Synthesis, properties, and application of 4-nitrosemicarbazones*

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The studies of the condensation of 4-nitrosemicarbazide (4-NSC) with various aldehydes and ketones resulted in the development of an approach to the synthesis of *N*-nitrosemicarbazones, promising high-energy and biologically active compounds. Subsequent treatment with amines and alkalis led to the synthesis of water-soluble salts of nitrosemicarbazones, as well as the corresponding semicarbazones. The reaction of *N*,*N*´-diisopropyl- or *N*,*N*´-di-*tert*-butyl-1,2-ethanediimine with 4-nitrosemicarbazide led to the synthesis of glyoxal bis(nitrosemicarbazone) derivatives. A computer-aided screening using the PASS software showed a probability of high biological activity for the compounds obtained, whereas antiarrhythmic properties of camphor nitrosemicarbazone potassium salt were confirmed in experiments in rats.

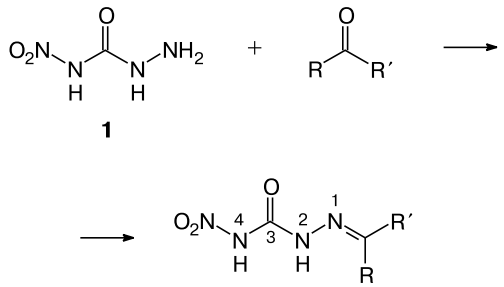
Key words: nitrosemicarbazones, nitrosemicarbazide, condensation.

Earlier, we reported a new direction in the preparation of nitramides and nitramines from dinitrourea,[1] including the synthesis of 4-nitrosemicarbazide[2] (**1**, 4-NSC). A relatively new compound **1** currently is being studied in different fields of chemistry and technique: mainly this is the preparation of nanopowders by the explosion and burning.[3] In the last years, the scope of application of semicarbazide **1** is considerably broadening, with the studies being carried out in the direction of the synthesis of both high-energy explosives[4] and organic compounds possessing biological activity.[5] It is known that many semicarbazones (analogs of **1**) possess potential biological activity and are widely used in clinical practice as antileukemic, tuberculostatic, antitumor, bacteriostatic, and antiseptic agents.[6—10] In this connection, it is interesting to study nitrosemicarbazones obtained by the condensation of compound **1** and its derivatives with aldehydes and ketones.

In the present work, we for the first time study the condensation reaction of compound **1** with different aldehydes and diacetyl, which leads to the formation of 4-nitrosemicarbazones (Scheme 1, Table 1). Reaction conditions were optimized for the synthesis of new compounds **2—8** in a series of 4-nitrosemicarbazones containing aromatic substituents, five-membered heterocyclic rings, and different functional groups (see Table 1).

The PubChem database contains analogs of compounds **2—8** (see Scheme 1) with the substituents R = = R´ = NH_2 (see Ref. 11) and R = Ph, R´ = Me (see Ref.

Scheme 1



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2—8

Compound	R	R´
2	3-MeO(4-HO)C_6H_3	H
3	2-HOC_6H_4	H
4	HC=NNHC(O)NH(NO_2)	H
5	2-Furyl	H
6	5-Nitro-2-furyl	H
7	MeC=NNHC(O)NH(NO_2)	Me
8	Bn	H

* Dedicated to Academician of the Russian Academy of Sciences N. S. Zefirov on the occasion of his 80th birthday.

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Table 1. Optimal conditions for the synthesis of compounds **2—8**

Carbonyl compound	Solvent	*t*/h	*T*/°C	Product	Yield* (%)
3-MeO(4-HO)C_6H_3CHO	Water	1	20	**2**	50
2-HOC_6H_4CHO	80% Aqueous ethanol	2	40	**3**	82
OHCCHO	Water	8	60	**4**	68
Furfural	Water	2	20	**5**	92
5-Nitrofurfural	Ethanol	2	20	**6**	43
MeC(O)C(O)Me	Water	4	20	**7**	79
BnCHO	Water	4	40	**8**	40

* Yield of isolated product.

12), however, there is no literature information on their preparation.

The condensation of 4-NSC **1** with aldehydes and ketones has a number of specific features: theoretically, acid catalysts should accelerate the reaction;[13] however, in our case an additional acidification decreased the yield of hydrazone **4** to 40% (Fig. 1). Such a dependence can be explained by the acidic properties of the starting 4-NSC **1**, that is why an additional introduction of an acid leads to the acid hydrolysis of the synthesized hydrazone in the course of the reaction.

