COMPETITION OF THE HANTZSCH AND BOESE REACTIONS

IN THE INTERACTION OF 1-THIOCARBAMOYLTHIOSEMICARBAZIDE

AND PHENYLCHLOROPYRUVIC ACID METHYL ESTER

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1-Thiocarbamoylthiosemicarbazide, the synthetic equivalent of thiourea and thiosemicarbazide, reacts with phenylchloropyruvic acid methyl ester exclusively as thiourea (Hantzsch reaction) forming 2-hydrazo-4-methoxycarbonyl-5-phenylthiazole. Diacetylation and reductive fission of this hydrazo compound was carried out, and also oxidation to the corresponding azo compound, readily accomplished with using dimethyl sulfoxide.

Esters [1] and amides [2] of arylchloropyruvic acid (α-chlorobenzyl glyoxylates and -glyoxylamides) ArCHClCOCOA (A = OR, NR_2), which are available due to our works, are the synthetic equivalents of the synthon ArCHC$^+$(O$^-$)C(O)A and react with 1,3- and 1,4-S,N-binucleophiles forming functionalized nitrogen-containing heterocyles, *viz.* thiazoles [3-7], thiazolidines [8], 1,3,4-thiadiazines [8,9], perhydro-1,3,4-thiadiazines [8,9], and 5,6-dihydro-1,4-thiazines [10-12]. Closing of these or other rings in these reactions frequently depends on the conditions and on the structure of the reactants.

It seems of interest in this connection to clarify how 1-thiocarbamoylthiosemicarbazide (bisthiourea) (II) behaves in condensation with phenylchloropyruvic acid methyl ester (I), the simplest electrophile of this type: as bisthioamide by the Hantzsch reaction with the formation of bisthiazolylhydrazine dihydrochloride (III), as the substituted thiosemicarbazide by the Boese reaction with the formation of perhydro-1,3,4-thiadiazine hydrochloride (IV), or by a mixed scheme with the formation of compound V. It turned out that bisthiourea II gave bisthiazole dihydrochloride III almost quantitatively with two moles of compound I, i.e. the hydrazine moiety was not affected. In other words, the competition between the Hantzsch and Boese reactions was directed in favor of the former.

Like other disubstituted hydrazines the bisthiazole free base VI was readily diacetylated and also underwent reductive splitting of the N–N bond. On heating in dimethyl sulfoxide the hydrazo compound VI is oxidized readily and in good yield to the corresponding azo compound IX. That the azo compound and not its dithiazolotetrazine isomer X is actually formed, was shown by X-ray crystallographic analysis.

