Chemistry of Heterocyclic Compounds, Vol. 43, No. 3, 2007

SYNTHESIS OF NEW 2-AMINO-5-HYDROXYMETHYL-2-THIAZOLINES

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A simple and convenient method is proposed for the synthesis of 2-amino-5-hydroxymethylthiazolines with various substituents in the amino group, which is based on hydrolysis of the corresponding 5-halomethyl derivatives of thiazoline in the presence of divalent lead oxide.

Keywords: 2-amino-5-hydroxymethyl-2-thiazoline, nitric oxide, hydrolysis, X-ray structural analysis, NMR.

It is familiar [1] that 2-amino-2-thiazoline derivatives provide radiation protection. Recently, interest has been shown in their capacity to act selectively on certain enzymes (e.g., NO synthase isoforms) [2, 3]. This has led to a search for a convenient method of synthesizing previously unknown 2-amino-5-hydroxymethyl-2-thiazolines with alkyl, benzyl, alkylbenzyl, dibenzyl, and hetaryl substituents in the amino group. The literature bears isolated items of information on the synthesis of such compounds from the corresponding 5-haloderivatives of thiazoline in the presence of silver salts [4, 5], but unfortunately they lack descriptions of the experimental methods and proof of the structures of the substances.

We have examined the hydrolysis of the hydrohalides of 2-amino-substituted 5-halomethyl-2-thiazolines **1a-h** made by traditional methods: iodination of the corresponding N'-derivatives of N-allylthiourea or reaction of N-(2,3-dibromopropyl)isothiocyanate with amines [6-8].

Previous studies have shown that isomeric six-membered rings (thiazines) are formed in these reactions as well as thiazolines [9, 10]. However, these reactions are usually performed in polar media with heating, and from the reaction mixtures one isolates only five-membered thiazoline rings, because under these conditions there is an easy dihydrothiazine-thiazoline rearrangement [11]. There is published evidence for the reversibility of that rearrangement [12], so particular attention has been given to establishing the structures of the resulting hydroxyl derivatives.

In order to choose the hydrolysis conditions, we examined the behavior of compounds **1a-h** at various pH; according to [13] and our studies, these compounds are unstable in the presence of bases and may give rise to polymeric compounds of variable composition. Therefore, for the hydrolysis we examined the systems PbO-H_2O or PbO-H_2O-EtOH as appropriate to the solubility of the initial hydrogen halides of the 2-aminothiazolines **1a-h**. The lead halides formed in the reaction are virtually insoluble in water, i.e., the halogen ions are removed from the reaction sphere and the equilibrium is displaced towards the formation of 2-amino-5-hydroxy-2-methylthiazolines. We found that the best conditions for the experiments were pH from 4 to 7.

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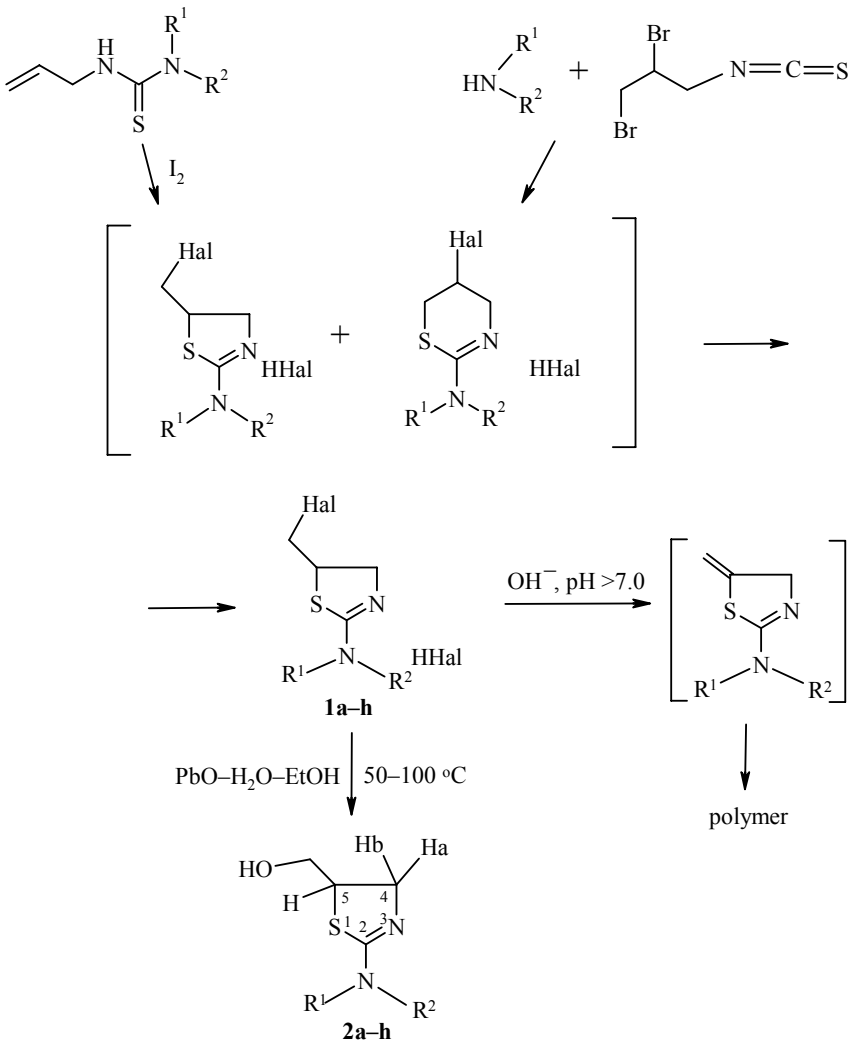