An increase in the temperature leads to the increase in the reaction rate, but at a temperature above 60 °C 4-nitrosemicarbazide **1** undergoes decomposition, which results in the decrease in the condensation product yield (Fig. 2).

Despite of this, the obtained compound have proved to be quite stable due to the presence of the nitroamine substituent, which, apparently, strongly hinders cyclization to pyrazoline.

The IR spectra of compounds **2—8** do not contain absorption bands characteristic of the stretching vibrations of the NH_2 bond of the starting 4-NSC **1** at 3473—3371 cm^{-1}, with the absorption band of the NH bond vibrations retaining in the region of 3308—3117 cm^{-1}. The absorption band of the C=O bond shifts from 1666 to 1750—1693 cm^{-1} and the appearance of new absorption bands is observed at

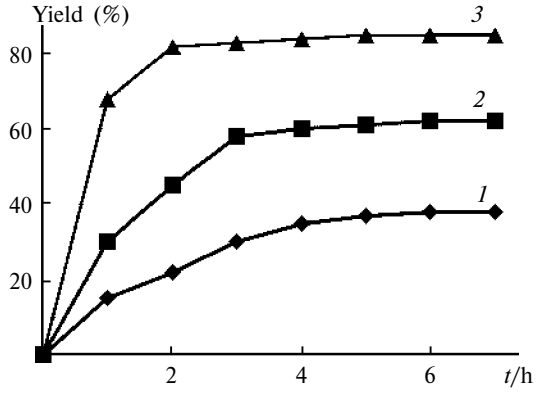


Fig. 1. Yield of glyoxal bis(nitrosemicarbazone) **4** *versus* reaction time (*t*) at pH = 2 (*1*), 4 (*2*), and 6 (*3*).

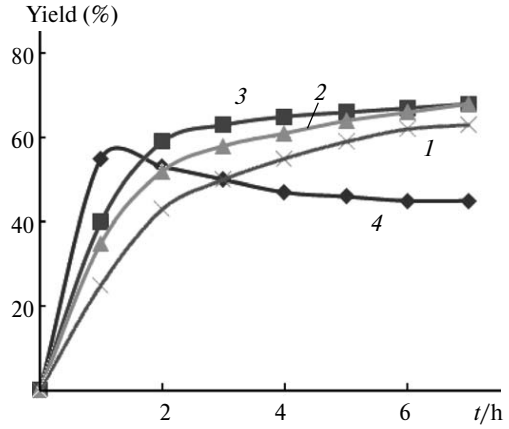


Fig. 2. Yield of glyoxal bis(nitrosemicarbazone) **4** *versus* reaction time (*t*) at the reaction temperature of 20 (*1*), 40 (*2*), 60 (*3*), and 80 °C (*4*).

1630—1583 cm^{-1}, which confirms the formation of the C=N bond and agrees with the literature data.[14—16] In the case of furfural nitrosemicarbazone **5** and 5-nitrofurfural nitrosemicarbazone **6**, a doublet of vibrations for the C=N bond is observed in the ranges of 1631—1601 and 1626—1603 cm^{-1}, respectively, the IR spectrum of compound **6** also exhibits a doublet of vibrations for the C=O bond at 1740 and 1703 cm^{-1} that indicates the presence of the isomeric forms of these compounds.

If the UV spectra of aliphatic aldehyde alkylhydrazones exhibit an absorption band at 230—240 nm, the absorption of semicarbazones of aromatic aldehydes and dicarbonyl compounds is characterized by a bathochromic shift of the absorption band to 300—320 nm attributed to the $\pi\rightarrow\pi^*$ transition.[13,17] As it was expected, compounds **2—8** have a characteristic absorption in the range 302—332 nm. Simultaneously, the peak at 258 nm corresponding to the nitroamide group retains; in the case of compounds **2**, **3**, and **8** this peak overlaps with absorption of the aromatic ring.

The ^{1}H NMR spectra of obtained compounds exhibit signals characteristic of the methine protons of the double bond at δ 7.73—8.65. The signals at δ 12.50—13.34 indicate the presence of the proton of the nitroamide group, while the

absence of a singlet for the protons of the NH_2 group at δ 6.42 agrees with the structure of semicarbazones.[17]