The molecule of compound IX is in a particular position in the crystal, the center of symmetry is in the middle of the $N_{(6)}=N_{(6a)}$ azo group bond (see Fig. 1). Consequently the coordinates and geometric parameters of half the molecule are given in the Tables. The thiazole rings of the molecule IX compound are planar within the limits of 0.008(5) Å. The deviation of the $N_{(6)}$ atom from the plane of the heterocycle is 0.011(5) Å, i.e. it also practically lies in this plane. Since the center of symmetry lies on the $N_{(6)}=N_{(6a)}$ bond all the central fragment of the molecule containing both thiazole rings and the azo group is planar and has the *trans* configuration. The planes of the phenyl substituents and the methoxycarbonyl groups are disposed with dihedral angles of 44.4° and 14.3° respectively relative to the central plane, which is somewhat greater than in 2-(3',5'-dimethyl-1'-pyrazolyl)-4-
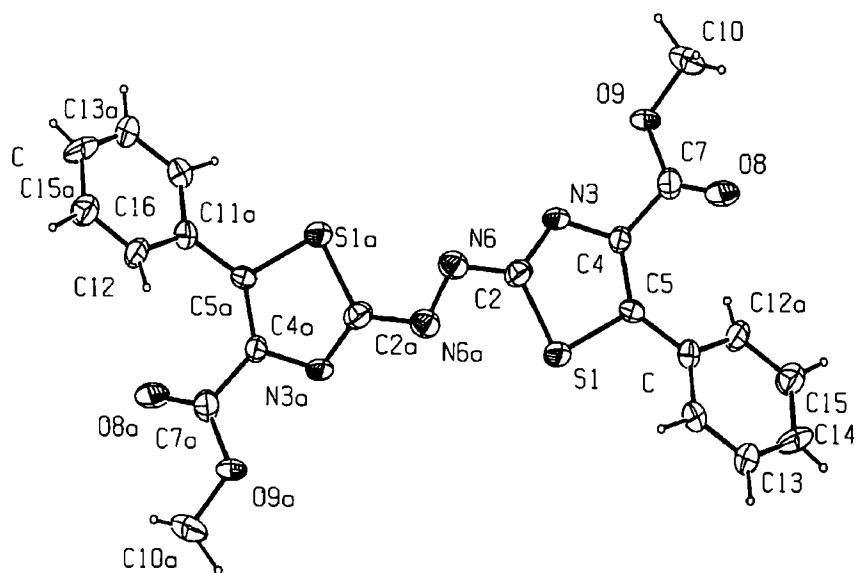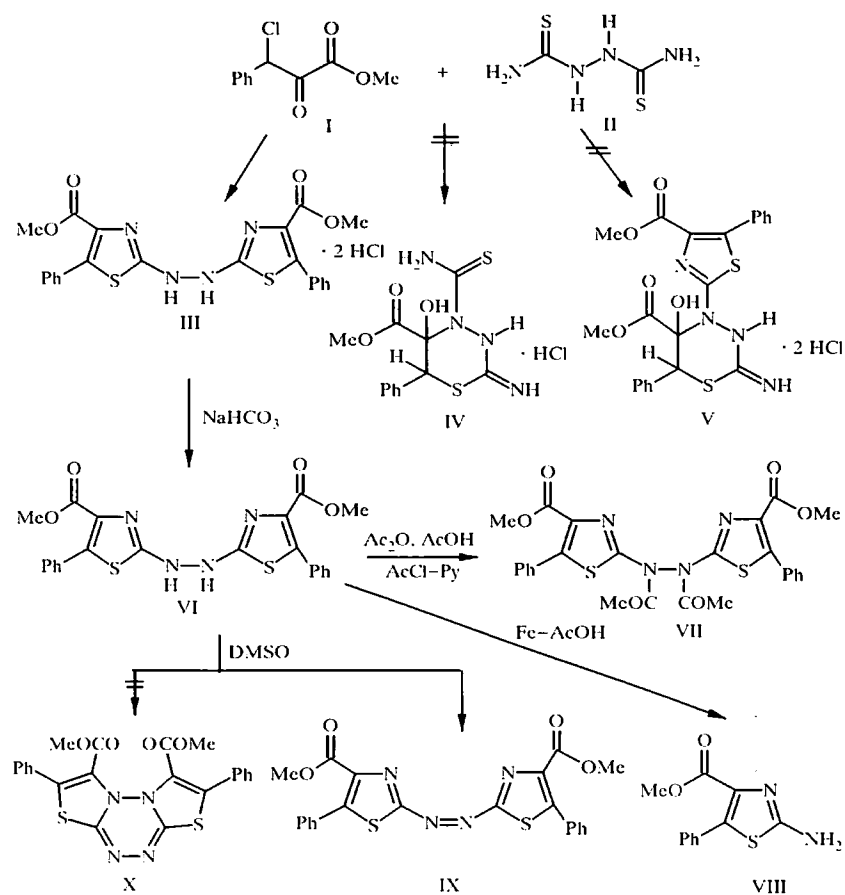
Fig. 1. Geometry of 2,2'-azobis(4-methoxycarbonyl-5-phenylthiazole) molecule in the crystal.

