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RAPID ACID HYDROLYSIS OF 5-ARYL-3-(β-THIOMORPHOLINOETHYL)-1,2,4-OXADIAZOLES

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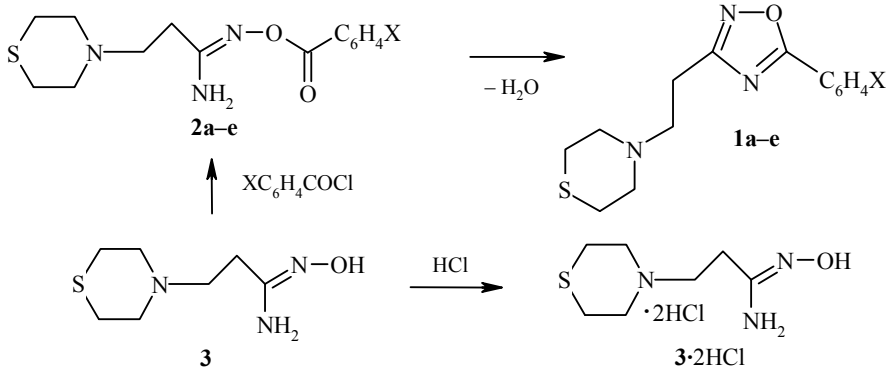
The acid hydrolysis of a series of 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles gave substituted benzoic acids and 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride hydrate, whose structure was demonstrated by spectral methods and X-ray diffraction structural analysis.

Keywords: 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles, 2-amino-8-thia-1-aza-5-azoniaspiro-[4.5]dec-1-ene chloride hydrate, substituted benzoic acids, acid hydrolysis, X-ray diffraction structural analysis.

The possibility that β-amino-O-aroylpropioamidoximes and 3-(β-aminoethyl)-5-aryl-1,2,4-oxadiazoles exist both as stable bases and hydrochlorides has been demonstrated in our previous work, in which β-piperidine, β-morpholine, and β-benzimidazole derivatives are described. These compounds do not undergo structural change upon isolation from the reaction mixture and recrystallization. Physicochemical and spectral data as well as X-ray diffraction structural data were obtained for these compounds [1-3].

Scheme 1



1,2 a X = *p*-MeO, **b** X = *p*-Me, **c** X = H, **d** X = *p*-Br, **e** X = *m*-Cl

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In the present work, we studied the reaction of hydrogen chloride with 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles **1a-e** obtained by the dehydration of O-aroyl-β-(thiomorpholino)propioamidoximes **2a-e.** These amidoximes were prepared by the acylation of β-(thiomorpholino)propioamidoxime (**3**) using acid chlorides of substituted benzoic acids [4, 5] (Scheme 1).

An ethereal solution of HCl with traces of moisture was added dropwise at room temperature to ethanolic solutions of 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles **1a-e** to lower the pH to 2. In all cases, a precipitate of 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride hydrate (**4**) formed immediately after addition of the hydrogen chloride solution. This precipitate has low solubility in ethanol. The filtrates were evaporated and the corresponding substituted benzoic acids **5a-e** were isolated (Tables 1-3).

The formation of compound **4** may be seen as a series of steps involving acid hydrolysis and intramolecular heterocyclization through intermediates **1**·HCl - **1**·2HCl·2H_2O - **1**·HCl·2H_2O (Scheme 2) during the reaction of 1,2,4-oxadiazoles bases **1a-e** with undried HCl. We propose that the determining factor is the formation ammonium compound **1**·HCl and the hydrolysis product **1**·2HCl·2H_2O upon the attack of the oxygen atom of the hydroxonium chloride on N(2) atom and of the water molecule oxygen on C(5) atom in the 1,2,4-oxadiazole ring of compounds **1a-e**. Stabilization of the positive charge on the ammonium nitrogen atom of the thiomorpholine ring by the unshared electron pair of the oxime nitrogen atom and loss of a water molecule in **1**·HCl·2H_2O completes the heterocyclization to give spiro compound **4**.