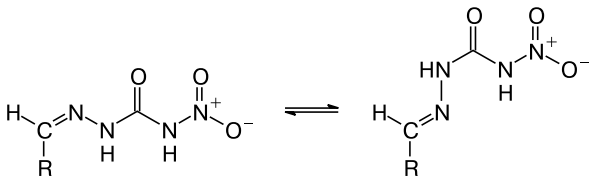
For hydrazones, there are known examples of both spatial and structural isomerism and in some case a tautomeric equilibrium of two or three forms. Geometric isomerism of hydrazones is a particular case of isomerism in the azomethine system due to the sp^2-hybridization of the imine nitrogen atom with a 120° angle between the bonds. By analogy with oximes, the isomer in which the substituted amino group and the methine hydrogen atom are in the *cis*-position relative to the C=N bond is usually regarded as a *syn*-isomer (*Z*-isomer), whereas the isomer with the *trans*-arrangement of this functional fragments, as an *anti*-isomer (*E*-isomer).[13]

The identification of compounds based on ^1H and ^{13}C NMR spectra is complicated by broadening of signals, which can be caused by the presence of the exchange processes due to the existence of *Z*- and *E*-isomers (Scheme 2).

Because of instability of compounds **2** and **3** in DMSO, it was impossible to accelerate exchange by increasing the temperature and observe the exchange-narrowed lines. Therefore, the NMR spectra were recorded at decreased temperature in acetone. Thus, for compound **2** the exchange was "frozen" at −90 °C, and the ^1H NMR spectrum exhibited a double set of signals with the ratio of intensities 4 : 6 assigned to *Z*- and *E*-isomers (Fig. 3). Attempted recording of the ^{13}C NMR spectrum for compound **2** did not give an acceptable signal-to-noise ratio because of its poor solubility in acetone.

The low-temperature ^1H and ^{13}C NMR spectra were recorded for compound **3**. In this case, the exchange was "frozen" already at −70 °C. However, in this case according to the ^1H NMR spectra (Figs 4 and 5) one of the isomers was found to be a predominant (more than 95%). It is possible that the stabilizing factor became the formation of the hydrogen bond between the hydroxy group at *ortho*-position of the aromatic ring and the C=O group.

Scheme 2



2, 3

In the present work, we did not study the structure of the isomers in detail. However, using the low-temperature spectra we clearly identified the signals undergoing exchange at room temperature, thus confirming the structure of the synthesized compounds.

Unfortunately, with ketones such as camphor the reaction proceeds with the formation of a mixture of unseparable products, and it was impossible to isolate camphor nitrosemicarbazone **9** (Scheme 3) in the pure form. Therefore, we attempted to select reaction conditions directed on the formation of hydrazones. The molecule of compound **1** is a multidentate one, therefore, three nitrogen atoms of compound **1** are regarded as potential centers for the attack by an active aldehyde molecule: the amine, the amide, and the nitroamine atoms. The probability of the formation of chemical bond is equal for each of the nitrogen atoms. The reactivity of the nitramine nitrogen atom can be blocked by

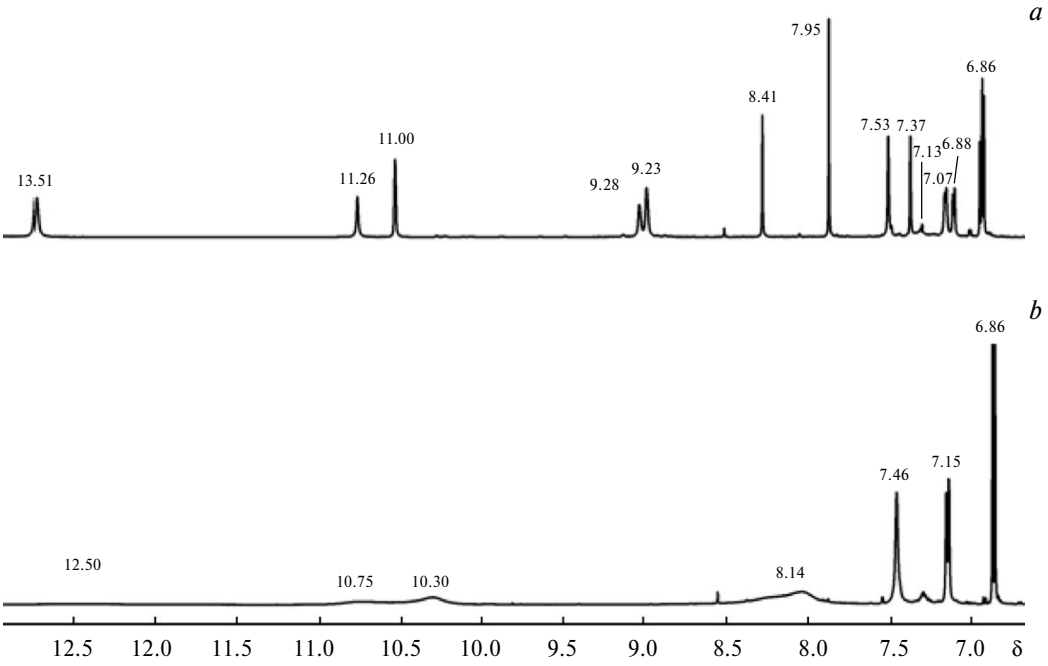


Fig. 3. Fragments of the ^1H NMR spectra of compound **2** recorded at −90 (*a*) and 20 °C (*b*).

