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Spiropyrazolinium compounds as a result of β-aminopropioamidoximes intramolecular rearrangements: monograph / L.A. Kayukova, A.V. Vologzhanina, E.M. Yergaliyeva. – Almaty: Daryn, 2022. – 156 p.
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The monograph deals with the β-aminopropioamidoximes reactivity in aroylation and arylsulfochlorination reactions. A set of the reaction products is presented, depending on the structure of the initial substrates – β-aminopropioamidoximes and reagents – chlorides of substituted benzoic and benzenesulfonic acid. Among the reaction products, O-aroyl(sulfoaroyl)-β-aminopropioamidoximes, 5-substituted phenyl-3-β-aminoethyl-1,2,4-oxadiazoles, 2-aminospiropyrazolilammonium chlorides, benzoates, and arylsulfonates were found. A characteristic structural feature for β-aminopropioamidoximes with six-membered heterocycles in the β-position is the formation of new 2-aminospiropyrazolilammonium chlorides, benzoates, arylsulfonates; this phenomenon is due to their thermodynamic advantage. Among the products of aroylation and sulfoaroylation, samples with *in vitro* antitubercular and antidiabetic activity were found that are higher than the reference drugs.
The monograph was written in accordance with research under a grant from the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan «Study of the regioselectivity of the reaction of arylsulfochlorination of β-aminopropioamidoximes; *in vitro* antidiabetic and antitubercular product screening» (IRN: AP08856440).
This collection of the works is intended for an audience of organic chemists and the specialists related to the applications of organic chemistry in medical practice.

Bibliography 200 titles, ill. 56, tab. 26.

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The monograph with DOI: https://doi.org/10.51580/2022-ebook.01 is in free access on the website of JSC "A.B. Bekturov Institute of Chemical Sciences".

PREFACE

Purpose: To present the competitive formation of products at the oxygen atom of the amidoxime group, O-aroyl- and O-arylsulfo-derivatives, products of their further transformations to 5-aryl-3-β-(amino)ethyl-1,2,4-oxadiazoles and 2-amino-spiropyrazolilammonium benzoates, sulfonates and chlorides in the series of products of aroylation and arylsulfochlorination of multifunctional substrates – β-aminopropioamidoximes.

Subject, study object: Series of β-aminopropioamidoximes with six-membered heterocycles in the β-position (β-amino group: piperidine, morpholine, thiomorpholine and phenylpiperazine), as well as with a β-benzimidazole fragment and their linear and heterocyclic derivatives: 5-aryl-3- β-(amino)ethyl-1,2,4-oxadiazoles and 2-amino-spiropyrazolilammonium benzoates, sulfonates and chlorides.

Relevance and significance: The issue of organic synthesis regioselectivity of multifunctional substrates is relevant. There are knowledge gaps, ambiguity of research in the field of arylsulfochlorination of amidoximes and β-aminopropioamidoximes, in particular. The authors found that 3,5-disubstituted 1,2,4-oxadiazoles are unstable compounds and rearrange during hydrolysis into benzoates of spiropyrazoliline compounds; arylsulfochlorination of β-aminopropioamidoximes immediately leads to arylsulfonates of spiropyrazolinium compounds. The latter disagrees with the results existing so far in the world on arylsulfochlorination of amidoximes. In rare cases, it has been shown to lead to O-arylsulfoamidoximes, and mainly to Tiemann-

rearranged products (ureas and cyanamides). The formation of 2-aminospiropyrazolilammonium arylsulfonates upon arylsulfochlorination of amidoximes observed by us is the first example of an intramolecular rearrangement to spiropyrazolinic compounds.

The monograph is the generalization of the works performed in the field of chemistry of β-aminopropioamidoximes, which have a structural feature characteristic of this class of compounds, which determines the thermodynamic advantage of the formation of spiropyrazolinium systems for β-aminoderivatives with six-membered heterocycles in the β-position.

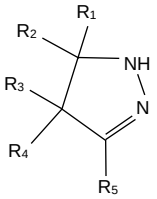
The authors found that there is no reasons to postulate the structure of O-aroyl-β-aminopropioamidoximes kinetically formed upon dehydration – 3,5-disubstituted 1,2,4-oxadiazoles or O-sulfoderivatives of β-aminopropioamidoximes – as unchanged. There is a thermodynamic advantage of the transition of both 3,5-disubstituted 1,2,4-oxadiazoles to spiropyrazolinium systems, which is consistent with the previously established Boulton-Katritzky rearrangement, and a thermodynamic advantage of the existence of sulfonates of spiropyrazolinium compounds, and not of the O-sulfoaryl derivatives of β-aminopropioamidoximes.

The set of sulfochlorination products of amidoximes, including the spectrum of products (O-sulfoderivatives of amidoximes, Tiemann rearranged ureas and cyanamides), postulated earlier, did not include pyrazolinium systems with a sulfonate counterion. In the longterm work of the authors, interesting intramolecular rearrangements of β-aminopropioamidoxime derivatives to spiropyrazolinium systems were discovered, which inspired the writing of this monograph.

Pyrazoline-containing compounds act as active pharmaceutical ingredients in commercially available drugs such as aminopyrine (aminophenazone; analgesic and antipyretic agent), dipyrone (metamisole, noramidopyrine; analgesic), antipyrine (benzocaine; non-narcotic analgesic, antipyretic and antirheumatic agent), zaleplon (hypnotic and sedative). agent), celecoxib (Aclarex,

Celebrex; antiinflammatory and antirheumatic agent), allopurinol (xanthine oxidase inhibitor) [1].

Therefore, in the group of pyrazoline derivatives, there is always a need for new molecules and improved synthetic methods. The five-membered pyrazoline heterocycle contains two neighboring nitrogen atoms. The vast majority of biologically active pyrazolines are 2-pyrazolines:



2-Pyrazoline

Practical interest to the class of β-aminopropioamidoxime derivatives is supported by their pronounced local anesthetic, antitubercular, and antidiabetic activity [2–4].

Analysis of the stability of biologically active compounds requires an accurate determination of their structure. We have found that 5-aryl-3-(2-aminoethyl)-1,2,4-oxadiazoles are generally unstable in the presence of acids and bases and rearrange to form salts of the compounds (benzoates or chlorides) of spiropyrazolinium. Therefore, there is a significant possibility that it is the rearranged products that should be attributed to the observed biological activity, and not the 5-aryl-3-(2-aminoethyl)-1,2,4-oxadiazoles initially taken for screening [5–7].

These facts are consistent with the spontaneous thermally induced Boulton-Katritzky monomolecular rearrangement known for 3,5-substituted 1,2,4-oxadiazoles having a saturated side chain and represent the first examples of the formation of spiropyrazoline compounds obtained by such a rearrangement [8].

In addition, spiropyrazolinium structures, 2-amino-8-oxa-1,5-diazaspiro[4.5]deca-1-ene-5-ammonium arylsulfonates, are formed upon arylsulfochlorination of β-aminopropioamidoximes [9, 10].

The issue of regiospecificity and regioselectivity of organic synthesis of multifunctional substrates has always remained relevant. Structural studies in the series of aroylation and arylsulfochlorination products of β-aminopropioamidoximes, depending on the reaction conditions and the structure of the starting amidoxime, should reveal the boundaries of the competing formation of spiropyrazolinium compounds, O-aroyl- and O-sulfoaryl derivatives, and products according to Tiemann.

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INTRODUCTION

The authors: L.A. Kayukova,
A.V. Vologzhanina, E.M. Ergaliyeva

The monograph consists of 9 chapters, which consider a structural feature characteristic of the class of β-aminopropioamidoximes, which determines the thermodynamic advantage of the formation of spiropyrazolinium systems for β-aminoderivatives with six-membered heterocycles in the β-position.

In the chapters 1–3 data on the Boulton-Katritzky rearrangement found on the example of 5-substituted phenyl-3-(β-amino)ethyl-1,2,4-oxadiazoles are presented. The chapters are complementary as they represent the development of studies on the Boulton-Katritzky rearrangement, which began with 5-substituted phenyl-3-(β-thiomorpholin-1-yl)ethyl-1,2,4-oxadiazoles and continued with β-piperidine and β-morpholine derivatives.

The chapters 4, 5, 8 describe the formation of spiropyrazoline systems during arylsulfochlorination of β-aminopropioamidoximes. In this case, researchers were surprised by the almost instantaneous formation of spiroheterocycles for β-aminopropioamidoximes with six-membered heterocycles (piperidine, morpholine, thiomorpholine and phenylpiperazine) in the β-position without isolating the initially formed assumed O-sulfoaryl derivatives of amidoximes.

The chapter 6 discusses the conformational structure of 2-amino-8-thia-1,5-diazaspiro [4.5]dec-1-en-5-ium chloride

monohydrate with a refinement of the geometry previously defined for it as the chiral P212121 space group to centrosymmetric Pbca.

The chapters 7 and 9 substantiate the thermodynamic advantage of the formation of arylsulfonates of spiropyrazolinium systems during the arylsulfochlorination of β-aminopropioamidoximes in comparison with the formation of O-sulfoaryl-β-aminopropioamidoximes, and also, for an exceptional case, for the arylsulfochlorination of β-(thiomorpholin-1-yl)propioamidoxime, the thermodynamic advantage of formation of the spiropyrazolinium compound chloride compared to the formation of the spiropyrazolinium compound arylsulfonates.

The generalization of the results in the field of chemistry of β-aminopropioamidoximes was carried out in accordance with the research under the grant from the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan «Study of the regioselectivity of the reactionof arylsulfochlorination of β-aminopropioamidoximes; *in vitro* antidiabetic and antitubercular product screening» (IRN: AP08856440).

The monograph is intended for an audience of organic chemists and for specialists associated with specific applications of organic chemistry in medical practice.

We express our deep gratitude to the scientists who were related to the issues considered in the monograph: organic chemists: G.P. Baitursynova, A.B. Uzakova and G.T. Dyusembayeva from the JSC «A.B. Bekturov Institute of Chemical Sciences», Almaty, Kazakhstan; biological activity testers from the Republican State Enterprise «National Scientific Center for Phthisiopulmonology of the Republic of Kazakhstan», Almaty, Kazakhstan and the Republican State Enterprise «National Center for Biotechnology», Nur-Sultan, Kazakhstan: V.L. Bismilda, L.T. Chingisova, B.T. Toksanbayeva, Z.T. Shulgau, A.E. Gulyaev,

Sh.D. Sergazy; spectroscopist K. Akatan from S. Amanzholov East-Kazakhstan State University, Ust-Kamenogorsk, Kazakhstan.

The monograph includes: Bibliography 200 titles, 56 illustrations, 26 tables.

Chapter 1

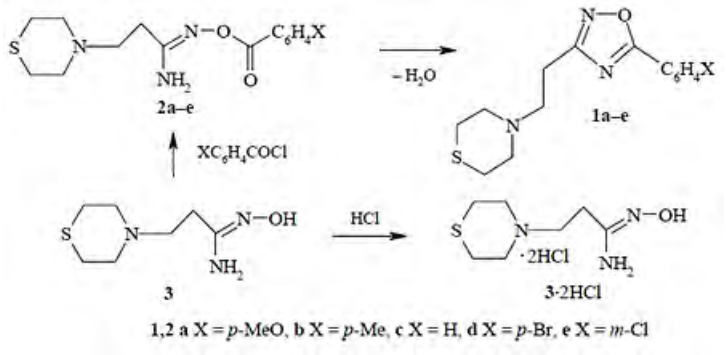
RAPID ACID HYDROLYSIS OF 5-ARYL - 3-(β-THIOMORPHOLINOETHYL)-1,2,4-OXADIAZOLES

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].

In the present work, we studied the reaction of hydrogen chloride with 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles **1a-e** obtainned 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).



Scheme 1

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 melting point (Tables 1-3).

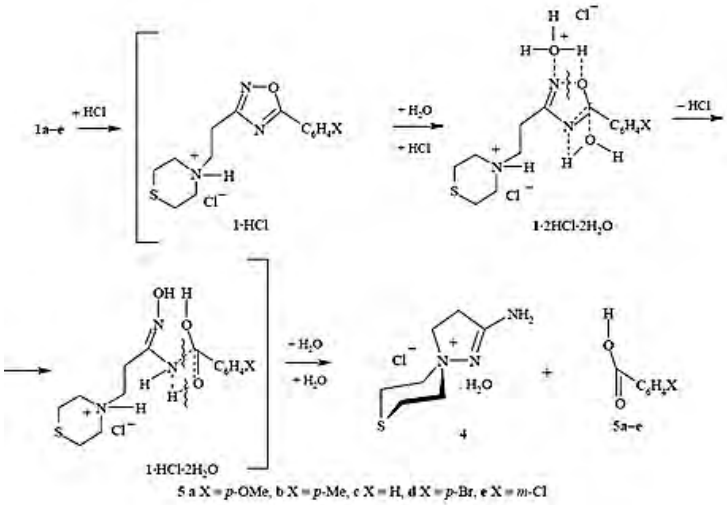
Table 1

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

Compd	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

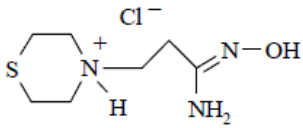
*The literature data from the Acros Organics 2004-2005 Catalog are given in parentheses.
*[2]The values given for Found in the elemental analysis of compound **4** correspond to the values calculated corresponding to the syntheses of these compounds from **1a-e**.

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

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

Table 2

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

Compd	ν, δ, cm^{-1} (KBr pellets)									
	νC=O (v. s)	νC=N (v. s)	δN–H, δN(+)–H, δO(–H)2	νC=C	δO–H	νC–O (v. s)	νC–S (s)	νN(+)–H (m)	νN–H (s)	νO–H (s)
3	—	1659	1598 m	—	1421 m	—	779	—	3092; 3153; 3279	3459
3·2HCl	—	1688	1632 w	—	1409 m	—	719	2525; 2628;	—	3268
4								2851; 2934; 2989		
	—	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

Compd	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** δ 3.14 ppm for the protons of the $C(3)H_2$ group coincide with the signals of the $S(CH_2)_2$ group at

*[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.

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.

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 (Figure 2). The geometry of the intermolecular interactions is given in Table 5.

Table 4

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

Angle	φ, deg	Angle	φ, deg
Pynazolinium 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···A, deg
	D–H	H···A	D···A	
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*.

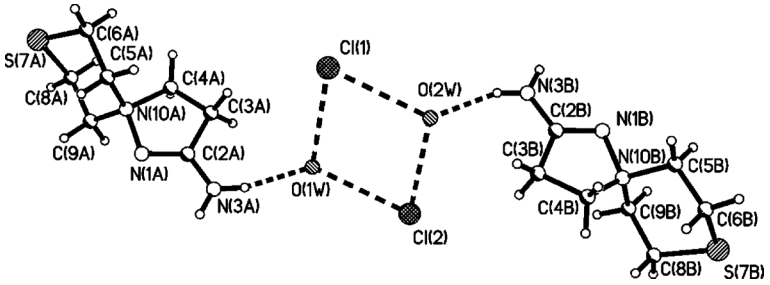


Figure 1. Association of molecules of **4** (independent part) with numbering of the non-hydrogen atoms

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 chloridehydrate (**4**).

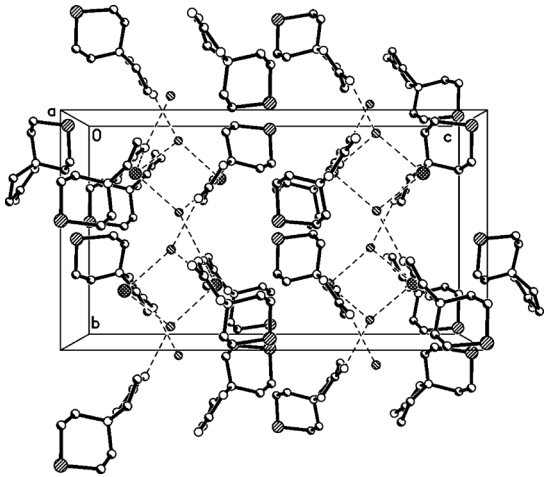


Figure 2. Crystal structure of compound **4**

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.

Table 6

Crystallographic Parameters and Unit Cell Data for Compound 4

Empirical formula Unit cell parameters	$C_7H_{14}ClN_3OS$
1	2
a, Å	10.166(2)
b, Å	11.060(2)
c, Å	19.610(4)
Space group	$P2_12_12_1$

1	2
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

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
1	2	3	4
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)

1	2	3	4
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)

*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 ofthe 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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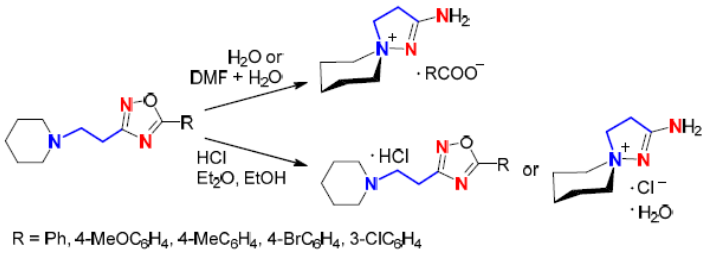
Citation: Kayukova, L.A.; Orazbaeva, M.A.; Gapparova, G.I.; Beketov, K.M.; Espenbetov, A.A.; Faskhutdinov, M.F.; Tashkhodjaev, B.T. Rapid acid hydrolysis of 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles. *Chem. Heterocycl. Compd.* **2010**, *46*, 879–886. DOI: https://doi.org/10.1007/s10593-010-0597-8

Chapter 2

RAPID BOULTON–KATRITZKY REARRANGEMENT OF 5-ARYL-3-[2-(PIPERIDIN-1-YL)ETHYL]-1,2,4-OXADIAZOLES UPON EXPOSURE TO WATER AND HCL

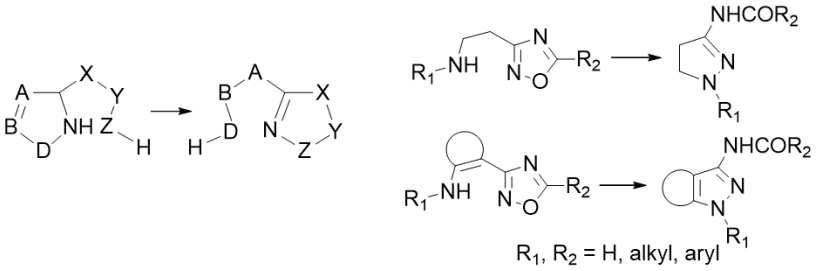


Graphical abstract

Recently we found that the 3,5-substituted 1,2,4-oxadiazoles are of interest for practical medicine since they possess local anaesthetic and anti-tuberculosis properties [1,3]; besides there is evidence of their anti-diabetic activity [3]. Thus, the chemical stability of 1,2,4-oxadiazoles is an area of increased interest. Conversion of these heterocycles during Boulton-Katritzky rearrangement, which is dependent on structural and external factors has been actively studied at present. Mononuclear heterocyclic Boulton-Katritzky rearrangement occurres in accord to the scheme ABD → XYZ at heating (Scheme 1) [4].

Substituted 1,2,4-oxadiazoles under “hard” conditions (in DMF at 150 °C or without solvent at 240 °C) undergo Boulton-Katritzky rearrangement to form pyrazolines and pyrazoles with a planar structure [5]. As reported, electronic properties of aromatic substituents on Boulton-Katritzky rearrangement of 3-(2-aminoaryl)-1,2,4-oxadiazoles to 3-(acylamino)-1H-indazoles have the same significance as the thermal conditions. To avoid the effect of thermal factors in the preparation of rearranged 3-(acylamino)-1H-indazoles microwave reaction conditions were used [6]. Thermal rearrangement of N-(1,2,4-oxadiazol-3-yl)hydrazones to 1,2,4-triazole derivatives is the first example of a triatomic side chain rearrangement involving a sequence of atoms NNC, attached to the atom C(3) of 1,2,4-oxadiazoles. Reactions were held in an environment free of solvents and gave the final products with high yelds [7].

The interconversion of the Z-hydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into the corresponding triazole was experimentally investigated in dioxane/water in the pS(+) range 5.5(5)÷13.9. The uncatalyzed region was examined by the DFT (*Density Functional Theory* – computational quantum mechanical modelling method) method using a model system formed by the Z-hydrazone of 3-formyl-1,2,4-oxadiazole and one or two water molecules. The environmental effect of the solvent was emulated using a continuum model COSMO (COnductor- like Screening MOdel – a calculation evaluation for determining the electrostatic interaction of a molecule with a solvent) approach [8].



Scheme 1

The effect of several modifications of the substrate structures (the *E* and/or *Z* structures of the arylhydrazones of 3-benzoyl-5-X-1,2,4-oxadiazoles), the possible influence of substituents in the arylhydrazone moiety, and the nature of substituents at C-5 of the 1,2,4-oxadiazole ring on the course of the photochemical Boulton-Katritzky rearrangement were examined [9].

Rearrangement rate of eleven 5-amino-3-benzoyl-1,2,4-oxadiazole (Z)-arylhydrazones into the corresponding 2-aryl-5-phenyl-2H-1,2,3-triazol-4-yl)ureas was identified in toluene in the presence of trifluoroacetic acid or piperidine at 40 °C. The results were correlated with the effects of aryl substituents using Hammett correlations and/or correlations Ingold/Yukawa-Tsuno. It was concluded that there is the difference between the chemical reactivity of the compounds studied in polarprotic (or dipolar aprotic) and apolar solvents [10].

A new variation on the Boulton−Katritzky reaction involving the use of CNC side chain was reported. 3-Benzoyl-1,2,4-oxadiazole imines in the presence of strong base underwent Boulton−Katritzky rearrangement to afford novel 4(5)-acylaminoimidazoles [11].

Previously we synthesized series of 5-substituted phenyl-3-(β-amino)ethyl-1,2,4-oxadiazoles (Figure 1). It seemed that they are stable during the isolation, purification, obtaining of physico-chemical and spectral characteristics as well as at storage (Sheme 2) [12-15]. Molecular structure of a representative of this series [5-phenyl-3-(β-benzimidazol-1-yl)ethyl-1,2,4-oxadiazole] was confirmed by X-ray diffraction [16].

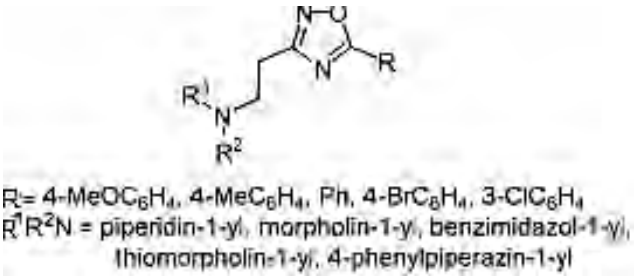
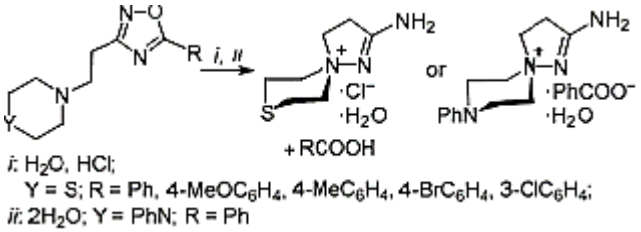


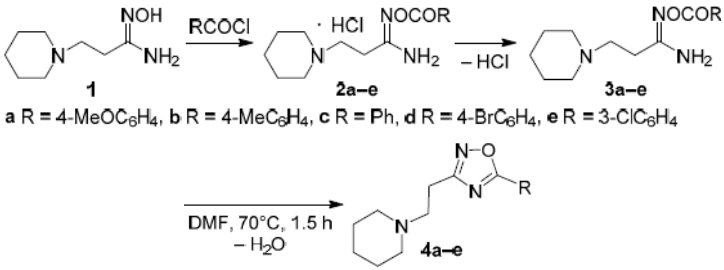
Figure 1. Series of 5-aryl-3-(2-amino)ethyl-1,2,4-oxadiazole

During our attempts to obtain hydrochlorides of 5-aryl-3-[2-(thiomorpholin-1-yl)ethyl]-1,2,4-oxadiazoles and to grow a single crystal for performing X-ray structural analysis of 5-phenyl-3-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,4-oxadiazole by prolonged keeping in 2-PrOH in the presence of air moisture we occasionally observed the lability of the investigated 1,2,4-oxadiazoles (Scheme 2) [17, 18]. Thus, 3-(2-aminoethyl)-5-aryl-1,2,4-oxadiazoles having tertiary amino groups at the β-position of substituent located at the ring position 3 were capable of rearranging to spiropyrazoline compounds. These transformations provided the first examples of spiro compound formation through such rearrangements and could be regarded as a variety of Boulton–Katritzky rearrangement.



Scheme 2

In the present work, the Boulton–Katritzky rearrangement of 3,5-disubstituted 1,2,4-oxadiazoles was performed by using the example of 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles **4a**–**e**. 1,2,4-Oxadiazoles **4a**–**e** as crystalline precipitates were obtained by heating of *O*-aroyl-(2-piperidin-1-yl)propioamidoximes **3a**–**e** in DMF at 70°C. An additional amount of products **4a**–**e** were isolated after evaporating of the solvent under oil pump vacuum and treating the residue with acetone (Scheme 3). The synthesis of the starting compounds **1**, **2a**–**e**, **3a**–**e**, and 1,2,4-oxadiazoles **4a**–**e** has been described earlier, where compounds **4a–e** were obtainted by dehydration of *O*-aroyl-(2-piperidin-1-yl)propioamidoximes **3a**–**e** by heating in DMF in the presence of molecular sieves [12].



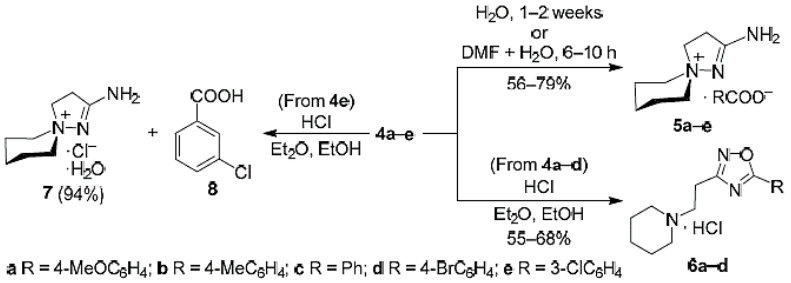
Scheme 3

IR spectra of compounds **4a**–**e** contained absorption bands at 1595–1600 (C=C) and 1662–1664 cm^{-1} (C=N). Compounds **4a**–**e** also exhibited absorption at 1358–1377 cm^{-1} (C–O), which is a characteristic feature of 1,2,4-oxadiazoles. ^1H NMR spectra of 1,2,4-oxadiazoles **4a**–**e** showed peaks in the range of 3.12–3.14 and 3.82 ppm (triplets of α- and β-methylene groups), as well as 3.30–3.36 and 3.42–3.50 ppm (multiplets of two methylene groups bonded to the nitrogen atom of the piperidine heterocycle). Each of the latter signals can be attributed to the axial and equatorial protons of the heterocycle, differentiated by the slow inversion of piperidine ring during the acquisition of NMR spectra.

We investigated the behavior of 5-aryl-3-[2-(piperidin-1-yl) ethyl]-1,2,4-oxadiazoles **4a**–**e** in Boulton–Katritzky rearrangement at 25°C in the following media: H_2O, DMF–H_2O, 10:1, and HCl in ether. The transition from 1,2,4-oxadiazoles **4a**–**c** with electron-donating substituents or an unsubstituted phenyl ring to 1,2,4-oxadiazoles **4d**,**e** with electron-withdrawing substituents occurs with a shortening of the regrouping time from 2 weeks to 1 week in the method I and from 10 to 6 h in the method II.

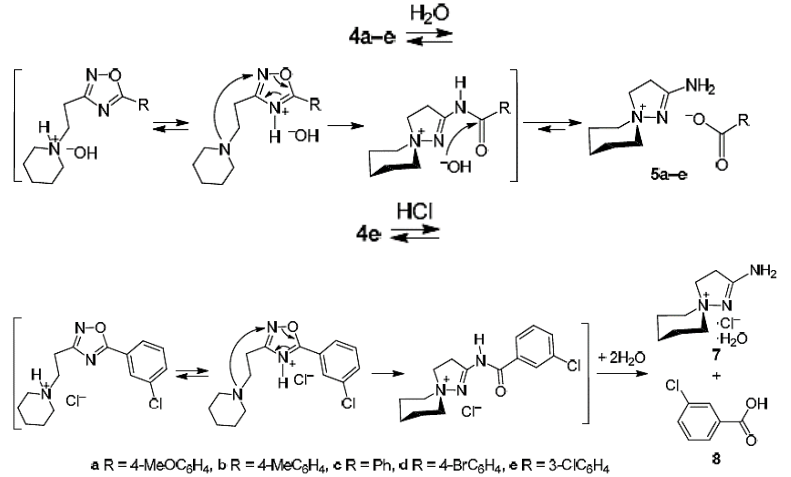
The physicochemical and spectral characteristics of the obtained products, as well as the X-ray diffraction data (see below) indicated that in H_2O and DMF–H_2O 1,2,4-oxadiazoles **4a**–**e** were converted to spiropyrazolines **5a**–**e**, but in ethereal HCl only compound **4e** was converted to spiropyrazoline **7**, while 1,2,4-oxadiazoles **4a**–**d** were recovered in the form of hydrochlorides **6a**–**d**. Spiropyrazolines

5a–**e** contained the respective benzoate anions, and compound **7** contained chloride as a counterion to the quaternary ammonium cation (Scheme 4).



Scheme 4

The formation of compounds **5a**–**e**, **7** can be represented as a series of protonation, proton transfer, and nucleophilic attack steps, effectively constituting hydrolysis during the reaction of 1,2,4-oxadiazoles **4a**–**e** with water and wet HCl (Scheme 5).



Scheme 5

The comparison of benzoates **5a**–**e** with 1,2,4-oxadiazoles **4a**–**e** revealed that the former have higher melting points (mp 216–238°C) and R_f 0.58–0.78, compared to the latter – mp 206–230°C and R_f 0.47–0.65. The main distinguishing feature in IR spectra of spiro compounds **5a**–**e** and **7** compared to the IR spectra of 1,2,4-oxadiazoles **4a**–**e** was the presence of symmetric and asymmetric ν(N–H) stretching bands at 3300 and 3500 cm^{-1}, respectively. IR spectrum of chloride hydrate **7** did not contain the characteristic ν(C–O) absorption band of 1,2,4-oxadiazoles at 1358–1377 cm^{-1}. ^{1}H NMR spectra of benzoates **5a**–**e** differed from the spectra of 1,2,4-oxadiazoles **4a**–**e** by the presence of NH_2 proton signal with the integral of 2H at 7.42–7.70 ppm. ^{1}H NMR spectra of 1,2,4-oxadiazole hydrochlorides **6a**–**d** featured the NH^+ proton signals at 12.63–13.20 ppm. ^{1}H NMR spectrum of spiro compound **7** contained the expected proton signals, and no aromatic proton signals were observed. 3-Chlorobenzoic acid (**8**) precipitated during the evaporation of mother liquors obtained after chloride hydrate **7** was collected by filtration.

After recrystallization of compounds **4a**–**e** from 2-PrOH, only in one case a crystal suitable for X-ray structural analysis could be grown over 9 months. It turned out that a rearrangement and the inclusion of one water molecule in the structure of the resulting spiropyrazoline 4-bromobenzoate occurred, giving hydrate **5d** (Figure 2).

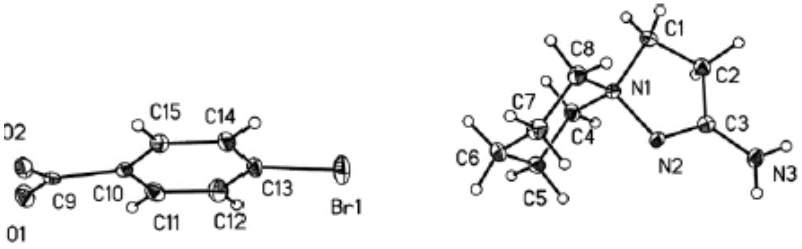


Figure 2. Molecular structure of 2-amino-1,5-diazaspiro [4,5]decan-1-en -5-ammonium (**5d**) with atoms represented by thermal vibration ellipsoids of 50% probability

The location of all hydrogen atoms allowed to unambiguously confirm that this structure is a salt, namely, 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromobenzoate. It crystallized in chiral space group *P*21, and Flack 0.018(6) indicated the correctness of its absolute configuration. The six- and five-membered rings of this cation adopted the conformations of chair and envelope, respectively. The deviation of the C(1) atom from the mean plane of five-membered ring was equal to 0.446(5) Å. The positive charge located on the N(1) atom caused elongation of C(1)–N(1) and N(1)–N(2) bonds compared to the average values for single bonds, which was previously also observed for 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene [17], for 1-(*tert*-butyl)-4,5-dihydro-1*H*-pyrazol-1-ium [19], and for 1,1,3-trimethyl-Δ2-pyrazolinium ions [20]. It would be reasonable to assume that the high antitubercular activity of water-soluble 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles **4a**,**b**,**d** previously observed during prolonged *in vitro* screening experiments was actually due to the rearranged 2-amino-1,5-diazaspiro[4.5]-dec-1-en-5-ium benzoates **5a**,**b**,**d** [21].

From all above mentioned one can conclude the following: in the series **4a**–**e** electronegative substituents of phenyl ring accelerate the rearrangement; hydrolysis under **c**) takes place immediately; hydrolysis under **b**) is faster than under **a**) conditions. Finally, 5-substituted phenyl-3-[β-(piperidin-1-yl)]ethyl-1,2,4-oxadiazoles can be considered as compounds that require control of their stability at room temperature and in the presence of external acids and bases. Thus, there is high level of probability that in the biological screening they have structure of rearranged products.

