Article

Reaction Products of β-Aminopropioamidoximes Nitrobenzenesulfochlorination: Linear and Rearranged to Spiropyrazolinium Salts with Antidiabetic Activity

Lyudmila Kayukova 1,*, Anna Vologzhanina 2,*, Pavel Dorovatovskii 3, Gulnur Baitursynova 1, Elmira Yergaliyeva 1, Ayazhan Kurmangaliyeva 1, Zarina Shulgau 4, Sergazy Adekenov 5, Zhanar Shaimerdenova 5 and Kydymolla Akatan 6,*

1 JSC A. B. Bekturov Institute of Chemical Sciences, 106 Shokan Ualikhanov St., Almaty 050010, Kazakhstan; guni-27@mail.ru (G.B.); erg_el@mail.ru (E.Y.); ayazhankb98@mail.ru (A.K.)
2 A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilova St., B-334, 119991 Moscow, Russia
3 NRC “Kurchatov Institute”, 1, Akademika Kurchatova pl., 123182 Moscow, Russia; paulgemini@mail.ru
4 RSE National Center for Biotechnology, Science Committee of ME&S RK, 13/5 Kuralzhinskoe Highway, Nur-Sultan 010000, Kazakhstan; shulgau@biocenter.kz
5 JSC International Research and Production Holding Phytochemistry, 4 M. Gazalieva St., Karaganda 100009, Kazakhstan; info@phyto.kz (S.A.); zh.shaimerdenova@phyto.kz (Z.S.)
6 National Scientific Laboratory, S. Amanzholov East Kazakhstan State University, 18/1 Amurskaya St., Ust-Kamenogorsk 070002, Kazakhstan; ahnur.hj@mail.ru
* Correspondence: lkayukova@mail.ru (L.K.); vologzhanina@mail.ru (A.V.); Tel.: +7-(705)-168-81-53 (L.K.)

Abstract: Nitrobenzenesulfochlorination of β-aminopropioamidoximes leads to a set of products depending on the structure of the initial interacting substances and reaction conditions. Amidoximes, functionalized at the terminal C atom with six-membered N-heterocycles (piperidine, morpholine, thiomorpholine and phenylpiperazine), as a result of the spontaneous intramolecular heterocyclization of the intermediate reaction product of an S_N2 substitution of a hydrogen atom in the oxime group of the amidoxime fragment by a nitrobenzenesulfonyl group, produce spiropyrazolinium ortho- or para-nitrobenzenesulfonates. An exception is ortho-nitrobenzenesulfochlorination of β-(thiomorpholin-1-yl)propioamidoxime, which is regioslective at room temperature, producing two spiropyrazolinium salts (ortho-nitrobenzenesulfonate and chloride), and regiospecific at the boiling point of the solvent, when only chloride is formed. The para-Nitrobenzensulfochlorination of β-(benzimidazol-1-yl)propioamidoxime, due to the reduced nucleophilicity of the aromatic β-amine nitrogen atom, is regiospecific at both temperatures, and produces the O-para-nitrobenzenesulfochlorination product. The antidiabetic screening of the new nitrobenzenesulfochlorination amidoximes found promising samples with in vitro α-glucosidase activity higher than the reference drug acarbose. 1H-NMR spectroscopy and X-ray analysis revealed the slow inversion of six-membered heterocycles, and experimentally confirmed the presence of an unfavorable stereoisomer with an axial N–N bond in the pyrazolinium heterocycle.

Keywords: β-aminopropioamidoximes; nitrobenzenesulfochlorination; spiropyrazolinium salts; X-ray diffraction

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
Spiropyrazolines, also termed as spirocyclic hydrazine moiety, are rigid asymmetric heterocyclic structures with a chirality axis and with possible centers of chirality 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 an enantiomeric advantage, regioisomeric composition, reactivity, and tautomeric transformations. Essentially, 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, the spiropyrazolinium salts with a 1,5-diazaspiro-1-en-5-i um fragment that we obtained via the hydrolysis of 3-(β-heteroamino)ethyl-5-aryl-1,2,4-oxadiazoles and the arylsulfochlorination of β-aminopropioamidoximes exist, under standard conditions, as the Δ2 isomer [5–8]. The thermodynamic advantage of possible tautomers of the key pyrazoline moiety was estimated; it turns out that, in the case of pyrazolines, the Δ2 isomer is much more stable than the others [9].

![Figure 1](image)

**Figure 1.** Structural isomers of spiropyrazolines.

Two comprehensive reviews on functionalized spiropyrazolines were published in 2013 and 2019 [10,11].

The most common methods for the construction of the 1,2- and 2,3-spiro-1-pyrazolines involve the formation of a new ring on an existing carbo- or heterocycle, having exocyclic C=C double bonds. The essential steps in the formation of spiropyrazoline systems in these cases are 1,3-cycloaddition reactions of nitrogen-containing molecules (nitrilimines [12–15] and diazoalkanes [16,17]) to double bonds, or a condensation reaction of substituted chalcones with hydrazine or its derivatives in an acidic or alkaline medium [18,19].

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

![Scheme 1](image)

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

Symmetrical spiropyrazoline systems are formed by the 1,3-dipolar cycloaddition reaction of (2E,2′E)-2,2′-(1,4-phenylene bis(methanylylidene)) bis(3,4-dihyronaphthalen-1(2H)-one) with a hydrazinoyl halides (nitrile imines). The reaction proceeds regioselectively and only one of two possible spiropyrazoline regioisomers (the 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-diazaspiropyrazolines adduct is made using the molecular orbital theory in the interaction of HOMO and LUMO reagents (Scheme 2) [22].

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

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

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

At a 1,3-dipolar addition of diphenylldiazomethane 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 diphenylldiazomethane 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′- (3H-pyrazole)]-3-carboxylates up to 75%. The change of the alkylidene substituent to COt-Bu leads to a stereoselective, but regiosomeric, 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′- (3H-pyrazole)]-3-carboxylate and (6R)-3-benzhydryl1′-acetyl-1′,5′-dihydrospiro[penicillanate-6,4′- (4H-pyrazole)]-3-carboxylate in a ratio of 46 and 10% (Scheme 4) [24].