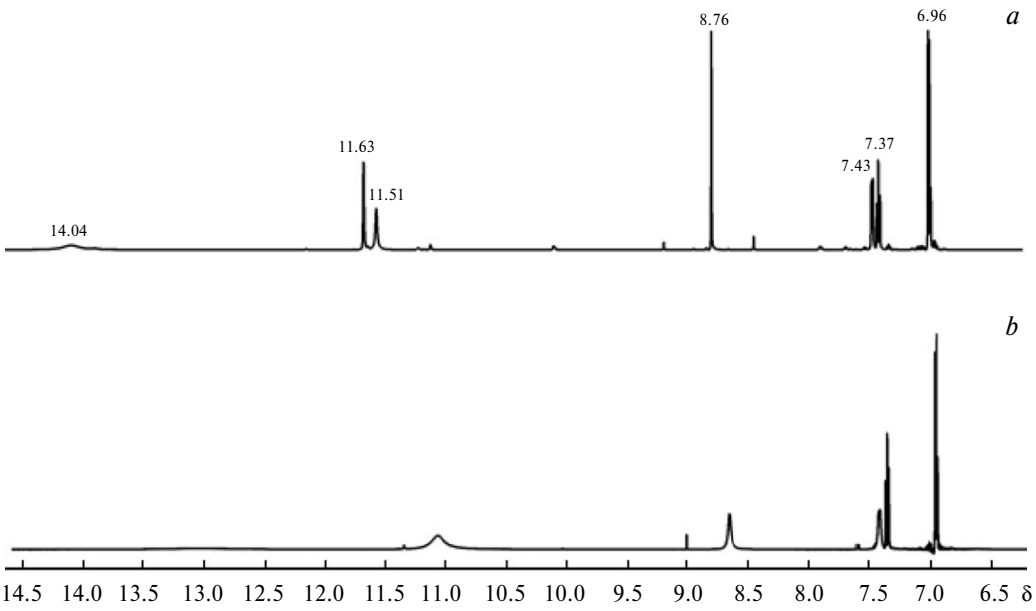


Fig. 4. ^{1}H NMR spectra of compound **3** recorded at −70 (*a*) and 20 °C (*b*).

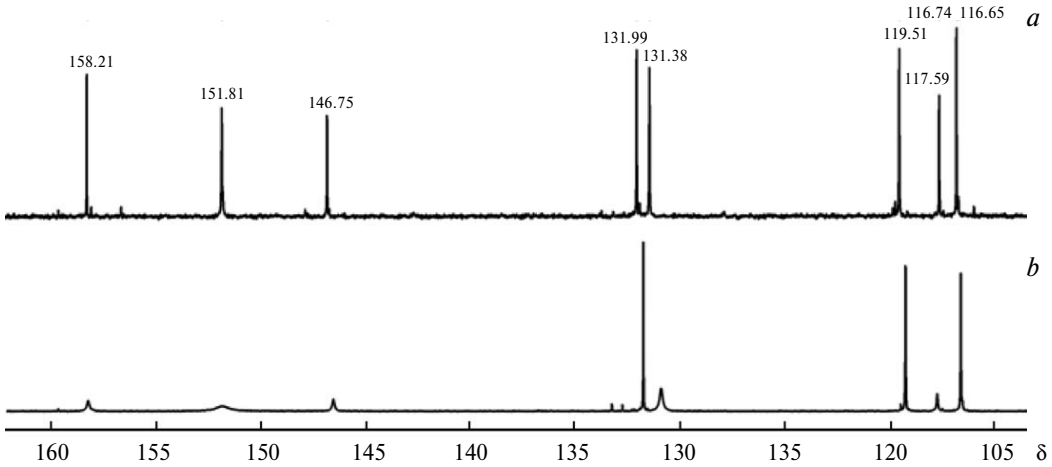


Fig. 5. ^{13}C NMR spectra of compound **3** recorded at −70 (*a*) and 20 °C (*b*).

the conversion of 4-NSC to the potassium salt. Its subsequent condensation with camphor leads to camphor nitrosemicarbazone potassium salt [**9**]K^+ (see Scheme 3).