Experimental

IR spectra were obtained on a NICOLET 5700 FTIR instrument in KBr tablets. The (^{1}H and ^{13}C) NMR spectra were recorded on a NMR Spectrometer Avance III 500 MHz (11.74 Tesla) with an operating frequency for nuclei ^{1}H – 500 MHz and ^{13}C – 126 MHz. As internal standard was used hexamethyldisiloxane (HMDS); as solvent – DMSO-d_6. Chemical shifts (δ) are in parts per million. All IR and NMR spectra were obtained at ambient temperature. Control over the progress of the reaction and product purity were performed using TLC plates Sorbfil (Company Sorbpolymer) coated sorbent – layer silica CTX-1A, grain size 5–17 microns, with UV-254 UV

indicator. As the eluent was used system benzene–EtOH, 1:3. Melting points were determined in glass capillaries on the device "PTP (M)" production of JSC "Himlabpribor". Chemicals were purchased from different chemical suppliers and were purified before using. The solvents used in the synthesis, recrystallization and TLC (ethanol, *i*–PrOH, benzene, DMF, acetone, diethyl ether) were prepared by standard techniques.

*Dehydration of O-aroyl-β-(piperidin-1-yl)propioamidoximes (**3a**–**e**) to form 5-substituted phenyl-3-[(β-piperidin-1-yl)]ethyl-1,2,4-oxadiazoles (**4a**–**e**) (Scheme 4).*

*5-p-Methoxyphenyl-3-[β-(piperidin-1-yl)]ethyl-1,2,4-oxadiazole (**4a**).* Solution of O-*p*-methoxyphenyl-β-(piperidin-1-yl)propioamidoxime (**3a**) (1.04 g, 3.410 mmol) in dry DMF (10 mL) was heated in an oil bath at 70 °C for 1.5 h with TLC control. Then at room temperature formed technical precipitate of **4a** (0.36 g, 1.183 mmol) was filtered and filtrate was evaporated to dryness in an oil pump vacuum at 50 °C/1 mm Hg. Organic residue was treated with dry acetone (10 mL). Additional quantity of 1,2,4-oxadiazole (**4a**) (0.44 g, 1.531 mmol) was filtered. Technical combined residues of **4a** were recrystallizated from *i*-PrOH to obtain colorless solid of 5-*p*-methoxyphenyl-3-[β-(piperidin-1-yl)]ethyl-1,2,4-oxadiazole (**4a**). Yield 0.50 g (51%); R_f 0.60, mp 224 °C. IR spectrum (KBr), ν, cm^{-1}: 1662, 1598, 1560, 1363. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.60 (2H, m), 1.70–1.78 (2H, m), and 1.85–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.13 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.35 ($2H_{eq}$, m) and 3.43–3.47 ($2H_{ax}$, m, $N(CH_2)_2$); 3.72 (3H, s, *p*-CH_3O); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 6.75 (2H, d, *J* = 8.7, *o*-H Ar); 7.74 (2H, d, *J* = 8.7, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.4; 55.4; 60.7; 64.3; 112.4; 130.9; 135.1; 159.8; 168.6; 168.7. Found, %: C 66.53; H 7.42. $C_{16}H_{21}N_3O_2$. Calculated, %: C 66.88; H 7.37.

*3-[2-(Piperidin-1-yl)ethyl]-5-(p-tolyl)-1,2,4-oxadiazole (**4b**)* was obtained analogously to compound **4a** from 3-(piperidin-1-yl)-*N*'-{[(*p*-tolyloxy)carbonyl]-oxy}propanimid- amide (**3b**) (1.30 g, 4.498 mmol) in dry DMF (10 ml). Yield 0.86 g (71%), colorless solid, mp 219–220°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1662 (C=N), 1595 (C=N), 1550 (C=C), 1359 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.60 (2H, m), 1.69–1.77 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 2.27 (3H, s, *p*-$CH_3$); 3.14 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.30–3.35 ($2H_{eq}$, m) and 3.42–3.50 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0 $C\underline{H}_2N(CH_2)_2$); 7.01 (2H, d, *J* = 8.0, *o*-H Ar); 7.70 (2H, d, *J* = 8.0, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.3; 21.9; 31.5; 60.7; 64.3; 127.9; 129.5; 137.4; 139.7; 168.6; 168.9. Found: C 70.53; H 7.42. $C_{16}H_{21}N_3O$. Calculated, %: C 70.82; H 7.80.

*5-Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4c**)* was obtained analogously to compound **4a** from *N*'-[(phenoxycarbonyl)oxy]-3-(piperidin-1-yl)propanimid- amide (**3c**) (0.73 g, 2.652 mmol) in dry DMF (5 ml). Yield 0.29 g (43%), colorless solid, mp 205–206°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 1663 (C=N), 1598 (C=N), 1553 (C=C), 1377 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.60

(2H, m), 1.70–1.78 (2H, m), and 1.85–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, J = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.36 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, J = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.23–7.81 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.6; 60.7; 127.4; 128.4; 129.4; 168.6; 168.9. Found, %: C 70.29; H 7.39. $C_{15}H_{19}N_3O$. Calculated: C 70.01; H 7.44.

*5-(4-Bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4- oxadiazole (**4d**)* was obtained analogously to compound **4a** from *N*'-{[(4-bromophenoxy)carbonyl]oxy}-3-(piperidin-1-yl)propanimidamide (**3d**) (0.98 g, 2.770 mmol) in dry DMF (10 ml). Yield 0.66 g (71%), colorless solid, mp 228– 230°C, R_f 0.47. IR spectrum, ν, cm^{-1}: 1662 (C=N), 1598 (C=N), 1547 (C=C), 1358 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.61 (2H, m), 1.69–1.77 (2H, m), and 1.83–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, J = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.35 ($2H_{eq}$, m) and 3.42–3.49 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, J = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.41 (2H, d, J = 8.0, *o*-H Ar); 7.74 (2H, d, J = 8.0, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.5; 60.7; 64.3; 122.1; 130.2; 131.6; 141.4; 167.7; 168.6. Found, %: C 53.71; H 5.46. $C_{15}H_{18}BrN_3O$. Calculated, %: C 53.58; H 5.40.

*5-(3-Chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4- oxadiazole (**4e**)* was obtained analogously to compound **4a** from *N*'-{[(3-chlorophenoxy)carbonyl]oxy}-3-(piperidin- 1-yl)propanimidamide (**3e**) (3.94 g, 1.272 mmol) in dry DMF (15 ml). Yield 2.97 g (80%), colorless solid, mp 207– 208°C, R_f 0.56. IR spectrum, ν, cm^{-1}: 1664 (C=N), 1600 (C=N), 1557 (C=C), 1360 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.61 (2H, m), 1.70–1.77 (2H, m), and 1.84–1.91 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, J = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.30–3.35 ($2H_{eq}$, m) and 3.44–3.49 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, J = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.25–7.78 (4H, m, C_6H_4Cl-*m*). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 127.8; 128.2; 129.2; 129.3; 132.4; 144.6; 167.1; 168.6. Found, %: C 61.71; H 6.46. $C_{15}H_{18}ClN_3O$. Calculated, %: C 61.75; H 6.22.

*Hydrolysis of 5-aryl-3-[(2-piperidin-1-yl)ethyl]-1,2,4- oxadiazoles **4a–e** in H_2O and in DMF–H_2O to form 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates 5a–e. 2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-methoxy- benzoate (**5a**).* Method I. 5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4a**) (0.5 g, 1.740 mmol) was dissolved in distilled water (5 ml). The solution was left at room temperature with daily TLC control. After hydrolysis for 2 weeks, the aqueous solution was concentrated under water aspirator vacuum. The organic residue was treated with diethyl ether (10 ml). The hydrolysis product was collected by filtration as a white precipitate, then recrystal- lized from 2-PrOH. Yield 0.40 g (75%), colorless solid, mp 230–232°C, R_f 0.78. IR spectrum, ν, cm^{-1}: 3500 (NH_2 as), 3300 (NH_2 sy), 1663 (C=N), 1599 (C=C), 1551 (COO^- sy), 1363 (COO^- as). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.60 (2H, m), 1.68–1.78 (2H, m), and 1.82–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.14 (2H, t, J = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.29–3.36 ($2H_{eq}$, m) and 3.42–3.49 ($2H_{ax}$, m, $N(CH_2)_2$); 3.73 (3H, s, *p*-CH_3O); 3.82 (2H, t, J = 7.0, $C\underline{H}_2N(CH_2)_2$); 6.75 (2H, d, J = 8.7, *o*-H Ar); 7.45 (2H, br. s, NH_2); 7.74 (2H, d, J = 8.7, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.4; 55.4; 60.7; 64.3;

112.5; 130.9; 134.7; 160.0; 168.9. Found, %: C 63.11; H 7.30. $C_{16}H_{23}N_3O_3$. Calculated, %: C 62.93; H 7.59.

Method II. 5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)- ethyl]-1,2,4-oxadiazole (**4a**) (0.5 g, 1.740 mmol) was dissolved in DMF (5 ml) and distilled water (0.5 ml). The solution was left at room temperature and checked by TLC at the intervals of 1 h. After hydrolysis for 10 h, the reaction solution was concentrated under water aspirator vacuum and the organic residue was treated with diethyl ether (10 ml). Product **5a** was collected by filtration as a white precipitate, then recrystallized from 2-PrOH. Yield 0.35 g (66%), colorless solid, mp 230–232°C, R_f 0.78. Found, %: C 63.25; H 7.80. $C_{16}H_{23}N_3O_3$. Calculated, %: C 62.93; H 7.59.

*2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-methyl- benzoate (**5b**)* was obtained analogously to compound **5a** from 3-[2-(piperidin-1-yl)ethyl]-5-(*p*-tolyl)-1,2,4-oxadiazole (**4b**) (0.5 g, 1.843 mmol). Method I (2 weeks). Yield 0.34 g (64%), colorless solid, mp 227–228°C, R_f 0.75. IR spectrum, ν, cm^{-1}: 3500 (NH_2 as), 3320 (NH_2 sy), 1663 (C=N), 1599 (C=C), 1550 (COO^- sy), 1368 (COO^- as). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.60 (2H, m), 1.70–1.80 (2H, m), and 1.82–1.93 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.13 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.29–3.36 ($2H_{eq}$, m) and 3.41–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.73 (3H, s, *p*-CH_3); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 6.75 (2H, d, *J* = 8.7, *o*-H Ar); 7.44 (2H, br. s, NH_2); 7.70 (2H, d, *J* = 8.7, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 20.1; 22.0; 31.6; 55.4; 60.2; 64.4; 112.6; 130.9; 134.7; 160.0; 168.3. Found, %: C 66.52; H 7.55. $C_{16}H_{23}N_3O_2$. Calculated, %: C 66.41; H 8.01.

Method II (10 h). Yield 0.30 g (56%), colorless solid, mp 227–228°C, R_f 0.75. Found, %: C 66.72; H 8.25. $C_{16}H_{23}N_3O_2$. Calculated, %: C 66.41; H 8.01.

*2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoate (**5c**)* was obtained analogously to compound **5a** from 5-phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4c**) (0.5 g, 1.943 mmol). Method I (2 weeks). Yield 0.39 g (73%), colorless solid, mp 220–222°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 3510 (NH_2 as), 3436 (NH_2 sy), 1663 (C=N), 1598 (C=C), 1554 (COO^- sy), 1377 (COO^- as). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.60 (2H, m), 168–1.77 (2H, m), and 1.83–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.13 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.30–3.35 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.45 (2H, br. s, NH_2); 7.24–7.82 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.5; 60.7; 64.3; 127.4; 130.4; 131.8; 132.2; 167.0; 168.5. Found, %: C 64.95; H 7.30. $C_{15}H_{21}N_3O_2$. Calculated, %: C 65.43; H 7.69.

Method II (10 h). Yield 0.30 g (56%), colorless solid, mp 220–222°C, R_f 0.70. Found, %: C 65.35; H 7.45. $C_{15}H_{21}N_3O_2$. Calculated, %: C 65.43; H 7.69.

*2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromo-benzoate (**5d**)* was obtained analogously to compound **5a** from 5-(4-bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4- oxadiazole (**4d**) (0.5 g, 1.487 mmol). Method I (1 week). Yield 0.39 g (74%), colorless solid, mp 237–238°C, R_f 0.58. IR spectrum, ν, cm^{-1}: 3480 (NH_2 as), 3320 (NH_2 sy), 1664 (C=N), 1595 (C=C), 1550 (COO^- sy), 1359 (COO^-

as). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.61 (2H, m), 1.70–1.80 (2H, m), and 1.82–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.29–3.36 ($2H_{eq}$, m) and 3.41–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.41 (2H, d, *J* = 7.0, *o*-H Ar); 7.60 (2H, br. s, NH_2); 7.75 (2H, d, *J* = 7.0, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 122.2; 130.3; 131.6; 141.3; 167.8; 168.6. Found, %: C 50.78; H 5.31. $C_{15}H_{20}BrN_3O_2$. Calculated, %: C 50.86; H 5.69.

Method II (6 h). Yield 0.30 g (57%), mp 237–238°C, R_f 0.58. Found, %: C 50.65; H 5.87. $C_{15}H_{20}BrN_3O_2$. Calculated, %: C 50.86, H 5.69.

*2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 3-chloro-benzoate (**5e**)* was obtained analogously to compound **5a** from 5-(3-chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4- oxadiazole (**4e**) (0.5 g, 1.714 mmol). Method I (1 week). Yield 0.41 g (77%), colorless solid, mp 214–216°C, R_f 0.68. IR spectrum, ν, cm^{-1}: 3350 (NH_2 as), 3340 (NH_2 sy), 1664 (C=N), 1599 (C=C), 1557 (COO^- sy), 1377 (COO^- as). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.51–1.61 (2H, m), 1.70–1.79 (2H, m), and 1.83–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.11 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.35 ($2H_{eq}$, m) and 3.43–3.47 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.27–7.77 (4H, m, C_6H_4Cl-*m*); 7.42 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.5; 60.7; 64.3; 127.8; 128.1; 129.2; 129.3; 132.4; 144.9; 166.9; 168.6. Found, %: C 58.56; H 6.14. $C_{15}H_{20}ClN_3O_2$. Calculated, %: C 58.16; H 6.51.

Method II (6 h). Yield 0.42 g (79%), colorless solid, mp 214–216°C, R_f 0.68. Found, %: C 58.55; H 6.35. $C_{15}H_{20}ClN_3O_2$. Calculated, %: C 58.16; H 6.51.

*Action of ethereal HCl solution on 5-aryl-3-[2- (piperidin-1-yl)ethyl]-1,2,4-oxadiazoles **4a–e** to form 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydro- chlorides **6a–d** or 2-amino-1,5-diazaspiro[4.5]dec-1-en- 5-ium chloride hydrate (**7**) and 3-chlorobenzoic acid (**8**). 5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (**6a**).* 5-(4-Methoxyphenyl)- 3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4a**) (0.3 g, 1.044 mmol) was dissolved in a minimum amount of absolute ethanol. Then ethereal HCl solution was added dropwise to pH 2. The resultant white precipitate was triturated with a glass rod and filtered through a micro funnel. Double volume of ether was added to the filtrate. The white precipitate was collected by filtration and combined with the first precipitate. After recrystallization from 2-PrOH, 5-(4-methoxyphenyl)-3-[2-(piperidin-1-yl)-ethyl]-1,2,4-oxadiazole hydrochloride (**6a**) was isolated. Yield 0.23 g (68%), white opaque powder, mp 168–170°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 2850–2450 (N^+–H), 1685 (C=N), 1604 (C=C), 1261 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.62 (2H, m), 1.70–1.80 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.10 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.32–3.38 (4H, m, $N(CH_2)_2$); 3.47 (2H, t, *J* = 7.0, $CH_2C\underline{H}_2N(CH_2)_2$); 3.82 (3H, s, *p*-$CH_3O$); 7.01 (2H, d, *J* = 7.0, *o*-H Ar) and 7.89 (2H, d, *J* = 7.0, *m*-H Ar); 12.63 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9 (2C); 31.5 (2C); 55.9; 60.7; 64.3; 114.3, 123.4, 131.8, 163.5 (6C); 167.4; 168.5. Found, %: C 59.81; H 7.30. $C_{16}H_{22}ClN_3O_2$. Calculated, %: C 59.35; H 6.85.

*5-(4-Methylphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (**6b**)* was obtained analogously to compound **6a** from 5-(4-methylphenyl)-3-[2-(piperidin- 1-yl)ethyl]-1,2,4-oxadiazole (**4b**) (0.3 g, 1.106 mmol). Yield 0.19 g (56%), white opaque powder, mp 165–168°C, R_f 0.60. IR spectrum, ν, cm^{-1}: 2800–2480 (N^+–H), 1664 (C=N), 1603 (C=C), 1320 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48–1.63 (2H, m), 1.71–1.81 (2H, m), and 1.83–1.91 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.33–3.39 (4H, m, $N(CH_2)_2$); 3.47 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.70 (2H, d, *J* = 7.0, *o*-H Ar); 7.90 (2H, d, *J* = 7.0, *m*-H Ar); 13.20 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.2; 22.0; 23.5; 31.6; 60.8; 64.5; 113.4; 123.5; 130.5; 163.5; 167.8; 169.2. Found, %: C 62.72; H 7.45. $C_{16}H_{22}ClN_3O$. Calculated, %: C 62.43; H 7.20.

*5-Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (**6c**)* was obtained analogously to compound **6a** from 5-phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4- oxadiazole (**4c**) (0.3 g, 1.167 mmol). Yield 0.19 g (55%), white opaque powder, mp 237–240°C, R_f 0.57. IR spectrum, ν, cm^{-1}: 2900–2480 (N^+–H), 1664 (C=N), 1603 (C=C), 1321 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.69 (2H, m), 1.72–1.82 (2H, m), and 1.83–1.91 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 2.35 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.32–3.38 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.25–7.83 (5H, m, C_6H_5); 13.18 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.7; 60.9; 64.5; 127.4; 128.4; 129.6; 143.0; 168.7; 169.2. Found, %: C 61.55; H 6.98. $C_{15}H_{20}ClN_3O$. Calculated, %: C 61.32; H 6.86.

*5-(4-Bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (**6d**)* was obtained analogously to compound **6a** from 5-(4-bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4d**) (0.3 g, 0.892 mmol) dissolved in absolute EtOH (0.5 ml). Yield 0.22 g (66%), white opaque powder, mp 185–186°C, R_f 0.81. IR spectrum, ν, cm^{-1}: 2900–2554 (N^+–H), 1678 (C=N), 1610 (C=C), 1296 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.61 (2H, m), 1.70–1.78 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.10 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.36 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.71 (2H, d, *J* = 7.0, *o*-H Ar); 7.86 (2H, d, *J* = 7.0, *m*-H Ar); 13.19 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 127.4; 130.4; 131.8; 132.2; 167.0; 168.5. Found, %: C 48.78; H 5.31. $C_{15}H_{19}BrClN_3O$. Calculated, %: C 48.34, H 5.14.

*Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**7**).* When ethereal HCl solution was added drop- wise to a solution of 5-(3-chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4e**) (0.3 g, 1.028 mmol) in EtOH (0.5 ml) to pH 2, white precipitate of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**7**) was formed at once and collected by filtration. Yield 0.2 g (94%), white opaque powder, mp 257–260°C, R_f 0.21. IR spectrum, cm^{-1}: 3338 (NH_2 ν as), 3260 (NH_2 ν sy), 1678 (C=N ν), 1610 (NH_2 δ). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.61 (2H, m), 1.70–1.78 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$; 3.10 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.36 (2Heq, m) and 3.45–3.50 (2Hax, m,

N(CH_2)$_2$); 3.83 (2H, t, *J* = 7.0, $CH_2C\underline{H_2}N(CH_2)_2$); 7.34 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 168.5. Found, %: C 46.56; H 8.54. $C_8H_{18}ClN_3O$. Calculated: C 46.26; H 8.74.

*2-Chlorobenzoic acid (**8**)* was precipitated during the evaporation of mother liquors obtained after the filtration of choride hydrate **7**. All characteristics of acid **8** corresponded to previously available data [22].

X-ray diffraction analysis. Inclusion of one water molecule in the structure of 1,2,4-oxadiazole **4d** during its crystallization from 2-PrOH over 9 months gave a single crystal of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromobenzoate (**5d**). The intensities of reflections were measured on a Bruker Apex II CCD diffractometer with MoKα radiation (λ 0.71073 Å, graphite monochromator). The crystal ($C_{15}H_{20}BrN_3O_2$, M_r 354.25) was monoclinic, space group $P2_1$, at 120.0 K: *a* 6.5058(5), *b* 7.9245(6), *c* 15.1028(11) Å; β 98.2190(10)°; *V* 770.63(10) Å^3; *Z* 2; *D*calc 1.527 g·cm–3; μ 2.675 mm–1. A total of 9361 reflections were measured, 4012 independent (*R*int 0.0561), final *R*1 ($I > 2\sigma(I)$) 0.0259, *wR*(*F*2) 0.0547 (all data), *GOF* 0.897. The structure was solved by direct method and refined by full-matrix least-squares method against *F*2. Non-hydrogen atoms were refined in anisotropic approximation. All hydrogen atoms could be located on difference Fourier maps. The H(C) atoms were included in the refinement by the riding model with *U*iso(H) = *nU*eq(C), where *n* = 1.5 for methyl groups and 1.2 for the other atoms. All calculations were performed using the SHELXL [23] and OLEX2 [24] software suites. The crystallographic dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1496456).

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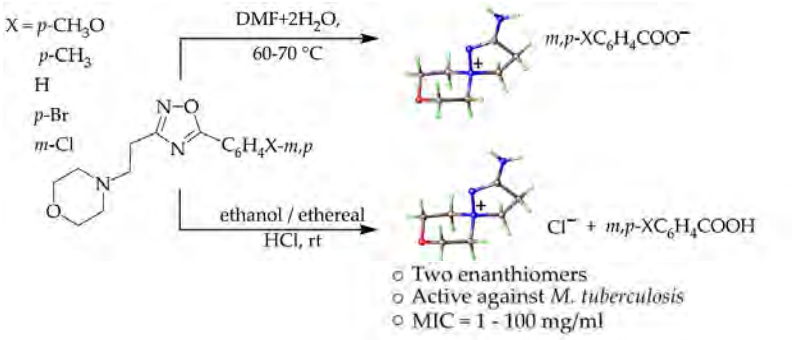
Chapter 3

BOULTON-KATRITZKY REARRANGEMENT OF 5-SUBSTITUTED PHENYL-3-[2-(MORPHOLIN-1-YL)ETHYL]-1,2,4-OXADIAZOLES AS A SYNTHETIC PATH TO SPIROPYRAZOLINE BENZOATES AND CHLORIDE WITH ANTITUBERCULAR PROPERTIES



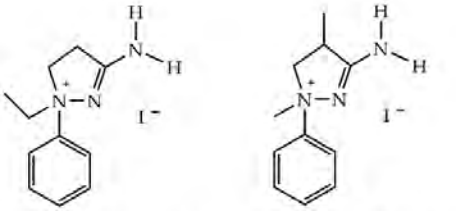
Graphical abstract

3.1. Introduction

There are pyrazoline-containing compounds that act as active pharmaceutical ingredients of such commercially available drugs as

aminopyrine (aminophenazone; analgesic and antipyretic), dipyrone (metamizole, noramidopyrine; analgesic), antipyrine (benzocaine; non-narcotic analgesic, an antipyretic and antirheumatic), zaleplon(hypnotic and sedative), celecoxib (Aclarex, Celebrex; anti-inflammatory and antirheumatic drug), allopurinol (uricostatic agent, xanthine oxidase inhibitor) [1]. Therefore, there is always a demand for new molecules,methodologies and improved synthetic approaches to novel pyrazoline derivatives. Pyrazolines, as noticeable, practically meaningful nitrogen-containing heterocyclic compounds, can be synthesized by a variety of methods. However, one of the most popular methods is the Fischer and Knoevenagel synthesis based on the reaction of *a*,*b*-unsaturated ketones with phenylhydrazine in acetic acid under refluxing conditions. However, depending on the reactivity of molecules and the need of the chemist, they had synthesized the pyrazolines under different solvent media and acidic or basic conditions [2–4].

Information on pyrazolinium structures with a quaternary nitrogen atom is limited. Thus, two examples of biologically active pyrazolinium salts were found: 3-amino-1-ethyl-1-phenyl-4,5-dihydro-1H-pyrazolinium iodide (PubChemCID: 13585073 structure, [5]) and 3-amino-1,4-dimethyl-1-phenyl-2-pyrazolinium iodide (PubChemCID: 13064197 structure, [6]) (Scheme 1):

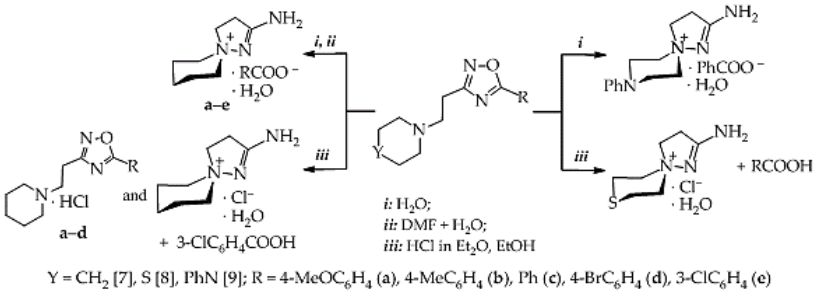


Scheme 1. Amino-1-phenyl-4,5-dihydro-1*H*-pyrazolinium iodides

In some works, we found spiropyrazolinium compounds with a quaternary nitrogen atom, which is common for two heterocycles. When studying the stability of 3-(2-aminoethyl)-5-aryl-1,2,4-

oxadiazoles having six-membered cyclic tertiary 2-amino groups towards hydrolysis, we found that they were capable of rearranging to spiropyrazolinebenzoates or chlorides [7–9].

Particularly, upon keeping 3-[2-(4-phenylpiperazin-1-yl)ethyl]-5-phenyl-1,2,4-oxadiazole recrystallized in 2-PrOH under conditions of air moisture access for ninemonths for growing single crystals for X-ray structural analysis or by exposure of 3-[2-thiomorpholin-1-yl)ethyl]-5-aryl-1,2,4-oxadiazoles in ethanol with ethereal HCl solution the above-mentioned 1,2,4-oxadiazoles underwent the rearrangement to spiropyrazolinium benzoates or chlorides (Scheme 2) [7,8]:

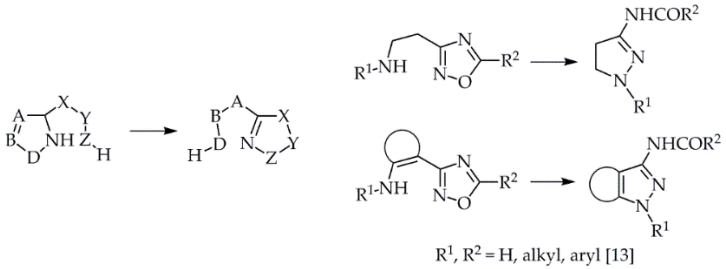


Scheme 2. 3-(2-Aminoethyl)-5-aryl-1,2,4-oxadiazoles in the conditions of exposure to H_2O and HCl

Furthermore, at targeted exposure on 3-[2-(piperidin-1-yl)ethyl]-5-aryl-1,2,4-oxadiazoles with: (*i*) water, (*ii*) water in DMF or (*iii*) ethereal HCl they underwent rearrangement with the formation 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates or chlorides (Scheme 2). In the latter case, along with the formation of spiropyrazolinium chloride hydrate from 3-[2-(piperidin-1-yl)ethyl]-5-(3-chloro-phenyl)-1,2,4-oxadiazole hydrochlorides of starting 1,2,4-oxadiazoles were obtained as secondary products [9].

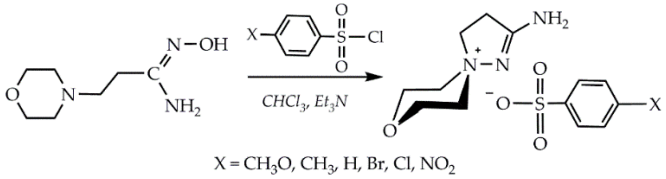
These facts are consistent with the known for 3,5-substituted 1,2,4-oxadiazoles with a saturated side chain spontaneous thermally induced monomolecular Boulton–Katritzky rearrangement and provided the first examples of spirocompound formation through such

reaction. In general, a variety of Boulton–Katritzky rearrangements could be represented as the following scheme (Scheme 3) [10,11]:



Scheme 3. Mononuclear heterocyclic Boulton-Katritzky rearrangement of 3,5-substituted 1,2,4-oxadiazoles

In addition, spiropyrazolinium structures – 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium arylsulfonates are formed at arylsulfochlorination of β-aminopropioamidoximes (Scheme 4) [12].



Scheme 4. Amino-4,5-dihydrospiropyrazolylammonium formation at arylsulfochlorination of β-aminopropioamidoximes

The practical interest in the class of β-aminopropioamidoxime derivatives is supported by their pronounced local anesthetic, antitubercular, and antidiabetic activities [13–16].

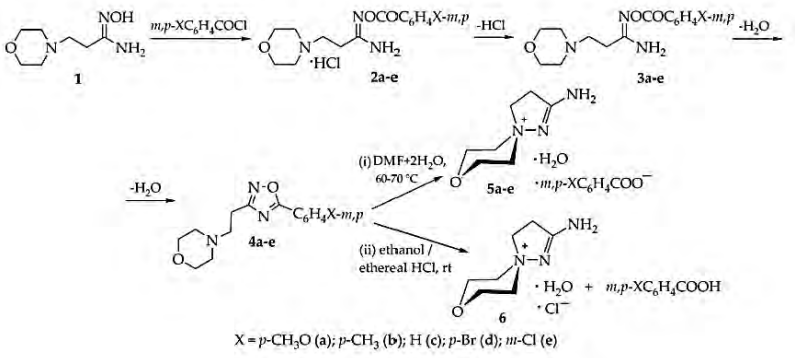
Herein we report on the stability of 5-aryl-3-[β-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles towards hydrolysis at: (*i*) DMF with the two equivalent amount of water when heated to 60–70 °C; (*ii*) alcohol/ethereal HCl mixture. A number of previously unknown spiropyrazolinium salts were obtained and characterized using FT-IR and NMR spectroscopy and X-ray diffraction. *In vitro* antitubercular

screening of spiropyrazoline benzoates and chloride was carried out, and their molecular docking was performed. It was shown that the hydrolysis of 1,2,4-oxadiazoles with a 3-morpholinoethyl substituent leads to spiropyrazoline compounds within 25–40 h. Acid hydrolysis of 1,2,4-oxadiazoles occurs immediately after reagents adding. In vitro antitubercular screening of benzoates and chloride of spiropyrazoline drug-susceptible and multidrug-resistant strains, *M. tuberculosis* revealed compounds with significant activity, and the results are in accordance with molecular docking studies.

3.2. Results and Discussion

3.2.1. Synthesis and Spectra

The synthesis of the starting compounds **1**, **2a**–**e**, **3a**–**e** and **4a**–**e** was described earlier [17]. 5-Substituted phenyl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (**4a**–**e**) were obtained by heating of O-aroyl-(β-morpholin-1-yl)propioamidoximes (**3a**–**e**) in DMF at 70 °C for several hours, evaporating off the solvent in an oil pump vacuum and treating of the residue with acetone. 1,2,4-Oxadiazoles (**4a**–**e**) are obtained as crystalline precipitates from acetone (Scheme 5).



Scheme 5. Obtaining of 5-Substituted phenyl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (**4a–e**), and 2-amino-8-oxa-1,5-diazaspiro [4.5]dec-1-en-5-ium benzoates and chloride (**5a**–**e**, **6**)

Physicochemical, FT-IR and NMR spectral characteristics of representatives of 1,2,4-oxadiazoles of the morpholine series (**4a**–**e**) were recorded immediately after isolation from DMF, and they correspond to the structure of 1,2,4-oxadiazoles. However, the X-ray diffraction analysis of single crystals grown for nine months from 1,2,4-oxadiazoles **4c**–**e** recrystallized from 2-PrOH showed a complete transition of 1,2,4-oxadiazoles into rearranged spiropyrazolinium compounds **5c**–**e** (Section 2.3.). This indicates the hydrolysis of 1,2,4-oxadiazoles **4a**–**e** by way of Boulton–Katritsky rearrangement to spiropyrazolinium compounds **5a**–**e** under the influence of air moisture. The rearrangement products **5a**–**e** have increased values of the mobility index R_f and m.p. in comparison with the initial compounds **4a**–**e** (Table 1).

Table 1

Physicochemical data of 5-substituted phenyl-3-[β-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (4a–e) and spiropyrazolinium compounds (5a–e) fixed in the conditions for obtaining single crystals for XRD analysis and in condition (*i*)

Compd	X	Yield, %	m.p., °C	R_f *	Compd	t, h **	Yield, %	m.p., °C	R_f *
4a	*p*-CH_3O	62	230	0.71	**5a**	40	63	248	0.80
4b	*p*-CH_3	70	220	0.62	**5b**	40	63	235	0.75
4c	H	92	216	0.66	**5c**	25	77	220	0.75
4d	*p*-Br	83	224	0.67	**5d**	25	80	240	0.77
4e	*m*-Cl	56	190	0.62	**5e**	25	43	200	0.70

* R_f determined in the system ethanol:benzene, 3:1; ** the heating time of 1,2,4-oxadiazoles **4a**–**e** in DMF+2H_2O.

Further in this work, we investigated the conditions for the Boulton–Katritsky rearrangement of 5-substituted phenyl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (**4a**–**e**) under the deliberate establishment of hydrolysis conditions: (*i*) DMF with the two equivalent amount of water when heated to 60–70 °C; (*ii*) alcohol/ethereal HCl mixture in the presence of air moisture (Scheme 5).

As can be seen from Table 1, the heating time has an increased value (40 h) for electron-donor substituents in the phenyl ring of 1,2,4-

oxadiazoles **4a**, **4b** in comparison with 1,2,4-oxadiazoles with an unsubstituted phenyl ring and with a phenyl ring having electron-withdrawing substituents–**4c**–**e** (25 h). Spiropyrazolinium compounds **5a**–**e** were obtained after evaporation of DMF in an oil pump vacuum, treatment of the residue with acetone with the isolation of rearranged products **5a–e** and their recrystallization from 2-PrOH. In the case of the action of ethereal HCl solution on alcohol solutions of 1,2,4-oxadiazoles **4a**–**e** in all cases, 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride (**6**) and the corresponding benzoic acids were isolated.