Scheme 4. 1,3-Dipolar addition of diphenylldiazomethane to 6-alkylidenepenicillanates (reaction conditions: DCM, 30 °C, 24 h).
Except for our own studies, no examples of 1,5-diazaspiro-1-en-5-ium spiropyrazolinium salts can be found in the literature. However, stable indazole derivatives, 1,1-disubstituted indazolium hexafluorophosphates with a nitrogen atom at the head of the bridge, were obtained utilizing the tosylation reaction. This transformation is similar to that observed in our previous studies, and includes intramolecular neighboring group participation, finally leading to strong bonding, which follows the $S_N 2$ reaction mechanism (Scheme 5) [25].

![Scheme 5](image)

**Scheme 5.** The attainment of stable 1,1-disubstituted indazolium hexafluorophosphates.

Previously, we obtained new spiropyrazolinium compounds via the hydrolysis of 3-(β-heteroamino)ethyl-5-aryl-1,2,4-oxadiazoles [5,6], by the arylsulfochlorination (Aryl: para-XC₆H₄SO₂Cl; X=CH₃O, CH₃, H, Br, Cl, NO₂) of β-(morpholin-1-yl)aminopropioamidoxime [7] and by the tosylation of β-aminopropioamidoximes (β-amino group: piperidin-1-yl, morpholine-1-yl, thiomorpholin-1-yl, 4-phenylpiperazin-1-yl, benzimidazol-1-yl) at r.t. [8]. In the present study, we are interested in the regioselectivity of β-aminopropioamidoximes ortho-, para-nitrobenzenesulfochlorination at reaction conditions (chloroform (CHCl₃), diisopropylamine (DIPEA), room temperature and 70 °C). Depending on the reactant’s structure and reaction temperature, 2-amino-1,5-diazathiaspiro[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 present work is the establishment of the ambiguity of amidoximes sulfochlorination and the possibility of obtaining a wide range of potentially biologically active products.

2. Results and Discussion

2.1. Synthesis and Spectra

The interaction of β-aminopropioamidoximes (1–5) with ortho-, para-nitrobenzenesulfochlorides in CHCl₃ was carried out at room temperature and by 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-nitrobenzenesulfochlorines, lead 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-nitrobenzenesulfochlorination, and up to 25–104 h for ortho-nitrobenzenesulfochlorination.

The heating of the reaction mixture at the CHCl₃ boiling point reduces the reaction time to 19–36 h, and to 24 h for para- and ortho-nitrobenzenesulfochlorination, respectively. The completion of β-aminopropioamidoximes arylsulfochlorination was confirmed by the physicochemical data (TLC, elemental analysis, m.p.), and the IR and NMR ($^1$H and $^{13}$C) spectra and X-ray data of the isolated products (6–14). On the basis of physicochemical and spectral data, it was concluded that, in the case of the nitrobenzenesulfochlorination of β-aminopropioamidoximes with six-membered heterocycles in the β-position (1–4), the main products were the nitrobenzenesulfonates of spiropyrazoline compounds 6–12, 13a, and 14; however, when the substrate was β-(benzimidazol-1-yl)propioamidoxime (5), only the product of para-nitrobenzenesulfochlorination 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 the nitrobenzenesulfochlorination of β-aminopropioamidoximes 1–4, the O-nitrobenzenesulphonates of β-propioamidoximes formed as intermediate B, due to the thermodynamic advantage, rearranging into spiropyrazoline nitrobenzenesulphonates (6–12, 13a, 14). Only in the case of the benzimidazole derivative, the intermediate B remains stable and produces O-para-nitrobenzenesulphonate 10.

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

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

Evidently, in this case, the para-nitrophenylsulfonate anion in the primarily formed 2-amino-1,5-diazaspiro[4.5]deca-1-en-5-ium para-nitrophenylsulfonate (13a) was exchanged for the chloride anion from DIPEA hydrochloride, releasing para-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 the single crystals of the ortho-nitrophenylsulfochlorination product of amidoxime 3 with atmospheric moisture.

When establishing the structure of nitrobenzenesulfochlorination products, a difference was noted in the values of the mobility index $R_t$ for the products produced by the nitrobenzenesulfochlorination of amidoximes with six-membered nitrogenous heterocycles in the β-position (6–9, 11–14) and for the para-nitrobenzenesulfonato derivative of β-(benzimidazol-1-yl)propioamidoxime (10) ($R_t$ 0.01–0.12 and 0.75). Compounds 7 and 13b were previously described in [7] and [26,27], respectively (Table 1).
In the IR spectra of compounds 6–12, 13a, and 14, there are two pairs of bands related to the characteristic stretching vibrations of a strong intensity of the NO₂ and SO₂ 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 for the bonds of the NO₂ and SO₂ groups.

It is interesting that, in the ¹H-NMR spectra of compounds 6–9, 13a, and 13b, it was possible to fix the diastereotopic nature of the geminal protons of the methylene groups located at the ammonium nitrogen atom, which produce pairs of multiple signals with an intensity of 2 protons at δ: 3.35 m, 3.44 m (6); 3.41 m, 3.65 m (7); 3.60 m, 3.72 m (8); 3.49 m, 3.98 m (9); 3.10 m, 3.68 m (13a); and 3.10 m, 3.68 m (13b).

Similarly, the geminal protons of the methylene groups at the S, O, S, S, and N atoms of the β-heterocycles of compounds 8, 12, 13a, 13b, and 14 also appear as pairs of proton signals with an intensity of 2 protons at δ: 2.87 m, 3.15 m (8); 3.35 m, 3.60 m (12); 2.84 m, 3.55 m (13a); 2.85 m, 3.55 m (13b); and 3.40 m, 3.71 m (14). Evidently, the effect of the slow rotation of β-heterocycles with the possibility of fixing the 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 the spiro compounds.