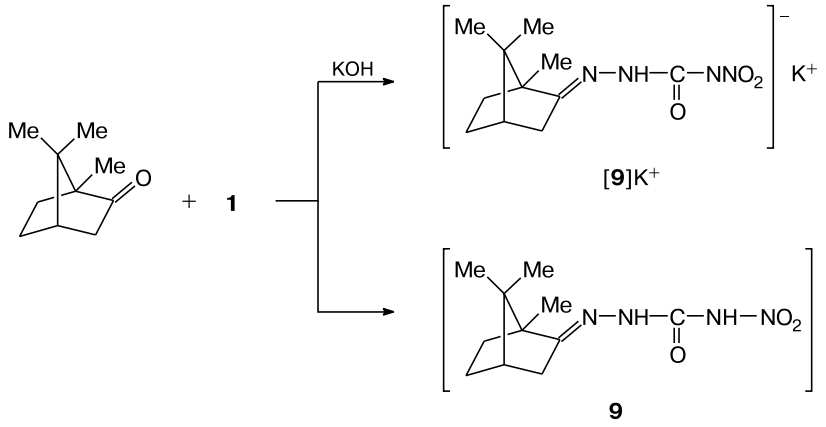
The use of K and Na salts of compound **1** in the condensation reactions with monofunctional aldehydes considerably increases the yield of hydrazones excluding the side reactions (Scheme 4).

A similar reaction of salt [**1**]K^+ with a bifunctional compound such as glyoxal leads to the formation of glyoxal bis(nitrosemicarbazone) dipotassium salt [**4**]K_2^+. The acidification of the reaction mixture removes the potassium cation to give glyoxal bis(nitrosemicarbazone) **4** in 98% yield (Scheme 5).

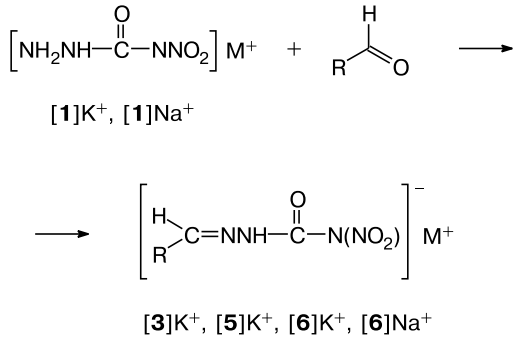
To sum up, we found that nitrosemicarbazones retain the salt-forming properties of starting nitrosemicarbazide[2] and readily form the corresponding onium salts upon treatment with bases.

Earlier, we have reported the synthesis of alkylsemicarbazides from 4-nitrosemicarbazide by the nucleophilic substitution reaction with amines.[18] A similar reaction is also characteristic of nitrosemicarbazones, which possess acidic properties and can be involved in the reaction with bases with the formation of both the salts and the alkyl-substituted semicarbazone derivatives. Taking glyoxal bis(nitrosemicarbazone) **4** as a model, we studied the reaction of nitrosemicarbazones with aqueous solutions of ammonia and amines. Thus, the onium salts of glyoxal bis(nitrosemicarbazone) **10—16** are formed upon cooling. Compound **4** was also obtained by the condensation of glyoxal with 4-nitrosemicarbazide ammonium salt at room

Scheme 3



Scheme 4



M = K, Na
R = 2-HOC_6H_4 (**3**), 2-furyl (**5**), 5-nitro-2-furyl (**6**)

temperature (Scheme 6). An excess of ammonia or amines upon reflux of the solution decomposes compound **4** to glyoxal bis(semicarbazone) and its alkyl-substituted derivatives **17—22** (see Scheme 6). The process of decomposition can be monitored using UV spectroscopy tracking the disappearance of the absorption maximum at 258 nm.

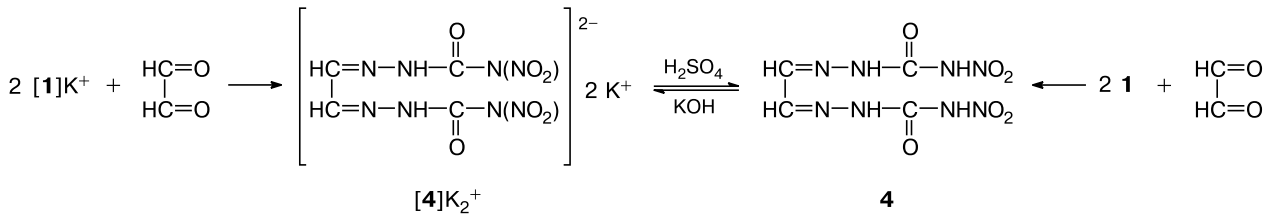
This property of the nitroamine group of nitrosemicarbazones was used in the counter synthesis of known hydrazones, which confirmed the structure of earlier unknown *N*-nitrohydrazones. Thus, nitrosemicarbazones **2** and **4—6** were treated with ammonia upon reflux to obtain known semicarbazones of salicylaldehyde, glyoxal, furfural, and nitrofurfural in quantitative yields.