IR spectra view of spirocompounds **5a**–**e** and **6** differ from the IR spectra of 1,2,4-oxadiazoles **4a**–**e**. First, the former compounds have symmetric and asymmetric ν(N–H) stretching bands at 3152–3485 and 3158–3457 cm^{-1}, respectively; second, there are pronounced bands of asymmetric and symmetric stretching vibrations of strong intensity ν(COO^-) at 1545–1557 cm^{-1} and 1420–1442 cm^{-1}, respectively for **5a**–**e** and no stretching bonds of aromatic protons for salt **6**.

The ^{1}H-NMR spectra of 1,2,4-oxadiazole **4a**–**e** were recorded immediately with isolation; if they were recorded after 1–2 weeks, then the emergence and increase in the intensity of the NH_2 group signal of the rearranged spiropyrazolinium products **5a**–**e** in the region of δ 7.51–7.57 ppm was observed. It indicates a transition of 1,2,4-oxadiazole to the spiropyrazolinium compounds **4a**–**e**→**5a**–**e** in the presence of air moisture.

Comparison of the NMR spectra (^{1}H and ^{13}C) of compounds **4a**–**e** and **5a**–**e** shows almost no differences in the regional characteristics of the groups of protons and carbon atoms of the structures of 5-substituted phenyl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (**4a**–**e**) and of 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates (**5a**–**e**). Hence, protons of α-CH_2 and β-CH_2 groups in the first case give signals in the range δ 3.15–3.17 ppm and δ 3.65–3.66 ppm and in the region δ 3.15–3.19 ppm and δ 3.64–3.66 ppm – in the second. The signals of the aromatic protons of *para*-substituted 1,2,4-oxadiazoles **4a**, **4b**, **4d** and spiropyrazolinium benzoates **5a**, **5b**, **5d** have the form of two symmetric doublets with the spin–spin coupling constant

J equal 7.5 and 8.0 Hz. Aromatic protons of 1,2,4-oxadiazoles and spiropyrazolinium benzoates with unsubstituted and *meta*-substituted phenyl rings have signals at δ 7.23–7.83 ppm (**4c**) and 7.22–7.80 ppm (**4e**) and 7.25–7.78 ppm (**5c**, **5e**). Proton-containing substituents CH_3O and CH_3 have singlet signals with an intensity of 3 protons at δ 3.73 and 2.27 ppm for compounds **4a**, **4b** and **5a**, **5b**.

A distinctive feature of ^{1}H-NMR spectra of benzoates **5a**–**e** from the spectra of 1,2,4-oxadiazoles **4a**–**e** is the presence of NH_2 proton signal with the integral intensity of 2H at δ 7.51–7.57 ppm.

The ^{1}H-NMR spectrum of spirocompound **6** contained the triplet proton signals of α- and β-CH_2 groups at δ 3.16 and 3.68 ppm and signals of $N(+)(CH_2)_2(C\underline{H}_2)_2O$ and $N(+)(C\underline{H}_2)_2(CH_2)_2O$ groups at δ3.40 and 3.92 ppm, respectively; no aromatic proton signals were observed.

Of the remarkable features of the ^{1}H-NMR spectra of compounds **4a**–**e**, **5a**–**e**, and **6**, is that the axial and equatorial protons of the methylene groups located at the nitrogen atom of the morpholine ring give independent multiplet signals. In one case, these signals are superimposed with the common signal of two groups methylene protons located at the oxygen atom of the morpholine ring at δ 3.91–3.93 ppm with a total intensity of six protons and in the other case have a multiplet signal at ~δ 3.40 ppm intensity of two protons. The diastereotopicity of discussed geminal protons of compounds **4a**–**e**, **5a**–**e**, and **6** is associated with a dynamic cause due to slow rotation of the morpholine heterocycle. The effect of hindered inversion of six-membered heterocycles, with a chair-like conformer with fixed positions of the axial and equatorial protons being predominant, in the ^{1}H-NMR spectra is a known fact reported in reference data [18]. In addition, the diastereotopicity of these geminal protons of compounds **5a**–**e** and **6** is associated with asymmetry due to the presence of the spirocyclic system.

In the ^{13}C spectra of the compounds **4a**–**e**, **5a**–**e** and **6,** all signals of aliphatic and aromatic protons were recorded in the expected regions.

So, in the ^{13}C NMR spectra the characteristic groups of compounds **4a**–**e**, **5a**–**e** and **6** include the signals of: α-methylene

groups at δ 31.4 ppm; β-methylene groups at δ 62.1 ppm; signals of carbon atoms of methylene groups with intensity 2C located at nitrogen and oxygen atoms of the heterocycle are in the regions δ 62.4–62.5 ppm and δ 63.2–63.3 ppm. Two signals of carbon atoms of C=N bonds of 1,2,4-oxadiazoles **4a**–**e** are in the regions δ 167.0–168.9 ppm and δ 169.2–169.5 ppm. The carbon atoms of the C=N bond of the pyrazoline ring of compounds **5a–e** have two signals at δ 167.0–168.8 ppm and δ 169.2 ppm, which may be due to the existence of enantiomers A and B. The carbon atom of the C=N bond of compound **6** has a chemical shift at δ 169.1 ppm. The signals of aromatic carbon atoms for compounds **4a**–**e** and **5a**–**e** are in the range δ 112.5–161.0 ppm; *para*-CH_3O and *para*-CH_3 groups of the compounds **4a**, **5a** and **4b**, **5b**, respectively, give signals at δ 55.4 ppm and δ 21.3 ppm.

As we have proved in this article, 1,2,4-oxadiazoles **4a**–**e** are recorded spectroscopically (FT-IR and NMR spectral data), and they are the initial ones during hydrolysis to pyrazolinium compounds. The Boulton–Katritsky rearrangement mechanism **4a**–**e**→**5a**–**e**, and **4a**–**e**→**6** can be represented as a sequence of protonation, proton transfer and nucleophilic attack steps, representing hydrolysis during the reaction of 1,2,4-oxadiazoles **4a**–**e** with water and wet HCl in the same way as we indicated for piperidine derivatives [9].

All these data demonstrate that the biological activity of compounds under discussion should be associated with their spiropirazolinium form.

3.2.2. In Vitro Antitubercular Screening of 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium Benzoates and Chloride (5a–e, 6)

In vitro antitubercular bacteriostatic activity of spiropyrazolinium compounds **5a**–**e** and **6** on drug-sensitive (DS) and multidrug-resistant (MDR) of *M. tuberculosis* (MTB) strains was studied using the method of serial dilution on the liquid Shkolnikova medium (Table 2).

Table 2

***In vitro* antitubercular activity (MIC) of 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates and chloride (5a–e, 6), μg/mL * on DS (H37Rv) and MDR (I) strains of MTB**

Compd		5a	5b	5c	5d	5e	6	Rifampicin
MIC, μg/mL	H37Rv	50	10	20	100	100	1	1
	I	50	50	50	100	100	2	2

* In the upper line of MIC values, the activity on the DS of MTB strains (H37Rv) is shown; in the lower–on the wild MDR strains (I), isolated from the patient, resistant to rifampicin and isoniazid.

A number of compounds **5a**–**e** on DS and MDR MTB strains exhibits an average antitubercular activity of 10–100 μg/mL. Moreover, an improvement in activity is observed with a decrease in MIC to 10 μg/mL (**5b**); 20 μg/mL (**5c**) and 50 μg/mL (**5a**) on the DS MTB strains and up to 50 μg/mL on the MDR MTB strains for the compounds **5a**–**c** containing donor substituents in the phenyl ring or with an unsubstituted phenyl ring**.** Spiropyrazolylammonium chloride **6** demonstrates high *in vitro* antitubercular activity equal to the activity of the basic antitubercular drug of the first-row rifampicin: on the DS strain as low as 1 μg/mL; on the wild MDR strain–2 μg/mL.

To rationalize the results of the antitubercular activity of 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium salts, X-ray diffraction studies and molecular docking studies were carried out.

3.2.3. X-Ray Diffraction

Molecular structures of compounds **5c**–**e** and **6** are given in Figure 1. Asymmetric units of **5c**, **5e** and **6** contain one water molecule besides the target ions, and the asymmetric unit of **5d** contains two cations and two symmetrically independent anions. All hydrogen atoms could be located on residual density maps; thus, it was confirmed that the structures are salts with deprotonated carboxylic acids. The six-membered oxo-containing cycles adopt the chair conformation, and the five-membered aza-containing cycles realize the envelope conformation. C(1) carbon atom deviates from the meanplane of N1=N2-C3-C2 atoms at 0.40(1)-0.49(1) Å. Although the cation is rather rigid, it can realize

two conformational isomers depending on the shift of the C(1) atom from the meanplane of the rest atoms of the five-membered ring. In crystals of **5c**, **5e** and **6**, these isomers are related with each other by an inversion center, and in acentric crystal 5d, two symmetrically independent cations realize different conformations (Figure 2a). Nevertheless, for cations in **5c**–**e** and **6** with similar conformations, the mean atomic deviation doesn′t exceed 0.5Å (Figure 2b). The positive charge on quaternary ammonium atom causes elongation of N(1)-N(2) and N(1)-C(1) bonds as it was previously demonstrated for 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles [11], 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene [9], 1-(*tert*-butyl)-4,5-dihydro-1*H*-pyrazol-1-ium [19] and 1,1,3-trimethyl-Δ^2-pyrazolinium [20] analogs.

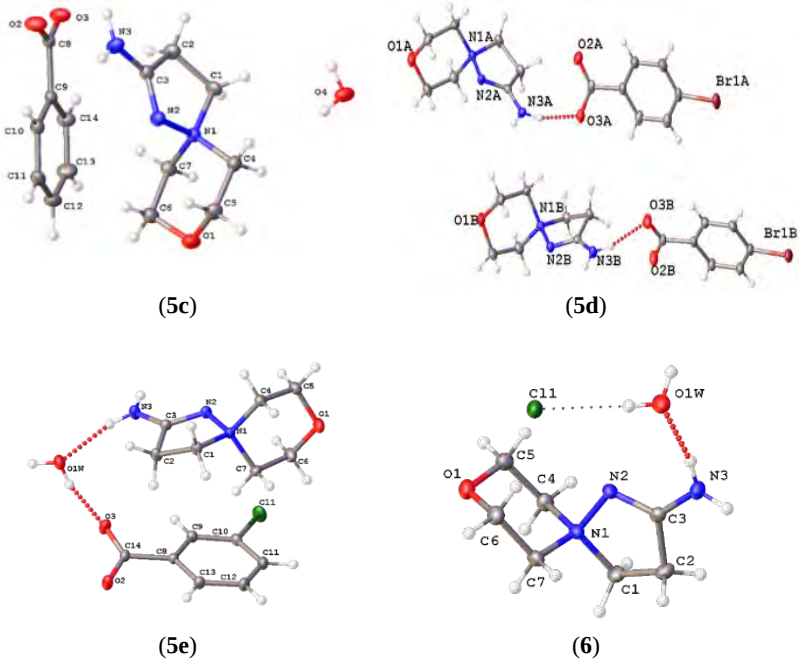


Figure 1. Molecular view of **5c**–**e** and **6** depicted in thermal ellipsoids (p = 50%)

(**a**) (**b**)

Figure 2. Molecular conformations of (**a**) two independent cations in **5d** (blue and red; H atoms are omitted); (**b**) similar conformations of cations in **5c** (red), **5d** (blue), **5e** (green) and **6** (magenta)

Crystal packing of a molecule can give valuable information about the most abundant intermolecular interactions of a polytopic molecule. The discussed cations can act as donors of two hydrogen bonds and, theoretically, acceptors of three H-bonds (through O(1), N(2) and N(3) atoms). However, the Full Interaction Maps tool [21, 22] implemented within the Mercury 2020.1 package [23] undoubtedly indicates the "inertness" of this cation as an acceptor of H-bonds (Figure 3). A monocarboxylate can only be an acceptor of 2–4 H-bonds. Thus, in the absence of water molecules, the cations and anions form simple H-bonded chains (Figure 4). In **5d**, these chains are further connected through halogen C-Br..O interactions (Figure 6a). In crystals of **5c**, **5e,** and **6,** water molecules act as linkers between the anion and cation and additionally bind two chains through O-H...O (anion) or O-H...Cl^- interactions (Figure 5) so that topologically identical H-bonded chains of the ladder-type are formed.

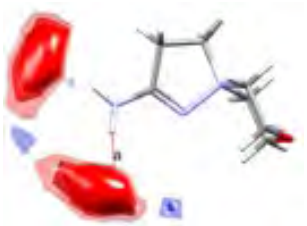
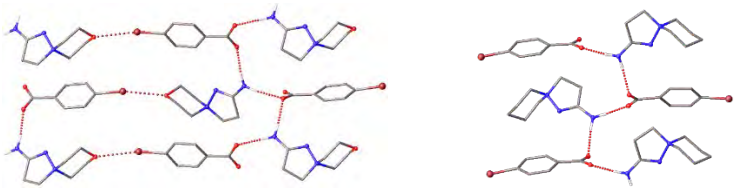
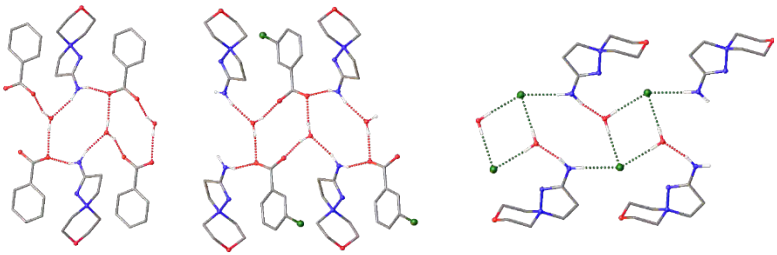


Figure 3. Interaction map in the crystal of **6** probed with H-bond donors (blue) and H-bond acceptors (red)



(**a**) (**b**)

Figure 4. Fragment of H-bonded chains in the crystal of (**a**) **5d** and (**b**) 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromobenzoate (deposit CCDC 1496456). Color code: Br–brown, C–grey, H–white, N–blue, O–red. The H(C) atoms are omitted. Intemolecular interactions are shown with dotted lines



(**a**) (**b**) (**c**)

Figure 5. Fragment of H-bonded chains in the crystal of (**a**) **5c**, (**b**) **5e**, (**c**) **6**. Color code: C–grey, Cl–green, H–white, N–blue, O–red. The H(C) atoms are omitted. Intemolecular interactions are shown with dotted lines

To sum up, X-ray diffraction data demonstrated that molecular docking studies should be carried out for two molecular conformations and that for stable ligand–receptor complexes, the most likely hydrogen bond occurs through the NH_2 group, while acceptor atoms of heterocycles less readily take part in the hydrogen bonds.

3.2.4. Molecular Docking Studies

Our results indicate that compounds **4a**–**e** at neutral pH in aqueous solutions undergo transformation to **5a**–**e**, and antitubercular activity demonstrated by the latter compounds can be referred to either anion of benzoic acids, or the cation, or a mixture of an anion and

cation. Some benzoic acids and their anions previously showed activity against *M. tuberculosis in vitro* [24–26]. However, it was assumed that benzoic acids do not have a specific cellular target for *M. tuberculosis* besides their general effect on disrupting the membrane function [25], which is supported by X-ray data of some benzoic acid derivatives with receptors, where ligands are situated on the protein surface [see, for example, PDB id 5TJZ, 5TJY, 2HRG]. Moreover, the activity of **5a**–**e** decreased in comparison with monocarboxylate-free salt **6** allows suggesting that the antitubercular activity of these salts should be referred to as the cation mainly.

As we mentioned above, the cation has a rigid conformation with spirocyclic motifs known to be present in some drugs [27,28]. Thus, the mutual disposition of donor, acceptor and hydrophobic fragments of this molecule can be compared with previously X-rayed drugs and ligand–receptor complexes. We used CSD-Crossminer 2020.1 package to search in the Protein Data Bank [29] ligand–receptor complexes where a ligand contains an (i) planar heterocycle with (ii) donor amine group involved in two H-bonds and (iii) neighboring ring, and a receptor was obtained from *M. tuberculosis*. The search gave three hits with PDB id codes 1NBU, 4FOG, and 4XT4, and R.M.S.D. of pharmacophore model from experimental ligand–receptor complexes of 0.398–0.717 Å. For all these hits,2-amino-8-oxa-1,5-diazaspiro [4.5]dec-1-ene-5-ammonium emulates the pterin moiety, known as a precursor of tetrahydrofolate synthesis, a coenzyme that acts as a carrier for one-carbon units in the biosynthesis of thymidylate, purine nucleotides, and some amino acids [30]. Receptors for these complexes include dihydroneopterin aldolase, thymidylate synthase or oxidoreductase Rv2671. The second search was carried out for structural analogs of spiro[4.5]decane in complexes with receptors obtained from *M. tuberculosis*. The second search gave two hits (PDB codes 5ICJ and 5N7O) of *M. tuberculosis* regulatory protein with 1-oxa-2,8-diazaspiro[4.5]-dec-2-en-8-y**l** derivatives. These receptors were taken as targets for molecular docking calculations together with more typical for theoretical antitubercular screening UDP-galactopyranose mutase.

For all cases, both stereoisomers of the cation were docked independently. Docking without constraints does not give any ligand:

receptor complexes; thus, docking was performed with H-bond constraints similar to that in the initial ligand–receptor complexes. Sterical clashes in the binding pocket of thymidylate synthase and UDP-galactopyranose mutase (PRB id codes, respectively, 4FOG and 4RPJ) do not allow the cation to realize appropriate H-bonding;thus, these receptors were excluded from consideration. For 1NBU and 4XT4, we succeeded in overcoming some steric clashes when flexible residues were allowed to rotate freely along with single bonds. Energies of interactions between the cations and three receptors are listed in Table 3; the closest environment of the cation is schematically represented in Figure 6.

Table 3

Energies of interactions for the 2-amino-8-oxa-1,5-diazaspiro[4.5] dec-1-ene-5-ammonium complexes with receptors [kcal/mol]

Receptor	**1NBU**		**4XT4**		**5ICJ**	
Ligand	**Type A**	**Type B**	**Type A**	**Type B**	**Type A**	**Type B**
H-bonds	−3.00	−2.00	−3.12	−2.00	−2.79	−3.00
Electrostatic	−4.37	−1.68	−6.34	−5.80	−0.51	−2.12
Nonpolar	−35.72	−32.51	−31.93	−34.80	−38.43	−35.43
Repulsive	0.25	0.35	0.99	0.36	0.04	0.01
Total	−42.84	−35.84	−40.40	−42.24	−41.69	−40.54

Overall, energies of ligand–receptor interactions vary from −35.84 to −42.84 kcal/mol, with the most prominent contribution from nonpolar C-H...π interactions. These values are close to the value of intermolecular pairwise interactions of the same cation in the crystal of **6** (−35.3 kcal/mol) estimated using UNI potentials [31,32]. The cation within binding pockets is involved in two or three hydrogen bonds, and for dihydroneopterin aldolase and thymidylate synthase complexes, the best solution for molecules type A and type B differs in H-bonding patterns. For 1NBU, the best docking solution for molecule type A includes three hydrogen bonds (two N-H...O interactions of amine and oxygen atoms of Tyr52 and Glu74 residues, additionally supported with N-H...N bonds between amide of Asn44

and heterocycle), while the solution for type B molecules includes two H-bonds (N-H...O between amine and Tyr52 and N-H...O between ammonium of Lys99 and the oxygen atom of the cation). The latter solution with the poorest system of H-bonds also has the highest energy of intermolecular interactions among the six solutions under discussion. For 4XT4, both isomers of cation form similar H-bonds with amide group of Asn44 and carboxylate group of Asp67, and interact not only with receptor but also cofactor. The nature of ligand-cofactor interactions differs for two isomers, as well as the system of H-bonds. Only in 5ICJ, both isomers realize nearly similar ligand–receptor interactions through two H-bonds between hydrogen atoms of NH_2 group, and OH group of Ser134 and COO group of Asp168 and numerous hydrophobic interactions with indolyl fragment of Trp100 additionally supported by hydrophobic interactions with Thr138 and Leu167. To summarize, based on molecular docking calculations, the cation is able to bind with *M. tuberculosis* dihydroneopterin aldolase, thymidylate synthase and regulatory proteins of transcription. Only in the latter case binding energy, the system of H-bonds and contributions of various types of interactions are independent on stereoisomer of the cation. However, other studies are needed to reveal the mechanism of antitubercular activity of compounds under discussion.

3.3. Materials and Methods

3.3.1. Synthesis

The reagents were purchased from different chemical suppliers and were purified before use. FT-IR spectra were obtained on a Thermo Scientific Nicolet 5700 FTIR instrument (Waltham, MA USA) in KBr pellets. ^{1}H- and ^{13}C-NMR spectra were acquired on a Bruker Avance III 500 MHz NMR spectrometer (500 and 126 MHz, respectively) (Bruker, BioSpin GMBH, Rheinstetten, Germany). The signals of DMSO-*d*6 were used as the internal reference for ^{1}H-NMR (2.50 ppm) and ^{13}C-NMR (39.5 ppm) spectra. Elemental analysis was carried out on a CE440 elemental analyzer (Exeter Analytical, Inc., Shanghai, China). Melting points were determined in glass capillaries on a PTP(M) apparatus (Khimlabpribor, Klin, Russia). The reaction progress and purity of the obtained products were controlled using Sorbfil (Sorbpolymer, Krasnodar, Russia) TLC plates coated with CTX-1A silica gel, grain size 5–17 μm, containing UV-254 indicator. The eluent for TLC analysis was a

mixture of benzene–EtOH, 1:3. The solvents for synthesis, recrystallization, and TLC analysis (ethanol, 2-PrOH, benzene, DMF, acetone) were purified according to the standard techniques.

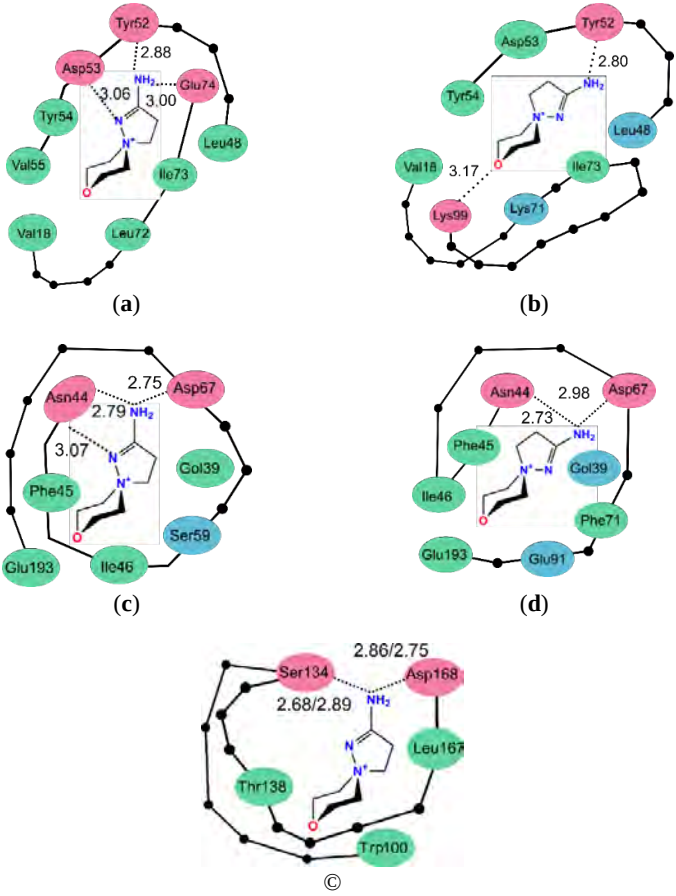


Figure 6. Schematic representation of the interactions between 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium and the residues within binding pockets of 1NBU (type A (**a**), type B (**b**)), 4XT4 (type A (**c**) and type B (**d**)), and 5ICJ (**d**). The colors of the residues indicate the character of bonding: pink correspond to H-bonds, green–hydrophobic interactions, blue–electrostatic interactions. H-bonds and their distances are depicted with dotted lines. **Left**–column corresponds to type A cations, and the **right**–to type B molecules

*3.3.1.1. A General Procedure for the Synthesis of 5-Aryl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (**4a–e**)*

A solution of O-aroyl-(β-morpholin-1-yl)propioamidoximes (**3a**–**e**) in dry DMF in a ratio of 1 g:5 mL, respectively, was heated on an oil bath at 70 °C for different times characteristic for compounds **3a**–**e**: 3.5 h (**3a**, **3b**), 2.5 h (**3c**), 2 h (**3d**), 1.5 h (**3e**) with TLC control (eluent was mixture benzene–EtOH, 1:3). The reaction mixture was evaporated to dryness under an oil pump vacuum at 50 °C/1 mm Hg. The organic residue was treated with dry acetone at a ratio of 1 g of parent compounds (**3a**–**e**): 5 mL of dry acetone. The obtained crude precipitates of the compounds **4a**–**e** were recrystallized from 2-PrOH.

5-*(4-Methoxyphenyl)-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazole* (**4a**). Starting from 4.93 g, (0.016 mol) of **3a** in 25 mL of dry DMF to the resulting 2.89 g (62%), colorless solid **4a**, m.p. 230 °C, R_f 0.71. IR (KBr, cm^{-1}): 1670 (C=N), 1597 (C=N), 1553 (C=C), 1362 (C–O). ^{1}H-NMR (500 MHz,DMSO-d_6): 3.17 (t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N), 3.40 [m, 2H, N(CH eq)$_2$] and 3.93 [m, 6H (2H, N(CH ax)$_2$ and 4H, O(CH$_2$)$_2$)], 3.65 (t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N), 3.73 (s, 3H, *p*-CH$_3$O), 6.75 (d, J = 8.0 Hz, 2H, *o*-H Ar), 7.75 (d, J = 8.0 Hz, 2H, *m*-H Ar). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 55.4, 62.0, 62.4, 112.5, 130.9, 136.0, 160.0, 168.9, 169.3. Anal. Calcd for $C_{15}H_{19}N_3O_3$ (289.33): C, 62.27; H, 6.62. Found: C, 62.60; H, 7.02.

5-(4-Tolyl)-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazole (**4b**). Starting from 2.81 g, (0.0096 mol) of **3a** in 15 mL of dry DMF to the resulting 1.84 g (70%), colorless solid **4b**, m.p. 220 °C, R_f 0.62. IR (KBr, cm^{-1}): 1648 (C=N), 1593 (C=N), 1553 (C=C), 1376 (C–O). ^{1}H-NMR (500 MHz,DMSO-d_6): 2.27 (s, 3H, *p*-CH$_3$), 3.15 (t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N), 3.40 [m, 2H, N(CHeq)$_2$] and 3.91 [6H, m: 2H, N(CH ax)$_2$ and 4H, O(CH$_2$)$_2$], 3.66 (t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N), 7.01 (d, J = 8.0 Hz, 2H, *o*-H Ar), 7.70 (d, J = 8.0 Hz, 2H, *m*-H Ar). ^{13}C-NMR (126 MHz, DMSO-d_6): 21.3, 31.4, 62.1, 62.4, 63.2, 112.5, 130.9, 136.0, 160.0, 169.0, 169.3. Anal. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01. Found: C, 65.50; H 7.22.

5-Phenyl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazole (**4c**). Starting from 1.00 g, (0.0036 mol) of **3c** in 5 mL of dry DMF to the resulting 0.86 g (92%) colorless solid **4c**, m.p. 216 °C, R_f 0.66. IR (KBr, cm^{-1}): 1650 (C=N), 1596 (C=N), 1559 (C=C), 1381 (C–O). ^{1}H-NMR (500 MHz,DMSO-d_6): 3.18 (t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N), 3.40 [2H, m, N(CHeq)$_2$] and 3.93 [6H, m: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.65 (2H, t, J = 7.0 Hz, CH$_2$C$\underline{H_2}$N), 7.23–7.83 (m, 5H, C$_6$H$_5$). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.1, 62.4, 63.3, 127.5, 127.8, 128.9, 129.1, 129.4, 167.0, 169.2. Anal. Calcd for $C_{14}H_{17}N_3O_2$ (259,30):C, 64.85; H, 6.61. Found: C, 65.30; H, 7.02.

5-(4-Bromophenyl)-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazole (**4d**). Starting from 1.44 g, (0.004 mol) of **3d** in 8 mL of dry DMF to the resulting 1.12 g (83%) colorless solid **4d**, m.p. 224 °C, R_f 0.67. IR (KBr, cm^{-1}):1650 (C=N), 1596 (C=N),

1559 (C=C), 1381 (C–O). ^{1}H-NMR (500 MHz,DMSO-d_6): 3.17 (t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N), 3.39 [m, 2H, N(CHeq)$_2$] and 3.93 [m, 6H: 2H, N(CH ax)$_2$ and 4H, O(CH$_2$)$_2$], 3.65 (2H, t, J = 7.0 Hz, CH$_2$C$\underline{H_2}$N), 7.40 (d, J = 7.5 Hz, 2H, *o*-H Ar), 7.74 (d, J = 7.5 Hz, 2H, *m*-H Ar). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.1, 62.4, 63.3, 122.7, 130.2, 131.6, 141.5, 168.3, 169.5. Anal. Calcd for $C_{14}H_{16}BrN_3O_2$ (338.20): C, 49.72; H, 4.77. Found,%: C, 49.29; H, 4.97.

*5-(3-Chlorophenyl)-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazole (***4e***).* Starting from 2.70 g, (0.0087 mol) of **3e** in 15 mL of dry DMF to the resulting 1.43 g (56%) colorless solid **4e**, m.p. 190 °C, R_f 0.62. IR (KBr, cm^{-1}):1680 (C=N), 1596 (C=N), 1557 (C=C), 1377 (C–O). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.15 (t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N), 3.40 [m, 2H, N(CHeq)$_2$] and 3.91 [m, 6H: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.65 (t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N), 7.25–7.78 (m, 4H, 3-Cl-C$_6$H$_4$). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.1, 62.4, 63.2, 127.7, 127.8, 129.2, 132.4, 144.5, 162.1, 169.2. Anal. Calcd for $C_{14}H_{16}ClN_3O_2$ (293.75): C, 57.24; H, 5.49. Found,%: C, 57.55; H, 5.92.

*3.3.1.2. A General Procedure of the Formation of 2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium benzoates (**5a**–**e**)*

To the solutions of 5-(3,4-substituted phenyl)-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazoles (**4a**–**e**) inDMF in a ratio of 0.5 g: 10 mL, respectively, two equivalents of H_2O was added dropwise. The reaction solutions were heated at 70 °C with TLC control during the time typical for groups of compounds **4a**–**e**: **4a**, **b** (40 h), **4c**–**e** (25 h). After the disappearance of the 1,2,4-oxadiazoles **4a–e** spots on the silufol plate and the appearance of products **5a–e** spots, the solvent was evaporated to dryness in an oil vacuum pump. Acetone was added to the viscous residues of the reaction mixtures **5a–e** at the rate of 0.5 g of the starting compounds **4a**–**e**: 15 mL of acetone. The formed precipitates of 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 3,4-substituted benzoates (**5a**–**e**) were filtered off and dried at room temperature.

2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 4-methoxybenzoate hydrate (**5a**). Starting from 0.5 g (0.0017 mol) of compound **4a** in 10 mL of DMF and 0.062 mL (0.0034 mol) H_2O to the resulting 0.35 g (63%) colorless solid **5a**, m.p. 235 °C, R_f 0.75. IR (KBr, cm^{-1}):1657 (C=N), 1594 (C=C), 1548 (νCOO$^-$ as), and 1420 (νCOO$^-$ sy), 3309, 3414, 3459 [νN(-H)$_2$]. ^{1}H-NMR (500 MHz,DMSO-d_6): 2.27 (s, 3H, *p*-CH$_3$O), 3.17 [t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N(+)], 3.41 [m, 2H, N(CHeq)$_2$] and 3.92 [m, 6H: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.65 [t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N(+)], 6.78 (d, J = 8.0 Hz, 2H, o-H Ar), 7.55 and 7.60 (s, 2H, NH$_2$), 7.78 (d, J = 8.0 Hz, 2H, *m*-H Ar). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.4, 63.2, 112.5, 130.9, 134.8, 159.9, 144.5, 168.8, 169.2. Anal. Calcd for $C_{15}H_{23}N_3O_5$ (325.36): C, 55.37; H, 7.13. Found,%: C, 55.79; H, 7.57.

2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 4-methylbenzoate hydrate (**5b**).Starting from 0.5 g (0.0018 mol) of the compound **4b** in 10 mL of DMF

and 0.066 mL (0.0036 mol) H_2O to the resulting 0.35 g (63%) colorless solid **5b**, m.p. 248 °C, R_f 0.80. IR (KBr, cm^{-1}):1655 (C=N), 1597 (C=C), 1550 (COO^-as), and 1442 (COO^- sy), 3157, 3312, 3457 [N(-H)$_2$]. ^{1}H-NMR (500 MHz,DMSO-d_6): 3.15 [t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N(+)], 3.41 [m, 2H, N(CHeq)$_2$] and 3.93 [m, 6H: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.64 [t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N(+)], 3.73 (s, 3H, *p*-CH$_3$), 7.02 (d, J = 8.0 Hz, 2H, *o*-H Ar), 7.54 (s, 2H, NH$_2$), 7.69 (d, J = 8.0 Hz, 2H, *m*-H Ar). ^{13}C-NMR (126 MHz, DMSO-d_6): 21.3, 31.38, 62.1, 62.4, 63.2, 127.9, 128.3, 129.4, 139.7, 168.8, 169.2. Anal. Calcd for $C_{15}H_{23}N_3O_4$. (309.36): C, 58.24; H, 7.49. Found: C, 58.29; H, 7.59.

2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium benzoate hydrate (**5c**). Starting from 0.5 g (0.0019 mol) of **4c** in 10 mL of DMF and 0.07 mL (0.0038 mol) H_2O to the resulting 0.43 g (77%) colorless solid **5c**, m.p. 220 °C, R_f 0.75. IR (KBr, cm^{-1}):1658 (C=N), 1596 (C=C), 1556 (COO^- as), and 1426 (COO^- sy), 3152, 3311, 3456 [N(-H)$_2$]. ^{1}H-NMR (500 MHz,DMSO-d_6): 3.19 [t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N(+)], 3.39 [m, 2H, N(CHeq)$_2$] and 3.93 [m, 6H: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.65 [t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N(+)], 7.22–7.80 (m, 5H, C$_6$H$_5$), 7.55 and 7.64 (s, 2H, NH$_2$). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 61.3, 62.4, 63.2, 127.26, 128.3, 129.4, 142.4, 168.7, 169.2. Anal. Calcd for$C_{14}H_{21}N_3O_4$ (295.33): C, 56.94; H, 7.17. Found: C, 56.79; H, 7.50.