At room temperature, spiroazonium chloride **4** has low solubility in the solution of HCl in aqueous ethanol serving as the reaction medium and forms a high-melting white precipitate. Evaporation of the filtrate gives the corresponding substituted benzoic acids **5a-e** identified using their spectral characteristics and

TABLE 1. Physicochemical Characteristics of Compounds **3**, **3**·2HCl, **4,** and Benzoic Acids **5a-e**

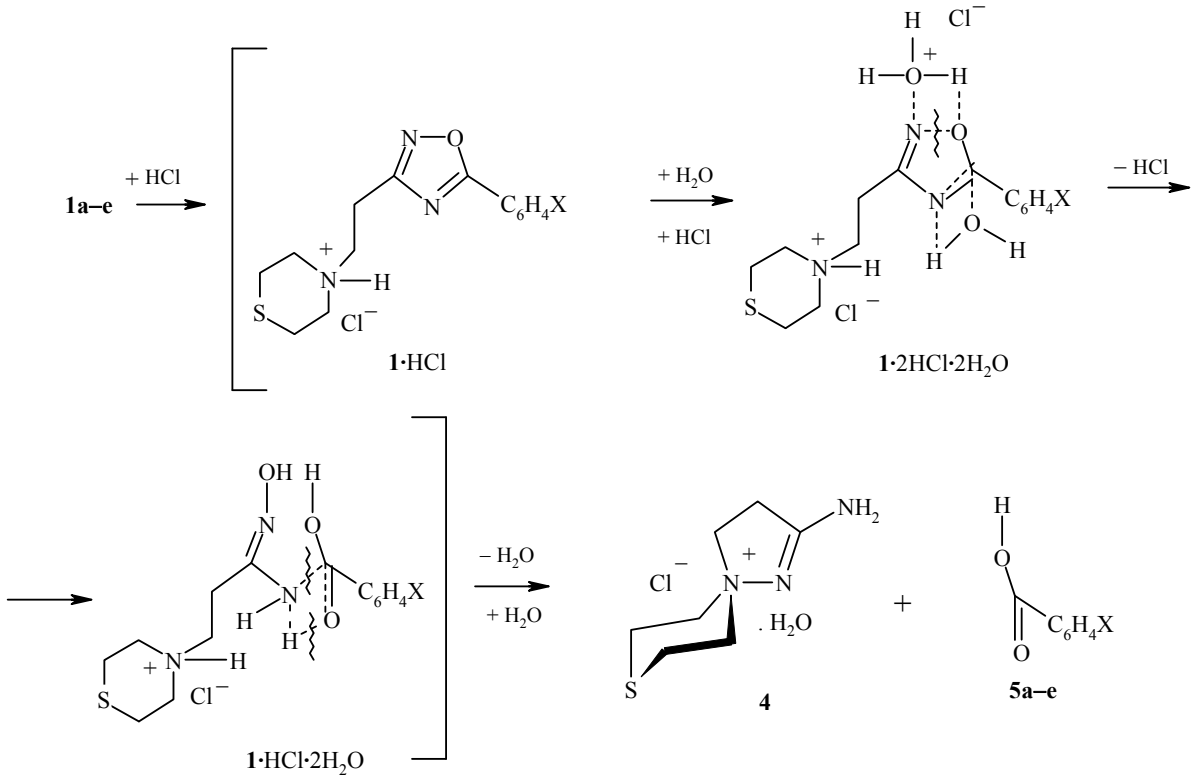
Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	R_f	Yield, %
		C	H	Hal			
3	$C_7H_{15}N_3OS$	44.20 / 44.42	8.10 / 7.99	—	170	0.54	92
3·2HCl	$C_7H_{17}Cl_2N_3OS$	32.50 / 32.06	6.46 / 6.53	27.30 / 27.04	178	0.07	98
4*[2]	$C_7H_{16}ClN_3OS$	a)37.10; b)37.88; c)37.23; d)37.84; e)37.74 / 37.25	a)7.52; b)7.40; c)6.56; d)6.95; e)6.86 / 7.14	a)15.02; b)15.24; c)15.41; d)15.80; e)16.03 / 15.71	302	0.09	40-47
5a	$C_8H_8O_3$	63.00 / 63.15	5.90 / 5.30	—	180 (181-186)	0.75	43
5b	$C_8H_8O_2$	70.20 / 70.57	6.33 / 5.92	—	178 (179-182)	0.76	45
5c	$C_7H_6O_2$	68.93 / 68.85	5.06 / 4.95	—	112 (121-123)	0.79	41
5d	$C_7H_5BrO_2$	42.20 / 41.83	3.04 / 2.51	39.55 / 39.75	247 (251-256)	0.81	40
5e	$C_7H_5ClO_2$	53.90 / 53.70	3.70 / 3.22	23.03 / 22.64	150 (154-157)	0.82	43

*The literature data from the Acros Organics 2004-2005 Catalog are given in parentheses.