a R^1 = H, R^2 = Me, Hal = I; **b** R^1 = H, R^2 = Et, Hal = I; **c** R^1 = H, R^2 = Bn, Hal = I;
d R^1 = Me, R^2 = Bn, Hal = Br; **e** N + R^1 + R^2 = pyrrolidin-1-yl, Hal = I;
f N + R^1 + R^2 = piperidin-1-yl, Hal = Br; **g** R^1 = H, R^2 = dibenzo[*b*,*d*]furan-3-yl, Hal = I;
h R^1 = R^2 = Bn, Hal = I

The use mainly of 5-iodomethyl-2-thiazolines not only reduced the reaction times but also simplified the purification of the final compound because the solubility of the lead iodide formed in the reaction is less by an order of magnitude than that of lead bromide. We also used water-alcohol mixtures instead of water with various alcohol contents because of the solubility differences of the initial hydrogen halides of the 2-amino-5-halomethyl-2-thiazolines **1a-h**. The stabilities of the initial and final compounds on heating were examined to choose the best reaction temperature for each substance and provided yields of 60-96% of the 5-hydroxymethyl derivatives **2a-h** (Table 1).

Most of the compounds synthesized were oils difficult to crystallize. All the 5-hydroxymethyl-2-thiazolines **2a-h** were obtained as bases, but on the hydrolysis of unsubstituted 2-amino-5-bromomethyl-2-thiazoline hydrobromide (**1i**) in the presence of PbO we were able to isolate the 2-amino-5-hydroxymethyl-2-thiazoline (**2i**) as the hydrobromide with almost quantitative yield. Previously, that compound had been obtained with a low (25%) yield by the hydrolysis of 2-amino-5-bromomethyl-2-thiazoline hydrobromide **1i** in the presence of $NaHCO_3$ [14].

TABLE 1. Reaction Conditions

Reaction product	Medium	Reaction temperature, ºC	Reaction time, h	Yield **2**, %
2a	Вода	50	3	66
2b	Вода	60	5	64
2c	Water–alcohol, 1:1	80	6	63
2d	Water–alcohol, 5:1	60	2	96
2e	Water–alcohol, 5:1	60	4	77
2f	Water	100	2.5	60
2g	Water–alcohol, 1:1	55	10.5	64
2h	Water–alcohol, 5:2	80	4	96

Table 2 gives spectral data on compounds **2a-h**.