The reaction with secondary amines is spatially hindered, therefore, more time is required for the reaction to reach completion. A side reaction of alkaline hydrolysis greatly decreases the yield of the target product. As it is seen from the data given in Table 2, the yield of the target products strongly depends on the amine basicity. Thus, in the formation of the salt the higher the basicity of amine, the higher is the yield of the target product. Apart from that, the yield of the product is affected by the steric and natural factors. In the nucleophilic substitution reaction, a reverse dependence is observed because of more drastic reaction conditions and acceleration in the proceeding of alkaline hydrolysis of the target product.

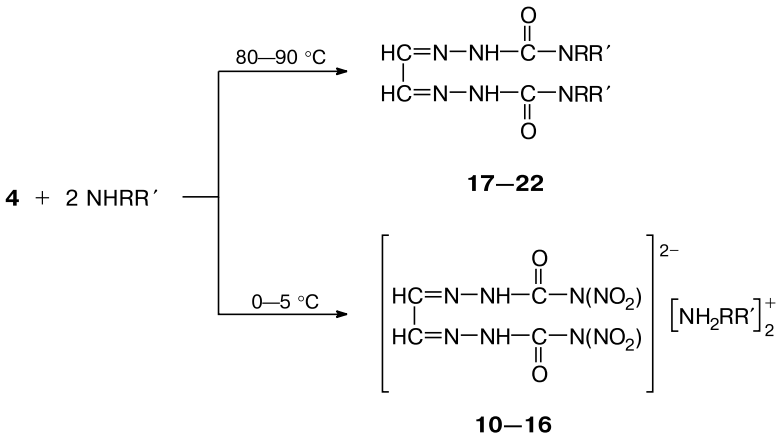
The use of dimethylsemicarbazide **23** and diethylsemicarbazide **24** in the condensation with glyoxal gives higher yields than bissemicarbazones **19** and **20**: 67 and 85%, respectively (Scheme 7).

To increase the yield of spatially branched salts of primary amines **15** and **16**, we suggested an alternative method consisting in transimination of *N*,*N*′-diisopropyl-[19] (**25**) or *N*,*N*′-di-*tert*-butyl-1,2-ethanediimines[20] (**26**) with

Scheme 5



Scheme 6



Compound	R	R′	Compound	R	R′
10, **17**	H	H	**14**, **20**	Et	Et
11	H	NH_2	**15**, **21**	H	Pr^i
12, **18**	H	Me	**16**, **22**	H	Bu^t
13, **19**	Me	Me			

4-nitrosemicarbazide **1** in aqueous acetonitrile. The yields of compounds **15** and **16** were increased to 88 and 78%, respectively (Scheme 8).

As it is seen from Tables 3 and 4 summarizing the data on the explosive properties and the sensitivity to impact[21] and friction[22] of glyoxal bis(nitrosemicarbazone) **4** and its salts **10** and **11**, these compounds are of interest as new high energy compounds.

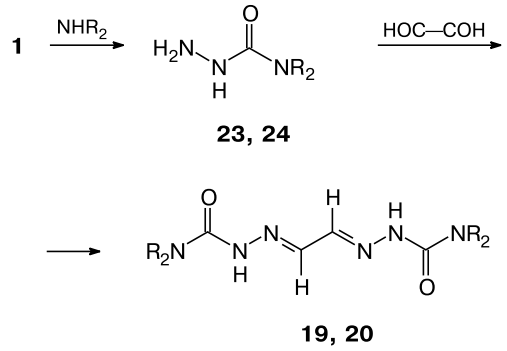
The tests of detonation velocity (Table 4) were carried out on the samples pressed in blocks prepared by a cold pressing method. An increase in the pressure above 1800 kg cm^{-2} led to disintegration (repressing) of the sample. To avoid this, we used wet pressing with EtOH or water. Compounds **10** and **11** possess properties allowing their use in ammunition as a combustion catalysts: the low sensitivity to mechanical action as compared to compound **4**, with retention of explosive characteristics. Therefore, we studied the burning rate of these products (Table 5). The flegmatization with urethane (5%) strongly decreases the burning rate of the glyoxal bis(nitrosemicarbazone) salts from 3800 to 1400 mm s^{-1}.