*[2]The values given for Found in the elemental analysis of compound **4** correspond to the values calculated corresponding to the syntheses of these compounds from **1a-e**.

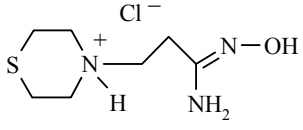
melting point (Tables 1-3). Spiroazonium chloride **4** is an isomer of the amidoxime hydrochloride **3**·HCl and the IR and ^{1}H NMR spectral data of **3**·HCl and the IR and ^{1}H NMR spectral data of **4** are in accord with the structure of **3**·HCl.

Scheme 2



5 a X = *p*-OMe, **b** X = *p*-Me, **c** X = H, **d** X = *p*-Br, **e** X = *m*-Cl

The melting points of compounds **3**, **3**·2HCl, and **4** are 170, 178, and 303°C, respectively. The characteristic stretching and deformation bands are given in Table 2. In going from compound **3** to **3**·2HCl and **4**, the ^{1}H NMR spectra show a shift in the signals of the protons of the α-CH_2 and β-CH_2 groups from δ 2.08 and 2.55 (compounds **3**) to 3.04 and 3.45 (**3**·2HCl) and to 3.14 (C(3)CH_2) and 3.88 ppm (C(4)H_2) in compound **4**. Furthermore, the signals of the protons of the N(+)CH_2)$_2$ and S(CH_2)$_2$ groups in the thiomorpholine ring of compound **4** are downfield relative to the analogous signals for compounds **3** and **3**·2HCl and divide into two groups of multiplets at δ 3.74, 3.62 and 2.88, 3.14 ppm with two-proton intensity (Table 3).



3 · HCl

The sharp difference between the physicochemical and spectral data of compound **4** and the corresponding data for β-(thiomorpholino)propioamidoxime (**3**) and its dichloride **3**·2HCl led us to carry out an X-ray diffraction structural analysis of this sample.

This structural analysis showed that compound **4** is 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride hydrate. Figure 1 shows the structures of the two crystallographically independent cations (**A** and **B**), which are bound to each other by intermolecular hydrogen bonds, with the chloride anions and water molecules.

TABLE 2. IR Spectra of Compounds **3**, **3**·2HCl, **4**, **5a-e**

Compound	ν, δ, cm^{-1} (KBr pellets)									
	$\nu_{C=O}$ (v. s)	$\nu_{C=N}$ (v. s)	δ_{N-H}, $\delta_{N(+)-H}$, $\delta_{O(-H)_2}$	$\nu_{C=C}$	δ_{O-H}	ν_{C-O} (v. s)	ν_{C-S} (s)	$\nu_{N(+)-H}$ (m)	ν_{N-H} (s)	ν_{O-H} (s)
3	—	1659	1598 m	—	1421 m	—	779	—	3092; 3153; 3279	3459
3·2HCl	—	1688	1632 w	—	1409 m	—	719	2525; 2628; 2851; 2934; 2989	—	3268
4	—	1657	1610 v. s	—	–	—	668	—	3137; 3229; 3381; 3382	
5a	1677	—	—	1612 v. s	1418 s	1286; 1320	—	—	—	3133-3400
5b	1677	—	—	1602 m	1418 m	1286; 1320	—	—	—	3130-3422
5c	1678	—	—	1602 m	1424 m	1293; 1327	—	—	—	3069-3414
5d	1679	—	—	1610 m	1427 m	1296; 1323	—	—	—	3080-3431
5e	1698	—	—	1600 m	1419 s	1260; 1303	—	—	—	3069-3382