2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 4-bromobenzoate (**5d**). Starting from 0.5 g (0.0015 mol) of **4d** in 10 mL of DMF and 0.05 mL (0.0028 mol) H_2O to the resulting 0.43 g (80%) colorless solid **5d**, m.p. 240 °C, R_f 0.77. IR (KBr, cm^{-1}):1657 (C=N), 1591 (C=C), 1545 (COO^-as), and 1423 (COO^- sy), 3302, 3411, 3485 [N(-H)$_2$]. ^{1}H-NMR (500 MHz,DMSO-d_6): 3.15 [t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N(+)], 3.40 [m, 2H, N(CHeq)$_2$] and 3.92 [m, 6H: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.65 [t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N(+)], 7.39 (d, J = 7.5 Hz, 2H, *o*-H Ar), 7.55 (s, 2H, NH$_2$), 7.73 (d, J = 7.5 Hz, 2H, *m*-H Ar). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.1, 62.4, 63.2, 121.9, 130.1, 131.6, 141.8, 167.4, 169.2. Anal. Calcd for $C_{14}H_{18}BrN_3O_3$ (356.22): C, 47.20; H, 5.09. Found: C, 47.49; H, 4.97.

2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 3-chlorobenzoate hydrate (**5e**). Starting from 0.5 g (0.0017 mol) **4e** in 10 mL of DMF and 0.06 mL (0.034 mol) H_2O to the resulting 0.24 g (43%) colorless solid **5e**, m.p. 200 °C, R_f 0.70. IR (KBr, cm^{-1}):1657 (C=N), 1594 (C=C), 1557 (COO^- as), and 1420 (COO^- sy), 3155, 3309, 3457 [N(-H)$_2$]. ^{1}H-NMR (500 MHz,DMSO-d_6): 3.16 [t, J = 7.0 Hz, 2H, C$\underline{H_2}$CH$_2$N(+)], 3.40 [m, 2H, N(CH eq)$_2$] and 3.93 [6H, m: 2H, N(CHax)$_2$ and 4H, O(CH$_2$)$_2$], 3.66 [t, J = 7.0 Hz, 2H, CH$_2$C$\underline{H_2}$N(+)], 7.25–7.78 (m, 4H, 3-Cl-C$_6$H$_4$), 7.57 and 7.61 (s, 2H, NH$_2$). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.1, 62.5, 63.2, 127.9, 128.2, 129.2, 129.3, 132.4, 144.7, 167.0, 169.2. Anal. Calcd for $C_{14}H_{20}ClN_3O_4$ (329.78): C, 50.99; H, 6.11. Found: C, 50.52; H, 6.47.

*3.3.1.3. A General Method of the Formation of 2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium chloride (**6**) and Substituted Benzoic Acids*

To a solution of 0.2 g (0.0007 mol) of 5-(3,4-substituted phenyl)-3-[2-(morpholin-1-yl)ethyl]- 1,2,4-oxadiazoles (**4a–e**) in 10 mL ethanol a HCl solution in ether was added dropwise to pH 2. A white precipitate of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**6**) in all cases was formed at once in 75–82% yields and collected by filtration. 3,4-Substituted benzoic acids were precipitated during the evaporation of mother liquors obtained after the filtration of chloride monohydrate **6**. All characteristics of substituted benzoic acids corresponded to the reference data.

2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium chloride hydrate (**6**)—white opaque powder, m.p. 257–260°C, R_f 0.21. IR (KBr, cm^{-1}): 1639 (νC=N), [1615, δN(–H)$_2$], 1362 (νC–O), 3158, 3310, 3457 [νN(-H)$_2$]. ^{1}H-NMR (500 MHz, DMSO-d_6): 3.16 [t, J = 7.0 Hz, 2H, C<u>H$_2$</u>CH$_2$N(+)], 3.40 [m, 2H, N(CH eq)$_2$] and 3.92 [m, 6H: 2H, N(CH ax)$_2$ and 4H, O(CH$_2$)$_2$], 3.68 [t, J = 7.0 Hz, 2H, CH$_2$C<u>H$_2$</u>N(+)], 7.51 (s, 2H, NH$_2$). ^{13}C-NMR spectrum, δ, ppm: 31.4, 31,5, 62.1, 62.4, 63.3, 169.2. Anal. Calcd for $C_7H_{16}N_3O_2$ (209.67): C, 40.10, H 7.69. Found: C, 40.29; H, 7.97.

3.3.2. Single-Crystal X-Ray Diffraction

The X-ray diffraction data of **5c–e, 6** were collected at 120 K on a Bruker Apex II diffractometer (Bruker AXS, Inc., Madison, WI, USA) equipped with an Oxford Cryostream cooling unit and a graphite monochromated Mo anode (λ = 0.71073 Å). Crystal structures were solved using SHELXT [33] program and refined with SHELXL [34] using OLEX2 software [35]. The structures were refined by full-matrix least-squares procedure against F^2. Non-hydrogen atoms were refined anisotropically. The H(C) positions were calculated, the H(N) and H(O) atoms were located on difference Fourier maps and refined using the riding model. Experimental details and crystal parameters are given in Table S1 (Electronic Supporting Information).

3.3.3. Molecular Docking Studies

The molecular docking studies were performed following the previously described protocol [36,37] and processed with GOLD software (version 2020.2.0, Cambridge Crystallographic Data Center, Cambridge, UK).

The three-dimensional (3D) crystal structures of *M. tuberculosis* regulatory protein (PDB ID: 5ICJ), 7,8-dihydroneopterin aldo-lase complexed with 2-amino-6-(hydroxymethyl)pteridin-4(3*H*)-one (PH2; PDB ID: 1NBO), thymidylate synthase in complex with 5-fluoro DUMP (UFP; PDB ID: 4FOG),UDP-galactopyranose mutase

from Mtb docked with UDP (UGM; PDB ID: 4RPJ), and Rv2671 proteinin complex with dihydropteridine (44W; PDB ID: 4XT4) were obtained from the RCSB Protein Data Bank [29], while the 3D-structure of cation was taken from X-ray diffraction data of **6** (two stereoisomers were analyzed independently).

To validate the molecular docking outcomes, 4,4,4-trifluoro-1-(3-phenyl-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)butan-1-one, PH2, UFP, UGM, and 44W were removed from their receptors and re-docked back into their receptors. The docking results were expressed as binding energy values (kcal/mol) of ligand–receptor complexes; these are based on hydrogen bond, hydrophobic, and electrostatic interactions. All required docking settings, including the preparation of mol2 files for the receptors and ligands, determination of binding sites, the protonation state, calculations, and the overall charges, were established as hitherto described [38].

3.4. Conclusions

5-Substituted phenyl-3-(2-aminoethyl)-1,2,4-oxadiazoles in the presence of moisture and acids undergo Boulton–Katritsky rearrangement to the salts of spiropyrazolinium compounds–2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates and chloride. Hence, biological screening results should be associated with rearranged products and not with the original taken on trials 5-substituted phenyl-3-(2-aminoethyl)-1,2,4-oxadiazoles. A small library of the newly 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates and chloride has been used in the drug design of antitubercular drugs. The tested compounds show moderate to high in vitro antitubercular activity with MIC values of 1–100 μg/mL. The highest activity in 1 μg/mL and 2 μg/mL on DS and MDR of *M. tuberculosis* strains, equal to the activity of the basic antitubercular drug rifampicin, was recorded for 2-amino-8-oxa-1,5-diazaspiro [4.5]dec-1-en-5-ium chloride. 3D molecular structure of the cation extracted from crystal structure was used for molecular docking studies with various *M. tuberculosis* receptors. It was demonstrated that two stereoisomers of the rigid cation form different sets of hydrogen bonds in complexes with dihydroneopterin aldolase or oxidoreductase Rv2671 and similar H-bonds in complex with thymidylate synthase. However, energies of all ligand–receptor complexes vary from −35.8 to −42.8 kcal/mol.

Supplementary Materials: The following are available online, supplementary data including the NMR spectra of 5-substituted phenyl-3-[2-(morpholin-1-yl)ethyl]-1,2,4-oxadiazole and 2-amino-8-oxa-1,5-diazaspiro [4.5]dec-1-en-5-ium benzoate and chloride associated with this article are available online. CCDC 2049798-2049801 contains crystallographic information for **5c**–**e**, **6**. Crystallographic information files are available from the Cambridge Crystallographic Data Center upon request (http://www.ccdc.cam.ac.uk/structures).

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Chapter 4

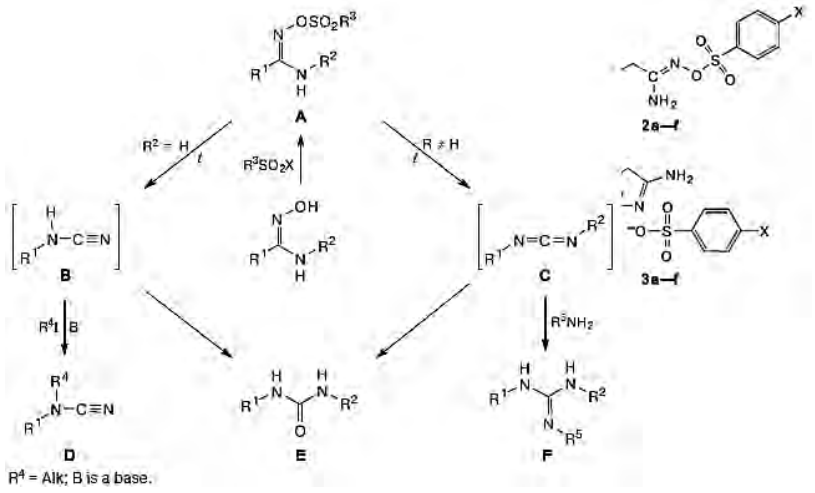
ARYLSULFOCHLORINATION OF β-AMINOPROPIOAMIDOXIMES GIVING 2-AMINOSPIROPYRAZOLYLAMMONIUM ARYLSULFONATES

Sulfochlorination of structurally different amidoximes can afford *O*-sulfonyl amidoximes, ureas, and cyanamides. Stable aromatic and heteroaromatic *O*-sulfonyl amidoximes derived by the reaction of substituted benzamidoximes and pyridinecarboxylic acid amidoximes with aromatic and aliphatic sulfonyl chlorides were described [1]. Besides, resulting from the structure of the starting amidoxime and the reaction conditions, the sulfochlorination of amidoximes gives unsymmetrically substituted ureas *via* the Tiemann rearrangement. The latter products are formed after the successive treatment of amidoximes with arylsulfonlyl chlorides and water [2-4]. In the presence of *N,N*-diisopropylethylamine (DIPEA) or pyridine, the sulfochlorination of amidoximes can produce substituted cyanamides [2]. Besides, the so-called modified Tiemann rearrangement provides a preparative route to various *N*-substituted cyanamides and is accomplished *via* the treatment of a solution of amidoxime and triethylamine in dichloromethane with an equivalent amount of arylsulfonyl chloride followed by the addition of alkyl halide in a 30% NaOH solution and a phase-transfer catalyst. This is a convenient method for the transformation of amidoximes into *N,N*-disubstituted cyanamides [5].

Despite the fact that cyanamides are highly labile in an acidic medium, they are stable under basic conditions at pH >10 due to deprotonation and the formation of the cyanamide anion. A series of aromatic, aliphatic, and terpenoid amidoximes are easily transformed into disubstituted unsymmetrical cyanamides in good yields (40–90%) *via* sulfochlorination followed by the reaction with alkyl halides.

In 2014, the conditions allowing the selective formation of *N*,*N*-disubstituted cyanamides or monosubstituted arylureas through arylsulfochlorination of *N*-substituted amidoximes were elaborated [6].

N-Substituted cyanamides can be produced *via* the Tiemann rearrangement of *NR*-substituted *O*-sulfoaryl amidoximes (**A**) (R2 ≠ H) on heating or upon the treatment with bases (Scheme 1). It was shown that *N*-substituted cyanamides or *N*,*N*´-disubstituted carbodiimides (**B** or **C**) are produced as intermediates in the Tiemann rearrangement. These intermediates are generally transformed into *N*,*N*-disubstituted cyanamides (**D**), ureas (**E**), or guanidines (**F**) and can be prepared under particular conditions indicated in Scheme 1.



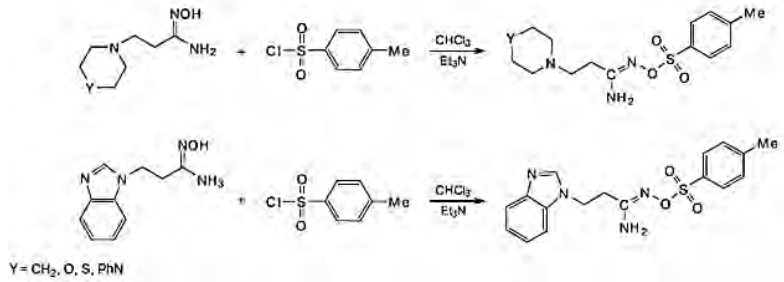
Scheme 1

Based on the spectroscopic data, we concluded that the reaction of β-aminopropioamidoximes with *p*-toluenesulfonyl chloride affords β-aminopropioamidoxime *O*-tosylates (Scheme 2) [7].

The formation of *O*-arylsulfochlorination products of β-aminopropioamidoximes would be expected based on the X-ray diff raction data on the reaction products of β-(piperidin-1-yl)propioamidoxime with substituted benzoic acid chlorides existing as *O*-aroyl-β-amino propioamidoxime hydrochlorides [8].

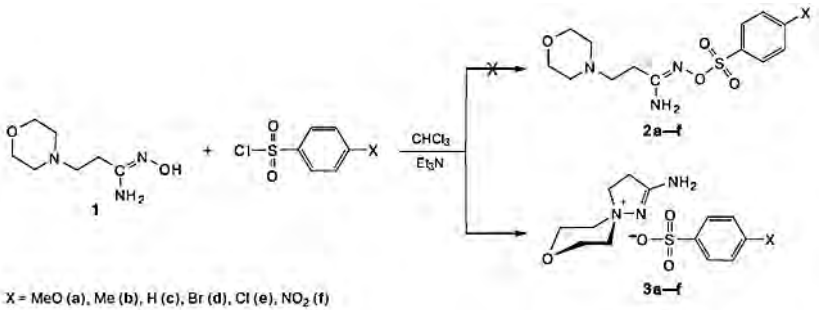
The goal of this study is to reveal the effect of the electronic properties of substituents in arylsulfonyl chlorides on the pathway of the reaction with β-(morpholin-1-yl)propioamidoxime (**1**).

We expected that the reaction of β-(morpholin-1-yl)propioamidoxime (**1**) with substituted arylsulfonyl chlorides in the presence of triethylamine, like the reaction of a series of β-aminopropioamidoximes with *p*-toluenesulfonyl chloride, would afford *O*-arylsulfonyl-β-(morpholin-1-yl)propioamidoximes (**2a**–**f**) [7]. The physicochemical and spectroscopic data are not contradictory to this assumption (Scheme 3).



Scheme 2

Meanwhile, *O*-arylsulfonyl-β-(morpholin-1-yl)propioamidoximes **2a**–**f** and 2-amino-4,5-dihydrospiropyrazolylammonium arylsulfonates **3a**–**f** are structural isomers. The stretching bands in the recorded IR spectra and the chemical shifts of protons and carbon atoms in the NMR spectra are consistent with both structures (see Scheme 3).



Scheme 3

However, the X-ray diffraction data provide unambiguous evidence that the reaction aff ords 2-aminospiropyrazolylmorpholineammonium arylsulfonates **3a**–**f**. The X-ray diffraction structures were determined for two extreme compounds of the series – sulfochlorination products with *p*-methoxy- and *p*-nitrosulfonyl chlorides (**3a** and **3f**, see Figure 1) [9].

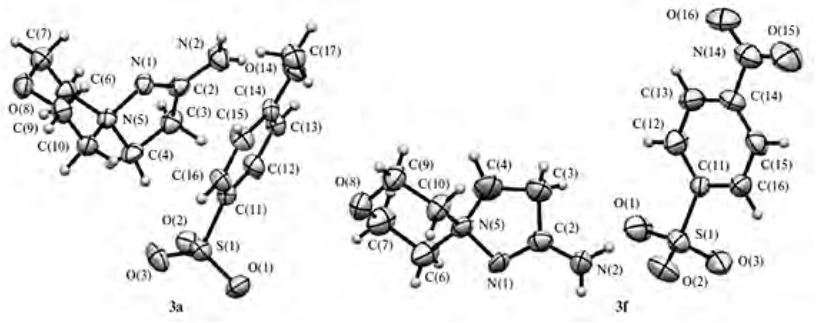


Figure 1. Molecular geometry of salts **3a** and **3f** in the crystals with thermal displacement ellipsoids drawn at the 50% probability level

The IR spectra of compounds **3a**–**f** display two characteristic symmetric and asymmetric stretching bands of the SO_2 group at ν 1119–1191 and 1195–1220 cm^{-1}. The stretching bands of C=C double bonds of compounds **3a**–**f** at ν 1596–1609 cm^{-1} and stretching bands

of the C_{sp2}–H bond at >3000 cm^{-1} are also evidence of sulfochlorination products. Other characteristic absorption bands typical of 2-amino-4,5-dihydrospiropyrazolylmorpholine-ammonium arylsulfonates **3a–f** are the stretching bands of C=N bonds at 1646–1664 cm^{-1}, symmetric and asymmetric stretching bands of the NH_2 group at 3176-3460 cm^{-1}, and stretching bands of C_{sp3}–H bonds at 2870–2985 cm^{-1}.

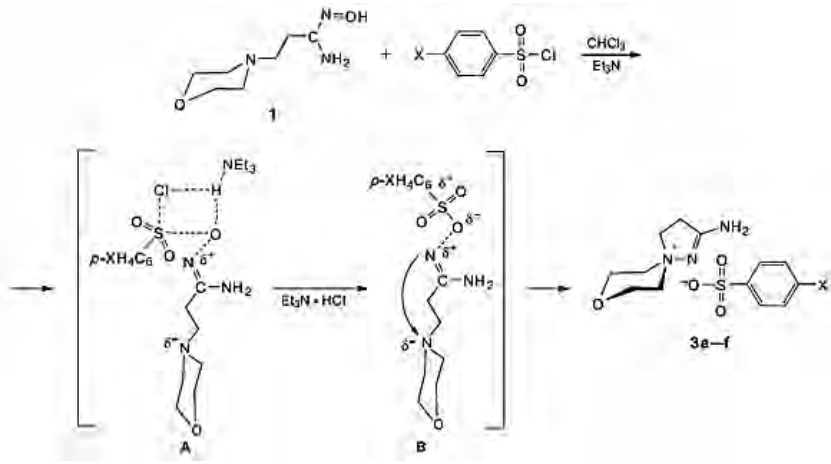
The ^{1}H NMR spectra of 2-amino-4,5-dihydrospiropyrazolylmorpholineammonium arylsulfonates **3a–f** show doublets of protons of the *p*-substituted phenyl group at δ_H 6.84–8.19 and a signal of the *p*-methoxy and *p*-methylsubstituents at δH 3.75 and 3.36 for compounds **3a** and **3f**, respectively, which are evidence that the sulfochlorination takes place. A broadened signal of the amino group NH_2 of compounds **3a–f** appears at δ_H 7.30–7.48. The interacting groups of methylene protons of the ethylene moiety $CCH_2CH_2N^+$ of the pyrazoline ring give two signals at δ_H 3.13–3.17 and 3.88–3.99. The former signal is a triplet. The latter one overlaps with the signal of methylene protons at the morpholine oxygen atom with an integral intensity of six protons.

The methylene protons at the nitrogen atom of the six-membered heterocycle of compounds **3a–f** exhibit a diastereotopic effect and appear as two multiplets each at δ_H 3.40–3.41 and δ_H 3.64–3.68 with two-proton intensity. The diastereotopicity of these geminal protons is primarily associated with asymmetry due to the presence of the spirocyclic system. Besides, the diastereotopicity of geminal protons should include the dynamic contribution due to retarded rotation of the morpholine heterocycle. These signals can be assigned to axial and equatorial protons, respectively. The effect of retarded inversion of six-membered heterocycles, with a chair-like conformer with fixed positions of the axial and equatorial protons being predominant, in the ^{1}H NMR spectra is a known fact reported in reference data [10, 11].

The ^{13}C NMR spectra show characteristic signals of carbon atoms corresponding to the structure of 2-amino-4,5-dihydrospiropyrazolylmorpholineammonium arylsulfonates **3a–f**: signals of carbon atoms of the *p*-$CH_3OC_6H_4SO_3$ – group at δC 55.64 and the *p*-$CH_3C_6H_4SO_3$ –

group at δ_C 21.25 and signals of sp^2-hybridized phenylcarbon atoms at δ_C 113.20–159.65; signals of carbon atoms of the C=N bond of products **3a**–**f** at δ_C 169.09-169.11; signals of methylene carbon atoms of the ethylene moiety $CC(3)H_2C(4)H_2N^+$ of the pyrazoline ring at δ_C 31.43–31.49 and 62.02–62.13, respectively; signals of methylene carbon atoms at the morpholine nitrogen atom $N^+(CH_2)_2$ of compounds **3a**–**f** at δ_C 62.08–62.46; signals of methylene groups at the oxygen atom at δ_C 63.23–63.35.

The presumptive mechanism of the reaction of β-(morpholin-1-yl)propioamidoxime (**1**) with arylsulfonyl chlorides is shown in Scheme 4.



Scheme 4

In this case, the state of the N–O bond plays a crucial role. The cleavage of this bond is facilitated by the formation of hydrochloride $Et_3N \cdot HCl$. and the stable arylsulfonate anion as a good leaving group in transition states **A** and **B**. The attack on the nitrogen atom of the heterocycle by the ammonium nitrogen resulted in the ring closure giving a spiropyrazoline structure, in which the arylsulfonate anion is a counterion for the bridging ammonium nitrogen.

The ease of the formation of spiro compounds is consistent with the fact that *O*-arylsulfonyl-β-(morpholin-1-yl)propioamidoximes **2a**–**f** are evidently thermodynamically less stable than 2-amino-4,5-dihydrospiropyrazolylmorpholineammonium arylsulfonates **3a**–**f** and with the fact that arylsulfonate anions are good leaving groups [12].

The formation of spiropyrazolinium structures *via* the Boulton–Katritzky rearrangement of 5-aryl-3-β-aminoethyl-1,2,4-oxadiazoles (the β-amino group: thiomorpholin-1-yl, 4-phenylpiperazin-1-yl) in the presence of HCl and H_2O was reported in our previous studies and was established by X-ray diffraction [13-15].

According to the single-crystal X-ray diffraction study of **3a** and **3f**, the cations in these compounds have the same structure and the six-membered morpholine rings adopt a chair conformation. The five-membered rings adopt an envelope conformation, with the C(4) atom deviating from the mean plane of the N(5) –N(1)=C(2) –C(3) atoms. The nitro group at the C(2) atom has a planar configuration and lies in the plane of the base of the five-membered ring. The arylsulfonyl anions have a standard geometry. Thus, the methoxy group in compound **3a** and the nitro group in compound **3f** lie in the planes of the benzene rings. The sulfonate groups are deprotonated and the S–O bond lengths in these groups are equalized, which is indicative of the negative charge delocalization.

The bond lengths, bond angles, and torsion angles in compounds **3a** and **3f** are typical of such structures.

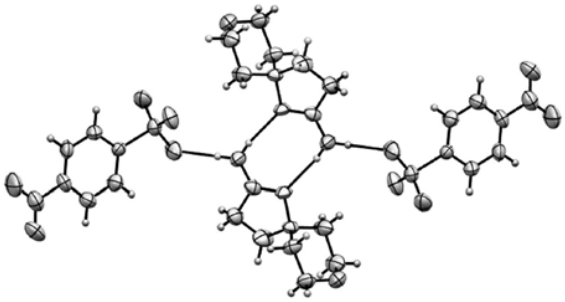


Figure 2. Hydrogen-bonding network in the crystal of **3a**

The crystal structures of compounds **3a** and **3f** are mainly determined by hydrogen bonds. Thus, a closed dimeric associate in the crystal of **3a** is formed by two cations and two anions linked by hydrogen bonds (Figure 2).

In the crystal of **3a**, one hydrogen atom of the amino group is linked to the oxygen atom of the morpholine ring of the adjacent cation. The parameters of the N(2)–H(2A)…O(8′) (1 – *x*, –*y*, 1 –*z*) hydrogen bond are *d*(N(2) –H(2A)) = 0.86 Å, *d*(H(2A)…O(8′) = 2.28 Å, *d*(N(2)…O(8′) = 3.099(5) Å, ∠N(2) –H(2A)…O(8) = 160°. The second hydrogen atom of the amino group forms a bond with the anion through an oxygen atom of the sulfonate group. The parameters of the (N(2)–H(2B)...O(2″) (1/2 + *x*, 1/2 – *y*, 1/2 + *z*) hydrogen bond are *d*(N(2)–H(2B)) = 0.86 Å, *d*(H(2B)…O(2″)) = 2.10 Å, *d*(N(2)…O(2″)) = 2.941(5) Å, ∠N(2) –H(2B)…O(2″) = 166°.

A different hydrogen-bonding network exists in the crystal of **3f** (Figure 3).

The cations are linked through centrosymmetric dimers by N(2) –H(2A)...N(1′) (2 – *x*, 1 – *y*, 1 – *z*) hydrogen bonds. The hydrogen-bond parameters are as follows: N(2)–H(2A), 0.86 Å; H(2A)…N(1′), 2.17 Å; N(2)…N(1′), 3.018(5) Å; the N(2) –H(2a)…N(1′) angle is 170°. The second hydrogen atom of the amino group forms a bond with the anion through the sulfonate oxygen atom, like in the crystal of **3a**. The parameters of the N(2)–H(2B)...O(1) hydrogen bond are as follows: N(2)–H(2B), 0.86 Å; H(2B)…O, 2.10 Å; N(2)…O(1), 2.931(5) Å; the N(2)–H(2B)…O(1) angle is 162°.

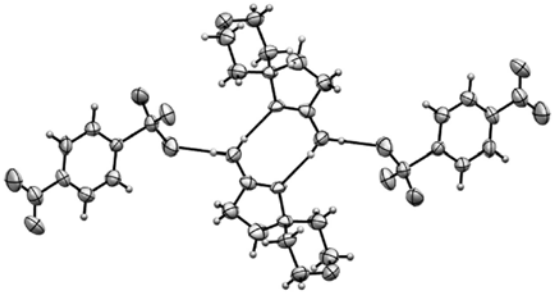


Figure 3. Hydrogen-bonding network in the crystal of **3f**

To summarize, we established that the reaction of β-aminopropioamidoximes with *p*-substituted arylsulfonyl chlorides in chloroform in the presence of an equivalent of triethylamine affords spiropyrazolinium arylsulfonates rather than expected *O*-sulfoaryl-β-amino propioamidoximes regardless of the electronic properties of substituents in arylsulfonyl chlorides.

Experimental

The IR spectra were recorded on a Thermo Scientifi c Nicolet 5700 FTIR spectrometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III NMR 500 MHz spectrometer (500 and 126 MHz, respectively). The elemental analysis was performed on a CE-440 elemental analyzer (Exeter Analytical, Inc., China). The melting points were measured on a TPL melting-point apparatus (Khimlabpribor, Russia). The course of reactions was monitored by TLC on Sorbfil plates (Sorbpolymer, Russia) pre-coated with STKh-1A silica gel with a particle size of 5–17 μm using a fluorescent indicator UV-254. A 1 : 3 benzene–EtOH mixture was used as the eluent.

The starting β-(morpholin-1-yl)propioamidoxime (**1**) was prepared in the following two steps: 1) the reaction of morpholine with acrylonitrile, which were distilled before use (EtOH as the solvent); 2) the resulting aminopropionitrile was distilled *in vacuo* and introduced into the reaction with commercial hydroxylamine hydrochloride, which was used as received (EtOH as the solvent).

β-(Morpholin-1-yl)propioamidoxime (**1**) that was isolated from the reaction mixture was recrystallized from Pr^{i}OH (benzene as the solvent for the extraction of amidoxime **1**) [16].

β-(Morpholin-1-yl)propioamidoxime (**1**) was subjected to arylsulfochlorination with substituted arylsulfonyl chlorides, which were purchased from Sigma-Aldrich and used as received (chloroform as the solvent, triethylamine distilled before use as the base).

The solvents for the synthesis, recrystallization, extraction, and TLC (EtOH, PriOH, benzene, chloroform) were purified according to standard procedures described for each solvent [17].

*Synthesis of 2-amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium arylsulfonates (**3a–f**) (general procedure).* Triethylamine (0.28 g, 0.0028 mol) was added to a solution of β-(morpholin-1-yl)-propioamidoxime (**1**) (0.5 g, 0.0028 mol) in chloroform (10 mL). The reaction mixture was cooled to 0 °C. A solution of arylsulfonyl chloride (0.55 g, 0.0028 mol) in chloroform (2 mL) was added dropwise with stirring. Then the reaction mixture was allowed to warm to room temperature and stirred for several days until the completion of the reaction. The course of the reaction was monitored by TLC. The resulting white precipitates of arylsulfonates **3a–f** were filtered off and recrystallized from Pr^{i}OH.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium 4-methoxybenzenesulfonate (**3a**).* The reaction time was 2 days. The yield of **3a** was 0.4 g (41.4%); m.p. 225—227 °C, R_f = 0.16. IR, ν/cm^{-1}: 3377 ν^{as} (NH_2), 3312 ν^{s} (NH_2), 1650 (C=N), 1597 (C=C), 1205 ν^{as} (SO_2), 1119 ν^{s} (SO_2). ^{1}H NMR, δ: 3.14 (t, 2 H, C$\underline{H}_2$CH_2N$^+$, J = 7.0 Hz); 3.41, 3.64 (both m, 2 H each, H_{ax} and H_{eq}, N$^+$(CH_2)$_2$); 3.75 (s, 3 H, OCH_3); 3.93 (m, 6 H, CH$_2$C$\underline{H}_2$N$^+$);* 3.93 (m, 6 H, O(CH_2)$_2$);* 6.84 (d, 2 H, CHsp^2, J = 7.0 Hz); 7.30 (br, 2 H, NH_2); 7.53 (d, 2 H, CHsp^2, J = 7.0 Hz). ^{13}C NMR, δ: 31.47 (C$\underline{H}_2$CH$_2$N$^+$), 55.64 (CH_3O), 62.02 (CH$_2$C$\underline{H}_2$N$^+$), 63.35 (N$^+$(CH_2)$_2$, 62.42 (O(CH_2)$_2$), 113.20 (2 C); 127.51 (2 C), 141.89 (1 C), 159.65 (1 C), 169.10 (C=N). Found (%): C, 48.75; H, 5.93; N, 12.70; S, 9.02. $C_{14}H_{21}N_3O_5S$. Calculated (%): C, 48.97; H, 6.16; N, 12.24; S, 9.34.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium 4-tosylate (**3b**).* The reaction time was 2 days. The yield of 2-aminospiropyrazolylammonium tosylate (**3b**) was 0.44 g (47.8%); m.p. 220–222 °C, R_f 0.14. IR, ν/cm^{-1}: 3422 ν^{as} (NH_2), 3367 ν^{s} (NH_2), 1654 (C=N), 1601 (C=C), 1195 ν^{as}(SO_2), 1120 vs (SO_2). ^{1}H NMR, δ: 3.14 (t, 2 H, C$\underline{H}_2$CH_2N$^+$, J = 7.0 Hz); 3.36 (s, 3 H, CH_3); 3.40, 3.65 (both m, 2 H each, H_{ax} and H_{eq}, N$^+$(CH_2)$_2$); 3.93 (m, 6 H, CH$_2$C$\underline{H}_2$N$^+$);* 3.93 (m, 6 H, O(CH_2)$_2$);* 7.11 (d, 2 H, CHsp^2, J = 7.0 Hz); 7.35 (br.s, 2 H, NH_2); 7.48 (d, 2 H, CHsp^2, J = 7.0 Hz). ^{13}C NMR, δ: 21.25 (CH_3), 31.43 (C$\underline{H}_2$CH$_2$N$^+$), 62.02 (CH$_2$C$\underline{H}_2$N$^+$), 62.42 (N$^+$(CH_2)^2), 63.23 (O(CH_2)$_2$), 125.95 (2 C); 128.55 (2 C), 138.13 (1 C), 146.16 (1 C), 169.10 (C=N). Found (%): C, 51.81; H, 6.59; N, 13.25; S, 9.37. $C_{14}H_{21}N_3O_4S$. Calculated (%): C, 51.36; H, 6.47; N, 12.83; S, 9.79.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium benzenesulfonate (**3c**).* The reaction time was 4 days. The yield of **3c** was 0.37 g (42.5%); m.p. 192–195 °C, R_f 0.75. IR, ν/cm^{-1}: 3326 ν^{as}(NH_2), 3176 ν^{s}(NH_2), 1656 (C=N), 1604 (C=C), 1220 ν^{as} (SO_2), 1181 as(SO_2). ^{1}H NMR, δ: 3.13 (t, 2 H, C$\underline{H}_2$CH_2N$^+$, J = 7.0 Hz); 3.40, 3.65 (both m, 2 H each, H_{ax} and H_{eq}, N$^+$(CH_2)$_2$); 3.92 (m, 6 H, CH$_2$C$\underline{H}_2$N$^+$);*^{2} 3.92 (m, 6 H, O(CH_2)$_2$);*^{2} 7.48–7.61 (m, 5 H, CHsp^2); 7.48 (br.s, NH_2). ^{13}C NMR, δ: 31.43 (C$\underline{H}_2$CH$_2$N$^+$), 62.08 (CH$_2$C$\underline{H}_2$N$^+$), 62.08 (N$^+$(CH_2)$_2$), 63.23 (O(CH_2)$_2$), 125.93 (2 C); 128.10 (2 C), 128.84 (1 C), 148.87 (1 C), 169.10 (C=N). Found (%): C, 49.29; H, 5.97; N, 13.87; S, 9.91. $C_{13}H_{19}N_3O_4S$. Calculated (%): C, 49.83; H, 6.11; N, 13.41; S, 10.23.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium 4-bromobenzenesulfonate (**3d**).* The reaction time was 4 days. The yield of **3d** was 0.58 g (53.2%); m.p. 230–232 °C, R_f 0.30. IR, ν/cm^{-1}: 3392 ν^{as}(NH_2), 3336 ν^{s}(NH_2), 1646 (C=N), 1609 (C=C), 1225 ν^{as}(SO_2), 1191 ν^{s}(SO_2). ^{1}H NMR, δ: 3.16 (t, 2 H, C$\underline{H}_2$CH_2N$^+$, J = 7.0 Hz); 3.40, 3.67 (both m, 2 H each, H_{ax} and H_{eq}, N$^+$(CH_2)$_2$); 3.87–3.98 (m, 6 H, CH$_2$C$\underline{H}_2$N$^+$);* 3.87–3.98 (m, 6 H, O(CH_2)$_2$);* 7.50 (d, 2 H, CHsp^2, J = 7.0 Hz); 7.39 (br.s, 2 H, NH_2); 7.54 (d, 2 H, CHsp^2, J = 7.0 Hz). ^{13}C NMR, δ: 31.48 (C$\underline{H}_2$CH$_2$N$^+$),

* Hereinafter, the overlapping signals of protons in the 1H NMR spectra of compounds **3a–f** are marked with an asterisk.