The signals of Csp³ and Csp² carbon atoms in the ¹³C-NMR spectra of compounds 6–14 are present in the characteristic regions.

We obtained a quantum-chemical confirmation of the advantageousness of the formation of spirocyclic tosylation and para-nitrobenzensulfochlorination products of β-aminopropropioamidoximes (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-(benzimidazole-1-yl)propioamidoxime (5), with positive values of the Gibbs energy for the tosylation and para-nitrobenzensulfochlorination products as 45.87 and 20.02 kJ/mol, respectively [28].

The thermodynamic advantage of the formation of 2-aminopropyrazoloylammonium sulfonates (tosylates, para- and ortho-nitrobenzensulfonates) for a number of β-aminopropropioamidoximes (1, 2, 4), in comparison to the formation of chloride hydrates, was identified, except for the case when the initial substrate was 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, −3.08 kJ/mol, respectively [29].

It should be noted that we attempted to react β-(benzimidazol-1-yl)propioamidoxime (5) with ortho-nitrobenzensulfonate several times, under the described conditions (CHCl₃, DIPEA, r.t. and 70 °C), but, each time, a resinous reaction mixture was obtained.

2.2. The In Vitro Antidiabetic Screening of 2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ammonium Nitrobenzensulphonates and Chloride Hydrate (6–9, 11–14) and 3-(1H-Benz[d]imidazol-1-yl)-N²-[(4-nitrophenyl)sulfonyl]oxy)propanimidamide (10)

The α-amylase and α-glucosidase inhibition tests, which hydrolyze starch in post-prandial hyperglycemia, are standard tests used 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 a 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 spiropyrazolium ammonium 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 via the degree of inhibition of the activity of α-amylase and α-glucosidase by the studied substances, compared to 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-Amlyase 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-Amlyase 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 the tested compounds had an average inhibitory activity against α-amylase, the values of which are less than the activity of acarbose. In regard to α-glucosidase, the products of para-nitrobenzenesulfochlorination 8 and 10 had 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 the 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 is derivative of para-nitrophenylsulfonic acid; the second subgroup is an ortho-nitrophenylsulfonic acid derivative. 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 ortho-nitrophenylsulfonic acid derivatives (10–14) are less efficient 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 previously described 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.

2.3. X-ray Diffraction

X-ray diffraction studies of all the reaction products were carried out. They confirmed that, regardless of the synthetic conditions, the 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. As a result of the ortho-nitrobenzenesulfochlorination of β-thiomorpholin-1-ylpropioamidoxime, nitrophenylsulfonate 13a and chloride monohydrate 13b of the corresponding spirocation, similar to the one previously reported [29], can be obtained depending on
the reaction conditions. No rearrangement was detected for benzenimidazol-1-yl-containing product 10 in accord with the B3LYP/6-31++G(d,p) calculations of the 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, ESI). The quality of XRD data allowed us to locate all of the hydrogen atoms on difference Fourier maps, and undoubtedly confirmed that none of the sulfonate groups contained any hydrogen atoms.

The molecular structures of these compounds are depicted on Figure S1 (ESI), and the main geometry parameters of the cations and anions are listed in Table 3. The X–CH2 bond distances increase and CH2–X–CH2 angles decrease, passing from O to NPh; CH2 and S. Valence angles at the positively charged N1 atom are close to ideal 109.5° values, however only N–CH2 bond distances within the 6-membered ring are typical for a single N–C bond. In 10, a similar N1–CH2 bond is equal to 1.458(2) Å, due to the mesomeric effect of the benzenimidazole substituent. The N–N bond in these salts varies from 1.460(2) to 1.470(2) Å, which is longer than 1.42–1.43 Å that is found for N-substituted aminopyrazoles [32,33].

Overall, the 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 examples of the inverted chair conformation (Figure 3) of this ring confirmed by means of X-ray diffraction. The difference in the two conformations manifests itself in the 1H-NMR spectra (see above), and also through the N1–C1 bond length, which is generally shorter in cations with ‘novel’ conformations. In our opinion, the overall conformation of the molecule and elongation of bond distances in the pyrazole ring can be attributed to the anomeric effect [33] of the (hetero)atom in the six-membered ring. The length of the N2=C bond in all the spirocations is nearly the same as the N2=C bond distance of 1.302(2) in 10.

Table 3. Selected geometrical parameters of spirocations 6–9, 11–14 (Å and °).

|      | 6    | 7   | 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  | 1.288(2) | 1.299(2) | 1.300(2) | 1.316(3) | 1.311(1) | 1.305(2) | 1.289(6) | 1.300(2) |
| X–Cn  | 1.492(4)– | 1.401(3)– | 1.791(3)– | 1.464(4)– | 1.519(1)– | 1.434(2)– | 1.794(5)– | 1.466(1)– |
| d(C…P) | 0.302(4) | 0.418(4) | 0.267(3) | 0.425(5) | 0.457(1) | 0.445(2) | 0.450(7) | 0.435(2) |
| Cn–NO2 | 1.472(2) | 1.470(2) | 1.477(2) | 1.474(4) | 1.472(1) | 1.474(2) | 1.454(6) | 1.474(2) |
| Cn–Cn | 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     | 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 the mean planes of the phenyl ring and the NO2 group for the anion.

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) and 14 (cyan). The superimposed atoms are N–N=C–C atoms in the 5-membered pyrazole ring.