The fragments X–CH_2–CH(S)–CH_2N of all the compounds given in Table 2 appear in the ^{1}H NMR spectrum as two ABX systems with common X parts. Sometimes, the CH-S signal overlaps with one of the signals from the CH_2N group protons. It is also difficult to analyze the spectra because of the hindered rotation around the exocyclic C-N bond, which leads to considerable broadening of the lines, so the coupling coefficients are given only for those groups where it occurs explicitly. In some cases we observed signals from two rotational isomers (with respect to the exocyclic C-N bond). Although the five-membered and six-membered isomers have a common type of spin system (two AB systems with a common X part), the forms of the spectra are different. In particular, in the salts and bases of the six-membered heterocyclics one gets spin-spin interaction through four bonds between the H-6 and H-4 protons, which has not been observed in any of the spectra for compounds **2a-h**.

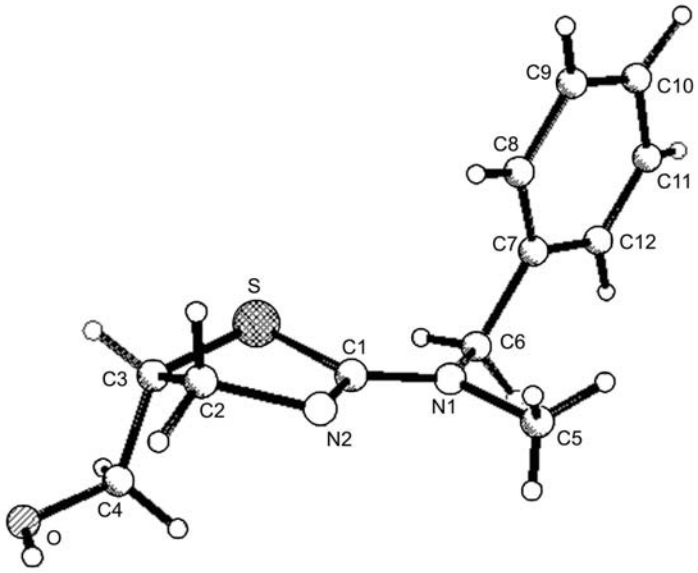

Fig. 1. General view of compound **2d** molecule with numbering of the atoms.

The X-ray data for thiazoline **2d** (Fig. 1) provide a further confirmation of the structures of these compounds. The XRD show that compound **2d** in the crystalline state is a 2-amino derivative of 2-thiazoline, which has a 5-hydroxomethyl substituent.

The maximum deviation of the $N_{(2)}$ atom from the plane formed by the atoms $C_{(1)}$,$C_{(2)}$,$C_{(3)}$ is -0.34, while that for the S atom is -0.62 Å, and the angle between the plane of the heterocycle and the benzene ring is 96.7°. Table 3 gives the bond lengths and valence angles for compound **2d**.

TABLE 2. ^{1}H NMR Spectra of Compounds **2a-b**

Com-pound	Chemical shifts (DMSO-d_6–CCl_4, 1:4), δ, ppm (*J*, Hz)					
	H-4a	H-4b	H-5	CH_2	NH	others signals
2a	3.8	3.8	3.8	3.36	6.45	4.7 (1H, br. s, OH); 2.7 (3H, s, CH_3)
2a	3.92	3.92	4.1	3.57	10.5, 10.2, 10.0	two isomers; 3.01 (d, *J* = 5.0) + 2.97 (d, *J* = 5.0) (3H, CH_3)*
2b	3.7	3.7	3.7	3.35	5.1, br. s (overlapping with OH)	5.1 (1H, br. s, OH); 3.15 (2H, q, $\underline{CH_2}CH_3$); 1.15 (3H, t, CH_3)
2b	3.9	3.9	4.0	3.5	10.5, s + 10.35, s (minor isomer); 10.0 s + 9.9 s (2H)	3.4 (2H, m, $C\underline{H_2}CH_3$); 1.2 (3H, m, CH_3)*
2c	3.8	3.8	3.8	3.3	7.2 (overlapping with C_6H_5)	7.2 (5H, m, C_6H_5); 4.9 (1H, t, *J* =5.6, OH); 4.4 (2H, s, $\underline{CH_2}C_6H_5$)
2d	3.9	3.9	3.9	3.4	—	7.2 (5H, m, C_6H_5); 4.5 (2H, s, $CH_2C_6H_5$); 2.9 (3H, s, CH_3); 5.0 (1H, t, *J* = 5.6, OH)
2e	3.8	3.8	3.8	~3.4	—	~3.4 (4H, m, CH_2N); 1.95 (4H, m, $\underline{CH_2}CH_2N$); OH in exchange with H_2O
2e	3.85	3.85	4.05	3.55	9.7	~3.45 (4H, m, CH_2N); 2.0 (4H, m, $\underline{CH_2}CH_2N$)*
2f	4.0–3.7	4.0–3.7	4.0–3.7	3.35	—	4.75 (1H, t, *J* = 5.6, OH); 3.35 (4H, m, CH_2N); 1.6 (6H, br. s, CH_2)
2f	3.75	3.65 (dd, ^2J = 12.0, ^3J = 3.5)	3.85	3.35	—	3.25 (4H, br. s, CH_2N); 1.45 (6H, br. s, CH_2)*^{2}
2g	4.0	3.8	4.0	3.5	9.5 + 8.0 (two isomers)	7.9–7.2 (7H, m, Aryl); 4.95 (1H, t, *J* = 5.6, OH)
2h	3.4	3.4	3.9	3.9	—	7.2 (10H, m, C_6H_5); 4.5 (4H, s, $CH_2C_6H_5$); 5.1 (1H, t, *J* = 5.5, OH)*^{3}