TABLE 3. ^{1}H NMR Spectra of Compounds **3**, **3**·2HCl, **4**, **5a-e**

Compound	Chemical shifts (DMSO-d_6), δ, ppm. (*J*, Hz)							
	$N(CH_2)_2$ (**3** and **3**·2HCl) or $N(+)(CH_2)_2$ (**4**)	$S(CH_2)_2$	α-CH_2 (**3** and **3**·2HCl); $C(3)H_2$ (**4**)	β-CH_2 (**3** and **3**·2HCl); $C(4)H_2$ (**4**)	NH_2, (2H, br. s)	NOH (**3**); N(+)H (**3**·2HCl); H_2O (**4**)	C_6H_4X	COOH, br. s
3	2.64 (4H, m)	2.55 (6H, m)*	2.08 (2H, t, *J* = 7.0)	—*	5.40	8.74 (br. s)	—	—
3·2HCl	3.45 (6H, m)*[2]	3.04 (6H, m)*[2]	—*[2]	—*[2]	—	8.94 (br. s) and 11.10 (br. s)	—	—
4	3.62 (2H, m); 3.74 (2H, m)	2.88 (2H, m); 3.14 (4H, m)*	—*	3.88 (2H, t, *J* = 7.0)	7.48	3.37 (2H, br. s)	—	—
5a	—	—	—	—	—	—	3.82 (3H, s); 7.01 (2H, m); 7.88 (2H, m)	12.62
5b	—	—	—	—	—	—	2.85 (3H, s); 7.29 (2H, m); 7.83 (2H, m)	12.79
5c	—	—	—	—	—	—	7.47-7.96 (5H, m)	12.96
5d	—	—	—	—	—	—	7.74 (2H, m); 7.85 (2H, m)	13.19
5e	—	—	—	—	—	—	7.52-7.90 (4H, m)	13.35

*The signals in compound **3** for the protons of the β-CH_2 groups coincide with the signals of the protons of the $S(CH_3)_2$ group, while the signals in compound **4** for the protons of the $C(3)H_2$ group coincide with the signals of the $S(CH_2)_2$ group at δ 3.14 ppm.

*[2]The signals of the protons of the α-CH_2 and β-CH_2 groups coincide with the signals of the $S(CH_2)_2$ and $N(+)(CH_2)_2$ groups.

TABLE 4. Some Torsion Angles (φ) in the Structure of Compound **4**

Angle	φ, deg	Angle	φ, deg
Imidazolidine ring		Thiomorpholine ring	
N(10A)–N(1A)–C(2A)–C(3A)	-5(2)	N(10A)–C(5A)–C(6A)–S(7A)	60.7(17)
N(1A)–C(2A)–C(3A)–C(4A)	-8(2)	C(5A)–C(6A)–S(7A)–C(8A)	-55.8(13)
C(2A)–C(3A)–C(4A)–N(10A)	15.2(17)	C(6A)–S(7A)–C(8A)–C(9A)	58.1(14)
C(3A)–C(4A)–N(10A)–N(1A)	-18.4(17)	S(7A)–C(8A)–C(9A)–N(10A)	-63.9(16)
C(2A)–N(1A)–N(10A)–C(4A)	14.7(17)	C(8A)–C(9A)–N(10A)–C(5A)	58.7(18)
N(10B)–N(1B)–C(2B)–C(3B)	-0.4(18)	C(6A)–C(5A)–N(10A)–C(9A)	-57.9(19)
N(1B)–C(2B)–C(3B)–C(4B)	16(2)	N(10B)–C(5B)–C(6B)–S(7B)	64.6(16)
C(2B)–C(3B)–C(4B)–N(10B)	-24.3(17)	C(5B)–C(6B)–S(7B)–C(8B)	-55.3(14)
C(8B)–C(9B)–N(10B)–N(1B)	174.0(13)	C(6B)–S(7B)–C(8B)–C(9B)	56.9(15)
C(2B)–N(1B)–N(10B)–C(4B)	-16.4(16)	S(7B)–C(8B)–C(9B)–N(10B)	-65.1(17)
		C(8B)–C(9B)–N(10B)–C(4B)	-67.2(18)
		C(6B)–C(5B)–N(10B)–C(9B)	-63.9(18)