A prominent variation in the 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 the H bonds is the amino group, while the sulfonate groups of the anions and heteroatoms of the cations compete to act as acceptors of H bonding. As a 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). The $D_{33}^3(9)$ tetramers in 6, 7, and 11 are formed through two N–H…N interactions and two N–H…O ones. Similar $D_{33}^3(13)$ tetramers in 12 and 14 are obtained through a similar N–H…O cation…anion interactions, but the cations are shifted along each other to allow for the bonding with a heteroatom of the six-membered ring. The $R_{44}^3(12)$ cycles in 9 and the H-bonded chains in 8 and 13 are formed by the interactions of the amino group with sulfonate groups of two neighboring molecules. The $G_{a_d}(n)$ notation of H-bonded architectures is presented in terms of [33], where $G$ represents the type of pattern (C for chain, S for intramolecular hydrogen bonds, R for ring, and 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 the similar crystal parameters and space group of 11–13 (Table S1, ESI), these compounds cannot be regarded as isostructural, as they 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.

![Figure 4](image-url)

*Figure 4. Cont.*
3. Materials and Methods

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 (Thermo Fisher Scientific, Inc., Waltham, MA, USA) in KBr pellets. The $^1$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 the $^1$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). The 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 (Sorbopolymer, Krasnodar, Russia) TLC plates coated with CTX-1A silica gel, grain size 5–17 $\mu$m, containing UV-254 indicator. The eluent for TLC analysis was a mixture of benzene–EtOH, 1:3. The solvents for the synthesis, recrystallization, and TLC analysis (ethanol, 2-PrOH, benzene, DMF, and acetone) were purified according to the standard techniques.

3.1.1. A General Procedure for the Synthesis of 2-Amino-1,5-diazaspiro[4.5]-dec-1-ene-5-carboxamido derivatives

The synthesis of $\beta$-aminopropioamidoximes 4-nitrobenzenesulfochlorination products 6–10 (general method). To a solution of 0.0029 mol of $\beta$-aminopropioamidoxime 1–5 in 20 mL of CHCl$_3$, 0.0029 mol of DIPEA was added. The reaction mixture was cooled to $-1^\circ$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 (b.p.) of CHCl$_3$) and stirred until the completion of the reaction. The

![Figure 4. H-bonding patterns in the crystal structures of the studied compounds. H bonds are depicted with dotted lines.](image-url)
progress of the reaction was monitored by TLC. The formed white precipitates of the products 6–10 were filtered off and recrystallized from 2-ProOH.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-aminium 4-nitrobenzenesulfonate (6). The reaction mixture consisting of 0.5 g (0.0029 mol) of compound 1 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to -1°C. Then, 0.64 g (0.0029 mol) of 4-nitrobenzenesulfonyl chloride was added dropwise. When the reaction mixture was kept at r.t. for 38 h, 0.80 g (77%) of white solid 6 was obtained (when the reaction mixture was kept at CHCl₃ b.p. for 27 h, 0.48 g (46%) of white solid 6 was obtained); m.p. 151 °C, Rf 0.12. IR (KBr, cm⁻¹): 1665 (C=N), 1607 (C=C), 1232 (SO₂ as) and 1190 (SO₂ sy), 1529 (NO₂ as) and 1352 (NO₂ sy), 3302 [N-(H)₂], 2938, 2864, 2815 (Csp₃s − H), 3032, 3257 (Csp₂ − H). ¹H-NMR (500 MHz, DMSO-d₆): 3.10 (t, J = 7.0 Hz, 2H, α-CH₂), 3.81 (t, J = 7.0 Hz, 2H, β-CH₂), 1.55 m, 1.75 m, 1.87 m, [6H, (CH₂)₃], 3.35 [m, 2H, N+(CH₃)₂] and 3.44 [m, 2H, N+(CH₃)₂], 7.23 (s, 2H, NH₂), 7.83–8.21 (m, 4H, Csp₂-H). ¹C-NMR (126 MHz, DMSO-d₆): 21.0, 21.9, 31.5, 60.7, 64.3 (2C), 125.3 (2C), 128.5 (2C), 138.0 (1C), 145.3 (1C), 168.5. Anal. Calcd for C₁₄H₂₀N₆O₂S (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-en-5-aminium 4-nitrobenzenesulfonate (7). The reaction mixture consisting of 0.5 g (0.0029 mol) of compound 2 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to -1 °C. Then, 0.64 g (0.0029 mol) of 4-nitrobenzenesulfonyl chloride was added dropwise. When the reaction mixture was kept at r.t. for 120 h, 0.73 g (70%) of white solid 7 was obtained (when the reaction mixture was kept at CHCl₃ b.p. for 24 h, 0.77 g (74%) of white solid 7 was obtained); m.p. 187–188 °C, Rf 0.10. IR (KBr, cm⁻¹): 1650 (C=N), 1600 (C=C), 1231 (SO₂ as) and 1194 (SO₂ sy), 1520 (NO₂ as) and 1362 (NO₂ sy), 3466 [N-(H)₂], 2967, 2854 (Csp₃s − H), 3236, 3328, 3388 (Csp₂ − H). ¹H-NMR (500 MHz, DMSO-d₆): 3.13 (t, J = 7.0 Hz, 2H, α-CH₂), 3.92 (t, J = 7.0 Hz, 2H, β-CH₂), 3.32 [m, 4H, O(CH₃)₂], 3.41 [m, 2H, N+(CH₃)₂] and 3.65 [m, 2H, N+(CH₃)₂], 7.28 (s, 2H, NH₂), 7.80–8.19 (m, 4H, Csp₂-H). ¹C-NMR (126 MHz, DMSO-d₆): 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 C₁₅H₁₈N₄O₆S (385.37): C, 43.57; H, 5.06. Found: C, 43.48; H, 5.13.