* In DMSO-d_6 + CCl_4 + CF_3COOH.

*^{2} In D_2O + 5% D_2SO_4.

*^{3} In DMSO-d_6.

The length of the endocyclic $N_{(2)}$–$C_{(1)}$ bond is 1.273(5) Å, which corresponds to a standard N(sp^2)=C(sp^2) double bond for these heterocycles (1.28 Å) [15, 16]. The exocyclic bond $N_{(1)}$–$C_{(1)}$ (1.346(5) Å) is somewhat shorter than a single one C(sp^2)–N (1.37–1.38 Å) [15, 17, 18]. The molecule contains two single S–C(sp^3) bonds and S–C(sp^2), where the difference between the lengths of these bonds is only 0.014 Å. The S–$C_{(3)}$ bond of 1.794(4) Å agrees well with the published data (1.79 [15] and 1.803 Å [19]), while the S–$C_{(1)}$ – 1.780(4) Å bond is somewhat longer (1.77 [15], 1.741 Å [19]). The $C_{(1)}$–S–$C_{(3)}$ angle is 88.9° (17), which agrees well with the data for the 2-aminothiazolines (88°) [15].

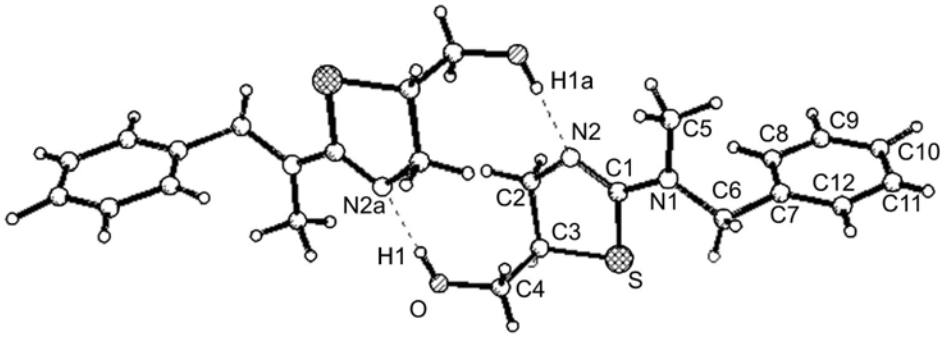

Fig. 2. Dimer formation in the crystal of compound **2d** (hydrogen bonds shown dotted).

The hydroxymethyl group in position 5 of the thiazoline molecule **2d** leads to the formation of layers of dimers in the crystal, which are joined by intermolecular OH...N hydrogen bonds (Fig. 2). The parameters of the hydrogen bond are *d* O–H 0.84(7), H...$N_{(2)}$ 2.03(7), O...$N_{(2)}$ 2.831(5) Å, angle (OH…$N_{(2)}$) 161(6)°.

The compounds were tested for NOS-inhibiting activity *in vivo* with white mice. The best results were obtained with compounds **2c** and **2g**.