TABLE 1. Characteristics of the Compounds Synthesized

Com-pound	Empirical formula	Found, % / Calculated				mp, °C (solvent)	IR spectrum, ν, cm⁻¹	PMR spectrum, δ, ppm, J, Hz (solvent)	Yield, %
		C	H	N	S				
III	$C_{22}H_{18}N_4O_2S_2 \cdot 2HCl$	48.79 / 48.99	3.33 / 3.70	10.47 / 10.38	11.58* / 11.89	223-224	1720 (C–O), 2400-3200 (NH)	3.85 (6H, s, MeO); 7.51-7.72 (10H, m, Ph); 8.12 (1H, s, NH) (DMF-d₇)	90
VI	$C_{22}H_{16}N_4O_4S_2$	56.23 / 56.65	4.01 / 3.85	12.22 / 12.00	13.41 / 13.75	202-204	1720 (C–O), 2700-3340 (NH)	3.93 (6H, s, MeO); 7.46 (10H, s, Ph) (CF₃COOH)	92
VII	$C_{26}H_{22}N_4O_4S_2$	56.38 / 56.73	3.98 / 3.99	10.55 / 10.17	11.23 / 11.65	216-217 (i-PrOH)	1710 (C–O amide), 1730 (C–O ester)	2.63 (6H, s, MeOCO); 3.78 (6H, s, MeCO); 7.55-7.75 (10H, m, Ph) (DMSO-d₆+acetone-d₆)	89 (A) 76 (B) 81 (C)
IX	$C_{22}H_{16}N_4O_4S_2$	56.85 / 56.90	3.44 / 3.44	12.01 / 12.06	13.77 / 13.81	265-266 (DMSO)	1460 (N–N), 1760 (C–O)	3.84 (6H, s, MeO); 7.50-7.75 (10H, m, Ph) (DMSO-d₆)	75

*Found, %: Cl 12.87. Calculated, %: Cl 13.14

TABLE 2. Coordinates of the Atoms of Compound X, Equivalent Isotropic Temperature Factors of the Nonhydrogen Atoms $B = \frac{1}{3} \cdot \sum_{i=1}^{3} \sum_{j=1}^{3} (a_i \cdot a_j) \cdot B(i,j)(\text{Å}^2)$ and Isotropic Temperature Factors of the Hydrogen Atoms $B_{iso}(\text{Å}^2)$

Atom	x	y	z	c
$S_{(1)}$	0.5871(5)	0.03754(6)	0.2477(2)	2.69(3)
$O_{(8)}$	1.131(1)	0.1872(1)	0.2796(4)	3.8(1)
$O_{(9)}$	1.001(1)	0.1825(1)	0.4929(4)	3.3(1)
$N_{(3)}$	0.782(1)	0.0933(2)	0.4589(5)	2.5(1)
$N_{(6)}$	0.574(1)	0.0192(1)	0.5266(5)	2.9(1)
$C_{(2)}$	0.655(2)	0.0507(2)	0.4252(5)	2.6(2)
$C_{(4)}$	0.839(1)	0.1174(2)	0.3433(6)	2.0(1)
$C_{(5)}$	0.747(2)	0.0943(2)	0.2164(6)	2.1(1)
$C_{(7)}$	1.004(2)	0.1660(2)	0.3649(6)	2.6(1)
$C_{(10)}$	1.166(2)	0.2285(2)	0.5288(7)	4.5(2)
$C_{(11)}$	0.745(2)	0.1080(2)	0.0718(6)	2.4(1)
$C_{(12)}$	0.849(2)	0.0752(2)	-0.0224(6)	2.8(2)
$C_{(13)}$	0.836(2)	0.0875(2)	-0.1602(6)	3.1(2)
$C_{(14)}$	0.712(2)	0.1318(2)	-0.2068(6)	3.9(2)
$C_{(15)}$	0.602(2)	0.1651(2)	-0.1169(6)	3.5(2)
$C_{(16)}$	0.622(2)	0.1532(2)	0.0223(6)	2.8(2)
$H_{(12)}$	0.942	0.044	0.013	3.5*
$H_{(13)}$	0.921	0.064	-0.223	4.0*
$H_{(14)}$	0.691	0.137	-0.288	6.0*
$H_{(15)}$	0.497	0.199	-0.144	6.0*
$H_{(16)}$	0.513	0.170	0.083	6.0*
$H_{(101)}$	1.137	0.233	0.632	6.0*
$H_{(102)}$	1.425	0.223	0.537	6.0*
$H_{(103)}$	1.133	0.247	0.464	6.0*

* Not defined more accurately.