2-Amino-thia-1,5-diazaspiro[4.5]dec-1-en-5-aminium 4-nitrobenzenesulfonate (8). The reaction mixture consisting of 0.55 g (0.0029 mol) of compound 3 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to -1 °C. Then, 0.64 g (0.0029 mol) of 4-nitrobenzenesulfonyl chloride was added dropwise. When the reaction mixture was kept at r.t. for 84 h, 0.74 g (68%) of white solid 8 was obtained (when the reaction mixture was kept at CHCl₃ b.p. for 21 h, 0.51 g (47%) of white solid 8 was obtained); m.p. 230 °C, Rf 0.10. IR (KBr, cm⁻¹): 1642 (C=N), 1588 (C=C), 1229 (SO₂ as) and 1197 (SO₂ sy), 1519 (NO₂ as) and 1349 (NO₂ sy), 3308, 3396 [N-(H)₂], 2944 (Csp₃s − H), 3105, 3199, 3245 (Csp₂ − H). ¹H-NMR (500 MHz, DMSO-d₆): 3.11 (t, J = 7.0 Hz, 2H, α-CH₂), 3.86 (t, J = 7.0 Hz, 2H, β-CH₂), 2.87 [m, 2H, S(CH₃)₂] and 3.15 [m, 2H, S(CH₃)₂], 3.60 [m, 2H, N+(CH₃)₂] and 3.72 [m, 2H, N+(CH₃)₂], 7.37 (s, 2H, NH₂), 7.83–8.20 (m, 4H, Csp₂-H). ¹C-NMR (126 MHz, DMSO-d₆): 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 C₁₃H₁₈N₄O₆S (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-aminium 4-nitrobenzenesulfonate (9). The reaction mixture consisting of 0.72 g (0.0029 mol) of compound 4 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to -1 °C. Then, 0.64 g (0.0029 mol) of 4-nitrobenzenesulfonyl chloride was added dropwise. When the reaction mixture was kept at r.t. for 60 h, 0.88 g (70%) of white solid 9 was obtained (when the reaction mixture was kept at CHCl₃ b.p. for 19 h, 0.87 g (69%) of white solid 9 was obtained); m.p. 203 °C, Rf 0.15. IR (KBr, cm⁻¹): 1649 (C=N), 1599 (C=C), 1240 (SO₂ as) and 1189 (SO₂ sy), 1515 (NO₂ as) and 1350 (NO₂ sy), 3421 [N-(H)₂], 2790, 2880, 2915 (Csp₃s − H), 3118, 3290 (Csp₂ − H). ¹H-NMR (500 MHz, DMSO-d₆): 3.17 (t, J = 7.0 Hz, 2H, α-CH₂), 3.95 (t, J = 7.0 Hz, 2H, β-CH₂), 3.56 [m, 4H, (CH₃)₂], 3.49 [m, 2H, N+(CH₃)₂] and 3.98 [m, 2H, N+(CH₃)₂], 7.25 (s, 2H, NH₂), 7.81–8.53 (m, 9H, Csp₂-H). ¹C-NMR (126 MHz, DMSO-d₆): 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 C₁₉H₂₃N₅O₅S (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]oxypropanimidamide (10). The reaction mixture consisting of 0.59 g (0.0029 mol) of compound 5 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to −1 °C. Then, 0.64 g (0.0029 mol) of 4-nitrobenzenesulfonyl chloride was added dropwise. When the reaction mixture was kept at r.t. for 80 h, 0.93 g (82%) of white solid 10 was obtained (when kept at CHCl₃ b.p. for 36 h, 0.41 g (36%) of white solid 10 was obtained); m.p. 158 °C, Rf 0.75. IR (KBr, cm⁻¹): 1648 (C=N), 1617 (C=C), 1124 (SO₂) as and 1187 (SO₂ sy), 1520 (NO₂ sy) and 1365 (NO₂ sy), 3417 [N-(H₂)], 2791, 2920 (C(sp³)–H), 3110, 3237 (C(sp²)–H). ¹H-NMR (500 MHz, DMSO-d₆): 2.50 (t, J = 7.0 Hz, 2H, α-CH₂), 3.33 (m, 4H, O(CH₂)₂), 3.34 (m, 2H, NH₂), 3.85 (m, 2H, C(sp²)H), 4.85 (m, 2H, C(sp³)H). ¹³C-NMR (126 MHz, DMSO-d₆): 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 C₁₆H₁₅N₃O₅S: C, 49.35; H, 3.88. Found: C, 49.28; H, 3.45.