TABLE 3. Bond Lengths *d* and Valence Angles ω in the Molecule of Compound **2d**

Bondь	*d*, Å	Angle	ω, deg
S–$C_{(1)}$	1.780(4)	$C_{(1)}$–S–$C_{(3)}$	88.6(17)
S–$C_{(3)}$	1.794(4)	$C_{(1)}$–$N_{(1)}$–$C_{(6)}$	124.0(4)
O–$C_{(4)}$	1.411(5)	$C_{(1)}$–$N_{(1)}$–$C_{(5)}$	119.6(4)
$N_{(1)}$–$C_{(1)}$	1.346(5)	$C_{(6)}$–$N_{(1)}$–$C_{(5)}$	116.4(4)
$N_{(1)}$–$C_{(6)}$	1.439(5)	$C_{(1)}$–$N_{(2)}$–$C_{(2)}$	110.1(3)
$N_{(1)}$–$C_{(5)}$	1.453(6)	$N_{(2)}$–$C_{(1)}$–$N_{(1)}$	124.1(4)
$N_{(2)}$–$C_{(1)}$	1.273(5)	$N_{(2)}$–$C_{(1)}$–S	117.1(3)
$N_{(2)}$–$C_{(2)}$	1.472(5)	$N_{(1)}$–$C_{(1)}$–S	118.9(3)
$C_{(2)}$–$C_{(3)}$	1.509(6)	$N_{(2)}$–$C_{(2)}$–$C_{(3)}$	109.3(3)
$C_{(3)}$–$C_{(4)}$	1.521(6)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	113.6(4)
$C_{(6)}$–$C_{(7)}$	1.520(6)	$C_{(2)}$–$C_{(3)}$–S	103.6(3)
$C_{(7)}$–$C_{(8)}$	1.370(6)	$C_{(4)}$–$C_{(3)}$–S	111.1(3)
$C_{(7)}$–$C_{(12)}$	1.375(6)	O–$C_{(4)}$–$C_{(3)}$	111.0(4)
$C_{(8)}$–$C_{(9)}$	1.380(6)	$N_{(1)}$–$C_{(6)}$–$C_{(7)}$	113.5(4)
$C_{(9)}$–$C_{(10)}$	1.348(7)	$C_{(8)}$–$C_{(7)}$–$C_{(12)}$	118.8(4)
$C_{(10)}$–$C_{(11)}$	1.372(8)	$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	121.6(4)
$C_{(11)}$–$C_{(12)}$	1.383(7)	$C_{(12)}$–$C_{(7)}$–$C_{(6)}$	119.6(4)
		$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	120.6(4)
		$C_{(10)}$–$C_{(9)}$–$C_{(8)}$	120.6(5)
		$C_{(9)}$–$C_{(10)}$–$C_{(11)}$	119.5(5)
		$C_{(10)}$–$C_{(11)}$–$C_{(12)}$	120.4(5)
		$C_{(7)}$–$C_{(12)}$–$C_{(11)}$	120.0(5)

We have thus developed a synthesis methods in the search for compounds with NO modulating activity for the synthesis of previously unknown 5-hydroxymethyl derivatives of thiazoline **2a-h** by hydrolysis of the corresponding 5-halomethyl derivatives **1a-h** in the presence of lead oxide. The method gives heterocyclic aminoalcohols **2a-h** in preparative amounts and with good yield. The ^{1}H NMR spectra and X-ray data reliably confirm the structures of the compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded with a Bruker CXP-200 spectrometer '200 MHz), internal standard TMS. The course of the reactions was monitored and the individuality of the compounds was established by TLC on Silufol UV-254 plates in the system butanol-acetone-formic acid 1:1:1.

X-ray structure analysis of compound 2d. Crystals of compound **2d** formed from alcohol are platy and at 293 K: a = 6.1070(10), b = 8.996(2), c = 11.367(2) Å, a = 99.79(3), b = 103.05(3), g= 95.60(3)°, V = 593.45(19) Å^3, d_{calc} = 1.323 g/cm^3, space group P-1, Z = 2. The measurements were made with an Enraf-Nonius CAD-4 automatic diffractometer by θ/2θ scanning in MoKα radiation, wavelength 0.71073 Å. The intensities of three standard reflections measured every 60 min remain stable within a range of 0.3%. A correction was applied for the X-ray absorption, absorption coefficient 0.253 mm^{-1}. The experimental data were processed and the subsequent calculations were performed on the SHELXT program. In the calculation we used 1002 reflections having $I > 2\sigma(I)$. The structure was interpreted by a direct method and refined by least-squares fitting in the full-matrix anisotropic approximation for the non-hydrogen atoms. All the hydrogen atoms were included in the refinement with fixed parameters in the isotropic approximation. The final value for the divergence factor was R = 0.0401. The full XRD data have been deposited in the Cambridge database: depositor CCDC 297910.