methoxycarbonyl-5-phenylthiazole studied by us previously [7]. Since the thiazole ring is a heteroaromatic system, and the degree of conjugation is proportional to the cosine of the angle between the planar fragments, the 2-azothiazole structure IX may be considered as conjugated within the limits of the overall molecule, including (to a lesser extent) the methoxycarbonyl and even the phenyl substituents. Judging by the bond lengths in the azothiazole fragment (apart from $C_{(4)}=C_{(5)}$), which are no different within the limits of experimental error from the corresponding lengths in thiazole-2-azo-1'-naphth-2'-ol [13] structurally close to 2-azothiazole IX, the degree of conjugation in these two related compounds is approximately the same. The $C_{(4)}=C_{(5)}$ double bond in the investigated 2-azothiazole IX, as in the mentioned 2-(3',5'-dimethyl-1'-pyrazolyl)-4-methoxy-carbonyl-5-phenylthiazole [7], is significantly longer – its length amounts to 1.379(7) Å [as against 1,332(9)] and reflects the conjugation in the system $MeOC(O)-C_{(4)}=C_{(5)}-Ph$, absent from the naphthol analog, which has no substituent at the $C_{(4)}$ and $C_{(5)}$ atoms of the heterocycle. In both azothiazoles cis orientation of the heterocyclic sulfur atom relative to the azo group is realized. This, according to quantum-chemical calculations made for thiazole-2-azo-1'-naphth-2'-ol [13], is related to the more strong attracting electrostatic interaction of the azo group with the sulfur atom compared with the $N_{(3)}$ atom in the alternative trans orientation of the sulfur atom. In both of the 2-azo-substituted thiazoles being considered the azo bond was somewhat longer than in trans-azobenzene [14] and trans-azo-p-toluene [15], which may also be considered as a sign of stronger conjugation involving the azo group.

It must be said that all comparisons with thiazolyl-2-azo-1'-naphth-2'-ol were carried out for the one of the two independent molecules in its crystal [13] which is closer in geometry to the actual azo compound, the hydrazone-like molecule was disregarded.

TABLE 3. Bond Lengths (d) and Valence Angles (ω) of the Compounds Synthesized

Bond	d, Å	Bond	d, Å
$S_{(1)}-C_{(2)}$	1.738(5)	$C_{(4)}-C_{(5)}$	1.379(7)
$S_{(1)}-C_{(5)}$	1.741(6)	$C_{(4)}-C_{(7)}$	1.493(8)
$O_{(8)}-C_{(7)}$	1.196(7)	$C_{(5)}-C_{(11)}$	1.455(8)
$O_{(9)}-C_{(7)}$	1.329(7)	$C_{(11)}-C_{(12)}$	1.402(8)
$O_{(9)}-C_{(10)}$	1.443(7)	$C_{(11)}-C_{(16)}$	1.397(8)
$N_{(3)}-C_{(2)}$	1.298(7)	$C_{(12)}-C_{(13)}$	1.375(8)
$N_{(3)}-C_{(4)}$	1.361(7)	$C_{(13)}-C_{(14)}$	1.367(8)
$N_{(6)}-N_{(6a)}$	1.274(6)	$C_{(14)}-C_{(15)}$	1.391(9)
$N_{(6)}-C_{(2)}$	1.397(7)	$C_{(15)}-C_{(16)}$	1.382(8)

Angle	ω, deg.	Angle	ω, deg.
$C_{(2)}-S_{(1)}-C_{(5)}$	89.4(3)	$C_{(4)}-C_{(5)}-C_{(11)}$	134.4(5)
$C_{(7)}-O_{(9)}-C_{(10)}$	116.7(5)	$O_{(8)}-C_{(7)}-O_{(9)}$	123.9(5)
$C_{(2)}-N_{(3)}-C_{(4)}$	110.6(4)	$O_{(8)}-C_{(7)}-C_{(4)}$	124.7(5)
$N_{(6)}-N_{(6a)}-C_{(2)}$	112.4(4)	$O_{(9)}-C_{(7)}-C_{(4)}$	111.4(5)
$S_{(1)}-C_{(2)}-N_{(3)}$	115.0(4)	$C_{(5)}-C_{(11)}-C_{(12)}$	120.8(5)
$S_{(1)}-C_{(2)}-N_{(6)}$	123.9(4)	$C_{(5)}-C_{(11)}-C_{(16)}$	120.5(5)
$N_{(3)}-C_{(2)}-N_{(6)}$	121.1(5)	$C_{(12)}-C_{(11)}-C_{(16)}$	118.6(5)
$N_{(3)}-C_{(4)}-C_{(5)}$	117.2(5)	$C_{(11)}-C_{(12)}-C_{(13)}$	120.9(5)
$N_{(3)}-C_{(4)}-C_{(7)}$	117.4(4)	$C_{(12)}-C_{(13)}-C_{(14)}$	119.6(6)
$C_{(5)}-C_{(4)}-C_{(7)}$	125.4(5)	$C_{(13)}-C_{(14)}-C_{(15)}$	121.2(5)
$S_{(1)}-C_{(5)}-C_{(4)}$	107.8(4)	$C_{(14)}-C_{(15)}-C_{(16)}$	119.5(5)
$S_{(1)}-C_{(5)}-C_{(11)}$	117.7(4)	$C_{(11)}-C_{(16)}-C_{(15)}$	120.3(5)