3.1.2. A General Procedure for the Synthesis of 2-Amino-1,5-diazaspiro[4.5]dec-1-ene-5-ammonium 2-Nitrobenzenesulfonate (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 CHCl₃, 0.0029 mol of DIPEA was added. The reaction mixture was cooled to −1 °C, and a solution of 0.0029 mol of 2-nitrobenzenesulfonyl chloride in 2 mL of CHCl₃ was added dropwise with stirring. The reaction mixture was then allowed to warm to r.t. (or up to the b.p. of CHCl₃) and stirred until the 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-ProOH.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 2-nitrobenzenesulfonate (11). The reaction mixture consisting of 0.5 g (0.0029 mol) of compound 1 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to −1 °C. Then, 0.64 g (0.0029 mol) of 2-nitrobenzenesulfonfchloride was added dropwise. When the reaction mixture was kept at r.t. for 35 h, 0.80 g (77%) of white solid 11 was obtained (when kept at CHCl₃ b.p. for 29 h, 0.78 g (75%) of white solid 11 was obtained); m.p. 153 °C, Rf 0.05. IR (KBr, cm⁻¹): 1657 (C=N), 1593 (C=C), 1221, 1232 (SO₂ as) and 1024 (SO₂ sy), 1541 (NO₂ as) and 1377 (NO₂ sy), 3399 [N-(H₂)], 2949 (C(sp³)–H), 3204, 3398 (C(sp²)–H). ¹H-NMR (500 MHz, DMSO-d₆): 2.05 (t, J = 9.95 Hz, 2H, α-CH₂), 3.77 (t, β-CH₂), 1.54, 1.71, 1.84, 6.0, (CH₂)₂, 3.35 [m, 4H, N(+)(CH₂)₂], 7.20d, 7.46–7.81 (m, 4H, C(sp²)H). ¹³C-NMR (126 MHz, DMSO-d₆): 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 C₁₄H₁₄N₂O₄S (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-en-5-ium 2-nitrobenzenesulfonate (12). The reaction mixture consisting of 0.5 g (0.0029 mol) of compound 2 in 20 mL of CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to −1 °C. Then, 0.64 g (0.0029 mol) of 2-nitrobenzenesulfonfchloride was added dropwise. When the reaction mixture was kept at r.t. for 25 h, 0.97 g (93%) of white solid 12 was obtained (when the reaction mixture was kept at CHCl₃ b.p. for 24 h, 0.67 g (64%) of white solid 12 was obtained); m.p. 148 °C, Rf 0.01. IR (KBr, cm⁻¹): 1637 (C=N), 1593 (C=C), 1207, 1228 (SO₂ as) and 1922 (SO₂ sy), 1549 (NO₂ as) and 1377 (NO₂ sy), 3387 [N-(H₂)], 2907 (C(sp³)–H), 3250, 3306, 3328 (C(sp²)–H). ¹H-NMR (500 MHz, DMSO-d₆): 2.09 (t, J = 9.75 Hz, 2H, α-CH₂), 3.88 (m, 2H, β-CH₂), 3.35 [m, 2H, O(CH₂)₂] and 3.60 [m, 2H, O(CH₂)₂], 3.88 [m, 4H, N(+)(CH₂)₂], 7.20 (s, 2H, NH₂), 7.45–7.81 (m, 4H, C(sp²)H). ¹³C-NMR (126 MHz, DMSO-d₆): 31.5, 62.2 (2C), 63.2, 122.0, 129.5, 130.6, 131.3, 140.0, 148.3, 169.2. Anal. Calcd for C₁₃H₁₄N₄O₄S (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-ium 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 CHCl₃ and 0.36 g (0.0029 mol) of DIPEA was cooled to −1 °C. Then, 0.64 g (0.0029 mol) of 2-nitrobenzenesulfonfchloride was added dropwise. When the reaction mixture was kept at r.t. for 104 h, the white precipitate
of the mixture of products 13a and 13b was obtained. After recrystallization, 0.16 g (25%) of 13b was obtained. After the evaporation of the filtrate from the recrystallization to 1/2 volume. 0.27 g (25%) of 2-nitrobenzenesulfonyl fluoride 13a was formed. When the reaction mixture was kept at CHCl₃ b.p. for 24 h, only 0.37 g (56%) of white solid 13b was obtained.

13a: m.p. 138–140 °C, Rᵣ 0.08. IR (KBr, cm⁻¹): 1647 (C=\text=N), 1604 (C=C), 1207, 1215 (SO₂ as) and 1024 (SO₂ sy), 1545 [N-(H₂)], 2936, 2964 (C(sp³-H)), 3152, 3258, 3302 (C(sp²-H)). ¹H-NMR (500 MHz, DMSO-d₆): 3.10 (t, J = 7.0 Hz, 2H, α-CH₂), 3.83 (t, J = 7.95 Hz, 2H, β-CH₂), 3.10 [m, 2H, S(CH₃)₂] and 3.55 [m, 2H, S(CH₂)₂], 3.10 [m, 2H, N+(CH₂)₂] and 3.68 [m, 2H, N(CH₂)₂], 7.26 (s, 2H, NH₂), 7.47–7.81 (m, 4H, C(sp²-H)). ¹³C-NMR (126 MHz, DMSO-d₆): 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 C₁₃H₁₃N₄O₅S₂ (374.44): C, 41.70; H, 4.85. Found: C, 41.67; H, 4.46.

13b: m.p. > 280 °C, Rᵣ 0.08. IR (KBr, cm⁻¹): 1659 (C=N); 1612 [H–N; (H₂)–O]; 670 [S–C]; 3135, 3230, 3380, 3384 (H–O, H–N). ¹H-NMR (500 MHz, DMSO-d₆): 3.10 (t, J = 7.0 Hz, 2H, α-CH₂), 3.85 (t, J = 7.95 Hz, 2H, β-CH₂), 2.85 [m, 2H, S(CH₃)₂] and 3.55 [m, 2H, S(CH₂)₂], 3.10 [m, 2H, N+(CH₂)₂] and 3.68 [m, 2H, N(CH₂)₂], 7.26 (s, 2H, NH₂). ¹³C-NMR (126 MHz, DMSO-d₆): 23.2, 31.5, 62.6, 64.7, 169.1. Anal. Calcd for C₁₉H₁₄ClN₃O₅S₂ (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 CHCl₃ and 0.38 g (0.0029 mol) of DIPEA was cooled to −1 °C. Then, 0.64 g (0.0029 mol) of 2-nitrobenzenesulfonyl chloride was added dropwise. When the reaction mixture was kept at r.t. for 34 h, 0.99 g (79%) of white solid 14 was obtained (when reaction mixture was kept at CHCl₃ b.p. for 24 h 1.02 g (81%) white solid 14 was obtained); m.p. 185–187 °C, Rᵣ 0.08. IR (KBr, cm⁻¹): 1647 (C=N), 1217, 1224 (SO₂ as) and 1024 (SO₂ sy), 1535 (NO₂ as) and 1366 (NO₂ sy), 3373 [N-(H₂)], 2837 (C(sp³-H)), 3161, 3300 (C(sp²-H)). ¹H-NMR (500 MHz, DMSO-d₆): 3.12 (t, J = 7.91 Hz, 2H, α-CH₂), 3.91 (t, J = 7.91 Hz, 2H, β-CH₂), 3.40 [m, 2H, N(CH₂)₂], 3.71 [m, 2H, N+(CH₂)₂], 3.54 [m, 4H, N(CH₂)₂], 6.82–7.81 (m, 11H, NH₂, C(sp²-H)). ¹³C-NMR (126 MHz, DMSO-d₆): 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 C₁₉H₁₄ClN₃O₅S₂ (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 CHCl₃ b.p. for 24 h 1.02 g (81%) white solid 14 was obtained].