62.07 ($\underline{C}H_2CH_2N^+$), 2.46 ($N^+(CH_2)_2$), 63.34 ($O(CH_2)_2$), 122.00 (1 C); 128.23 (2 C), 131.04 (2 C), 148.33 (1 C), 169.11 (C=N). Found (%): C, 40.25; H, 4.85; Br, 19.89; N, 10.28; S, 8.17. $C_{13}H_{18}BrN_3O_4S$. Calculated (%): C, 39.80; H, 4.63; Br, 20.37; N, 10.71; S, 8.17.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium 4-chlorobenzenesulfonate (**3e**).* The reaction time was 6 days. The yield of **3e** was 0.36 g (37%); m.p. 160–162 °C, R_f 0.19. IR, ν/cm^{-1}: 3405 $\nu^{as}(NH_2)$, 3305 $\nu^{s}(NH_2)$, 1647 (C=N), 1596 (C=C), 1220 $\nu^{as}(SO_2)$, 1191 $\nu^{s}(SO_2)$. ^{1}H NMR, δ: 3.17 (t, 2 H, $C\underline{H}_2CH_2N^+$, J = 7.0 Hz); 3.40, 3.67 (both m, 2 H each, H^{ax} and H^{eq}, $N^+(CH_2)_2$); 3.88–3.98 (m, 6 H, $CH_2C\underline{H}_2N$+); *3.88–3.98 (m, 6 H, $O(CH_2)_2$); * 7.37 (d, 2 H, CHsp^2, J = 7.0 Hz); 7.44 (br.s, 2 H, NH_2); 7.61 (d, 2 H, CHsp^2, J = 7.0 Hz). ^{13}C NMR, δ: 31.49 ($\underline{C}H_2CH_2N^+$), 62.04 ($CH_2\underline{C}H_2N^+$), 62.46 ($N^+(CH_2)_2$), 63.33 ($O(CH_2)_2$), 127.93 (2 C); 128.11 (2 C), 133.38 (1 C), 147.89 (1 C), 169.11 (C=N). Found (%): C, 44.68; H, 5.47; Cl, 10.47; N, 12.50; S, 8.85. $C_{13}H_{18}ClN_3O_4S$. Calculated (%): C, 44.89; H, 5.22; Cl, 10.19; N, 12.08; S, 9.22.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium 4-nitrobenzenesulfonate (**3f**).* The reaction time was 3 days. The yield of **3f** was 0.49 g (48.5%); m.p. 192–195 °C, R_f 0.17. IR, ν/cm^{-1}: 3405 $\nu^{as}(NH_2)$, 3305 $\nu^{s}(NH_2)$, 1664 (C=N), 1601 (C=C), 1204 $\nu^{as}(SO_2)$, 1120 $\nu^{s}(SO_2)$. ^{1}H NMR, δ: 3.14 (t, 2 H, $C\underline{H}_2CH_2N^+$, J = 7.0 Hz); 3.41, 3.64 (both m, 2 H each, H^{ax} and H^{eq}, $N^+(CH_2)_2$); 3.88–3.99 (m, 6 H, $CH_2C\underline{H}_2N^+$); * 3.88–3.99 (m, 6 H, $O(CH_2)_2$);* 7.29 (br.s, 2 H, NH_2); 7.85 (d, 2 H, Csp^{2}H, J = 7.0 Hz); 8.19 (d, 2 H, Csp^{2}H, J = 7.0 Hz). ^{13}C NMR, δ: 31.47 ($\underline{C}H_2CH_2N^+$), 62.13 ($CH_2\underline{C}H_2N^+$), 62.44 ($N^+(CH_2)_2$), 63.35 ($O(CH_2)_2$), 123.71 (2 C); 127.39 (2 C), 147.79 (1 C), 155.00 (1 C), 169.09 (C=N). Found (%): C, 43.96; H, 5.29; N, 16.01; S, 9.28. $C_{13}H_{18}N_4O_6S$. Calculated (%): C, 43.57; H, 5.06; N, 15.63; S, 8.95.

X-ray diffraction study. Crystals of compounds **3a** and **3f** suitable for X-ray diffraction were grown from Pr^{i}OH. The X-ray diffraction data were collected from the crystals of compounds **3a** and **3f** on a Bruker Kappa APEX II CCD automated diffractometer equipped with a graphite monochromator (λ(Mo-Kα) = 0.71073 Å; ω- and φ-scanning technique) at 100 K. Semiempirical absorption corrections were applied with the SADABS program [18]. The structures were solved by direct methods using the SHELXT 2014/4 program package [19] and refined first with isotropic and then with anisotropic displacement parameters using the SHELXL-2018/3 program package [20].

Hydrogen atoms were positioned geometrically and refined using a riding model. All calculations were carried out with the WinGX[21] and APEX2 programs [22]. All figures were prepared and intermolecular interactions were analyzed with the PLATON [23] and ORTEP programs [21].

The crystallographic data and the X-ray diffraction data collection and structure refinement statistics for compounds **3a** and **3f** are given in Table 1.

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Single crystals of **3a** and **3f** were investigated in the Assigned Spectral-Analytical Center for Studies of Structure, Composition and Properties of Substances and Materials of the A.E. Arbuzov Institute of Organic and Physical Chemistry (Kazan, Russia). We are grateful to staff members of the Spectral-Analytical Center I.A. Litvinov, O.A. Lodochnikova, and F.A. Karamov for performing X-ray diffraction experiments and to the staff member of the A.B. Bekturov Institute of Chemical Sciences (Almaty, Kazakhstan) A.A. Espenbetov for help in interpreting the X-ray dif raction data.

Table 1

Crystallographic data and the X-ray diffraction data collection and structure refinement statistics for compounds 3a and 3f

Parameter	3a	3f
Molecular formula	$C_{14}H_{21}N_3O_5S$	$C_{13}H_{18}N_4O_6S$
M	343.40	358.37
Color	Colorless	Colorless
Crystal habit	Prismatic	Prismatic
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
a/deg	9.2401(14)	15.706(3)
b/deg	18.448(2)	6.6935(10)
c/deg	9.5149(14)	16.144(2)
β/Å	100.361(6)	111.884(8)
V/Å^3	1595.5(4)	1574.9(4)
Z	4	4
d_{calc}/g cm^{-3}	1.430	1.512
μ(Mo)/mm^{-1}	0.233	0.245
θ-Scan range/deg	2.20—28.30	3.30—26.00
Number of reflections		
measured	9873	11400
unique	3959	3046
with $I \geq 2\sigma(I)$	1746	1319
Final R factor		
based on all reflections	3959	3046
R	0.1660	0.1598
R_w	0.2280	0.1414
based on observed reflections with $F > 2\sigma(F^2)$		
R	0.0669	0.0581
R_w	0.1541	0.1060
GOOF	0.926	0.906
CCDC	1957795	1957796

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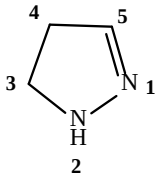
Chapter 5

ARYLSULPHONATES OF SPIROPYRAZOLINES AND O-TOSYLATE-β-(BENZIMIDAZOL-1-YL) PROPIOAMIDOXIME AS THE PRODUCTS OF β-AMINOPROPIOAMIDOXIMES TOSYLATION

5.1. Introduction

The drugs currently sold in the pharmaceutical market are based on heterocyclic compounds. From the point of view of the breadth of biological activity, pyrazoline is of paramount importance among them. The five-membered pyrazoline heterocycle contains two adjacent nitrogen atoms. The vast majority of of biologically active pyrazolines are 2-pyrazolines or 3,4-dihydropyrazoles [1,2].



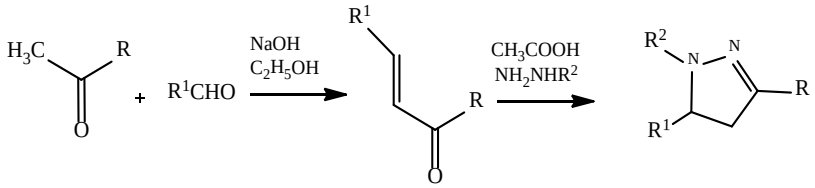
2-pyrazolines (3,4-dihydro-2H-pyrazole)

To develop effective and potent drugs molecules with a pyrazoline fragment of natural and synthetic origin are being investigated

all over the world. In the last decade reviews summarizing certain aspects of the well-developed field of medicinal chemistry of pyrazoline derivatives have appeared [5–12].

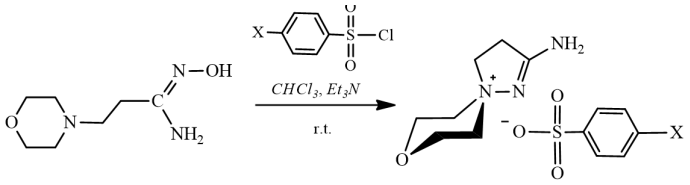
Thus, the review [5] summarizes this area, beginning from the pyrazoline structures that have found application in therapy, then examines the developed pyrazoline compounds that have reached the phases of clinical trials, and then draws attention on a wide range of *in vitro* and *in vivo* results of studies of the potentially highly active pyrazoline derivatives.

Methods for the synthesis of pyrazolines mainly consist in the reactions of interaction of steroid compounds – chalcones containing an enone fragment with substituted hydrazines [11, 17–19].



Innovative, «green» methods for the synthesis of substituted pyrazolines are being developed: activation of the reaction by ultrasound [11], microwave radiation [18], thermal reactions without a solvent using a biodegradable maltose catalyst [19].

Among the derivatives of β-aminopropioamidoximes, we have accumulated experience of spiropyrazolinium compounds formation [20–22]. Boulton-Katritsky rearrangement is a transition pathway of 3-(β-heteroamino)ethyl-5-aryl-1,2,4-oxadiazoles to 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium spiropyrazoline benzoates and chloride. It turned out that the spiropyrazonium structure is synthetically available already upon arylsulfochlorination of β-(morpholin-1-yl)propioamidoxime [23]. In this case, the formation of structural isomers, O-arylsulfo-β-(morpholin-1-yl)propioamidoximes, was not observed.



The aim of this work is the study of the effect of the base strength and the structure of amidoximes on the structure of tosylation products of β-aminopropioamidoximes, which may include spiropyrazoline derivatives. We carried out interaction of β-aminopropioamidoxime (β-amino group: piperidin-1-yl, morpholin-1-yl, thiomorpholin-1-yl, 4-phenylpiperazin-1-yl, β-(benzimidazol-1-yl) with tosyl chloride (TsCl) in $CHCl_3$in the presence of diisopropylethylamine (DIPEA) at room temperature.

5.2. Results and discussion

Products (**6**–**10**) were isolated in 45–65% yields and identified using physicochemical characteristics and data from IR spectroscopy and NMR (^1H and ^{13}C) spectroscopy (Tables 1–4).

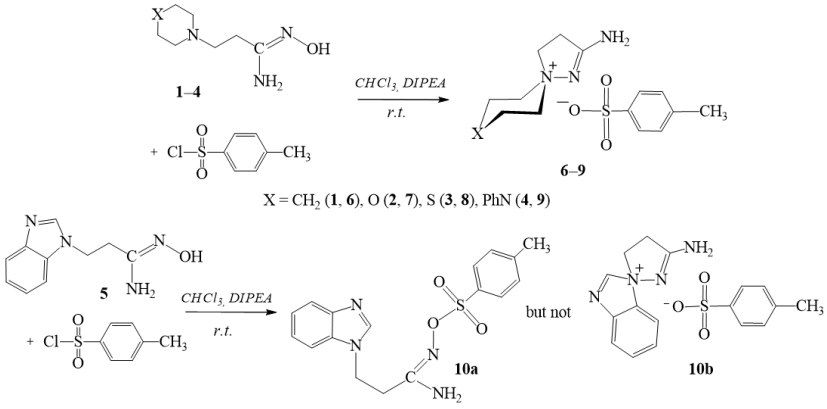


Table 1

Physicochemical characteristics of β-aminopropioamidoximestosylation products 6–10.

Compd	Yield,%	Time, h	M.p., °C	R_f	MW	Found,% Calculated,%			Gross formula
						C	H	N	
6	62	15	230	0.24	325.43	55.36 54.86	7.12 6.63	12.91 12.41	$C_{15}H_{23}N_3O_3S$
7*	65	15	218–220	0.13	327.40	51.36 50.86	6.47 5.99	12.83 12.51	$C_{14}H_{21}N_3O_4S$
8	56	20	255	0.08	343.46	48.96 48.23	6.16 5.71	12.23 11.69	$C_{14}H_{21}N_3O_3S_2$
9	50	15	290	0.10	402.51	59.36 59.68	6.47 6.51	13.53 13.92	$C_{20}H_{26}N_4O_3S$
10a	45	15	163–165	0.67	358.42	56.55 56.97	5.06 5.45	15.63 15.11	$C_{17}H_{18}N_4O_3S$

*Note. M.p. of compound **7** obtained in [23], is 220–222 °C; R_f – 0.14.

In the IR spectra of the synthesized substances **6**–**10**, there are bands of asymmetric and symmetric stretching vibrations of the SO_2 group in the region ν 1131–1190 cm^{-1} and 1347–1380 cm^{-1}, bands of stretching vibrations of double bonds C=C in the region ν 1600–1617 cm^{-1} and the bands of stretching vibrations of the C_{sp2} –H bonds in the region> 3000 cm^{-1} (Table 2).

Table 2

IR spectra of β-aminopropioamidoximestosylation products 6–10

Compd	Stretching vibrations of bonds, ν, cm^{-1}						
	$\nu_{C=N}$	$\nu_{C=C}$	ν_{SO2} asym.	ν_{SO2} sym.	$\nu_{(N-H)2}$	ν_{Csp3-H}	ν_{Csp2-H}
6	1641	1616	1131	1380	3415	2848, 2912	3115, 3210
7	1643	1600	1190, 1127	-	3466	-	3236, 3328, 3388
8	1652	1611	1132, 1189	1347	3427	2810, 2913, 2985	3162, 3233, 3289
9	1642	1599	1131, 1189	1347	3421	2770, 2848,2910	3115, 3286
10a	1648	1617	1190	1358	3417	2791, 2920	3110, 3237

The ^{1}H NMR spectra of the products **6**–**10** contain doublet signals of the *para*-substituted phenyl group in the region of δ 7–8 ppm and the signal of the *para*-methyl substituent in the range δ 2.29–2.38 ppm. The signal of the amino group of compounds **6**–**10** is observed in the range of δ 6.80–7.33 ppm. The interacting groups of α- and β-methylene protons give two triplet signals in the regions δ 2.50–3.17 ppm and δ 3.82–4.33 ppm (Table 3).

Products **6**–**9** are characterized by a high melting point (214–290 °C) and low R_f values (0.08–0.24) (Table 1), which are characteristic for the spirocyclic compounds –arylsulfonatesof 2-amino-8-oxa-1,5-diazaspiro[4.5]-dec-1-en-5-ammonium [23].

Compound **10** has m.p. 163–165 °C and, in contrast to the compounds **6**–**9**, has a significantly higher value of R_f 0.67.

In addition, the broadened signal of the protons of the NH_2 group of compounds **6**–**9** is in the range of δ 7.28–7.33 ppm (Table 3) – in the same region as the analogous signal of 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium arylsulfonates (δ 7.29–7.48 ppm) [23]; while the signal of the NH_2 group of the compound **10** was determined at δ 6.80 ppm, which is close to the position of the analogous signal of NH_2 group of the O-acylation products of β-(piperidin-1-yl)propioamidoxime (δ 6.58–6.77 ppm) [24].

Table 3

^{1}H NMR spectra of the tosylation products of β-aminopropioamidoximes 6–10

Compd	Chemical shift, δ, ppm (J, Hz)						
	α-CH_2	β-CH_2	$(CH_2)_3$ (**11**) $X(CH_2)_2$ (**12**–**14**)	$N(+)(CH_2)_2$ [ax (2H); eq (2H)]	*para*-CH_3(3H)	NH_2 (2H)	$C_{(sp2)}H$
1	2	3	4	5	*6*	7	8
6	3.09t (2H, 7.0)	3.82t (2H, 7.0)	1.57m, 1.75m, 1.87m (6H)	3.34m (2H), 3.44m (2H)	2.29	7.28	7.11d(2H, 7.0), 7.47d (2H, 7.0)
7	3.13t (2H, 7.0)	3.92t (2H, 7.0)	3.32m (4H)	3.41m (2H), 3.65m (2H)	2.29	7.28	7.11d(2H, 7.0), 7.48d (2H, 7.0)
8	3.12t (2H, 7.0)	3.87t (2H, 7.0)	3.32m (4H)	2.88m (2H), 3.59m (2H)	2.29	7.33	7.11d(2H, 7.0), 7.47d (2H, 7.0)

1	2	3	4	5	*6*	7	8
9	3.17t (2H, 7.0)	3.95t (2H, 7.0)	3.56m (4H)	3.48m (2H), 3.95m (2H)	2.29	7.32	7.10d(2H, 7.0), 7.48d (2H, 7.0) and 6.87, 7.02, 7.27m (5H)
10a	2.50t (2H, 7,0)	4.33t (2H, 7.0)	-	-	2.38	6.80	7.18–7.64 m, 7.99 s, 7.36d(2H, 7.0), 7.70d (2H, 7.0)

In the ^{13}C NMR spectra the signal of the carbon atom of the C=N bond of the pyrazolinium ring of compounds **6**–**9** is present at δ 169.10 ppm; and for compound **10** – at δ 158.04 ppm (Table 4).

Based on a comparison of physicochemical and IR and NMR spectral data of products **6**–**9** and product **10**, it is assumed that product **10** is an O-tosylsulfoderivative of β-(benzimidazol-1-yl)propioamidoxime–3-(1H-benzo[d]imidazol-1-yl)-N'-(tosyloxy)-propanimidamide (**10a**).

Table 4

^{13}C NMR spectra of the tosylation products of β-aminopropioamidoximes 6–10

Compd	Chemical shift, δ, ppm						
	α-CH_2	β-CH_2	N(+)(CH_2)$_2$	X(CH_2)$_2$	*para*-CH_3	C_{sp2}	C=N
6	31.5	60.7	64.3 (2C)	21.0 (2C), 21.9 (1C)	21.2	126.0 (2C), 128.5 (2C), 138.0 (1C), 146.3 (1C)	168.5
7	31.4	62.1	63.2 (2C)	62.4 (2C)	21.2	126.0 (2C), 128.6 (2C), 138.1(1C), 146.2(1C)	169.0
8	31.4	62.5	64.7 (2C)	23.2 (2C)	21.2	126.0 (2C), 128.5 (2C), 138.0 (1C), 146.0 (1C)	169.0
9	31.5	61.5	62.9 (2C)	44.5 (2C)	21.3	126.0 (2C), 128.5 (2C),138.0 (1C),146.3 (1C), 116.3 (2C), 129.6 (2C), 120.4 (1C), 149.9 (1C)	169.1
10a	31.2	41.6	-	-	21.6	128.5 (2C), 130.0 (2C), 133.5(1C), 144.7 (1C),110.8 (1C), 119.8 (1C), 121.9 (1C), 122.7 (1C),134.0 (1C), 143.7 (1C), 144.3 (1C)	158.0

X-Ray structural analysis data will be useful confirmation of the compounds **6**–**10** structure.

Experimental part

IR spectra were obtained on a Thermo Scientific Nicolet 5700 FTIR instrument in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 MHz NMR spectrometer (500 and 126 MHz, respectively). Melting points were determined on a TPL apparatus (Khimlabpribor, Russia). The progress of the reaction was monitored using Sorbfil TLC plates (Sorbpolymer, Russia) coated with CTX-1A silica gel, grain size 5–17 μm, UV-254 indicator. The spots were developed in I_2 vapors and in the UV light of a chromatoscope (λ 254 nm) «ТСХ 254/365» (PETROLASER). The eluent for the analysis is a mixture of EtOH–benzene, 1:1 + a few drops of a 25% aqueous solution of NH_3. Microanalysis according to the Pregl method was carried out on an elemental analyzer with the absorption of CO_2 and O_2 isolated during combustion with a two-degree repetition of combustion.

Tosylation of β-aminopropioamidoximes (**1**–**5**) was performed in dried $CHCl_3$ with tosyl chloride with the participation of diisopropylethylamine, purchased from Sigma-Aldrich and used without purification. Solvents for synthesis, recrystallization, extraction and TLC analysis (EtOH, i-PrOH, benzene, $CHCl_3$) were purified according to the standard procedures described for each solvent.

*Synthesis of β-aminopropioamidoximes tosylation products **6**–**10** (general method).* To a solution of 0.0029 mol of β-aminopropioamidoximes **1**–**5** in 20 ml of $CHCl_3$ 0.0029 mol of DIPEA was added. The reaction mixture was cooled to -1 °C, and a solution of 0.0029 mol of tosyl chloride in 2 ml of chloroform was added dropwise with stirring. The reaction mixture was then allowed to warm to room temperature and stirred until completion of the reaction. The progress of the reaction was monitored by TLC. The formed white precipitates of tosylchlorides **6**–**10** were filtered off and recrystallized from i-PrOH.

*2-Amino-1,5-diazospiro[4.5]dec-1-en-5-ammonium tosylate (**6**).* The reaction time was 15 h. The yield of 2-aminospiropyrazolylammonium tosylate (**6**) was 0.59 g (62%), m.p. 230 °C, R_f 0.24.

*2-Amino-8-oxa-1,5-diazospiro[4.5]dec-1-ene-5-ammonium tosylate (**7**).* The reaction time was 15 h. The yield of 2-aminospiropyrazolylammonium tosylate (**7**) was 0.65 g (65%); m.p. 218–220 °C, R_f 0.13.

*2-Amino-8-thio-1,5-diazospiro[4.5]dec-1-ene-5-ammonium tosylate (**8**).* The reaction time was 20 h. The yield of 2-aminospiropyrazolylammonium tosylate (**8**) was 0.5 g (56%); m.p. 255 °C, R_f 0.08.

*2-Amino-8-phenyl-1,5,8-triazaspiro[4.5]dec-1-ene-5-ammonium tosylate (**9**).* The reaction time was 15 h. The yield of 2-aminospiropyrazolylammonium tosylate (**9**) was 0.15 g (50%); m.p. 290 °C, R_f 0.10.

*3-(1H-Benzo[d]imidazol-1-yl)-N '-(tosyloxy)propanimidamide (**10**).*

The reaction time was 15 h. The yield of O-tosylation product of β-(benzimidazol-1-yl)propioamidoxime **10** was 0.4 g (45%); m.p. 163–165 °C, R_f 0.67.

5.3. Conclusion

Thus, the tosylation of β-aminopropioamidoximes (β-amino group: piperidin-1-yl, morpholin-1-yl, thiomorpholin-1-yl, 4-phenyl-piperazin-1-yl) proceeds to obtain spirocyclic compounds – tosylates 2-amino-1,5-diazaspiro [4.5]-dec-1-en-5-ammonium; tosylation of β-(benzimidazol-1-yl)propioamidoxime gives the product at the oxygen atom of the amidoxime group. As a result of our studies, along with the expected product – O-tosyl-β-(benzimidazol-1-yl)propioamidoxime, a number of the structurally new, isomeric spiropyrazolinium compounds was obtained. This indicates on their thermodynamic advantage in comparison with the products of O-acylation. Analysis of the literature data shows that among the derivatives of pyrazolines there are no examples of doubly charged spirocompounds with ammonium nitrogen in the head of the bridge and any anion as a counterion.

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Chapter 6

REDETERMINATION OF THE STRUCTURE OF 2-AMINO-8-THIA-1,5-DIAZASPIRO[4.5] DEC-1-EN-5-IUM CHLORIDE MONOHYDRATE

6.1. Chemical context

Sulfochlorination of amidoximes is known to afford stable products of acylation at the oxygen atom of the amidoxime group; at the same time, the sulfochlorination reaction of derivatives of primary amidoximes can, depending on the structure of the starting amidoxime and reaction conditions, lead to rearranged products with the formation of ureas and substituted cyanamides (Tiemann, 1891; Bakunov et al., 2000; Doulou et al., 2014).

Previously, in our studies of the acylation of β-aminopropioamidoximes with acid chlorides of substituted benzoic acids, only O-acyl-β-aminopropioamidoximes were identified as acylation reaction products. Their structures have been determined by the complex use of spectroscopic methods, as well as X-ray structural analysis (Kayukova, 2003; Beketov et al., 2004; Kayukova et al., 2010a). The dehydration of the products of the O-acylation of β-aminopropioamidoximes allows for 3,5-disubstituted 1,2,4-oxadiazoles to be obtained, which under conditions of acid hydrolysis and in the presence of moisture are capable of undergoing a Boulton–Katritsky rearrangement to 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium salts (Kayukova et al., 2010b, 2018, 2021a).

Recently, we found that the arylsulfochlorination reaction of β-aminopropioamidoximes at room temperature afforded 2-amino-8-(hetera)-1,5-diazaspiro[4.5]dec-1-en-5-ium arylsulfonates as the main products (Kayukova et al., 2020, 2021b). Herein we report on the result of β-(thiomorpholin-1-yl)propioamidoxime tosylation at the boiling point of the solvent. By means of such a high-temperature process, the formation of the most stable reaction product is expected.

Under such conditions of thermodynamic control of the tosylation reaction of β-(thiomorpholin-1-yl)propioamidoxime (**1**) upon prolonged heating for 8 h at the boiling point of the solvent [$CHCl_3$, 8 h, 343 K (bath temperature)], in the presence of DIPEA, the title hydrated salt, 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate (**3**) was obtained in good yield (84%). In our opinion, the source of hydrate formation was air moisture, since the formation of single crystals took place over a long time under conditions of natural evaporation of the solvent for crystallization with air access. This result of the amidoxime (**1**) tosylation differs from the result of the same reaction performed at room temperature, when the main kinetic product of the reaction was 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium tosylate (**2**) (Figure 1, yield 56%; Kayukova et al., 2021b).

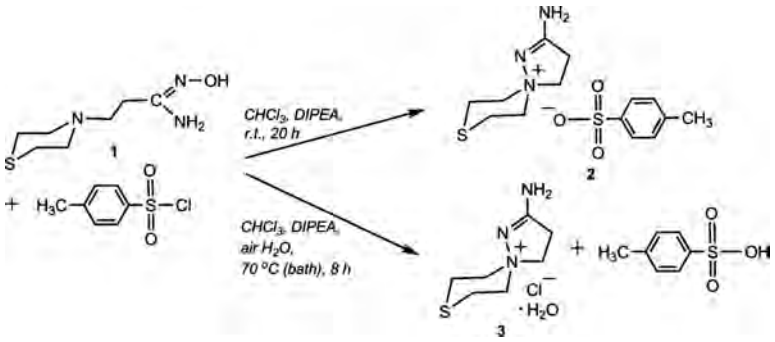

Figure 1. Results of the β-(thiomorpholin-1-yl)propioamidoxime (**1**) tosylation reaction at r.t. and at the boiling point of the solvent

Spiropyrazolinium chloride monohydrate **3** is a white opaque precipitate, poorly soluble in chloroform. When the reaction was

complete, it was filtered off from the reaction mixture and re-crystallized from propanol-2 solution over three weeks in the form of transparent prisms with a melting point of 575 K. We previously isolated a compound with the same chemical composition and melting point during the acid hydrolysis of 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles (Kayukova et al., 2010b).

Not only the composition, but also the orthorhombic unit-cell parameters were similar for 3 and the previously reported structure; however, the space groups were different: P212121 at room temperature (Kayukova et al., 2010b) and Pbca at 120.0 (2) K for 3, thus a single crystal of the reaction product was also determined at 295.0 (2) K and the resulting crystal structures were compared with the previously reported one.

6.2. Structural commentary

The molecular structure of **3** is shown in Figure 2. The C3–N1 and N1–N2 bonds are elongated as compared with typical single bonds at 1.521 (1) and 1.463 (1) Å, respectively, which can be related to the anomeric effect of the lone pair of atom N2. The six- and five-membered rings of the $C_7H_{14}N_3S^+$ cation adopt chair and envelope conformations, respectively.

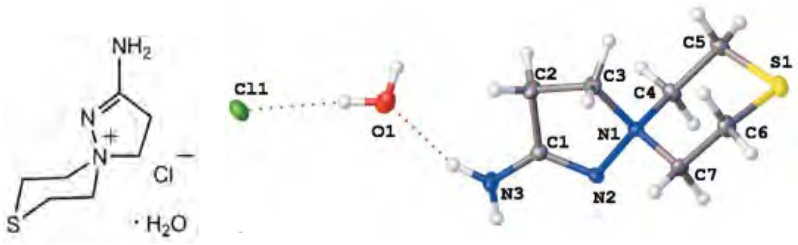

Figure 2. Asymmetric unit of 3 at low temperature
with displacement ellipsoids at the 50% probability level

It may be noted that in respect to a chair conformation of the sixmembered ring, atom N2 can be situated in the equatorial and axial

positions of the N1 atom; however, in this and previously reported salts, only the axial disposition of the N2 atom is observed. This is in accord with our B3LYP/6-31++G(d,p) calculations of standard Gibbs free energies of reactions leading to the formation of various products. We established that the axial stereoisomer is more stable than the equatorial one (ΔG = 144.29 and –124.23 kJ mol^{-1}, respectively; Yergaliyeva et al., 2021).

The envelope conformation of the C1/C2/C3/N1/N2 five-membered ring in **3** is expressed as the deviation of C3 from the mean plane formed by atoms N1/N2/C1/C2 (r.m.s. deviation = 0.005 Å): it is equal to 0.401 (1) Å, and the two molecular conformers (corresponding to different directions of this carbon atom shifted in respect to the N–N C–C mean plane) are equally present in this centrosymmetric crystal. However, the previously reported crystal structure (Kayukova et al., 2010b) [refcode APOBOX in the Cambridge Crystallographic Database (CSD; Groom et al., 2016)] contains two independent spiro-cations in the asymmetric unit with two different conformations of the five-membered ring (Figure 3). A question arises as to whether these structures are polymorphs of the same salt, or if the previously reported structure was incorrectly solved and refined.

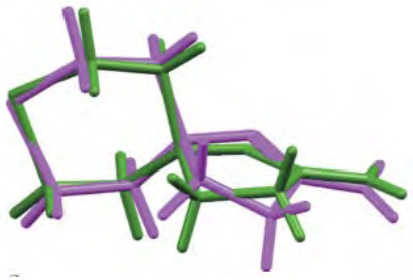

Figure 3. The two independent 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium cations observed in APOBOX depicted as overlaid molecules

Our study of the same single crystal of **3** at room temperature confirmed that no phase transition occurs between 120 and 295 K.

Unfortunately, crystallographic data for APOBOX stored in the CSD could not be re-refined. Thus, we compared the crystal packing and the system of hydrogen bonds for the two models refined in different space groups.

Table 1

Hydrogen-bond geometry (Å, °) for the low-temperature structure

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*A*···Cl1^{i}	0.88	2.38	3.2560 (9)	175
N3—H3*B*···O1	0.88	1.95	2.7970 (11)	161
O1—H1*A*···Cl1	0.85	2.26	3.1042 (9)	175
O1—H1*B*···Cl1^{ii}	0.85	2.27	3.1152 (9)	176
C5—H5*B*···N2^{iii}	0.99	2.58	3.3778 (12)	138
C6—H6*A*···N2^{iv}	0.99	2.55	3.3346 (12)	136

Symmetry codes: (i) x + ½, -y +3/2, -z + 1; (ii) –x, -y + 1, -z + 1; (iii) - x + 1, y - ½, -z + 3/2; (iv) –x + 3/2, y -1/2, z.

6.3. Supramolecular features

First, the system of hydrogen bonds was compared for the two solids at 120.0 (2) and 295.0 (2) K (Tables 1 and 2) and they are essentially the same, apart from a slight lengthening of the H…X contacts at the higher temperature. In both cases, the amine acts as a donor of hydrogen bonds with a water molecule, an anion and the water molecules act as acceptors of N–H…O bonds and as donors in two O–H…Cl interactions, and the chloride anion is an acceptor of three hydrogen bonds. As a result, infinite layers parallel to the (001) plane are observed (Figure 4). A topological analysis of the system of hydrogen bonds, where the spiro-cations act as linkers and water molecules and anions are three-connected nodes, indicates that both layers are isoreticular and have the fes topology (the three-letter code is given in terms of the RSCR notation; O'Keeffe et al., 2008).