Table 2. Reaction conditions and yields of products **10—22**[a]

Amine	pK_a[b]	Product	Yield (%)
NH_3	9.25	**10**	84
NH_2NH_2	5.9	**11**	97
NH_2Me	10.66	**12**	59
$NHMe_2$	10.73	**13**	100
$NHEt_2$	10.93	**14**	27
NH_2Pr^i	10.53	**15**	48
NH_2Bu^t	10.6	**16**	70
NH_3	9.25	**17**	98
NH_2Me	10.66	**18**	40
$NHMe_2$	10.73	**19**	27
$NHEt_2$	10.93	**20**	20
NH_2Pr^i	10.53	**21**	32
NH_2Bu^t	10.6	**22**	39

[a] Reaction temperature 0—5 °C for salts **10—16** and 85—90 °C for semicarbazones **17—22**.
[b] Water, 25 °C.

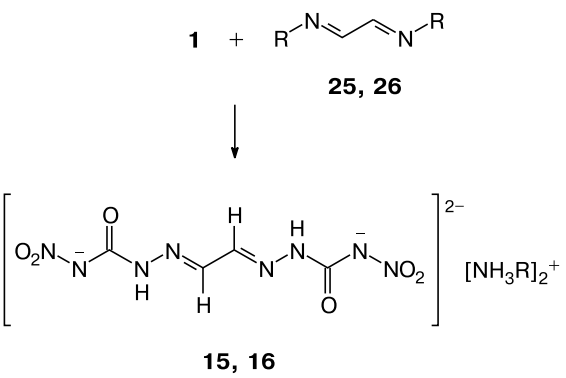
Scheme 7



R = Me (**19**, **23**), Et (**20**, **24**)

To assess the potential of these compounds as biologically active agents, we carried out a virtual screening using the PASS program.[23] This program proceeding from the structural formula of compounds and using a uniform de-

Scheme 8



R = Pr^i (**15**, **25**), Bu^t (**16**, **26**)

scription of chemical structure and a universal mathematical algorithm of finding the "structure—activity" relationship makes it possible to predict the probability of different kinds of pharmacological activity. Based on this prediction, it was shown that with a high probability the nitrosemicarbazones should possess antacid, cytoprotective, antiischemic, antiinfective, antiprotozoal, and antituberculosis properties. In this connection, the compounds possessing high coefficients of probability of exhibiting antiarrhythmic activity were studied *in vivo*.

Biological experiments were carried out in the Laboratory of Pharmacological Studies of the N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences. Acute toxicity of nitroderivatives **2—6** and salt [**9**]K$^+$ was determined in rats, using a single intragastric administration by Kerber's method. The studies showed that the half lethal dose (LD_{50}) for all the compounds is higher than 1000 mg kg^{-1}, therefore, these substances belong to the 3 class of moderately toxic compounds. The studies of antiarrhythmic activity were carried out by intravenous administration of test compounds in different doses. It was shown that compound [**9**]K$^+$ exhibited high activity in the doses 4 and 0.4 mg kg^{-1} on the calcium chloride arrhytmia and in the dose of 0.4 mg kg^{-1} on a model of adrenalin arrhytmia it prevented development of the arrhytmia in 80% of cases.

It is known that vanillin, being a source of a methoxyphenol substituent and a methine fragment to the structure of aminoketones, plays an exclusive role in the synthesis of biologically active compounds, analogs of cardioprotectors, analgesics, bactericides, *etc.*[24] Vanyllal ni-

Table 4. Determination of the rate of explosive conversion of compounds **4**, **10**, and **11**

Compound	Sample				Detonation /m s^{-1}
	Mass /g	Diameter /mm	Height /mm	Density /g cm^{-3}	
4[a]	33.0	25.3	49.5	1.33	8000
4[a]	32.5	25.3	48	1.35	8130
10[b]	20	25.2	38.3	1.05	4740
10[b]	20	25.2	39	1.03	4640
11[c]	20.5	20.1	45.8	1.41	6890

[a] Specific pressure of pressing 430 kg cm^{-1}.
[b] Specific pressure of pressing 1000 kg cm^{-1}.
[c] Specific pressure of pressing 1800 kg cm^{-1}.