3.2. Screening

The in vitro antidiabetic activity of 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. A total of 100 µL of α-amylase or α-glucosidase (1 U/mL) and 200 µL of the 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 incubated again at +37 °C for 20 min. The reaction was stopped by the addition of 500 µL of sodium carbonate (0.1 M). Since 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 obtained at a concentration of 10.0 mg/mL (positive control).

Simultaneously, a negative control was placed without the addition of the test compounds. All the samples were examined in triplets. The inhibitory activity was expressed as a percentage (%) of the degree of inhibition of α-glucosidase, in comparison to the negative control.
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 (\(\lambda = 0.71073 \text{ Å}\)). The intensities of the 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 the absorption using the Scala program [36]. The crystal structures were solved using SHELXT [37] program and refined with SHELXL [38] using OLEX2 software [39]. The structures were refined by the 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. The details of the experiment and the crystal parameters are presented in Tables S1 and S2 (Electronic Supporting Information).

4. Conclusions

The set of the reaction products of \(\beta\)-aminopropioamidoximes nitrobenzenesulfochlorination depends on the structure of the initial substrates and temperature. \(\beta\)-Aminopropioamidoximes with six-membered heterocycles in the \(\beta\)-aminogroup produce 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-nitrobenzenesulfochlorination of \(\beta\)-(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-nitrobenzenesulfonate and chloride hydrate. Heating leads to a regiospecific course of the reaction with the formation of only chloride hydrate.

The para-Nitrobenzenesulfochlorination of \(\beta\)-(benzimidazol-1-yl)propioamidoxime produces the O-para-nitrobenzenesulfochlorination product. The reaction time when the reaction mixture is heated is reduced by 2–3 times. The in vitro screening of the library of nitrobenzenesulfochlorination products for antidiabetic activity reveals two samples with high \(\alpha\)-glucosidase activity exceeding the activity of the acarbose standard: products of para-nitrobenzenesulfochlorination of \(\beta\)-(thiomorpholin-1-yl)propioamidoxime. The arsenal of the 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 the \(^1\)H NMR spectra, the slow inversion of six-membered nitrogen-containing \(\beta\)-heterocycles can be observed. These spiropyrazoline derivatives can be interesting objects in dynamic NMR spectroscopy, which would allow for the rotational barriers of six-membered heterocycles to be measured. 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. The 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 the six-membered cycle.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27072181/s1, Figure S1: Asymmetric units of the X-rayed compounds in a representation of atoms with thermal ellipsoids (\(p = 50\%\)); Table S1: Crystallographic data and the experimental details for compounds 6 and 8–10; Table S2: Crystallographic data and the experimental details for compounds 11–14; Compounds 6 and 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).
Author Contributions: Conceptualization, L.K.; methodology, G.B., E.Y. and A.K.; software, A.V., Z.S. (Zhanar Shaimerdenova); investigation, A.V., P.D., G.B., E.Y., A.K. and Z.S. (Zarina Shulgina), S.A., Z.S. (Zhanar Shaimerdenova) and K.A.; data curation, L.K.; writing—original draft preparation, L.K. and A.V.; writing—review and editing, L.K.; visualization, L.K., A.V. and E.Y.; project administration, E.Y.; funding acquisition, L.K. All authors have read and agreed to the published version of the manuscript.

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References
1. de la Torre, B.G.; Albericio, F. The Pharmaceutical Industry in 2021. An Analysis of FDA Drug Approvals from the Perspective of Molecules. Molecules 2022, 27, 1075. [CrossRef] [PubMed]
2. Global Diphenyl Pyrazoline Market Research Report 2021—Impact of COVID-19 on the Market. Available online: https://www.businessgrowthreports.com/TOC/19091429 (accessed on 26 March 2022).
3. Lévai, A.; Simon, A.; Jenei, A.; Kálmán, G.; Jekô, J.; Tóth, G. Synthesis of spiro-1-pyrazolines by the reaction of exocyclic α,β,γ,δ-unsaturated ketones with diazomethane. Arkivoc 2009, 12, 161–172. [CrossRef]
4. Dadiboyena, S.; Valente, E.J.; Hamme, A.T., II. Synthesis and Tautomerism of Spiro-Pyrazolines. J. Org. Chem. 2015, 80, 5514–5521. [CrossRef] [PubMed]
5. Dadiboyena, S.; Valente, E.J.; Hamme, A.T., II. Synthesis and Tautomerism of Spiro-Pyrazolines. J. Org. Chem. 2015, 80, 5514–5521. [CrossRef] [PubMed]
6. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid 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. Molecules 2021, 26, 967. [CrossRef]
7. Kayukova, L.A.; Praliyev, K.D.; Myrzabek, A.B.; Kainarbayeva, Z.N. Arylsulfochlorination of β-Arylsulphonates. Eur. J. Org. Chem. 2018, 27, 643–649. [CrossRef]
8. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
9. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
10. Kayukova, L.A.; Praliyev, K.D.; Myrzabek, A.B.; Kainarbayeva, Z.N. Arylsulfochlorination of β-Aminopropioamidoximes giving 2-Aminospiropyrazolylammonium arylsulfonates. Eur. J. Med. Chem. 2020, 197, 1075. [CrossRef] [PubMed]
11. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
12. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
13. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
14. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
15. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
16. Kayukova, L.A.; Uzakova, A.B.; Vologzhanina, A.V.; Akatan, K.; Shymardan, E.; Kabdrakhmanova, S.K. Rapid Boulton–Katritzky Rearrangement of 5-Substituted Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl. Chem. Heterocycl. Compd. 2018, 54, 643–649. [CrossRef]
17. Adamus-Grabicka, A.A.; Markowicz-Piasiecka, M.; Cieślak, M.; Królewska-Golińska, K.; Hikisz, P.; Kusz, J.; Malecka, M.; Budzisz, E. Biological Evaluation of 3-Benzylidenecromanes and Their Spiropyrazolines-Based Analogue. *Molecules* **2020**, *25*, 1613. [CrossRef]