Standard deviation is given in parentheses.

TABLE 4. Torsion Angles τ

Angle	τ, deg.	Angle	τ, deg.
$C_{(5)}-S_{(1)}-C_{(2)}-N_{(3)}$	0.29 (0.49)	$S_{(1)}-C_{(5)}-C_{(11)}-C_{(12)}$	-43.50 (0.77)
$C_{(5)}-S_{(1)}-C_{(2)}-N_{(6)}$	179.08 (0.53)	$S_{(1)}-C_{(5)}-C_{(11)}-C_{(16)}$	133.40 (0.52)
$C_{(2)}-S_{(1)}-C_{(5)}-C_{(4)}$	0.55 (0.46)	$C_{(4)}-C_{(5)}-C_{(11)}-C_{(12)}$	139.79 (0.70)
$C_{(2)}-S_{(1)}-C_{(5)}-C_{(11)}$	-176.98 (0.50)	$C_{(4)}-C_{(5)}-C_{(11)}-C_{(16)}$	-43.31 (1.03)
$C_{(10)}-O_{(9)}-C_{(7)}-O_{(8)}$	-0.90 (0.85)	$C_{(5)}-C_{(11)}-C_{(12)}-C_{(13)}$	177.77 (0.58)
$C_{(10)}-O_{(9)}-C_{(7)}-C_{(4)}$	177.49 (0.49)	$C_{(16)}-C_{(11)}-C_{(12)}-C_{(13)}$	0.82 (0.92)
$C_{(4)}-N_{(3)}-C_{(2)}-S_{(1)}$	-1.06 (0.65)	$C_{(5)}-C_{(11)}-C_{(16)}-C_{(15)}$	-176.52 (0.59)
$C_{(4)}-N_{(3)}-C_{(2)}-N_{(6)}$	-179.89 (0.51)	$C_{(12)}-C_{(11)}-C_{(16)}-C_{(15)}$	0.44 (0.92)
$C_{(2)}-N_{(3)}-C_{(4)}-C_{(5)}$	1.57 (0.75)	$C_{(11)}-C_{(12)}-C_{(13)}-C_{(14)}$	-1.47 (0.95)
$C_{(2)}-N_{(3)}-C_{(4)}-C_{(7)}$	-176.78 (0.52)	$C_{(12)}-C_{(13)}-C_{(14)}-C_{(15)}$	0.86 (0.99)
$N_{(3)}-C_{(4)}-C_{(5)}-S_{(1)}$	-1.32 (0.67)	$C_{(13)}-C_{(14)}-C_{(15)}-C_{(16)}$	0.38 (1.01)
$N_{(3)}-C_{(4)}-C_{(5)}-C_{(11)}$	175.62 (0.63)	$C_{(14)}-C_{(15)}-C_{(16)}-C_{(11)}$	-1.03 (0.97)
$C_{(7)}-C_{(4)}-C_{(5)}-S_{(1)}$	176.88 (0.48)	$C_{(5)}-C_{(4)}-C_{(7)}-O_{(9)}$	168.10 (0.55)
$C_{(7)}-C_{(4)}-C_{(5)}-C_{(11)}$	-6.18 (1.10)	$N_{(3)}-C_{(4)}-C_{(7)}-O_{(9)}$	-13.70 (0.74)
$N_{(3)}-C_{(4)}-C_{(7)}-O_{(8)}$	164.67 (0.57)	$C_{(5)}-C_{(4)}-C_{(7)}-O_{(8)}$	-13.53 (0.98)

EXPERIMENTAL

Melting points were determined on a Boetius stage. The IR spectra were taken on an UR 20 spectrometer (Nujol mull). The ^{1}H NMR spectra of compounds VI, VIII, and X were recorded on a Bruker WV 250 spectrometer with an operating frequency of 250.13 MHz, and of compound VI on a Varian T 60 spectrometer with an operating frequency of 60 MHz.