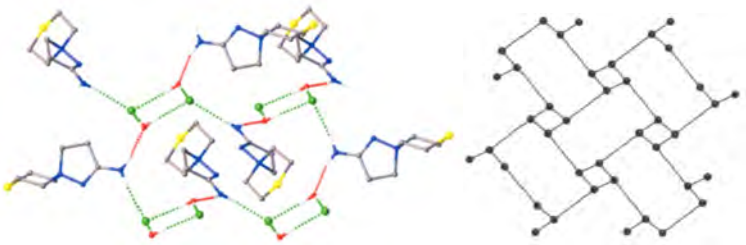

Figure 4. Top: fragment of the hydrogen-bonded layers in **3**. Hydrogen bonds are depicted as dotted lines. C-bound H atoms are omitted. Bottom: underlying net of hydrogen bonds in **3** with a **fes** topology

Table 2

Hydrogen-bond geometry (Å, °) for the room-temperature structure

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*A*···Cl1^{i}	0.86	2.42	3.2786 (18)	174
N3—H3*B*···O1^{ii}	0.86	1.99	2.821 (2)	162
O1—H1*C*···Cl1	0.85	2.28	3.1244 (17)	173
O1—H1*D*···Cl1^{iii}	0.85	2.29	3.1343 (17)	175
C6—H6*B*···N2^{iv}	0.97	2.61	3.391 (2)	138

Symmetry codes: (i) x, y + 1, z; (ii) x +1/2, -y + 1/2, -z + 1; (iii) - x + 1, -y, -z + 1; (iv) –x + 1/2, y -1/2, z.

Additional analysis of the crystal packing by means of the PLATON package (Spek, 2020) suggests that the Pbca space group is correct for both solids, and by means of the ‘Crystal Packing Similarity’ tool implemented within Mercury (Macrae et al., 2020) as described by Childs et al. (2009) or by Vologzhanina (2019) denotes that the packings of 30-molecule clusters for the two solids are also very close to each other (the average r.m.s. deviation of 0.15 Å can be explained by the different experimental temperatures). Thus, we propose that 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate crystallizes in the Pbca space group both at low and room temperatures in contrast with the data given previously in space group P212121(Kayukova et al., 2010b).

6.4. Synthesis and crystallization

IR spectra were obtained on a Thermo Scientific Nicolet 5700 FTIR instrument in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 MHz NMR spectrometer (500 and 126 MHz, respectively). Melting points were determined on a TPL apparatus (Khimlabpribor, Russia). The progress of the reaction was monitored using Sorbfil TLC plates (Sorbpolymer, Russia) coated with CTX-1A silica gel, grain size 5–17 μm, UV-254 indicator. The spots were developed in I_2 vapours and in the UV light of a chromatoscope (λ= 254 nm) TSX 254/365 (PETROLASER). The eluent for the analysis was a mixture of EtOH: benzene = 1:1 + a few drops of a 25% aqueous solution of NH_3. Microanalysis according to the Pregl method was carried out on an elemental analyser with the absorption of CO_2 and O_2 isolated during combustion with a two-degree repetition of combustion.

The tosylation of β-(thiomorpholin-1-yl)propioamidoxime (**1**) was performed in dried $CHCl_3$ with tosyl chloride in the presence of DIPEA, purchased from Sigma–Aldrich and used without purifycation. Solvents for synthesis, recrystallization and TLC analysis (EtOH, 2-PrOH, benzene, $CHCl_3$) were purified according to the standard procedures described for each solvent.

*Synthesis of 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**3**):*

To a solution of 1.00 g (0.0053 mol) of β-(thiomorpholin-1-yl) propioamidoxime (**1**) in 40 ml of $CHCl_3$, 0.92 ml (0.0053 mol) of DIPEA were added. The reaction mixture was cooled to 272 K, and a solution of 1.01 g (0.00530 mol) of tosylchloride in 4 ml of $CHCl_3$ was added dropwise under stirring. The reaction mixture was stirred for 1 h at room temperature and was then heated and stirred at the reflux temperature of $CHCl_3$ for 8 h until the completion of the reaction, the progress of the reaction being monitored by TLC. The formed white precipitate of the chloride hydrate 3 was filtered off and recrystallized from 2-PrOH solution. The yield of **3** was 1.01 g (84%), m.p. 575 K, R_f 0.08. Found, %: C 37.67, H 7.49. $C_7H_{16}ClN_3OS$. Calculated, %: C 37.24, H 7.14. IR, cm^{-1}: 1659 (ν C=N); 1612 [d C–N; d (H)2–O]; 670 (ν S–C); 3135, 3230, 3380, 3384 (ν H–O, ν H–N). ^{1}H NMR, δ, ppm (*J*, Hz): 2.88 [*m*, 2H, $S(CH_{eq})_2$], 3.14 [*m*, 2H, $S(CH_{ax})_2$], 3.14 [*m*, 2H, $N(+)CH_2C\underline{H}_2$], 3.37 (*br. s*, 2H, H_2O), 3.62 [*m*, 2H, $N(+)C(H_{eq})_2$], 3.74 [*m*, 2H, $N(+)C(H_{ax})_2$], 3.88 [*t*, 2H, *J* = 7.0, $N(+)C\underline{H}_2CH_2$], 7.48 (*br s*, 2H, NH_2). The signals for the methylene protons of the $N(+)CH_2CH_2$ group in **3** coincide with the signals of the $S(CH_{ax})_2$ group at 3.14 ppm.

6.5. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3.

Table 3

Experimental details

	120 K	295 K
Crystal data		
Chemical formula	$C_7H_{14}N_3S^+ \cdot Cl^- \cdot H_2O$	$C_7H_{14}N_3S^+ \cdot Cl^- \cdot H_2O$
M_r	225.74	225.74
Crystal system, space group	Orthorhombic, *Pbca*	Orthorhombic, *Pbca*
a, b, c (Å)	11.0360 (18), 10.1005 (16), 19.291 (3)	11.0924 (4), 10.1898 (4), 19.6434 (8)
V (Å^3)	2150.4 (6)	2220.28 (15)
Z	8	8
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.52	0.50
Crystal size (mm)	0.41 × 0.36 × 0.32	0.41 × 0.36 × 0.32
Data collection		
Diffractometer	Bruker APEXII CCD	Bruker D8 Quest PHOTON area detector
Absorption correction	Multi-scan (*SADABS*; Bruker, 2016)	Multi-scan (*SADABS*; Bruker, 2016)
T_{min}, T_{max}	0.633, 0.747	0.518, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	29600, 5145, 3893	29622, 2969, 2269
R_{int}	0.032	0.106
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.830	0.684
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.030, 0.087, 1.06	0.048, 0.124, 1.05
No. of reflections	5145	2969
No. of parameters	121	118
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.44, −0.34	0.29, −0.34

Computer programs: APEX2 and SAINT (Bruker, 2016), SHELXT (Sheldrick, 2015a), SHELXL (Sheldrick, 2015b) and OLEX2 (Dolomanov et al., 2009).

The positions of hydrogen atoms were calculated and included in the refinement in isotropic approximation using a riding model with Uiso(H) = 1.5Ueq(O) and 1.2Ueq(X) for the other atoms.

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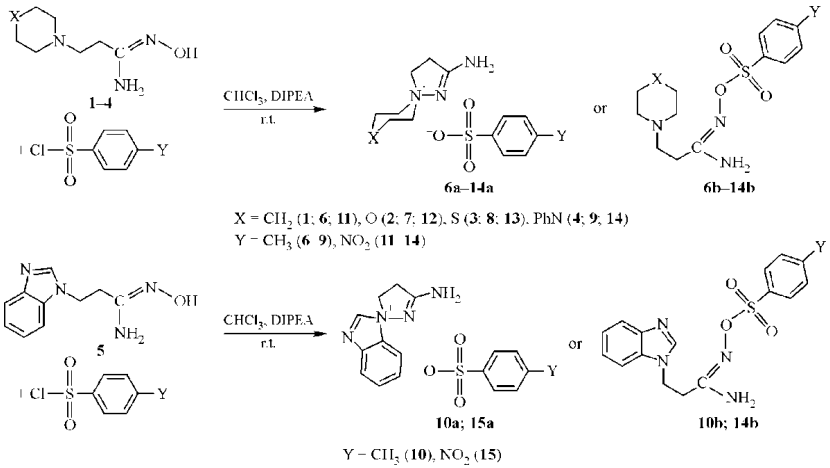
Chapter 7

COMPUTATIONAL STUDIES OF THE PRODUCTS OF TOSYLATION AND *PARA*-NITROBENZENESULFOCHLORINATION OF β-AMINOPROPIOAMIDOXIMES

7.1. Introduction

Amidoximes serve as intermediate products for the synthesis of many heterocyclic compounds and are used in some methods to introduce functional groups when preparing biologically active compounds [1, 2]. One such method is arylsulfochlorination [3, 4] leading to the formation of O-substitution products [3] or spiropyrazolinium compounds [1, 5]. We earlier reported *para*-toluenesulfochlorination of β-aminopropioamidoximes (Scheme 1, **1**-**5**) in the presence of diisopropylethylamine (DIPEA) to obtain toluenesulfonates of spiropyrazolinium compounds **6a**-**9a** from the initial β-aminopropioamidoximes **1**-**4**, while the tosylation of β-(benzimidazol-1-yl)propioamidoxime (**5**) yielded its O-substitution product – 3-(1H-benzo[d]imidazole-1-yl)-N′-(tosyloxy)propanimidamide (**10b**) [6]. The structures of the synthesis products were determined by IR and NMR spectroscopies. In the present work, we report a theoretical study of β-aminopropioamidoxime tosylation using calculations of thermodynamic parameters of the corresponding reactions and quantum chemical HOMO–LUMO analysis of molecular structures of reaction products. The performed calculations explain the experi-

mental data. Similar calculations conducted also for thermodynamic parameters of *para*-nitrobenzenesulfochlorination reactions for the considered series of β-aminopropioamidoximes will allow predicting the structure of products of **11**–**15** and their properties such as reactivity and stability.



Scheme 1. Experimental and predicted products of β-aminopropioamidoximes arylsulfochlorination

Experimental

Full geometry optimization of molecules and calculations of vibrational frequencies were performed with the Gaussian09W package [7] by the DFT method using the B3LYP/6-31++G(*d*,*p*) theory level. The effect of solvent (chloroform) was considered within the polarizable continuum model (IEFPCM). The B3LYP functional (Becke′s three parameter hybrid functional using the Lee–Young–Parr (LYP) correlation) is a reliable functional with an average level of accuracy suitable for most tasks [8]; the 6-31++G(*d*,*p*) basis set provides a sufficient accuracy when calculating thermodynamic parameters such as the Gibbs free energy *G* [9–12].

Quantum chemical calculations allow determining thermodynamic parameters of reactions and revealing the thermodynamically preferable reaction product by comparing formation enthalpies [13] or Gibbs free energies [14] of the products. The thermodynamic parameters were estimated by calculating of all reactants according to Scheme 1 using Hess's law [15].

$$\Delta G_r = \sum \Delta G_{0\ \text{products}} - \sum \Delta G_{0\ \text{reactans}}$$

taking into account the formation of DIPEA hydrochloride.

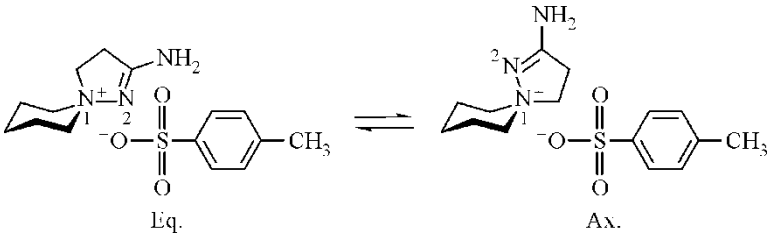
7.2. Results and discussion

The thermodynamic parameters of reactions calculated by DFT in the mentioned basis set may differ from the experimental ones; however, their comparison allows estimating which of the products **1a**–**15a** or **1b**–**15b** are more preferable. The calculated ΔG values are listed in Table 1.

By comparing standard Gibbs free energies of reactions leading to the formation of products **a** and **b**, the most preferable product is found as the one having the largest magnitude of the negative ΔG value. The calculations show that products **6a**–**9a** and **11a**–**14a** are thermodynamically more preferable during arylsulfochlorination of β-aminopropioamidoximes **1**–**4**, i.e. the most probable products are *para*-toluenesulfonates and *para*-nitrobenzenesulfonates of spiropyrazolinium compounds.

To the contrary, *para*-toluenesulfochlorination and *para*-nitrobenzenesulfochlorination of β-aminopropioamidoxime **5** lead to the formation of products via the substitution of the oxygen atom of the amidoxime group of **10b** and **15b**. As can be seen from Table 1, the formation of spiropyrazolinium products **10a** and **15a** is impossible under such conditions, since the calculated ΔG value is positive for the corresponding reactions. For the products of *para*-toluenesulfochlorination of β-aminopropioamidoximes, the above results are confirmed by ^{1}H and ^{13}C NMR spectroscopy data [6].

The calculated data allow one to predict that *para*-nitrobenzenesulfochlorination of β-aminopropioamidoximes **1**–**5** will lead to the formation of products similar to **6a**–**9a** and **10b** (Scheme 2).



Scheme 2. Structure of stereoisomers of spiropyrazolinium compounds with equatorial and axial positions of nitrogen (N2) of the pyrazolinium heterocycle on the example of compound **6a**

According to the calculations, the axial stereoisomer (ΔG = –144.29 kJ/mol) is more preferable than the equatorial one (ΔG = –124.23 kJ/mol). This conclusion may be useful when considering the possibility of formation of stereoisomers of compounds **6a**–**9a** and when analyzing their NMR spectra [1].

Table 1

Δ*G* Values of Reactions Yielding Products 6a–15a and 6b–15b (kJ/mol) Calculated by DFT at the B3LYP/6-31G++(d,p) Level of Theory in the Gas Phase and Taking into Account the Effect of Solvent (chloroform)

No.	In the gas phase				In chloroform			
	6a–15a		**6b–15b**		**6a–15a**		**6b–15b**	
	ΔG, u	ΔG, kJ/mol	ΔG, u	ΔG, kJ/mol	ΔG, u	ΔG, kJ/mol	ΔG, u	ΔG, kJ/mol
1	2	3	4	5	6	7	8	9
6	–0.0394	–103.32	–0.0147	–38.47	–0.0550	–144.29	–0.0099	–25.92
7	–0.0369	–96.75	–0.0150	–39.25	–0.0495	–129.96	–0.0100	–26.21
8	–0.0344	–90.41	–0.0121	–31.67	–0.0468	–122.80	–0.0078	–20.52
9	–0.0351	–92.07	–0.0149	–39.08	–0.0457	–119.99	–0.0093	–24.52
10	0.0228	59.80	–0.0054	–14.06	0.0175	45.87	–0.0027	–7.12
11	–0.0501	–131.42	–0.0199	–52.15	–0.0623	–163.57	–0.0141	–37.01

1	2	3	4	5	6	7	8	9
12	–0.0477	–125.31	–0.0094	–51.63	–0.0610	–160.02	–0.0137	–35.95
13	–0.0457	–119.86	–0.0176	–46.09	–0.0532	–139.70	–0.0119	–31.32
14	–0.0457	–119.96	–0.0185	–48.44	–0.0562	–147.61	–0.0131	–34.30
15	0.0121	31.76	–0.0102	–26.90	0.0076	20.02	–0.0061	–15.89

We calculated the energies of frontier orbitals and the HOMO–LUMO gap for the studied molecules **6a**–**15a** and **6b**–**15b**. The reactivity and stability of molecules are often estimated using the frontier molecular orbital theory by Fukui [16, 17]. The HOMO energy is related to the molecule's ability to donate an electron and to the ionization potential (according to Koopmans' theorem, the ionization potential $IP = -E$(HOMO), while the LUMO energy is related to the ability to accept an electron. The HOMO–LUMO gap characterizes the molecule's region of thermodynamic stability [18]. The calculated LUMO and HOMO energies as well as the energy gap [E(LUMO) –E(HOMO), eV] are listed in Table 2.

Table 2

E(HOMO) and E(LUMO) Values Calculated for 6a–15a and 6b–15b by the DFT B3LYP/6-31++G(d,p) (eV) Method in the Gas Phase and Taking into Account the Effect of Solvent (chloroform)

No.	E(HOMO), eV	E(LUMO), eV	ΔE, eV	No.	E(HOMO), eV	E(LUMO), eV	ΔE, eV
1	2	3	4	5	6	7	8
In the gas phase							
6a	–5.59	–0.06	5.53	**6b**	–6.03	–0.90	5.13
7a	–5.71	–0.24	5.47	**7b**	–6.14	–0.96	5.18
8a	–5.73	–0.31	5.42	**8b**	–6.16	–0.97	5.19
9a	–5.67	–0.40	5.27	**9b**	–5.59	–0.94	4.65
10a	–5.84	–2.32	3.52	**10b**	–6.18	–1.09	5.09
11a	–6.08	–2.03	4.05	**11b**	–6.38	–2.87	3.51

1	2	3	4	5	6	7	8
12a	–6.19	–2.09	4.10	**12b**	–7.58	–2.37	5.21
13a	–6.22	–2.10	4.11	**13b**	–6.43	–2.92	3.51
4	–6.00	–2.07	3.94	**14b**	–5.69	–2.89	2.80
15a	–6.29	–2.55	3.74	**15b**	–6.20	–3.01	3.19
In chloroform							
6a	–6.58	–0.58	6.00	**6b**	–6.40	–1.48	4.92
7a	–6.60	–0.60	6.00	**7b**	–6.55	–1.50	5.05
8a	–6.60	–0.62	5.98	**8b**	–6.36	–1.50	4.86
9a	–5.93	–0.69	5.24	**9b**	–5.73	–1.50	4.23
10a	–6.59	–2.35	4.24	**10b**	–6.44	–1.52	4.92
11a	–6.96	–3.01	3.95	**11b**	–6.48	–3.03	3.45
12a	–7.02	–3.03	3.99	**12b**	–6.67	–3.47	3.20
13a	–6.74	–3.01	3.73	**13b**	–6.40	–3.46	2.94
14a	–5.96	–3.02	2.94	**14b**	–5.75	–3.45	2.30
15a	–7.01	–3.03	3.98	**15b**	–6.47	–3.46	3.01

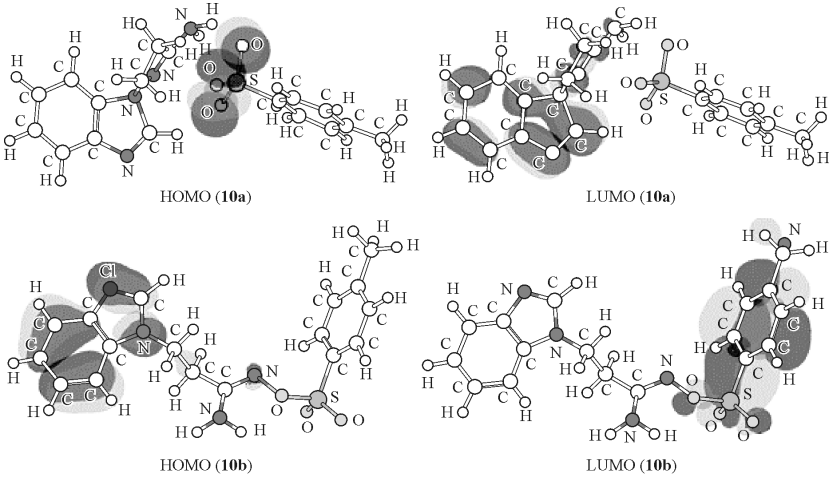


Figure 1. HOMO and LUMO orbitals of compounds **10a** and **10b** calculated by the B3LYP/6-311++G(*d*,*p*) method (the isosurface value is 0.02)

All the calculated structures have negative LUMO values and are therefore nucleophiles [19].

Small HOMO–LUMO gap of compounds **14a** and **14b** indicates that these compounds have a higher reactivity and a lower thermodynamic stability than their analogs.

The comparison of HOMO and LUMO energies of compounds **10a** and **10b** (4.24 eV and 4.92 eV, respectively) shows that structure **10b** is more stable than the hypothesized structure **10a**. At the same time, the situation is opposite for compounds **15a** and **15b** (3.98 eV and 3.01 eV, respectively). The same picture is obtained by the calculations in the gas phase. Figure 1 shows the HOMO and LUMO energies calculated for compounds **10a** and **10b** in the gas phase. The orbitals were visualized using the ChemCraft program [20].

The HOMO–LUMO analysis indicates that **6a**, **7a,** and **8a** are the most stable compounds. Figure 2 shows an example of HOMO of compound **8a** with the corresponding hydrogen bond (the length of the bond is 0.18 nm in chloroform and 0.19 nm in the gas phase).

As can be seen from the visualized HOMOs of the salts of spiropyrazolinium compounds **6a**–**9a** and **11a**–**14a**, the oxygen atoms of the sulfo group have lone electron pairs facilitating the formation of hydrogen bonds between the cation and the anion in these compounds.

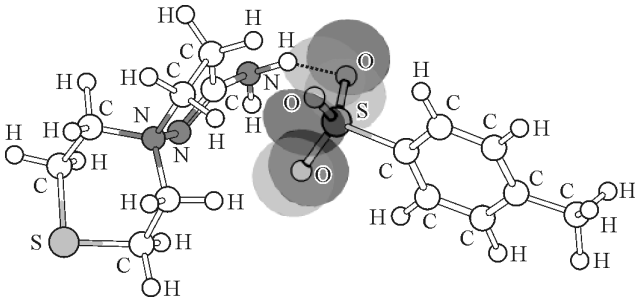


Figure 2. HOMO orbital of compound **8a** calculated by the B3LYP/6-311++G(*d*,*p*) method (the isosurface value is 0.02)

7.3. Conclusions

Theoretical calculations of thermodynamic parameters by the DFT method at the B3LYP/6-31G(*d*,*p*) level of theory showed that spiropyrazolinium structures **6a**–**9a** and **11a**–**14a** are most preferable products of *para*-toluenesulfochlorination and *para*-nitrobenzenesulfochlorination of β-aminopropioamidoximes **1**–**4**. In the case of **5**, *O*-substituted products **10b** and **15b** are most preferable. The calculations agree with the experimental data reported in [6]. The possibility for the formation of stereoisomers of spiropyrazolinium compounds was analyzed on the example of **6a**. The frontier orbital energies were calculated for all the studied compounds, whose negative LUMO values testify their nucleophilic nature.

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Conflict of interests: The authors declare that they have no conflict of interests.

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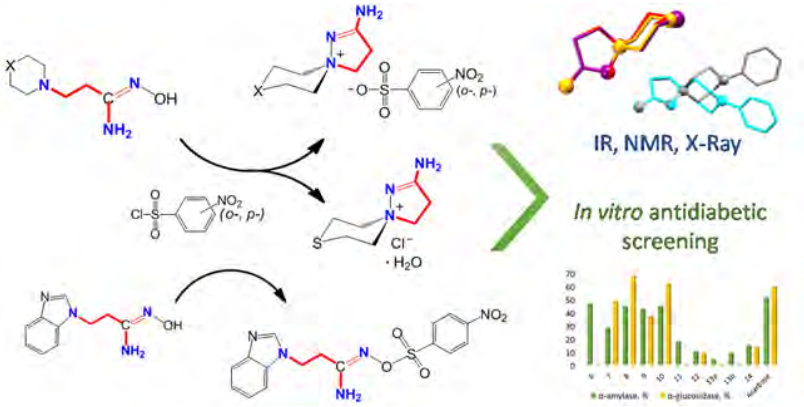
Chapter 8

REACTION PRODUCTS OF β-AMINOPROPIOAMIDOXIMES NITROBENZENESULFOCHLORINATION: LINEAR AND REARRANGED TO SPIROPYRAZOLINIUM SALTS WITH ANTIDIABETIC ACTIVITY



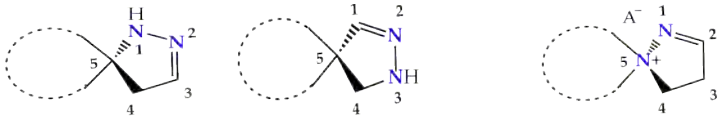
Graphical abstract

8.1. Introduction

Heterocycles with potential bioactive properties are of great interest, first of all, for medical chemists working in the field of

heterocyclic compounds synthesis. Among the new drugs approved by the FDA in 2021, almost 50% are substances with nitrogen-containing heterocycles [1]. Pyrazoline derivatives, as prominent representatives of nitrogen-containing heterocycles, became the subject of a report on the world market of diphenylpyrazolines from Market Strides (Global aggregator and publisher of Market intelligence research reports). The main segments of the diphenylpyrazoline market are divided into pharmaceutical and industrial and cover: textiles, detergents, paper production, cosmetics, plastics, ceramics, medicines [2].

Spiropyrazolines, also termed as spirocyclic hydrazine moiety, are rigid asymmetric heterocyclic structures with centers of chirality or chirality axis: C-5 carbon atoms in the most studied 1,2-diazospiro- and 2,3-diazospiropyrazolines or the ammonium nitrogen atom N(+)-5 in 1,5-diazospiropyrazolinium systems (Figure 1). Thus, these compounds exhibit great synthetic potential due to enantiomeric advantage, regioisomeric composition, reactivity, tautomeric transformations. Basically, 1,2- and 2,3-spiro-1-pyrazolines exist as spiro-2-pyrazolines (Δ2 isomers) [3]; although in solutions they exhibit an equilibrium of the imine and enamine forms [4]. As we know, spiropyrazolinium salts with 1,5-diazaspiro-1-en-5-ium fragment obtained by us by hydrolysis of 3-(β-heteroamino)ethyl-5-aryl-1,2,4-oxadiazoles and by arylsulfochlorination of β-aminopropioamidoximes, under standard conditions exists as the Δ2 isomer [5–8]. The thermodynamic advantage of possible tautomers of the key pyrazoline moiety has been estimated. It turned out that in the case of pyrazolines, the Δ2 isomer is much more stable than the others [9].



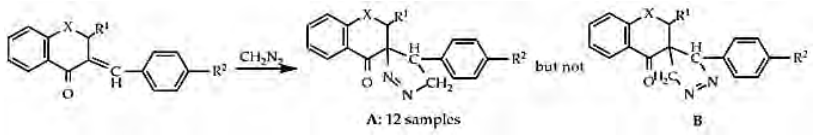
1,2-diazaspiro-2-ene 2,3-diazaspiro-1-ene 1,5-diazaspiro-1-en-5-ammonium

Figure 1. Structural isomers of spiropyrazolines

On functionalized spiropyrazolines has been published there are two comprehensive reviews in 2013 and 2019 [10, 11].

Most common methods for the construction of the 1,2- and 2,3-spiro-1-pyrazolines involves the formation of a new ring on an existing carbo- or heterocycle, having exocyclic C=C double bonds [12]. The essential steps in the formation of spiropyrazoline systems in these cases are 1,3-cycloaddition reactions of nitrogen-containing molecules (diazoalkanes [13, 14], nitrilimines [15–17]) to double bonds or condensation reaction of substituted chalcones with hydrazine or its derivatives in an acidic or alkaline medium [18, 19].

There is information about regioselective and regiospecific syntheses of spiropyrazolines. The synthesis of only one stereoisomer of spiro-1-pyrazolines **A** – Δ2 1,2-diazospiropyrazolines obtained by 1,3-dipolar cycloaddition of diazomethane to 3-arylideneflavanones/chromanones proceeds regioselectively in one step (Scheme 1). Alternative structures **B** were rejected based on ^{1}H NMR and XRD data as well as DFT calculations [20, 21].

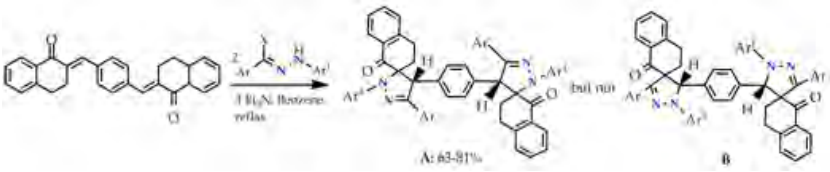


X	CH_2	S	S	S	O	O	O	O	O	O	O	O
R^1	H	H	H	H	H	H	H	H	Ph	Ph	Ph	Ph
R^2	H	H	*iso*-Pr	NO_2	H	*iso*-Pr	OMe	Br	H	*iso*-Pr	OMe	NO_2

Scheme 1. 1,3-Dipolar cycloaddition of diazomethane to 3-arylideneflavanones

Symmetrical spiropyrazoline systems are formed by 1,3-dipolar cycloaddition reaction of (2E,2'E)-2,2'-(1,4-phenylene bis(methanylylidene)) bis(3,4-dihydronaphthalen-1(2*H*)-one) with a hydrazinoyl halides (nitrile imines). The reaction proceeds regioselectively and only one of two possible spiropyrazoline regioisomers (1,2-diazaspiropyrazoline but not 2,3-diazaspiropyrazoline)is formed. The best explanation for the regioselectivity of the reaction and the

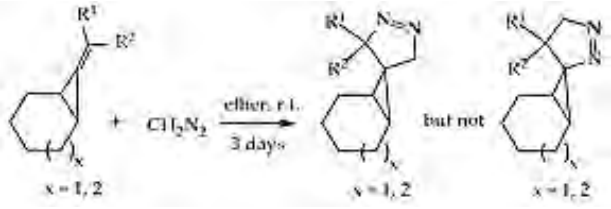
impossibility of the formation of the 2,3-diazospiropyrazolines adduct is made using the molecular orbital theory in the interaction of HOMO and LUMO reagents (Scheme 2) [22].



Ar^1 = Ph, PhCl, PhCH=CH, thiophene, furan; Ar^2 = Ph, $PhNO_2$; X = Cl, Br

Scheme 2. Cycloaddition of bis-exocyclic olefins with nitrile imines

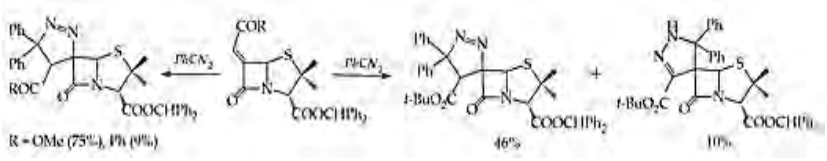
1,3-Dipolar cycloaddition of diazomethane to a double bond activated by an electron-withdrawing group in alkylidenecyclopropanes gives 2,3-diazaspiropyrazolines in excellent amounts (95–99%). Determination of the stereochemistry of spiropyrazolines was carried out by NMR spectroscopy including NOE experiments, which indicated that the methylene protons of 2,3-diazaspiropyrazoline ring have NOE effects with cyclopropane protons, and it is possible when methylene group is in exo-position (Scheme 3) [23].



x	1	1	1	1	2	2	2	2
R^1	H	H	Me	$CH_2CH=CH_2$	H	H	Me	$CH_2CH=CH_2$
R^2	COOMe	COOEt	COOMe	COOMe	COOMe	COOEt	COOMe	COOMe

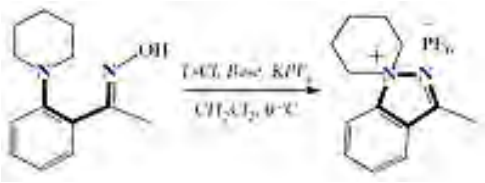
Scheme 3. Formation of 2,3-diazaspiro-2-ene isomers in the course of regiospecific addition of diazomethane to alkylidenecyclopropanes

At 1,3-dipolar addition of diphenyldiazomethane to 6-alkylidenepenicillanates examples of regioselective and regiospecific syntheses with the formation of 1,2- and 2,3-spiropyrazoline systems are observed. Regio- and stereospecificity is observed in the interaction of diphenyldiazomethane with penicylates having Ph and COMe alkylidene substituents R to form 1,2-spiropyrazolines: (4'S, 6S)-3-benzhydryl 4'-methoxycarbonyl- and (4'S,6S)-3-benzhydryl 4'-benzoyl-5',5'-diphenyl-4',5'-dihydrospiro [penicillanate-6,3'-(3*H*-pyrazole)]-3-carboxylates up to 75%. The change of the alkylidene substituent to CO_2t-Bu leads to a stereoselective but regioisomeric mixture of 1,2- and 2,3-spiropyrazolines: (4'S,6S)-3-benzhydryl 4'-tert-butoxycarbonyl-5',5'-diphenyl-4',5'-dihydrospiro[penicillanate-6,3'-(3*H*-pyrazole)]-3-carboxylate and (6R)-3-benzhydryl 3'-acetyl-1',5'-dihydrospiro[penicillanate-6,4 '-(4*H*-pyrazole)]-3-carboxylate in a ratio of 46 and 10% (Scheme 4) [24].



Scheme 4. 1,3-Dipolar addition of diphenyldiazomethane to 6-alkylidenepenicillanates (reaction conditions: DCM, 30°C, 24 h)

Except our own studies no examples of 1,5-diazaspiro-1-en-5-ium spiropyrazolinium salts could be found in literature. However, stable indazole derivatives – 1,1-disubstituted indazolium hexafluorophosphates, having a nitrogen atom at the head of the bridge have been obtained utilizing tosylation reaction. This transformation is similar to that seen in our previous studies and includes intramolecular neighboring group participation, finally leading to strong bonding, which follows the S_N2 reaction mechanism (Scheme 5) [25].



Scheme 5. Obtaining of stable 1,1-disubstituted Indazolium hexafluorophosphates

Previously we obtained new spiropyrazolium compounds by the hydrolysis of 3-(β-heteroamino)ethyl-5-aryl-1,2,4-oxadiazoles [5, 6], by arylsulfochlorination (Aryl: *para*-$XC_6H_4SO_2Cl$; X=CH_3O, CH_3, H, Br, Cl, NO_2) of β-(morpholin-1-yl)aminopropioamidoxime [7] and by tosylation of β-aminopropioamidoximes (β-amino group: piperidin-1-yl, morpholin-1-yl, thiomorpholin-1-yl, 4-phenylpiperazin-1-yl, benzimidazol-1-yl) at r.t. [8]. Here we were interested in the regioselectivity of β-aminopropioamidoximes *ortho*-, *para*-nitrobenzenesulphochlorination at reaction conditions [chloroform ($CHCl_3$), diisopropylamine (DIPEA), room temperature and 70 °C]. Depending on the reactants structure and reaction temperature 2-amino-1,5-diazathiospiro[4.5]-dec-1-ene-5-ammonium nitrobenzenesulfonates and chloride and the product of *para*-nitrobenzenesulfochlorination on the oxygen atom of β-(benzimidazol-1-yl)propioamidoxime were obtained; among them samples with high *in vitro* antidiabetic activity were found. The significance of the work is establishing the ambiguity of amidoximes sulfochlorination and the possibility of obtaining a wide range of potentially biologically active products.