Hydrohalides of 2-amino-5-halomethyl-2-thiazolines 1a-i. These were made by iodinating N' derivatives of N-allylthiourea (compounds **1a, b, c, e, g,** and **h**) or by bromination of N-allylthiourea (compound **1i**) or reaction of N-(2,3-dibromopropyl)isothiocyanate with the corresponding amines (compounds **1d** and **f**) [6-8].

5-Hydroxymethyl-2-methylamino-2-thiazoline (2a). We dissolve (1.0 g, 2.6 mmol) of 5-iodomethyl-2_methylamino-2-thiazoline hydroiodide (**1a**) at 50° in 75 ml of water and gradually add (0.87 g, 3.9 mmol) of lead oxide. The mixture is stirred at that temperature for 3 h. The precipitate is filtered off and the solvent is evaporated under vacuum, with the resulting oil treated with ether and stored in the cold. It crystallizes within 1-3 days and gives 0.25 g of thiazoline **2a**, m.p. 102-104°C. Found, %: C 41.09; H 6.99; N 19.01. $C_5H_{10}N_2OS$. Calculated, %: C 41.07; H 6.89; N 19.16.

Compounds 2b-h were made similarly with modification of certain aspects of the methods 'Table 1).

2-Ethylamino-5-hydroxymethyl-2-thiazoline (2b), mp 81-83°C. Found, %: C 45.24; H 7.76; N 17.80. $C_6H_{12}NOS$. Calculated, %: C 44.97; H 7.55; N 17.48.

2-(N-Benzyl)amino-5-hydroxymethyl-2-thiazoline (2c), mp 151-153°C. Found, %: C 59.57; H 6.13; N 12.98. $C_{11}H_{14}N_2OS$. Calculated, %: C 59.43; H 6.35; N 12.60.

2-(N,N-Methylbenzyl)amino-5-hydroxymethyl-2-thiazoline (2d), mp 117-119°C. Found, %: C 60.97; H 6.57; N 11.88. $C_{12}H_{16}N_2OS$. Calculated, %: C 60.97; H 6.57; N 11.88.

5-Hydroxymethyl-2-pyrrolidin-1-yl-2-thiazoline (2e), mp 104-106°C. Found, %: C 51.65; H 7.28; N 15.35. $C_8H_{14}N_2OS$. Calculated, %: C 51.58; H 7.58; N 15.04.

5-Hydroxymethyl-2-piperidin-1-yl-2-thiazoline (2f), mp 82-84°C. Found, %: C 53.89; H 8.17; N 14.12. $C_9H_{16}N_2OS$. Calculated, %: C 53.97; H 8.05; N 13.99.

2-(N-dibenzo[*b*,*d*]furan-3-yl)amino-5-hydroxymethyl-2-thiazoline (2g), mp 181-183°C. Found, %: C 64.32; H 5.69; N 9.14. $C_{16}H_{16}N_2O_2S$. Calculated, %: 63.98; H 5.37; N 9.33.

2-(N,N-Dibenzyl)amino-5-hydroxymethyl-2-thiazoline (2h), mp 112-113°C. Found, %: C 69.23; H 6.48; N 9.01. $C_{18}H_{20}N_2OS$. Calculated, %: C 69.20; H 6.45; N 8.97.

5-hydroxymethyl-2-amino-2-thiazoline hydrobromide (2i) was obtained by analogy with compound **2a**, reaction performed for 14 h at 80°C. This gave 3.53 g (91%) of thiazoline **2i**, mp 85-86°C (mp 84°C [14]).

The research was performed with financial support from the Russian Fund for Basic Research (grants No. 05-04-48794 and No. 05-03-01840 ofi-a).

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