The X-ray structural analysis was carried out on an Enraf-Nonius CAD-4 automatic four-circle diffractometer (λMoKα, graphite monochromator, $\omega/2\theta$-scanning, $\theta < 26.3°$). Crystals of $C_{22}H_{16}N_4O_4S_2$ are monoclinic, $a = 3.905(6)$, $b = 27.721(5)$, $c = 9.731(1)$ Å; $\beta = 100.59(5)°$; $V = 1035.5(9)$ Å^3; $d_{calc} = 1.39$ g/cm^3; $Z = 2$, space group $P2_1/c$. The parameters of the unit cell and the intensities of 2452 reflections, 723 of which had $I > 3\sigma$ (I) were measured at 20°C. No loss of intensity of three control reflections was observed during the time of the experiment. The structure was solved by the direct method using the SIR program [16] and was refined in an isotropic and then in an anisotropic approach. All hydrogen atoms were revealed from difference sets of electron density, their contribution to the structural amplitudes was calculated with fixed positional and isotropic temperature parameters. The final values of the divergence factors were $R = 0.04077$, $R_w = 0.04195$ on 636 independent reflections with $F^2 > 3\sigma$. All calculations were carried out on an Alpha Station 200 with the MolEN program set [17]. The coordinates of atoms, bond lengths, valence and torsion angles are given in Tables 2-4.

2-Hydrazo-4-methoxycarbonyl-5-phenylthiazole Dihydrochloride (III). Solution of compound I (9.14 g, 0.043 mol) and hydrazodithiocarbamide (3.2 g, 21.3 mmol) in methanol (100 ml) was boiled for 3 h. Methanol was removed in vacuum. Ether (50 ml) was added to the residue, the crystals which precipitated were filtered off, washed with ether, and dried in the air. Analytically pure product was obtained. Attempts at recrystallization made the quality worse.

2-Hydrazo-4-methoxycarbonyl-5-phenylthiazole (VI). Compound III dihydrochloride (10.0 g, 18.5 mmol) was stirred with aqueous 5% NaHCO$_3$ solution (50 ml). The crystals which precipitated were filtered off, washed with water, and dried. Analytically pure product was obtained. Attempts at recrystallization made the quality worse.

N,N'-Diacetyl-2-hydrazo-4-methoxycarbonyl-5-phenylthiazole (VII). A. Solution of hydrazobisthiazole VI (2.00 g, 4.3 mmol) in acetic anhydride (10 ml) was boiled for 3 h, the solvent was evaporated in vacuum, and the residue recrystallized.

B. Acetic acid was used in place of acetic anhydride, the reaction time was 5 h.

C. Acetyl chloride (0.70 g; 9 mmol) was added with stirring to suspension of hydrazo compound VI (2.00 g, 4.3 mmol) in benzene (50 ml) and Et$_3$N (1.00 g, 10 mmol) in atmosphere of argon at 10-15°C. Stirring was continued for 3 h at 20°C, and the mixture was then left overnight. The solvent was distilled off, the residue washed with water, dried, and recrystallized.

2-Azobis-4-methoxycarbonyl-5-phenylthiazole (IX). Solution of hydrazobisthiazole VI (2.00 g, 4.3 mmol) in DMSO (20 ml) was heated to boiling. The solution immediately became colored and red crystals were precipitated. The reaction mixture was cooled, the precipitated crystals were filtered off, washed with 2-propanol, and recrystallized.

Reductive Splitting of 2-Hydrazo-4-methoxycarbonyl-5-phenylthiazole (VI). Iron powder (5 g) was added to solution of hydrazothiazole VI (1.00 g, 2 mmol) in acetic acid (25 ml) containing water (3 ml). The mixture was boiled for 5 h, then decanted hot. Crystals separated from the solution on cooling were filtered off, dried in the air, and recrystallized from aqueous methanol, 1 : 1. 2-Aminothiazole VIII (0.45 g; 45%) was obtained having mp 223°C (literature [3] mp 223 °C).

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