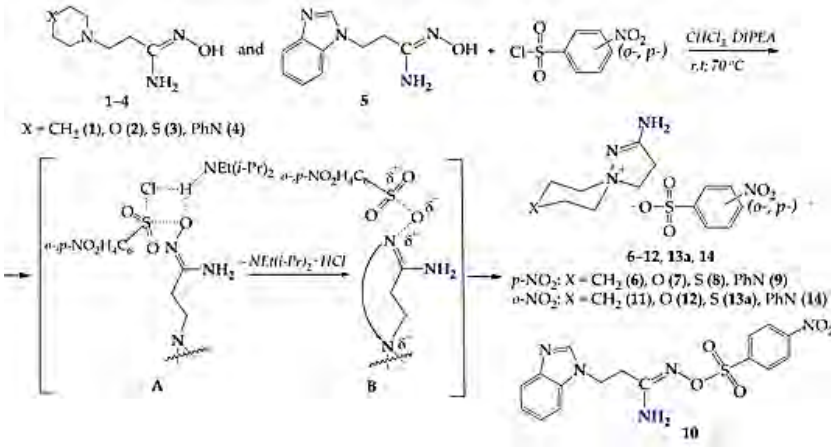
8.2. Results and Discussion

8.2.1. Synthesis and Spectra

The interaction of β-aminopropioamidoximes (**1**–**5**) with *ortho*-, *para*-nitrobenzenesulfochlorides in $CHCl_3$ was carried out at room temperature and heating the reaction mixture to the solvent boiling point. A change in the electronic properties of the sulfochlorinating

agent – the transition from tosyl chloride to *ortho*-, *para*-nitrobenzenesulfochlores leads to an increase in the reaction time at room temperature from 15 – 20 h in the case of tosylation [4] to 38 – 120 h for *para*-benzenesulfochlorination and up to 25–104 h for *ortho*-benzenesulfochlorination.

Heating the reaction mixture at the $CHCl_3$ boiling point reduces the reaction time to 19 – 36 h and to 24 h for *para*- and *ortho*-nitrobenzenesulfochlorination, respectively. Completion of β-aminopropioamidoximes arylsulfochlorination is confirmed by physicochemical data (TLC, elemental analysis, m.p.) and IR and NMR (^{1}H and ^{13}C) spectra and X-ray data of isolated products (**6**–**14**). On the basis of physicochemical and spectral data, it was concluded that in the case of nitrobenzenesulfochlorination of β-aminopropioamidoximes with six-membered heterocycles in the β-position (**1**–**4**), the main products are nitrobenzenesulfonates of spiropyrazoline compounds **6**–**12**, **13a**, and **14**; but when the substrate was beta-(benzimidazol-1-yl)propioamidoxime (**5**), only the product of *para*-nitrobenzensulfochlorination at the oxygen atom of the amidoxime fragment **10** was isolated from the reaction mixture (Scheme 6).



Scheme 6. Nitrobenzenesulfochlorination of β-aminopropioamidoximes

It is assumed that in the case of nitrobenzenesulfochlorination of β-aminopropioamidoximes **1**–**4** O-nitrobenzenesulphonates of β-propioamidoximes formed as intermediates **B**, due to thermodynamic advantage, rearrange into of spiropyrazoline nitrobenzenesulphonates (**6**–**12**, **13a**, **14**). Only in case of benzimidazole derivative intermediate **B** remains stable and gives O-*para*-nitrobenzenesulphonate **10**.

In addition, *ortho*-nitrobenzenesulfochlorination of β-(thiomorpholine-1-yl)propioamidoxime (**3**) has the following features: at room temperature a mixture of 2-aminospiropyrazolylammonium *ortho*-nitrobenzenesulfonate and chloride (**13a** and **13b**) were obtained; carrying out the reaction at 70 °C gives only chloride **13b**. Compound **13b** was characterized by us previously [26, 27].

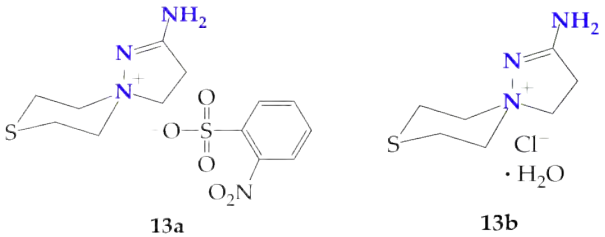


Figure 2. Salts of spiropyrazolinium compounds **13a** and **13b** isolated at the *ortho*-nitrobenzenesufochlorination of β-(thiomorpholin-1-yl)propioamidoxime

Apparently, in this case, the *ortho*-nitrophenylsulfonate anion in the primarily formed 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium *ortho*-nitrophenylsulfonate (**13a**) was exchanged for the chloride anion from DIPEA hydrochloride, releasing *ortho*-nitrobenzenesulfonic acid and DIPEA.

The stoichiometry of the reaction does not provide for the formation of a hydrate. We believe that the preparation of hydrate **13b** can be explained by the prolonged contact of the mother liquor during the preparation of single crystals of the product of *ortho*-nitrophenylsulfochlorination of amidoxime **3** with atmospheric moisture.

When establishing the structure of nitrobenzenesulfochlorination products a difference was noted in the values of the mobility index R_f for the products of nitrobenzenesulfochlorination of amidoximes with six-membered nitrogenous heterocycles in the β-position (**6**–**9**, **11**–**14**) and for the *para*-nitrobenzenesulfoderivative of β-(benzimidazol-1-yl)propioamidoxime (**10**) (R_f 0.01–0.12 and 0.75).

Table 1

Physicochemical data on the products of nitrobenzenesulfochlorination of β-aminopropioamidoximes (6–14)

Compd	Yield,%		Time, h		M.p., ˚C	R_f	Compd	Yield,%		Time, h		M.p., ˚C	R_f
	r.t.	70 ˚C	r.t.	70 ˚C				r.t.	70 ˚C	r.t.	70 ˚C		
6	77	46	38	27	151	0.12	**11**	77	75	35	29	153	0.05
7 [7]	70	74	120	24	187–188	0.10	**12**	93	64	25	24	148	0.01
8	68	47	84	21	230	0.10	**13a**	25	-	104	24	138–140	0.08
9	70	69	60	19	203	0.15	**13b** [26, 27]	25	56	104	24	>280	0.08
10	82	36	80	36	158	0.75	**14**	79	81	34	24	185–187	0.08

In the IR spectra of compounds **6**–**12**, **13a**, **14** there are two pairs of bands related to characteristic stretching vibrations of strong intensity of the NO_2 and SO_2 groups at 1515–1549 (as) cm^{-1} and 1349–1377 (sy) cm^{-1} and 1207–1240 (as) cm^{-1} and 1024–1197 (sy) cm^{-1}, respectively. Whereas in the IR spectrum of compound **13b** there are no bands of stretching vibrations of the bonds of NO_2 and SO_2 groups.

It is interesting that in the ^{1}H-NMR spectra of compounds **6–9**, **13a**, **13b** it was possible to fix the diastereotopic nature of the geminal protons of the methylene groups located at the ammonium nitrogen atom, which give pairs of multiplet signals with an intensity of two protons at δ: 3.35m, 3.44m (**6**); 3.41m, 3.65m (**7**); 3.60m, 3.72m (**8**); 3.49m, 3.98m (**9**); 3.10m, 3.68m (**13a**); 3.10m, 3.68m (**13b**).

Similarly, the geminal protons of the methylene groups at the S, O, S, S, N atoms of the β-heterocycles of compounds **8**, **12**, **13a**, **13b**, **14** also appear as pairs of proton signals with an intensity of two protons at δ: 2.87m, 3.15m (**8**); 3.35m, 3.60m (**12**); 2.84m, 3.55m (**13a**); 2.85m, 3.55m (**13b**); 3.40m, 3.71m (**14**). Obviously, the effect of slow rotation of β-heterocycles with the possibility of fixing equatorial and axial protons is observed here. In addition, the diastereotopicity of these protons may be associated with the presence of an asymmetry axis inherent in spiro compounds.

The signals of Csp^3 and Csp^2 carbon atoms in the ^{13}C-NMR spectra of compounds **6**–**14** are present in the characteristic regions.

We obtained quantum-chemical confirmation of the advantageousness of the formation of spirocyclic tosylation and *para*-nitrobenzenesulfochlorination products of β-aminopropioamidoximes (**1**-**4**) with negative values of the Gibbs energy of the chemical reaction in the range of -119.99 – -163.57 kJ/mol and the disadvantage of the formation of a spirostructure for β-(benzimidazol-1-yl)propioamidoxime (**5**) with positive values of the Gibbs energy for tosylation and *para*-nitrobenzenesulfochlorination products as 45.87 and 20.02 kJ/mol, respectively [28].

The thermodynamic advantage of the formation of 2-aminospiropyrazolylammonium sulfonates (tosylates, *para*- and *ortho*-nitrobenzenesulfonates) for a number of β-aminopropioamidoximes (**1**, **2**, **4**) in comparison with the formation of chloride hydrates was identified, except for the case when the initial substrate is β-(thiomorpholine-1-yl)propioamidoxime **3**; in this case, 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ammonium chloride monohydrate (**13b**) is preferred by -8.1, -6.18, -3.08kJ/mol, respectively [29].

It should be noted that we have several tries reacting of β-(benzimidazol-1-yl)propioamidoxime (**5**) with *ortho*-nitrobenzenesulfonate under the described conditions ($CHCl_3$, DIPEA, r.t. and 70°C), but each time a resinous reaction mixture was obtained.

8.2.2. The In vitro antidiabetic screening of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ammonium nitrobenzenesulphonates and chloride hydrate (6–9, 11–14) and 3-(1H-benzo[d]imidazol-1-yl)-N'-{[(4-nitrophenyl)sulfonyl]oxy}propanimidamide (10)

The α-amylase and α-glucosidase inhibition tests, which hydrolyze starch in postprandial hyperglycemia, are standard tests in the discovery and development of new antidiabetic drugs. Essentially, the regulation of α-amylase and α-glucosidase biological functions (inhibition) is critical to the treatment regimen. This implies that new drug candidates with potent inhibition of the α-glucosidase and α-amylase would be valuable to drug discovery and development for diabetes mellitus [30].

The in vitro antidiabetic activity of spiropyrazolilammonium *ortho*-, *para*-nitrobenzenesulfonates and chloride **6–9**, **11–14** and the product of O-*para*-nitrobenzenesulfochlorination of β-(benzimidazol-1-yl)propioamidoxime (**10**) was assessed by the degree of inhibition of the activity of α-amylase and α-glucosidase by the studied substances compared with the standard drug acarbose (Table 2). The table shows four series of experiments with different experimental values of the in vitro activity of acarbose in relation to α-amylase and α-glucosidase.

Table 2

***In vitro* α-amylase and α-glucosidase activity of nitrobenzenesulfochlorination products of β-aminopropioamidoximes (6–14)**

Compd	**6**	**7**	**8**	**9**	**10**	**Acarbose**
α-Amylase activity, %	46.0±2.8	27.7±1.9	43.9±2.1	42.0±2.3	44.1±2.9	50.3±1.1
α-Glucosidase activity, %	“0”	48.1±22.2	67.1±3.8	36.5±13.2	61.0 ±1.5	58.9±1.8
Compd	**11**	**12**	**13a**	**13b**	**14**	**Acarbose**
α-Amylase activity, %	17.2±1.2	9.6±2.2	3.4±1.1	8.4±0.8	14.3±4.1	34.6±0.4
α-Glucosidase activity, %	“0”	8.7±2.2	“0”	“0”	13.0±2.0	60.7±0.7

All tested compounds have an average inhibitory activity against α-amylase, the values of which are less than the activity of acarbose. Regarding α-glucosidase, the products of *para*-nitrobenzenesulfochlorination **8** and **10** have a pronounced inhibitory activity (61.0% and 67.1%). In the same series of experiments, the average inhibitory activity of 36.5% and 48.1% is shown by the compounds **7** and **9**. The reference drug acarbose exhibited standard inhibitory activity of 58.9% and 50.3% in terms of α-glucosidase and α-amylase, respectively. In two other series of experiments, the tested *ortho*-nitro derivatives (**11–14**) did not show activity against α-amylase and α-glucosidase, comparable to the activity of acarbose.

The apparent difference in the antidiabetic activity of the subgroups of compounds **6**–**10** and **11**–**14** can be explained by the difference in their chemical structure. The first subgroup are derivatives of *para*-nitrophenylsulfonic acid; the second subgroup is *ortho*-nitrophenylsulfonic acid derivatives. It is likely that binding to the sites of α-amylase and α-glucosidase enzymes responsible for increasing blood sugar is more efficient for *para*-nitrobenzenesulfonic acid derivatives (**6–10**), while for *ortho*-nitrophenylsulfonic acid derivatives (**10**–**14**) are less efficient than for the target reference antidiabetic drug acarbose.

The absence of α-glucosidase activity in representatives of the subgroup of compounds **11**–**14** may be associated with the above trend of a general decrease in antidiabetic activity in the series of *ortho*-nitrophenylsulfonic acid derivatives (**10**–**14**). Whereas the absence of α-glucosidase activity for compound **6** may be a random variable.

8.2.3. X-ray diffraction

X-ray diffraction studies of all reaction products were carried out. It confirmed that regardless synthetic conditions nitrobenzenesulfochlorination of β-aminopropioamidoximes containing piperidin-1-yl, morpholine-1-yl and 4-phenylpiperazin-1-yl as β-aminogroup affords spiropyrazolium nitrobenzenesulfonates **6**, **7**, **9** or **11**, **12**, **14**. By *ortho*-nitrobenzenesulfochlorination of β-(thiomorpholin-1-yl)pro-

pioamidoxime nitrophenylsolfonate **13a** and chloride monohydrate **13b** of corresponding spirocation similar with previously reported one [29] can be obtained depending on reaction conditions. No rearrangement was detected for benzimidazol-1-yl-containing product **10** in accord with B3LYP/6-31++G(d,p) calculations of standard Gibbs free energies of reaction [28, 29] found for N-substituted aminopyrazoles [31, 32]. All salts contain one cation and one anion in the asymmetric unit (Figure S1, ES1). Quality of XRD data allowed to locate all hydrogen atoms on difference Fourier maps and undoubtedly confirmed that none of sulfonate groups contains any hydrogen atoms.

Molecular structures of these compounds are depicted on Figure S1 (ES1) and the main geometry parameters of cations and anions are listed in Table 3.

Table 3

Selected geometrical parameters of spirocations 6–9, 11–14 (Å and º)

	6	**7** [7]	**8**	**9**	**11**	**12**	**13a**	**14**
N1–N2	1.470(2)	1.466(2)	1.468(2)	1.468(4)	1.469(1)	1.473(2)	1.460(5)	1.468(1)
N1–C1	1.526(2)	1.514(3)	1.526(2)	1.530(4)	1.513(1)	1.520(2)	1.493(7)	1.518(1)
C1–C2	1.485(3)	1.495(3)	1.497(3)	1.518(4)	1.517(2)	1.513(2)	1.526(9)	1.526(2)
N2=C	1.298(2)	1.299(2)	1.300(2)	1.316(3)	1.311(1)	1.305(2)	1.289(6)	1.300(2)
X–C_{Ar}	1.492(4)–1.529(4)	1.401(3)–1.406(3)	1.791(3)–1.796(3)	1.464(4)–1.467(4)	1.519(1)–1.522(1)	1.434(2)–1.439(2)	1.794(5)–1.799(5)	1.466(1)–1.473(2)
d(C...Pz)[1]	0.302(4)	0.418(4)	0.267(3)	0.425(5)	0.457(1)	0.445(2)	0.450(7)	0.435(2)
C_{Ph}–NO_2	1.472(2)	1.470(2)	1.477(2)	1.474(4)	1.472(1)	1.474(2)	1.454(6)	1.474(2)
C_{Ar}-X-C_{Ar}	112.1(2)	109.7(2)	98.2(1)	111.0(2)	109.83(9)	110.21(9)	95.5(2)	108.43(9)
Ω^2	8.9(1)	6.6(1)	4.9(1)	6.8(1)	112.63(4)	109.74(5)	113.20(2)	125.73(5)

[1]The deviation of the C(1) atom from the mean plane formed by N–N=C–C atoms in the 5-membered pyrazole ring.[2] The twist angle between meanplanes of phenyl ring and NO_2 group for the anion.

The X–CH_2 bond distances increase and CH_2–X–CH_2 angles decrease passing from O to NPh, CH_2 and S. Valence angles at

positively charged N1 atom are close to ideal 109.5° values, however only N–CH_2 bond distances within the six-membered ring are typical for a single N–C bond. In **10** similar N1–CH_2 bond is equal to 1.458(2) Å due to mesomeric effect of benzimidasole substituent. The N–N bond in these salts vary from 1.460(2) to 1.470(2) Å that is longer than 1.42–1.43 Å found for N-substituted aminopyrazoles [32, 33]. Overall conformations of the cations in **7**, **9**, **11**,**13a** and **13b** correspond to one conformation on the six-membered ring towards the five-membered ring, while **6**, **8**, **12** and **14** are the first example of the inverted chair conformation (Figure 3) of this ring confirmed by means of X-ray diffraction.

The difference in two conformations manifests itself in ^{1}H NMR spectra (see above), and also through the N1–C1 bond length which is generally shorterin cations with 'novel' conformation. In our opinion, overall conformation of molecule and elongation of bond distances in the pyrazole ring can be attributed to the anomeric effect [33] of (hetero)atom in the six-membered ring. Length of the N2=C bond in all spirocations is nearly the same as the N2=C bond distance of 1.302(2) in **10**.

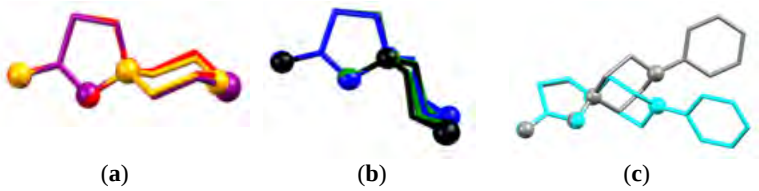


Figure 3. Molecular conformations of the spirocation in (a) **7** (orange), **11** (red), **13a** (violet),(b) **6** (green), **12** (blue), **14** (black), and (c) **9** (grey), **14** (cyan). Superimposed atoms are N–N=C–C atoms in the 5-membered pyrazole ring

A prominent variation in biological properties of these compounds can be accounted for the possibility of these cations to realize different conformations and to take part in different types of H-bonds [34]. In these solids, the only donor for H-bonds is the amino-group, while sulfonate groups of the anions and heteroatoms of the cations compete to act as acceptors of H-bonding. As result,

H-bonded chains are observed in 2-amino-1,5-diazathiospiro[4.5]-dec-1-ene-5-ammonium-containing salts, and tetramers in six other salts (Figure 4).

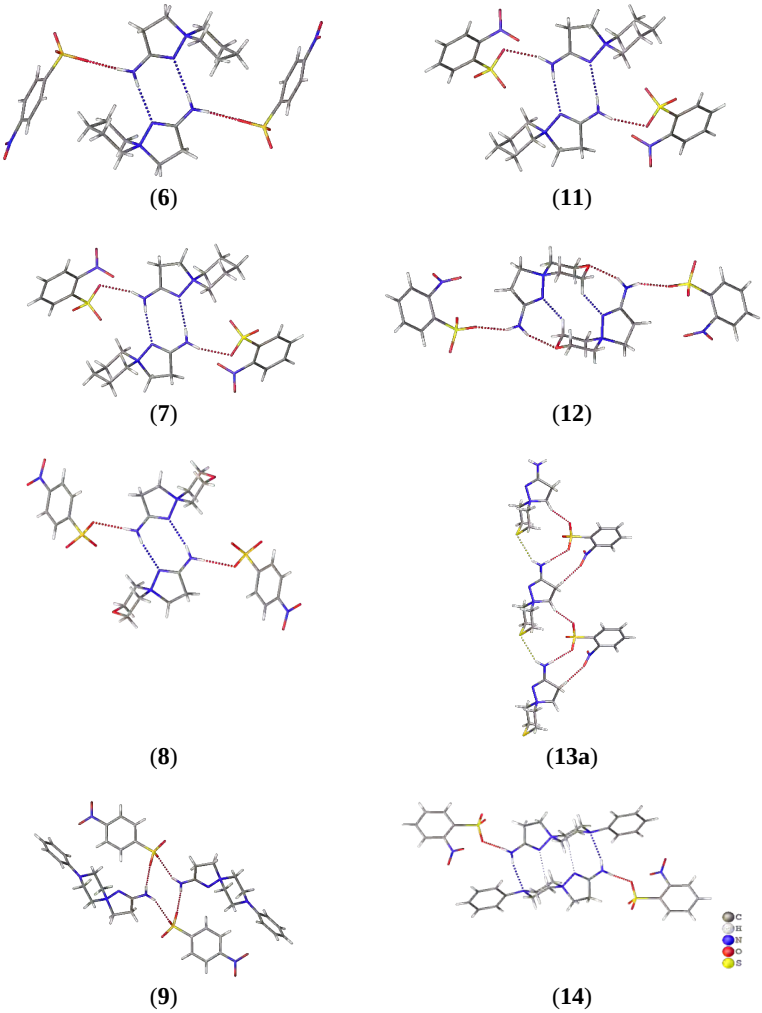


Figure 4. H-bonding patterns in crystal structures of studied compounds. H-bonds are depicted with dotted lines

The $D^3_3(9)$ tetramers in **6**, **7** and **11** are formed through two N-H…N interactions and two N-H…O ones. Similar $D^3_3(13)$ tetramers in **12** and **14** are obtained through similar N-H…O cation…anion interactions, but the cations are shifted along each other to allow bonding with a heteroatom of the six-membered ring. The $R^4_4(12)$ cycles in **9** and the H-bonded chains in **8** and **13** are formed by interactions of the amino-group with sulfonate groups of two neighboring molecules. The $\mathbf{G^a_d(n)}$ notation of H-bonded architecttures is given in terms of [33], where **G** represents the type of pattern (**C** for chain, **S** for intramolecular hydrogen bonds, **R** for ring, **D** for finite), **a** is the number of acceptors, **d** is the number of donors and **n** the number of atoms in the pattern. Note, that despite similar crystal parameters and space group of **11–13** (Table S1, ESI) these compounds can not be regarded isostructural, as these realize different packing and intermolecular (including H-bonding) interactions. Crystal packing demonstrates that for these spirocations heteroatoms of the six-membered cycle can take part in H-bonding, and different conformations can be stabilized by means of intermolecular bonding.

8.3. Materials and Methods

8.3.1. Synthesis

The reagents were purchased from different chemical suppliers and were purified before use. FT-IR spectra were obtained on a Thermo Scientific Nicolet 5700 FTIR instrument (Waltham, MA USA) in KBr pellets. ^{1}H- and ^{13}C-NMR spectra of compounds **6**–**10** were acquired on a Bruker Avance III 500 MHz NMR spectrometer (Bruker, BioSpin GMBH, Rheinstetten, Germany) and ^{1}H- and ^{13}C-NMR spectra of compounds **11–14** on a Jeol JNM-ECA 500 (Jeol, Tokyo 196-8558, JAPAN), (500 and 126 MHz, respectively).

The signals of the residual undeuterated solvents were used as a reference for ^{1}H-NMR (2.50 ppm) and ^{13}C-NMR (39.5 ppm) spectra. Elemental analysis was carried out on a CE440 elemental analyzer (Exeter Analytical, Inc., Shanghai, China). Melting points were determined in glass capillaries on a PTP(M) apparatus (Khimlabpribor, Klin, Russia). The reaction progress and purity of the obtained products were controlled using Sorbfil (Sorbpolymer, Krasnodar, Russia) TLC plates coated with CTX-1A silica gel, grain size 5–17 μm,

containing UV-254 indicator. The eluent for TLC analysis was a mixture of benzene–EtOH, 1:3. The solvents for synthesis, recrystallization, and TLC analysis (ethanol, 2-PrOH, benzene, DMF, acetone) were purified according to the standard techniques.

*8.3.1.1. A General Procedure for the Synthesis of 2-Amino-1,5-diazaspiro[4.5]-dec-1-ene-5-ammonium para-nitrobezenesulfonates **(6–9)** and 3-(1H-Benzo[d]imidazol-1-yl)-N'-{[(4-nitrobenzene)sulfonyl]oxy}propanimidamide **(10)***

*The synthesis of β-aminopropioamidoximes 4-nitrobenzenesulfochlorination products **6**–**10** (general method).* To a solution of 0.0029 mol of β-aminopropioamidoximes **1**–**5** in 20 ml of $CHCl_3$ 0.0029 mol of DIPEA was added. The reaction mixture was cooled to -1 °C, and a solution of 0.0029 mol of 4-nitrobenzenesulfochloride in 2 ml of $CHCl_3$ was added dropwise with stirring. The reaction mixture was then allowed to warm to r.t. (or heated to the boiling point of $CHCl_3$) and stirred until completion of the reaction. The progress of the reaction was monitored by TLC. The formed white precipitates of the products **6**–**10** were filtered off and recrystallized from 2-PrOH.

*2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ammonium 4-nitrobenzenesulfonate **(6)**.* The reaction mixture consisting of 0.5 g (0.0029 mol) of compound **1** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 4-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 38 h, 0.80 g (77%) white solid **6** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 27 h 0.48 g (46%) white solid **6** was obtained]; m.p. 151 °C, R_f 0.12. IR (KBr, cm^{-1}): 1665 (C=N), 1607 (C=C), 1232 (SO_2 as) and 1190 (SO_2 sy), 1529 (NO_2 as) and 1352 (NO_2 sy), 3302 [N(-H)$_2$], 2938, 2864, 2815 (C_{sp3}–H), 3032, 3257 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.10 (t, J = 7.0 Hz, 2H, α-CH_2), 3.81 (t, J = 7.0 Hz, 2H, β-CH_2), 1.55m, 1.75m, 1.87m, [6H, $(CH_2)_3$], 3.35 [m, 2H, N(+)(CH_{ax})$_2$] and 3.44 [m, 2H, N(+)(CH_{eq})$_2$], 7.23 (s, 2H, NH_2), 7.83–8.21 (m, 4H, $C_{(sp2)}$H). ^{13}C-NMR (126 MHz, DMSO-d_6): 21.0, 21.9, 31.5, 60.7, 64.3 (2C), 126.0 (2C), 128.5 (2C), 138.0 (1C), 145.3 (1C), 168.5. Anal. Calcd for $C_{14}H_{20}N_4O_5S$ (356.40): C, 47.18; H, 5.66. Found,%: C, 47.36; H, 5.37.

*2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 4-nitrobenzenesulfonate **(7)**.* The reaction mixture consisting of 0.5 g (0.0029 mol) of compound **2** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 4-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 120 h, 0.73 g (70%) white solid **7** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 24 h

0.77 g (74%) white solid **7** was obtained]; m.p. 187–188 °C, R_f 0.10. IR (KBr, cm^{-1}): 1650 (C=N), 1600 (C=C), 1231 (SO_2 as) and 1194 (SO_2 sy), 1520 (NO_2 as) and 1362 (NO_2 sy), 3466 [N(-H)$_2$], 2967, 2854 (C_{sp3}–H), 3236, 3328, 3388 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.13 (t, J = 7.0 Hz, 2H, α-CH_2), 3.92 (t, J = 7.0 Hz, 2H, β-CH_2), 3.32 [m, 4H, O(CH_2)$_2$], 3.41 [m, 2H, N(+)(CH_{ax})$_2$] and 3.65 [m, 2H, N(+)(CH_{eq})$_2$], 7.28 (s, 2H, NH_2), 7.80–8.19 (m, 4H, $C_{(sp2)}$H). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.4, 62.1, 62.4, 63.2, 123.8 (2C), 127.4 (2C), 147.7 (1C), 154.8 (1C), 170.1. Anal. Calcd for $C_{13}H_{18}N_4O_6S$ (358.37): C, 43.57; H, 5.06. Found,%: C, 43.48; H, 5.13.

*2-Amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ammonium 4-nitrobenzenesulfonate (**8**).* The reaction mixture consisting of 0.55 g (0.0029 mol) of compound **3** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 4-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 84 h, 0.74 g (68%) white solid **8** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 21 h 0.51 g (47%) white solid **8** was obtained]; m.p. 230 °C, R_f 0.10. IR (KBr, cm^{-1}): 1642 (C=N), 1588 (C=C), 1229 (SO_2 as) and 1197 (SO_2 sy), 1519 (NO_2 as) and 1349 (NO_2 sy), 3308, 3396 [N(-H)$_2$], 2944 (C_{sp3}–H), 3105, 3199, 3245 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.11 (t, J = 7.0 Hz, 2H, α-CH_2), 3.86 (t, J = 7.0 Hz, 2H, β-CH_2), 2.87 [m, 2H, S(CH_{ax})$_2$] and 3.15 [m, 2H, S(CH_{eq})$_2$], 3.60 [m, 2H, N(+)(CH_{ax})$_2$] and 3.72 [m, 2H, N(+)(CH_{eq})$_2$], 7.37 (s, 2H, NH_2), 7.83–8.20 (m, 4H, $C_{(sp2)}$H). ^{13}C-NMR (126 MHz, DMSO-d_6): 23.2, 31.4, 62.5, 64.7, 123.8 (2C), 127.3 (2C), 147.7 (1C), 154.8 (1C), 169.0. Anal. Calcd for $C_{13}H_{18}N_4O_5S_2$ (374.44): C, 41.70; H, 4.85. Found,%: C, 41.59; H, 4.33.

*2-Amino-8-phenyl-1,5,8-triazaspiro[4.5]dec-1-en-5-ammonium 4-nitrobenzenesulfonate (**9**).* The reaction mixture consisting of 0.72 g (0.0029 mol) of compound **4** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 4-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 60 h, 0.88 g (70%) white solid **9** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 19 h 0.87 g (69%) white solid **9** was obtained]; m.p. 203 °C, R_f 0.15. IR (KBr, cm^{-1}): 1649 (C=N), 1599 (C=C), 1240 (SO_2 as) and 1189 (SO_2 sy), 1515 (NO_2 as) and 1350 (NO_2 sy), 3421 [N(-H)$_2$], 2790, 2880, 2915 (C_{sp3}–H), 3118, 3290 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.17 (t, J = 7.0 Hz, 2H, α-CH_2), 3.95 (t, J = 7.0 Hz, 2H, β-CH_2), 3.56 [m, 4H, N(CH_2)$_2$], 3.49 [m, 2H, N(+)(CH_{ax})$_2$] and 3.98 [m, 2H, N(+)(CH_{eq})$_2$], 7.25 (s, 2H, NH_2), 7.81–8.53 (m, 9H, $C_{(sp2)}$H). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.5, 44.5, 61.5, 62.9, 115.3 (2C), 120.4 (1C), 123.8 (2C), 127.4 (2C), 129.5 (2C), 147.7 (1C), 149.9 (1C), 156.7 (1C), 169.0. Anal. Calcd for $C_{19}H_{23}N_5O_5S$ (433.48): C, 52.64; H, 5.35. Found,%: C, 52.35; H, 5.21.

*3-(1H-benzo[d]imidazol-1-yl)-N'-{[(4-nitrophenyl)sulfonyl]oxy}propanimidamide (**10**).* The reaction mixture consisting of 0.59 g (0.0029 mol) of compound **5** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 4-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 80 h, 0.93 g (82%) white solid **10** was obtained [when kept at $CHCl_3$ bp for 36 h 0.41 g (36%) white solid **10** was obtained]; m.p. 158 °C, R_f 0.75. IR (KBr, cm^{-1}): 1648 (C=N), 1617 (C=C), 1240 (SO_2 as) and 1187 (SO_2 sy), 1520 (NO_2 as) and 1365 (NO_2 sy), 3417 [N(-H)$_2$], 2791, 2920 (C_{sp3}–H), 3110, 3237 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 2.50 (t, J = 7.0 Hz, 2H, α-CH_2), 4.33 (t, J = 7.0 Hz, 2H, β-CH_2), 6.50 (s, 2H, NH_2), 7.78–8.44 (m, 8H, $C_{(sp2)}$H), 8.05 (s, 1H, $C_{(sp2)}$H). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.2, 42.9, 110.8 (2C), 119.8 (2C), 121.9 (1C), 122.7 (1C), 128.5 (2C), 130.0 (2C), 133.5 (2C), 134.0 (1C), 143.7 (1C), 144.3 (1C), 144.7 (1C), 160.0. Anal. Calcd for $C_{16}H_{15}N_5O_5S$ (389.39): C, 49.35; H, 3.88. Found, %: C, 49.28; H, 3.45.

*8.3.1.2 A General Procedure for the Synthesis of 2-Amino-1,5-diazaspiro[4.5]-dec-1-ene-5-ammonium 2-nitrobezenesulfonate (**11–13a, 14**) and 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**13b**)*

*The synthesis of β-aminopropioamidoximes 2-nitrobenzenesulfochlorination products **6**–**10** (general method).* To a solution of 0.0029 mol of β-aminopropioamidoximes **1**–**5** in 20 ml of $CHCl_3$ 0.0029 mol of DIPEA was added. The reaction mixture was cooled to -1 °C, and a solution of 0.0029 mol of 2-nitrobenzenesulfochloride in 2 ml of $CHCl_3$ was added dropwise with stirring. The reaction mixture was then allowed to warm to r.t. (or up to the b.p. of $CHCl_3$) and stirred until completion of the reaction. The progress of the reaction was monitored by TLC. The formed white precipitates of the products were filtered off and recrystallized from 2-PrOH.