TABLE 5. Intermolecular Interactions in the Structure of Compound **4**

Bond*	Distance, Å			Angle
	D–H	H···A	D···A	D–H···A, deg
O(1W)···Cl(1)i			3.12 (1)	
O(1W)···Cl(2)i			3.08(1)	
O(2W)···Cl(1)i			3.12(1)	
O(2W)···Cl(2)i			3.12(1)	
C(3A)–H(3AD)···O(1W)i	0.97	1.99	3.37(2)	94.9
C(3B)–H(3BD)···O(2W)i	0.97	2.01	3.31(2)	90.5
N(3B)–H(3BC)···Cl(1)ii	0.86	2.41	3.26(1)	170.6
N(3A)–H(3AC)···Cl(2)iii	0.86	2.44	3.30(1)	174.3

* Symmetry codes: (i) *x*, *y*, *x;* (ii) 1-*x*, 0.5+*y*, 0.5-*z;* (iii) -*x*, -0.5+*y*, 0.5-*z*.

The thiomorpholine rings in ammonium chloride hydrates **A** and **B** are isostructural within experimental error and have *chair* conformation, while the imidazolidines rings have *envelope* conformation and are mirror images of each other (Table 4).

Layers parallel to the *ab* plane are formed in crystals of compound **4** by means of a system of hydrogen bonds (Fig. 2). The geometry of the intermolecular interactions is given in Table 5.

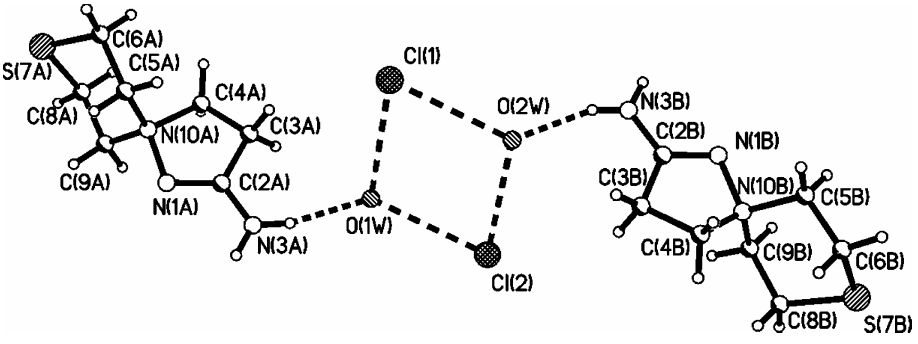


Fig. 1. Association of molecules of **4** (independent part) with numbering of the non-hydrogen atoms.

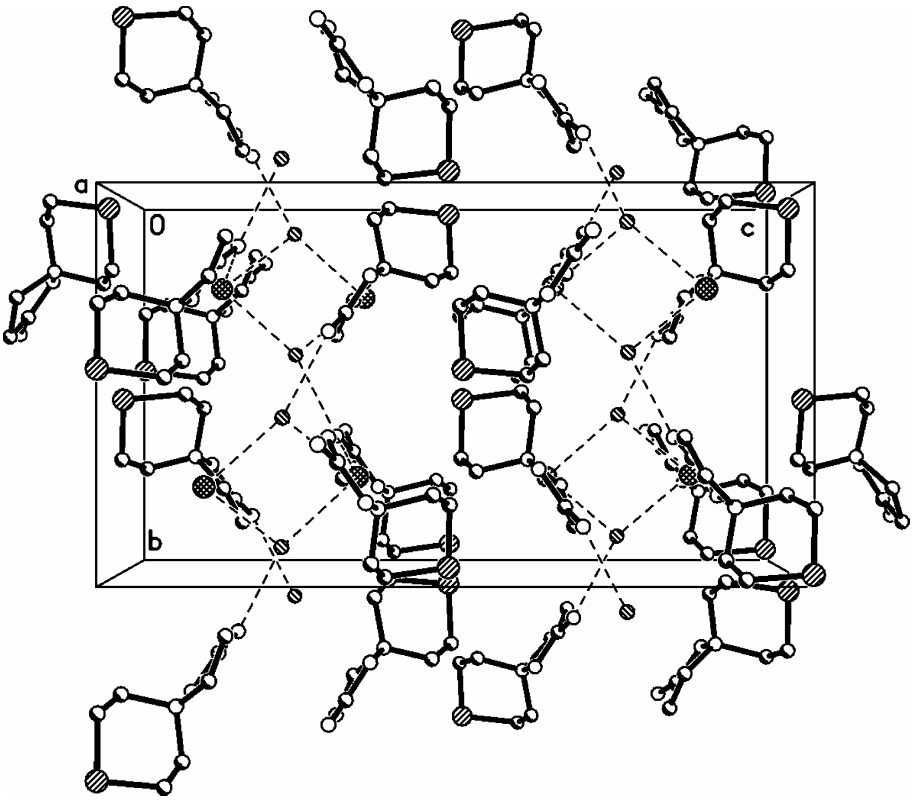


Fig. 2. Crystal structure of compound **4**.