18. Dandia, A.; Joshi, R.; Sehgal, V.; Sharma, C.; Saha, M. Synthesis of novel 3-spiro indolines containing benz(g) indazole, benz(h)pyrazolo(3,4-b)quinolone and naphthoisoaxol moiety. *Heterocycl. Commun.* **1996**, *2*, 281–286. [CrossRef]

19. Ibrahim, M.N.; El-Messmary, M.; Elarfi, M.G.A. Synthesis of Spiro Heterocyclic Compounds. *E-J. Chem.* **2010**, *7*, 55–58. [CrossRef]

20. Toh, G.; Szollosy, A. Synthesis and Stereochemistry of Spiropyrazolines. *J. Chem. Soc. Perkin Trans. II* **1986**, *12*, 1895–1898. [CrossRef]

21. Budzisz, E.; Paneth, P.; Geromino, I.; Muziol, T.; Rozalski, M.; Krajewska, U.; Pipiak, P.; Ponczek, M.B.; Malecka, M.; Kupcewicz, B. The cytotoxic effect of spiroflavanone derivatives, their binding ability to human serum albumin (HSA) and a DFT study on the mechanism of their synthesis. *J. Mol. Struct.* **2017**, *1137*, 267–276. [CrossRef]

22. Farghaly, T.; Abbas, I.; Hassan, W.; Loify, M. Study on regioselective synthesis of bioactive bis-spiropyrazolines using molecular orbital calculations. *Eur. J. Chem.* **2014**, *5*, 577–583. [CrossRef]

23. Chowdhury, M.A.; Senboku, H.; Tokuda, M. A New Synthesis of Ring-Fused Alkylidenecyclobutanes by Ring-Enlargement Reaction of Bicycle[5.1.0]alkylidene Derivatives. *Tetrahedron Lett.* **2003**, *44*, 3329–3332. [CrossRef]

24. Santos, B.S.; Gomes, C.S.B.; Pinho e Melo, T.M.V.D. Synthesis of chiral spipyrazoline-b-lactams and spirocyclopentyl-b-lactams from 6-alkylidenepenecillanates. *Tetrahedron* **2014**, *70*, 3812–3821. [CrossRef]

25. Ning, Y.; Kawahata, M.; Yamaguchi, K.; Otani, Y.; Ohwada, T. Synthesis, Structure and N-N Bonding Character of 1,1-Disubstituted Indazolium Hexafluorophosphate. *Chem. Commun.* **2018**, *54*, 1881–1884. [CrossRef]

26. 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. [CrossRef]

27. Kayukova, L.A.; Yergaliyeva, E.M.; Vologzhanina, A.V. Redetermination of the structure of 2-amino-8-thia-1,5-di azia spiro [4.5]dec-1-en-5-ium chloride monohydrate. *Acta Cryst.* **2022**, *E78*, 164–168. [CrossRef]

28. Yergaliyeva, E.M.; Kayukova, L.A.; Bazyrykova, K.B.; Gubenko, M.A.; Langer, P. Computational studies of the products of tosylation and para-nitrobenzenesulfochlorination. *J. Struct. Chem.* **2021**, *62*, 1969–1975. [CrossRef]

29. Yergaliyeva, E.M.; Kayukova, L.A.; Gubenko, M.A.; Baitursynova, G.P.; Uzakova, A.B. Free energies of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate. *Chem. J. Kaz.* **2022**, *75*, submitted.

30. Akinyede, K.A.; Oyewusi, H.A.; Hughes, G.D.; Ekpo, O.E.; Oguntibeju, O.O. In Vitro Evaluation of the Anti-Diabetic Potential of Aqueous Acetone Helichrysum petiolare Extract (AAHPE) with Molecular Docking Relevance in Diabetes Mellitus. *Molecules* **2022**, *27*, 155. [CrossRef]

31. Sbit, M.; Dupont, L.; Dideberg, O.; Goblet, M.; Dejardin, J.V. Structures de l’amino-3 phenyl-1 pyrazoline-2 et de l’amino-3 (m-trifluoromethylphenyl)-1 pyrazoline-2. *Acta Cryst.* **1988**, *C44*, 909–912. [CrossRef]

32. Claramunt, R.M.; Cozzini, P.; Domiano, P.; Elguero, J.; Fruchier, A. Structure of 3-amino-4,5-dihydropyrazoles in acid media: X-ray structure of 3-amino-1-phenyl-4,5-dihydropyrazol-2-ium picrate and the origin of broad signals in 1H NMR spectroscopy. *J. Chem. Soc. Perkin Trans. 2* **1995**, *1875–1878*.

33. Alabugin, I.V.; Kuhn, L.; Krivoshchakop, N.V.; Meahfyy, P.; Medvedev, M.G. Anomeric effect, hyperconjugation and electrostatics: Lessons from complexity in a classic stereoelectronic phenomenon. *Chem. Soc. Rev.* **2021**, *50*, 10212–10252. [CrossRef] [PubMed]

34. Motherwell, W.D.S.; Shields, G.P.; Allen, F.H. Automated assignment of graph-set descriptors for crystallographically symmetric molecules. *Acta. Cryst.* **2000**, *B56*, 466–473. [CrossRef] [PubMed]

35. Battye, T.G.G.; Kontogiannis, L.; Johnson, O.; Powell, H.R.; Leslie, A.G.W. iMOSFLM: A new graphical interface for diffraction-image processing with MOSFLM. *Acta Cryst.* **2011**, *D67*, 271–278. [CrossRef]

36. Evans, P. Scaling and assessment of data quality. *Acta Cryst.* **2006**, *62*, 72–82. [CrossRef] [PubMed]

37. Sheldrick, G.M. SHELXT—Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3–8. [CrossRef]

38. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3–8. [CrossRef]

39. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341. [CrossRef]