*2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ammonium 2-nitrobenzenesulfonate (**11**).* The reaction mixture consisting of 0.5 g (0.0029 mol) of compound **1** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 2-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 35 h, 0.80 g (77%) white solid **11** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 29 h 0.78 g (75%) white solid **11** was obtained]; m.p. 153 °C, R_f 0.05. IR (KBr, cm^{-1}): 1657 (C=N), 1593 (C=C), 1221, 1232 (SO_2 as) and 1024 (SO_2 sy), 1541 (NO_2 as) and 1377 (NO_2 sy), 3399 [N(-H)$_2$], 2949 (C_{sp3}–H), 3204, 3398 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.05 (t, J = 7.95 Hz, 2H, α-CH_2), 3.77 (t, J = 7.95 Hz, 2H, β-CH_2), 1.54m, 1.71m, 1.84m, [6H, $(CH_2)_3$], 3.35 [m, 4H, N(+)$(CH_2)_2$],

7.20d, 7.46–7.81 (m, 4H, $C_{(sp2)}H$). ^{13}C-NMR (126 MHz, DMSO-d_6): 21.0, 21.9(2C), 31.6, 60.7, 64.3, 122.0, 129.5, 130.5, 131.3, 140.0, 148.3, 168.6. Anal. Calcd for $C_{14}H_{20}N_4O_5S$ (356.40): C, 47.18; H, 5.66. Found,%: C, 47.57; H, 5.33.

*2-Amino-8-oxa-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 2-nitrobenzenesulfonate (**12**).* The reaction mixture consisting of 0.5 g (0.0029 mol) of compound **2** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 2-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 25 h, 0.97 g (93%) white solid **12** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 24 h 0.67 g (64%) white solid **12** was obtained]; m.p. 148 °C, R_f 0.01. IR (KBr, cm^{-1}): 1637 (C=N), 1593 (C=C), 1207, 1228 (SO_2 as) and 1022 (SO_2 sy), 1549 (NO_2 as) and 1377 (NO_2 sy), 3387 [$N(-H)_2$], 2907 (C_{sp3}–H), 3250, 3306, 3328 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.09 (t, J = 7.95 Hz, 2H, α-CH_2), 3.88 (m, 2H, β-CH_2), 3.35 [m, 2H, $O(CH_{ax})_2$] and 3.60 [m, 2H, $O(CH_{eq})_2$], 3.88 [m, 4H, $N(+)(CH_2)_2$], 7.20 (s, 2H, NH_2), 7.45–7.81 (m, 4H, $C_{(sp2)}H$). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.5, 62.2 (2C), 63.2, 122.0, 129.5, 130.6, 131.3, 140.0, 148.3, 169.2. Anal. Calcd for $C_{13}H_{18}N_4O_6S$ (358.37): C, 43.57; H, 5.06. Found, %: C, 43.89; H, 5.47.

*2-Amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ammonium 2-nitrobenzenesulfonate (**13a**) and 2-Amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**13b**).* The reaction mixture consisting of 0.55 g (0.0029 mol) of compound **3** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 2-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 104 h white precipitate of the mixture of products **13a** and **13b** was obtained. After recrystallization 0.16 g (25%) **13b** was obtained. After evaporation of the filtrate from the recrystallization to half volume 0.27 g (25%) of 2-nitrobenzenesulfonate **13a** was formed. When the reaction mixture was kept at $CHCl_3$ bp for 24 h only 0.37 g (56%) white solid **13b** was obtained.

13a: m.p. 138–140 °C, R_f 0.08. IR (KBr, cm^{-1}): 1647 (C=N), 1604 (C=C), 1207, 1215 (SO_2 as) and 1024 (SO_2 sy), 1545 (NO_2 as) and 1373 (NO_2 sy), 3497 [$N(-H)_2$], 2936, 2964 (C_{sp3}–H), 3152, 3258, 3302 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.10 (t, J = 7.0 Hz, 2H, α-CH_2), 3.83 (t, J = 7.95 Hz, 2H, β-CH_2), 3.10 [m, 2H, $S(CH_{ax})_2$] and 3.55 [m, 2H, $S(CH_{eq})_2$], 3.10 [m, 2H, $N(+)(CH_{ax})_2$] and 3.68 [m, 2H, $N(+)(CH_{eq})_2$], 7.26 (s, 2H, NH_2), 7.47–7.81 (m, 4H, $C_{(sp2)}H$). ^{13}C-NMR (126 MHz, DMSO-d_6): 23.2, 31.5, 62.6, 64.7, 122.9, 129.5, 130.6, 131.3, 139.7, 148.3, 169.1. Anal. Calcd for $C_{13}H_{18}N_4O_5S_2$ (374.44): C, 41.70; H, 4.85. Found,%: C, 41.67; H, 4.46.

13b: m.p. >280 °C, R_f 0.08. IR (KBr, cm^{-1}): 1659 (C=N); 1612 [H–N; $(H)_2$–O]; 670 [S–C]; 3135, 3230, 3380, 3384 (H–O, H–N). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.10 (t, J = 7.0 Hz, 2H, α-CH_2), 3.85 (t, J = 7.95 Hz, 2H, β-CH_2), 2.85

[m, 2H, S(CH_{ax})$_2$] and 3.55 [m, 2H, S(CH_{eq})$_2$], 3.10 [m, 2H, N(+)(CH_{ax})$_2$] and 3.68 [m, 2H, N(+)(CH_{eq})$_2$], 7.26 (s, 2H, NH_2). ^{13}C-NMR (126 MHz, DMSO-d_6): 23.2, 31.5, 62.6, 64.7, 169.1. Anal. Calcd for $C_7H_{16}ClN_3OS$ (225.74): C, 37.24; H, 7.14. Found,%: C, 37.52; H, 7.48.

*2-Amino-8-phenyl-1,5,8-triazaspiro[4.5]dec-1-en-5-ammonium 2-nitrobenzenesulfonate (**14**).* The reaction mixture consisting of 0.72 g (0.0029 mol) of compound **4** in 20 mL of $CHCl_3$ and 0.38 g (0.0029 mol) DIPEA was cooled to -1°C. Then 0.64 g (0.0029 mol) of 2-nitrobenzenesulfochloride was added dropwise. When reaction mixture was kept at r.t. for 34 h, 0.99 g (79%) white solid **14** was obtained [when reaction mixture was kept at $CHCl_3$ bp for 24 h 1.02 g (81%) white solid **14** was obtained]; m.p. 185–187 °C, R_f 0.08. IR (KBr, cm^{-1}): 1647 (C=N), 1593 (C=C), 1217, 1224 (SO_2 as) and 1024 (SO_2 sy), 1535 (NO_2 as) and 1366 (NO_2 sy), 3373 [N(-H)$_2$], 2837 (C_{sp3}–H), 3161, 3300 (C_{sp2}–H). ^{1}H-NMR (500 MHz, DMSO-d_6): 3.12 (t, J = 7.91 Hz, 2H, α-CH_2), 3.91 (t, J = 7.91 Hz, 2H, β-CH_2), 3.40 [m, 2H, N(CH_{ax})$_2$], 3.71 [m, 2H, N(CH_{eq})$_2$], 3.54 [m, 4H, N(+)(CH_2)$_2$], 6.82–7.81 (m, 11H, NH_2, $C_{(sp2)}$H). ^{13}C-NMR (126 MHz, DMSO-d_6): 31.6, 44.6, 61.5, 62.9, 116.4, 120.5, 122.9, 129.5, 129.7, 130.6, 131.3, 139.8, 148.3, 150.0, 169.2. Anal. Calcd for $C_{19}H_{23}N_5O_5S$ (433.48): C, 52.64; H, 5.35. Found,%: C, 52.92; H, 5.63.

When reaction mixture was kept at r.t. for 34 h, 0.99 g (79%) white solid **14** was obtained [when reaction mixture was kept at $CHCl_3$ b.p. for 24 h 1.02 g (81%) white solid **14** was obtained].

8.3.2. Screening

The *in vitro* antidiabetic activity of the samples **6**–**14** was assessed by the degree of inhibition of α-amylase and α-glucosidase activity. Pure DMSO was used as a solvent. The final concentration of the sample substances was 10 mg/ml. 100 µl of α-amylase or α-glucosidase (1 U/ml) and 200 µl of test sample solution (10 mg/ml) were added to 500 µl of phosphate buffer (0.1 M; pH 6.8). The resulting mixture was incubated for 15 min at +37°C and 200 µl of P-NPG solution (5 mM) was added.

Then the resulting mixture was again incubated at +37 ºC for 20 min. The reaction was stopped by the adding of 500 µl of sodium carbonate (0.1 M). Because the samples showed too much absorbance at 405 nm, they were diluted 5 times with 5 ml of water and 1 ml of sodium carbonate solution (0.1 M). A solution of α-amylase or α-glucosidase (1 U/ml) was used as a blank. As a negative control 200 µl of pure DMSO was used in triplicate. As a reference drug, acarbose was taken at a concentration of 10.0 mg/ml (positive control).

Simultaneously, a negative control was placed without adding the test compounds. All samples were examined in triplets. The inhibitory activity was

expressed as a percentage (%) of the degree of inhibition of α-glucosidase in comparison with the negative control.

8.3.3. Single Crystal X-ray Diffraction

The X-ray diffraction data of **8**, **9**, and **11 – 14** were collected on a Bruker Apex II diffractometer (Bruker AXS, Inc., Madison, WI, USA) equipped with an Oxford Cryostream cooling unit and a graphite monochromated Mo anode (λ = 0.71073 Å). Intensities of reflections for **10** were collected at 100 K at the "Belok" beamline of the Kurchatov Synchrotron Radiation Source (NRC "Kurchatov Institute", Moscow, Russia) at the wavelength of 0.745 Å using a MAR CCD 165 detector. The image integration was performed using the iMosflm software [35]. The integrated intensities were empirically corrected for absorption using the Scala program [36]. Crystal structures were solved using SHELXT [37] program and refined with SHELXL [38] using OLEX2 software [39]. The structures were refined by full-matrix least-squares procedure against F^2. Non-hydrogen atoms were refined anisotropically. The H(C) positions were calculated, the H(N) and H(O) atoms were located on difference Fourier maps and refined using the riding model. Experimental details and crystal parameters are given in Tables S1-S2 (Electronic Supporting Information).

8.4. Conclusions

The set of the reaction products of β-aminopropioamidoximes nitrobenzenesulfochlorination depends on the structure of the initial substrates and temperature. β-Aminopropioamidoximes with six-membered heterocycles in the β-aminogroup give good yields of 2-amino-1,5-diazaspiro[4.5]-dec-1-ene-5-ammonium nitrobenzenesulfonates at r.t. and $CHCl_3$ b.p. An exception is the *ortho*-nitrobenzensulfochlorination of β-(thiomorpholin-1-yl)propioamidoxime when the reaction is regioselective at r.t. as two products are formed: 2-amino-1,5-diazathiospiro[4.5]-dec-1-ene-5-ammonium *ortho*-nitrobezenesulfonate and chloride hydrate; heating leads to a regiospecific course of the reaction with the formation of only chloride hydrate.

The *para*-Nitrobenzenesulfochlorination of β-(benzimidazol-1-yl)propioamidoxime gives the O-*para*-nitrobenzenesulfochlorination product. The reaction time when the reaction mixture is heated is

reduced by 2–3 times. *In vitro* screening of the library of nitrobenzenelsulfochlorination products for antidiabetic activity revealed two samples with high α-glucosidase activity exceeding the activity of the acarbose standard: products of *para*-nitrobenzeneulfochlorination of β-(thiomorpholin-1-yl)- and β-(benzimidazol-1-yl)propioamidoximes. The arsenal of physicochemical and spectral methods made it possible to establish the structural features of the studied spiropyrazolinium organic salts. Thus, in DMSO-d_6 solutions in ^{1}H NMR spectra slow inversion of six-membered nitrogen-containing β-heterocycles is observed. These spiropyrazoline derivatives can be interesting objects in dynamic NMR spectroscopy, which would allow measuring the rotational barriers of six-membered heterocycles. It is assumed that the bulky substituted arylsulfonate anion anchors the spiroheterocycles in the most thermodynamically favorable chair-like position. According to X-ray diffraction data, the axial location of the N-N bond in the spiropyrazoline heterocycles is unambiguously determined. NMR and XRD data demonstrate that two various conformations of spirocation are present both in solution, and in solids. The cation can take part in different types of intermolecular interactions depending on the conformation and the nature of six-membered cycle.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: Asymmetric units of X-rayed compounds in representation of atoms with thermal ellipsoids (p = 50%).; Table S1: Crystallographic data and the experimental details for compounds **6**, **8–10**; The compounds **6**, **8 – 14**. are registered in CCDC with the numbers: 2154973-2154980. Crystallographic information files are available from the Cambridge Crystallographic Data Center upon request (http://www.ccdc.cam.ac.uk/structures).

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Data Availability Statement: The data presented in this study are available in this article.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds **6 – 14** are available from the authors.

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Chapter 9

FREE ENERGIES OF 2-AMINO-1,5-DIAZASPIRO[4.5] DEC-1-EN-5-IUM CHLORIDES MONOHYDRATES AND ARYLSULFONATES FORMATION AT β-AMINOPROPIOAMIDOXIMES ARYLSULFOCHLORINATION

9.1. Introduction

As we previously reported [1–3], tosylation and *para*-nitrobenzenesulfonchlorination of β-aminopropionamidoximes **1–4** (β-amino groups were: piperidin-1-yl, morpholin-1-yl, thiomorpholin-1-y- and 4-phenylpiperazin-1-yl) leads to the formation of the corresponding 2-amino-1,5- diazaspiro[4.5]dec-1-en-5-ium arylsulfonates, and in the case of β-(benzimidazole-1-yl)propioamidoxime products are O-arylsulfoderivatives.

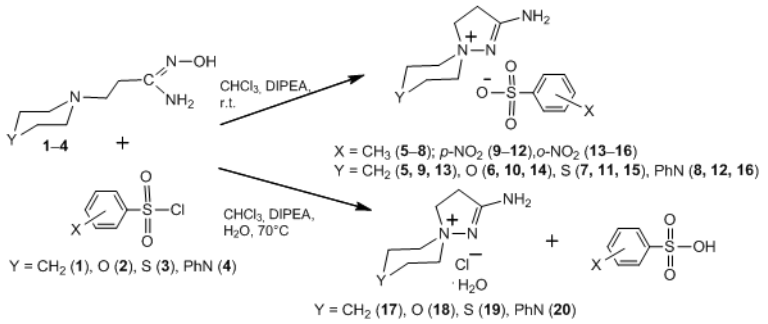
When optimizing the conditions for β-aminopropioamidoximes arylsulfochlorination, it was found that under certain conditions (when heating the reaction mixture in chloroform in the presence of N,N-diisopropylethylamine DIPEA), the main or by-product of β-(thiomorpholine-1-yl)propioamidoxime tosylation was 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate **19**. The experiment did not provide for carrying out β-aminopropioamidoximes arylsulfochlorination reactions in an inert medium. The high hygroscopicity of 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride determines its existence as a monohydrate.

In the case of other β-aminopropioamidoximes (**1**, **2** and **4**) arylsulfochlorination, only 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium arylsulfonates were isolated. Conditions of 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate obtaining, its physical and chemical characteristics, NMR ^{1}H and ^{13}C spectra and X-ray diffraction data were given in [4].

This paper presents the results of a theoretical comparative study of reactions and propability of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chlorides monohydrates **17–20** formation in the reactions of tosylation, *para*- and *ortho*-nitrobenzenesulfochlorination of β-aminopropioamidoximes **1–4** (Scheme 1).

Complete optimization of the molecular geometry and calculations of thermodynamic parameters were performed using Gaussian-09 software [5]. The reliability of DFT/B3LYP method in the calculations of thermodynamic parameters and HOMO-LUMO energies related to the heterocyclic compounds has been confirmed by previous studies [6–8].

The applied basis 6-31G++(d,p) shows sufficient accuracy in calculating the thermodynamic parameters of organic reactions [9]. Vibrational frequency analysis confirms that the ground states were found (no imaginary frequency). Ionization potential (IP), electrophilic index (ω), electronegativity (χ), chemical softness (σ) and hardness (η) were calculated using HOMO and LUMO energies as reported in literature [10–12].



Scheme 1. The reactions of tosylation, *para*- and *ortho*-itrobenzenesulfochlorination of β-aminopropioamidoximes

Solvation effects were accounted for by using the polarizable continuum model (IEFPCM) for chloroform. Thermodynamic functions were determined for standard conditions (1 atm. and 298.15 K).

9.2. Results and discussion

Thermodynamically preferred products were identified by comparing the Gibbs free energies of the corresponding chemical reactions calculated by the Hess equation as the difference between the free energies of the formation of reaction products and reagents. The calculation results are shown in Table 1.

Table 1

Δ*G* values of products 5–16 and 17–20 formation reactions

Product	ΔG_S*, kJ/mol	Product	ΔG_{Cl}**, kJ/mol	ΔG_{Cl} -ΔG_S, kJ/mol
tosylation				
5	-144.29	**17**	-142.14	2.15
6	-129.96	**18**	-130.79	-0.83
7	**-117.26**	**19**	**-125.36**	**-8.1**
8	-119.99	**20**	-129.47	-9.48
para-nitrobenzenesulfochlorination				
9	-163.57	**17**	-151.56	12.01
10	-160.02	**18**	-140.21	19.81
11	**-139.70**	**19**	**-145.88**	**-6.18**
12	-147.61	**20**	-138.89	8.72
ortho-nitrobenzenesulfochlorination				
13	-206.59	**17**	-162.66	43.93
14	-157.56	**18**	-151.31	6.25
15	**-142.80**	**19**	**-145.88**	**-3.08**
16	-154.66	**20**	-149.99	4.67
ΔG_S* – the free energy of formation reactions sulfonates (**5–16**) ΔG_{Cl}** – free energy for the formation of the monohydrates of chlorides (**17–20**)				

Calculations show that in most examples arylsulfonates are thermodynamically favorable, except cases when the initial substrate is β-(thiomorpholine-1-yl)propioamidoxime **3**. 2-Amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate **19**, based on

comparing the values of ΔG reactions, is more advantageous compared to 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium tosylate, *para*-nitrophenylsulphonate and *ortho*-nitrophenylsulphonate (**7**, **11** and **15**, respectively).

Thermodynamic calculations of the reactions of formation of product **18** compared to **6**, and product **20** compared to **8** are exceptions. For the first one, the advantage in free energy is rather insignificant (-0.83 kJ/mol), and for the second one, a difference of -9.48 kJ/mol is observed. However, under the conditions described in [1–3], the formation of chloride monohydrate salts was observed only for the 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium cation **19**.

The formation of monohydrate chloride **17** should be considered the least likely, since the energetic advantage of the formation *of ortho*-nitrophenylsulfonate in β-(piperidine-1-yl)propioamidoxime *ortho*-nitrobenzenesulfochlorination reaction is the largest among the obtained free energy differences in β-aminopropioamidoximes arylsulfochlorination reactions.

For obtained 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate **19** the molecular orbitals were simulated and frontier molecular orbitals (FMO) analysis was performed in comparison with tosylate, *para*-nitrophenylsulphonate and *ortho*-nitrophenylsulphonate of 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium (**7**, **11** and **15**, respectively).

FMO analysis is very important to predict chemical stability and reactivity parameters based on HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies. The HOMO energy in absolute value corresponds to the ionization of the orbitals and determines the electron-donor properties and, accordingly, the ability to interact with electrophilic reagents. The LUMO energy determines the electron affinity, i.e. electron accepting properties, their ability to interact with nucleophilic reagents. The reactivity parameters of products **7**, **11**, **15** and **19** reflecting their chemical properties are estimated. Results are presented in Table 2.

Table 2

Reactivity parameters of products 7, 11, 15 and 19

Reactivity parameters	**7**	**11**	**15**	**19**
HOMO energy (eV)	-6.60	-6.74	-6.72	-6.47
LUMO energy (eV)	-0.62	-3.02	-2.57	-0.61
Energy gap ΔE(LUMO-HOMO) (eV)	5.98	3.72	4.15	5.86
Ionization potential $IP = -E$(HOMO)(eV)	6.60	6.74	6.72	6.47
Electron affinity $EA = -E$(LUMO) (eV)	0.62	3.02	2.57	0.61
Electronegativity $\chi\,(eV) = (I + A)/2$ (eV)	3.61	4.88	4.65	3.54
Hardness $\eta = (IP - EA)/2$ (eV)	2.99	1.86	2.08	2.93
Chemical potential $\mu = -\chi$ (eV)	-3.61	-4.88	-4.65	-3.54
Electrophilicity $\omega = \mu^2/2\,\eta$ (eV)	2.18	6.40	5.20	2.14
Softness $\sigma = 1/\eta$ (eV)	0.33	0.54	0.48	0.34

Figure 1 shows 3D plots of HOMO and LUMO. GaussView 05 program [13] was used to visualize molecular orbitals.

A molecule with a high energy difference between HOMO and LUMO orbitals (energy gap) has low chemical reactivity and high kinetic stability [14]. Molecules with a high and low energy gap are called hard and soft molecules, respectively. Hard molecules are less polarizable than the soft ones and require more energy for excitation. Thus, it is clear from Table 2 that compounds **7** and **19** are less soft while **11** and **15** with relatively low energy gap are characterized by easy polarizability and high reactivity. Compound **11** having greater value of chemical potential (-4.88 eV) is the most reactive, while chloride monohydrate **19** is the least reactive (-3.54 eV) of all.

A highest electron affinity value is found to be 3.02 in **11**. The least value of electron affinity is 0.61 observed in **19**. The NO_2 group in compounds **11** and **15** is a very strong electrophile; these compounds exhibit higher electrophilicity then **7** and **19**. The results of calculations show that the E(LUMO) orbitals of all the calculated structures are negative, which indicate that studied molecules are nucleophiles.

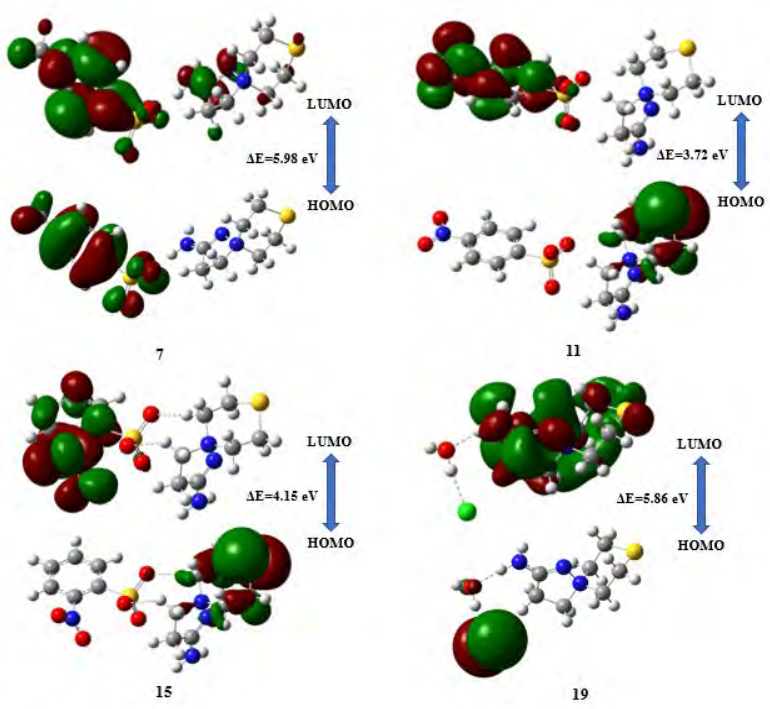


Figure 1. Frontier molecular orbitals of products **7**, **11**, **15** and **19**. Isovalue = 0.02

Experimental

Methods for obtaining 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium arylsulfonates, characteristics and identification were published in [1–3]. Conditions of 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate obtaining, its physical and chemical characteristics, NMR ^{1}H and ^{13}C spectra and X-ray diffraction data were given in [4].

The calculations were performed using Gaussian 09 package. The molecular structure of compounds was fully optimized using Density Functional Theory at the B3LYP levels with 6-31G++(d,p) basis set. The absence of imaginary (negative) frequencies in the calculation results indicates that a local minimum was found.

9.3. Conclusion

Calculations show that in most examples arylsulfonates are thermodynamically favorable, except when the initial substrate is β-(thiomorpholin-1-yl)propioamidoxime (**3**). 2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate (**19**), based on comparing the values of Δ*G* reactions, is more advantageous compared to 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium tosylate, *para*-nitrophenylsulphonate and *ortho*-nitrophenylsulphonate (**7**, **11** and **15**, respectively). Thermodynamic calculations of the reactions of formation of product **18** compared to **6**, and product **20** compared to **8** are exceptions**.** The formation of monohydrate chloride **17** should be considered the least likely. The possibility of the formation of chloride monohydrates from arylsulfonates and hydrochlorides of DIPEA was also evaluated.

For 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium tosylate, *para*-nitrophenylsulphonate, *ortho*-nitrophenylsulphonate and chloride monohydrate the molecular orbitals were simulated and FMO comparative analysis was performed. The results of calculations show that all the E(HOMO) and E(LUMO) orbitals are negative, which indicate that studied molecules are stable.

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CONCLUSION

The monograph deals with the reactivity of multifunctional substrates – β-aminopropioamidoximes (β-amino group: piperidine, morpholine, thiomorpholine and phenylpiperazine), as well as with a β-benzimidazole fragment) and the structure of their aroylation products (O-aroyl-β-aminopropioamidoximes), dehydration of O-aroyl-β-aminopropioamidoximes to 5-aryl-3-(β-amino)ethyl-1,2,4-oxadiazoles, Boulton-Katritzky rearrangement of 1,2,4-oxadiazoles to benzoates and 2-aminospiropyrazolilammonium chlorides; also structures of arylsulfochlorination products. That is, in the case when, along with the expected products of O-arylsulfochlorination of β-aminopropioamidoximes, sulfonates and chlorides of 2-aminospiropyrazolilammonium are formed.

In this work, the questions of the dependence of the reaction products structure and their rearrangements on the structure of the initial substrates – β-aminopropioamidoximes and reagents (substituted benzoic acid chlorides and arylsulfochlorides) were studied. The formation of the stable reactions and rearrangements products is confirmed by calculations of their thermodynamic stability.

A set of physicochemical and spectral methods (IR, ^{1}H and ^{13}C NMR spectroscopy, X-ray diffraction analysis) was used to determine the structure.

In addition, where possible, we studied the biological activity of the synthesized products and identified candidates for antitubercular, antidiabetic and local anesthetic agents.

As a result of the study the following conclusions were made:

- DFT/B3LYP/6-31G++(d,p)calculations of the arylsulfochlorination reaction products predict that *para*-toluenesulfonates and *para*-nitrobenzenesulfonates of spiropyrazolinium compounds are thermodynamically more preferable in case of four studied β-aminopropioamidoximes (β-aminogroup: piperidine, morpholine, thiomorpholine and phenylpiperazine), while the O-substitution product is more stable in the arylsulfochlorination of β-(benzimidazol-1-yl)propioamidoxime. The frontier orbital energies were calculated for all the studied compounds, whose negative LUMO values testify their nucleophilic nature. Of two conformers of spirocations, the equatorial one is more stable than the axial one [Yergaliyeva et al., *J. Struct. Chem.* **2021**, *62*, 1969–1975.]

We demonstrated that arylsulfonates are thermodynamically more favorable reaction products than chlorides in arylsulfochlorination of β-aminopropioamidoximes with six-member heterocycles in the β-position with an exception of β-(thiomorpholine-1-yl)propioamidoxime. 2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate based on Δ*G* reaction values, is more advantageous as compared to 2-amino-8-thia-1,5-diazaspiro[4.5]dec-1-en-5-ium tosylate, *para*-nitrophenylsulphonate and *ortho*-nitrophenylsulphonate. [Yergaliyeva et al. *Chem. J. Kaz.* **2022**, *75*, 172-180.]

Our conclusions were validated by a series of syntheses:

- The acid hydrolysis of a series of 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles gave 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride hydrate and substituted benzoic acids. Thus, 1,2,4-oxadiazoles with a 3-(β-thiomorpholino)ethyl substituent 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; their structures were confirmed by X-ray diffraction structural analysis. [Kayukova et al., *Chem. Heterocycl. Compd.* **2010**, *46*, 879–886.]

- Chemical stability of 5-substituted phenyl-3-[β-(piperidin-1-yl)]ethyl-1,2,4-oxadiazoles was studied in Boulton-Katritzky rearrangement to form spiropyrazolines. We observed instability of 5-substituted phenyl-3-[β-(piperidin-1-yl)]ethyl-1,2,4-oxadiazoles at room temperature in H_2O, DMF + H_2O and under the action of HCl. Hydrolysis of 3,5-disubstituted 1,2,4-oxadiazoles in the first two conditions gave benzoates of 2-amino-1-aza-spiro (4.5)decane-2-ene-5-ammonium; whilst action of HCl on the 3,5-disubstituted 1,2,4-oxadiazoles led to the hydrochlorides of 3,5-disubstituted 1,2,4-oxadiazoles and to 2-amino-1-aza-spiro (4.5)decane-2-ene-5-ammonium chloride hydrate. The reaction afforded spiropyrazoline compounds instead of compounds with a planar structure. [Kayukova et al., *Chem. Heterocycl. Compd.* **2018**, *54*, 643–649.]
- 5-Substituted phenyl-3-(2-aminoethyl)-1,2,4-oxadiazoles in the presence of moisture and acids undergo Boulton–Katritsky rearrangement to the salts of spiropyrazolinium compounds – 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates and chloride. Hence, biological screening results should be associated with rearranged products and not with the original taken on trials 5-substituted phenyl-3-(2-aminoethyl)-1,2,4-oxadiazoles. A small library of the newly 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates and chloride has been used in the drug design of antitubercular drugs. The tested compounds show moderate to high *in vitro* antitubercular activity with MIC values of 1–100 μg/mL. The highest activity in 1 μg/mL and 2 μg/mL on DS (drug sensitive) and MDR (multidrug resistant) of *M. tuberculosis* strains, equal to the activity of the basic antitubercular drug rifampicin, was recorded for 2-amino-8-oxa-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride. 3D-Molecular structure of the cation extracted from crystal structure was used for molecular docking studies with various *M. tuberculosis* receptors. It was demonstrated that two stereoisomers of the rigid cation form different sets of hydrogen bonds in

complexes with dihydroneopterin aldolase or oxidoreductase Rv2671 and similar H-bonds in complex with thymidylate synthase. However, energies of all ligand–receptor complexes vary from −35.8 to −42.8 kcal/mol. [Kayukova et al., *Molecules* **2021**, 26, 967.]

- We established that the reaction of β-(morpholin-1-yl)propioamidoxime with *para*-substituted arylsulfonyl chlorides in chloroform in the presence of an equivalent of triethylamine affords spiropyrazolinium arylsulfonates rather than expected *O*-sulfoaryl-β-aminopropioamidoximes regardless of the electronic properties of substituents in arylsulfonyl chlorides. [Kayukova et al., *Rus. Chem. Bul.* (Int. Ed.) **2020**, *69*, 496–503.]
- The tosylation of β-aminopropioamidoximes (β-amino group: β-amino group: piperidine, morpholine, thiomorpholine and phenylpiperazine) proceeds to obtain spirocyclic compounds – 2-amino-1,5-diazaspiro [4.5]-dec-1-en-5-ammonium tosylates; tosylation of β-(benzimidazol-1-yl)propioamidoxime gives the product at the oxygen atom of the amidoxime group. As a result of our studies, along with the expected product – O-tosyl-β-(benzimidazol-1-yl)propioamidoxime, a number of the structurally new, isomeric spiropyrazolinium compounds was obtained. This indicates on their thermodynamic advantage in comparison with the products of O-acylation. Analysis of the literature data shows that among the derivatives of pyrazolines there are no examples of doubly charged spirocompounds with ammonium nitrogen in the head of the bridge and any anion as a counterion. [Kayukova et al., *Chem. J. Kaz.*, **2021**, *2(74)*, 22–32.]
- Comparison of molecular conformations of spirocations indicates that thermodynamically more stable equatorial conformation is also predominant in their solid salts; however a number of nitrobenzenelsulfonates contain in their crystal structures cations in the less stable axial conformation [Kayukova et al., *Molecules* **2022**, *27*, 2181.]. The envelope conformation of the five-membered ring results in formation

of two conformers both present in centrosymmetric space groups. The only exception was previously reported crystal structure of 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene chloride monohydrate in the chiral $P2_12_12_1$ space group which was refined as two independent spiro-cations in the asymmetric unit with two different conformations of the five-membered ring. Multitemperature X-ray diffraction study allowed to correct the space group of this salt to centrosymmetric Pbca [Kayukova et al., *Acta Cryst.* **2022**, E78, 16].

- The set of the reaction products of β-aminopropioamidoximes nitrobenzenesulfochlorination depends on the structure of the initial substrates and temperature. β-Aminopropioamidoximes with six-membered heterocycles in the β-aminogroup give good yields of 2-amino-1,5-diazaspiro[4.5]-dec-1-ene-5-ammonium nitrobenzenesulfonates at r.t. and $CHCl_3$ b.p. An exception is the *ortho*-nitrobenzensulfochlorination of β-(thiomorpholin-1-yl)propioamidoxime when the reaction is regioselective at r.t. as two products are formed: 2-amino-1,5-diazathiospiro[4.5]-dec-1-ene-5-ammonium *ortho*-nitrobezenesulfonate and chloride hydrate; heating leads to a regiospecific course of the reaction with the formation of only chloride hydrate.

  The *para*-nitrobenzenesulfochlorination of β-(benzimidazol-1-yl)propioamidoxime gives the O-*para*-nitrobenzenesulfochlorination product. The reaction time when the reaction mixture is heated is reduced by 2–3 times. *In vitro* screening of the library of nitrobenzenelsulfochlorination products for antidiabetic activity revealed two samples with high α-glucosidase activity exceeding the activity of the acarbose standard: products of *para*-nitrobenzeneulfochlorination of β-(thiomorpholin-1-yl)- and β-(benzimidazol-1-yl)propioamidoximes. The arsenal of physicochemical and spectral methods made it possible to establish the structural features of the studied spiropyrazolinium organic salts. Thus, in DMSO-d_6 solutions in ^{1}H NMR spectra slow inversion of six-membered nitrogen-containing β-heterocycles is

observed. According to X-ray diffracttion data, the axial location of the N-N bond in the spiropyrazoline heterocycles is unambiguously determined. NMR and XRD data demonstrate that two various conformations of spirocation are present both in solution, and in solids. The cation can take part in different types of intermolecular interactions depending on the conformation and the nature of six-membered cycle. [Kayukova et al., *Molecules* **2022**, *27*, 2181.]

Content

Scientific issue

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