TABLE 6. Crystallographic Parameters and Unit Cell Data for Compound **4**

Empirical formula	$C_7H_{14}ClN_3OS$
Unit cell parameters	
a, Å	10.166(2)
b, Å	11.060(2)
c, Å	19.610(4)
Space group	$P2_12_12_1$
Unit cell volume, *V*, Å^3	2204.9(8)
Z (two independent formula units in a cell)	8
Crystal density, ρ_{calc}, g/cm^3	1.348
Absorption coefficient, μ, mm^{-1} *F*(000)	4.598
F(000)	944
Number of reflections measured	1885
Number of reflections for the calculation	1221
GOOF	1.008
Final *R*-factor [$I > 2\sigma(I)$]	$R_1 = 0.0666$, $wR_2 = 0.1992$
Residual electron density, e/Å^3	0.658 and -0.325

Thus, 1,2,4-oxadiazoles with a 3-(β-thiomorpholino)ethyl substituent **1a-e** are chemically unstable compounds and undergo acid hydrolysis to give 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride hydrate (**4**).

TABLE 7. Bond Lengths (*d*) in Compound **4**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
N(1A)–C(2A)	1.272(19)	C(6A)–S(7A)	1.790(16)	C(3B)–C(4B)	1.51(2)
N(1A)–N(10A)	1.463(18)	S(7A)–C(8A)	1.79(2)	C(4B)–N(10B)	1.48(2)
C(2A)–N(3A)	1.312(19)	C(8A)–C(9A)	1.56(2)	C(5B)–C(6B)	1.50(2)
C(2A)–C(3A)	1.50(2)	C(9A)–N(10A)	1.49(2)	C(5B)–N(10B)	1.525(16)
C(3A)–C(4A)	1.50(2)	N(1B)–C(2B)	1.320(19)	C(6B)–S(7B)	1.813(15)
C(4A)–N(10A)	1.559(18)	N(1B)–N(10B)	1.490(18)	S(7B)–C(8B)	1.800(17)
C(5A)–N(10A)	1.457(17)	C(2B)–N(3B)	1.345(18)	C(8B)–C(9B)	1.50(3)
C(5A)–C(6A)	1.53(2)	C(2B)–C(3B)	1.46(2)	C(9B)–N(10B)	1.541(18)

TABLE 8. Valence Angles (ω) in Compound **4**

Angle	ω, deg	Angle	ω, deg
C(2A)–N(1A)–N(10A)	108.7(12)	C(2B)–N(1B)–N(10B)	104.1(12)
N(1A)–C(2A)–N(3A)	124.1(15)	N(1B)–C(2B)–N(3B)	119.9(15)
N(1A)–C(2A)–C(3A)	115.4(15)	N(1B)–C(2B)–C(3B)	117.2(14)
N(3A)–C(2A)–C(3A)	120.5(13)	N(3B)–C(2B)–C(3B)	122.9(13)
C(2A)–C(3A)–C(4A)	103.5(14)	C(2B)–C(3B)–C(4B)	100.5(13)
C(3A)–C(4A)–N(10A)	102.5(12)	N(10B)–C(4B)–C(3B)	103.8(12)
N(10A)–C(5A)–C(6A)	115.3(12)	C(6B)–C(5B)–N(10B)	112.4(14)
C(5A)–C(6A)–S(7A)	111.9(11)	C(5B)–C(6B)–S(7B)	112.0(11)
C(6A)–S(7A)–C(8A)	95.9(8)	C(8B)–S(7B)–C(6B)	95.8(9)
C(9A)–C(8A)–S(7A)	111.2(13)	C(9B)–C(8B)–S(7B)	113.7(13)
N(10A)–C(9A)–C(8A)	111.8(16)	C(8B)–C(9B)–N(10B)	110.2(14)
C(5A)–N(10A)–N(1A)	108.5(11)	C(4B)–N(10B)–N(1B)	107.4(12)
C(5A)–N(10A)–C(9A)	112.9(12)	C(4B)–N(10B)–C(5B)	112.8(14)
N(1A)–N(10A)–C(9A)	106.9(13)	N(1B)–N(10B)–C(5B)	103.9(12)
C(5A)–N(10A)–C(4A)	110.6(13)	C(4B)–N(10B)–C(9B)	116.7(12)
N(1A)–N(10A)–C(4A)	106.5(10)	N(1B)–N(10B)–C(9B)	105.1(12)
C(9A)–N(10A)–C(4A)	111.0(13)	C(5B)–N(10B)–C(9B)	109.9(13)

