0.076(4)	1.019(9)	6(2)*
H(C6)	0.029(3)	0.062(4)	1.047(8)	5(1)*
H(C1')	0.122(3)	0.250(3)	1.123(6)	3(1)*
H(C2')	0.003(3)	0.190(3)	0.879(5)	2.1(8)*
H(C3')	-0.081(4)	0.307(4)	0.933(9)	5(1)*
H(C4')	-0.066(3)	0.284(3)	1.263(6)	2.6(9)*
H1(C5')	-0.191(3)	0.228(3)	1.155(6)	3.1(9)*
H2(C5')	-0.139(4)	0.158(5)	1.25(1)	7(2)*
H(N2')	0.136(4)	0.308(4)	0.849(9)	7(2)*
H1(CA4)	0.039(4)	0.566(4)	0.999(8)	8(2)*
H2(CA4)	0.024(4)	0.517(4)	1.159(8)	8(2)*
H3(CA4)	0.108(4)	0.497(4)	1.083(9)	9(2)*
H1(CA6)	-0.149(3)	0.064(4)	0.754(8)	5(1)*
H2(CA6)	-0.214(4)	0.125(4)	0.699(9)	7(2)*
H3(CA6)	-0.248(4)	0.042(3)	0.773(9)	7(1)*

starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab (cos gamma) * B(1,2) + ac (cos beta) * B(1,3) + bc (cos alpha) * B(2,3)].

the C(2')-endo- C(1')-exo {$^2T_1$} pucker with the pseudo rotation angle P of 152.8 (4)° and an amplitude of pucker, τ_m of 42.7 (3)°. The deviations of C(2'), C(1') and C(5') from the mean plane of the ribose ring are -0.259, 0.233 and -1.320Å respectively. Table 3 lists some of the torsion angles in the ribose ring. The conformation across the exocyclic C(4')- C(5') bond is gauche-gauche (g^+), the torsion angles ψ_{oo} and ψ_{oc} being -72.0 (5) and 47.5 (4)° respectively. The value of ψ' [(O(3')-C(3')-C(4')-C(5')] is 144.6 (5)°, well within the allowed range of 70 to 160°.

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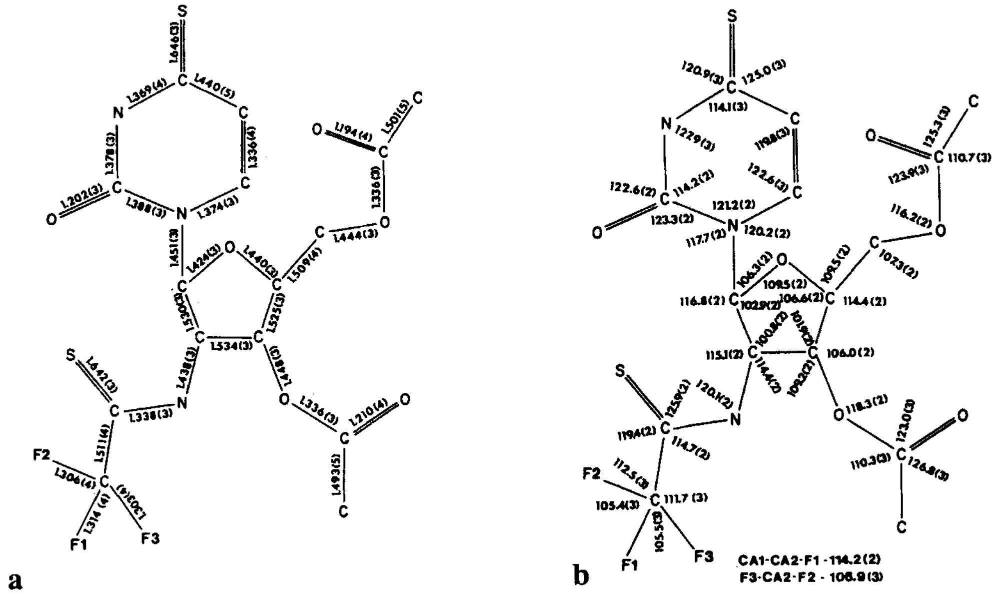

CA1-CA2-F1 - 114.2(2)
F3-CA2-F2 - 108.9(3)

Fig. 2(a) Bond distances involving non-hydrogen atoms in TTDR (b) Bond angles involving non-hydrogen atoms in TTDR

Table. 3.

Torsion angles	Values
τ_0	-30.9(4)°
τ_1	42.0(4)
τ_2	-37.2(4)
τ_3	20.1(4)
τ_4	6.7(4)
P	152.8(4)
τ_m	42.7(3)

HYDROGEN BONDING AND PACKING

The hydrogen bonding interactions are illustrated in the stereo view (Fig.3). The distances and angles involved in hydrogen bonding are listed in Table. 4. The oxygen atom of both the acetyl groups are hydrogen bond acceptors from N(3) and N2'. The C(3')-H...O2 hydrogen bond could be

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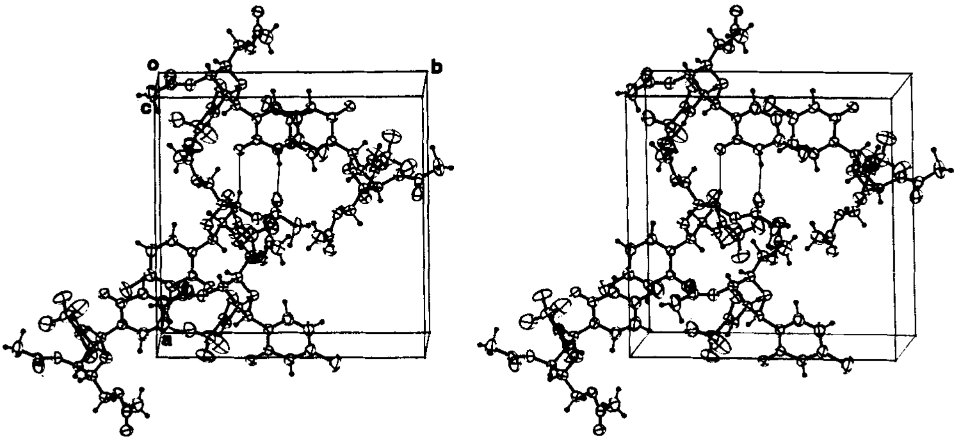

Fig.3. A stereo view of hydrogen bonding and packing in TTDR

Table.4 Hydrogen bond distances (in Å) and angles (°) in TTDR

Donor D	Hydrogen H	Acceptor A	Distances in Å D-H	H...A	D...A	Angle (°) D-H...A	Data set
C3'	HC3'	O2	0.98(4)	2.49(4)	3.366(3)	148(4)	x-1/2, -y+1/2, z+2
N2'	HN2'	OA2	0.91(5)	2.03(5)	2.910(3)	163(4)	x+1/2, -y+1/2, z+2
N3	HN3	OA1	0.96(5)	2.09(5)	3.008(4)	160(5)	x+1/2,-y+1/2, z +2
CA4	HCA4	OA2	1.17(5)	2.63(5)	3.591(6)	139(3)	x+1/2, -y+1/2, z+2

due to the partial positive charge on the C(3') atom, as pointed out by Renugopalakrishnan, Lakshminarayanan and Sasisekharan (15), It is noteworthy to mention that a dimer is formed using the C(3')-H(C3')...O(2) and N(3)-H(N3)...O(A1) hydrogen bonds involving the base, ribose ring and the acetyl group. The typical base-base hydrogen bonding interactions are not present in this structure.

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