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr pellets. The ^{1}H NMR spectra were taken on a Mercury-300 spectrometer at 300 MHz with HMDS as the internal standard (δ 0.05 ppm). The reaction course was monitored using thin-layer chromatography on Fluka silica gel plates with 3:1 ethanol–benzene as the eluent. The solvents used in these experiments were prepared in accord with standard procedures [6]. The yields, elemental analysis results, and spectral data of the products are given in Tables 1-3, while the X-ray diffraction structural data for compound **4** are given in Tables 4-8.

Synthesis of β-(Thiomorpholino)propioamidoxime (3) was given in our previous work [4].

Preparation of the Solution of Hydrogen Chloride in Diethyl Ether Containing Traces of Water Used for the Acid Hydrolysis of 1,2,4-Oxadiazoles 1a-e. Absolute diethyl ether was saturated with gaseous HCl formed upon the addition of concentrated sulfuric acid to commercial dry sodium chloride. Drying of the gaseous HCl in a trap filled with concentrated sulfuric acid was not carried out.

β-(Thiomorpholino)propioamidoxime Dichloride (3·2HCl). β-(Thiomorpholino)propioamidoxime (**3**) (0.2 g, 1.0 mmol) was dissolved in anhydrous chloroform (20 ml) and brought to pH 2 by the addition of ethereal HCl (the hydrogen chloride used for saturating the solution in absolute diethyl ether was passed

through a concentrated sulfuric acid trap). The white precipitate of the dichloride **3**·2HCl was filtered off. A precipitate of the dichloride **3**·2HCl formed upon evaporation of the filtrate in vacuum. All the portions of **3**·2HCl were collected and recrystallized from 2-propanol.

Acid Hydrolysis of 5-(*m*-Chlorophenyl)-3-(thiomorpholinoethyl)-1,2,4-oxadiazole (1e). 1,2,4-Oxadiazole **1e** (0.25 g, 0.81 mmol) was dissolved in 5 ml absolute ethanol and then brought to pH 2 by adding ethereal hydrogen chloride containing traces of water. The precipitate formed was filtered off and recrystallized from ethanol to give 0.073 g (0.32 mmol, 40%) 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride hydrate (**4**), mp 302°C. The filtrate was evaporated to dryness to give a white precipitate. Recrystallization of the precipitate from ethanol gave 0.051 g (43%) *m*-chlorobenzoic acid (**5e**), mp 150°C.

The hydrolyses of the other 1,2,4-oxadiazoles **1a-d** were carried out analogously.

X-ray Diffraction Structural Analysis of 4 was carried out on a STOE STADI-4 diffractometer at room temperature using CuKα radiation, graphite monochromator, and θ/2θ-scanning. Orthorhombic crystals of **4** were grown from solution in 2-propanol, ρ_{calc} = 1.357 g/cm^3. The structure was solved using the direct method. The hydrogen atoms at the nitrogen and carbon atoms were placed in geometrically calculated positions. The hydrogen atoms in the water molecules were not revealed. The structure was refined anisotropically for the non-hydrogen atoms (the hydrogen atoms were refined with fixed positional and temperature parameters) by the method of least squares using the *SHELX-97* programs [7]. The final *R*-factor was 0.0666 related to 1221 reflections with $I > 2\sigma(I)$.

The X-ray diffraction structural data were deposited in the Cambridge Crystallographic Data Center (CCDC 711438).

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