Table 3. Sensitivity to mechanical impact and explosive properties of hydrazones **4**, **10**, and **11**

Compound	Sensitivity			
	to impact[a]		to friction[b]	
	explosion frequency (%)[c]	low level/mm (load weight/kg)	low level /kgf cm^{-2}	explosion frequency (%)[d]
4	76	<50 (10) 200 (2)	2000	8
10	0	≥500 (10) — (2)	4000	—[e]
11	16	≥500 (10) — (2)	≥7000	—

Note. The low level of sensitivity to impact is the minimum height of the load drop at which at least in one out of 10 or 25 trials an explosion took place. The low level of sensitivity to friction is the maximum pressure of pressing of the blasting explosive sample placed between steel planes at which none of the explosions out of 25 trials took place at an impact shift of one plane relative to the other.
[a] The Kast brisance meter.[21]
[b] A K-44-111 instrument.[22]
[c] Explosion frequency at the dropped load weight P = 10 kg and the height from which the impact is produced H = 250 mm.
[d] Explosion frequency at P_{spec} = 2200 kgf cm^{-2}.
[e] Not tested, since the compound possesses low sensitivity to friction.

Table 5. Sample characteristics, parameters of combustion initiation, and combustion rate of the samples of compounds **10** and **11**

Compound	Sample[a,b]			Igniter mass[c] /g	Combustion rate /mm S^{-1}
	Mass/g	Height/mm	Density/g cm^{-3}		
			Without flegmatization		
10	9.7	32.5	0.94	3	1350
11	10.7	31.5	1.10	2	3100
			Flegmatization with urethane		
10[d]	10.0	32.5	0.97	2	8
11	10.2	29.0	1.10	2	1450
	12.0	37.8	1.00	3	1500
	17.2	48.5	1.12	5[e]	1400

[a] If not indicated otherwise, pressing force is 800 kg cm^{-2}.
[b] Diameter of samples 20.1 mm.
[c] If not indicated otherwise, igniter is trotyl.
[d] Pressing force is 1200 kg cm^{-2}.
[e] Igniter is ballistite.

trosemicarbazone **2** has proved inactive on a model of calcium chloride arrhytmia, but showed good activity in the dose of 0.5 mg kg^{-1} on a model of adrenalin arrhytmia. In the doses 5 and 0.05 mg kg^{-1} no recovery of electrocardiogram (ECG) occurred.

During studies of antihypertensive properties, compound [**9**]K^+ was found to decrease the pressure in rats with normal arterial pressure by 10% in a dose of 4 mg kg^{-1}. The decrease in the pressure was observed 5 min after the injection of the test compound in femoral vein. An increase in the dose of test compound led to insignificant (3%) decrease in the pressure.

In conclusion, in the present work we showed a possibility to synthesize 4-nitrosemicarbazones of various aldehydes and ketones, selected the optimal conditions for the synthesis of earlier unknown compounds **2—8**, their sodium, potassium, and onium salts, as well as alkyl derivatives. The synthesized compounds possess a number of interesting properties: glyoxal nitrosemicarbazone and its salts can be used as explosives; nitrosemicarbazones of other aldehydes are regarded as intermediants of pharmaceutical agents.

Experimental

Melting points were measured on a VEB Analytik Dresden PHMK device. UV spectra were recorded on a Varian Cary 50 spectrophotometer in water. IR spectra of the samples in KBr pellets were recorded on a FT-801 Fourier-transform spectrometer in the region from 4000 to 500 cm^{-1}. Elemental composition was determined on FlashEATM 1112 elemental C,H,N,O-analyzer. ^1H and ^{13}C NMR spectra of the samples were recorded on Bruker DRX-500 (500.13 and 125.75 MHz, respectively), Bruker AV-400 (400.13 and 100.62 MHz, respectively), and Bruker AV-600 spectrometers (600.30 and 150.95 MHz, respectively) in DMSO-d_6 (δ_H 2.50, δ_C 39.50), acetone-d_6 (δ_H 2.04, δ_C 29.8 and 206), and D_2O (δ_H 4.80). Chemical shifts in ^1H and ^{13}C NMR spectra are given relative to the residual signals of solvents (an internal standard). ^{15}N NMR spectra were recorded on a Bruker AV-600 spectrometer (60.84 MHz); chemical shifts are given relative to ammonia (an external standard).

The starting nitrosemicarbazide **1** was synthesized from dinitrourea upon treatment with hydrazine hydrate in aqueous solution at the temperature below 30 °C. Further treatment with KOH or NaOH gave its potassium ([**1**]K^+) and sodium ([**1**]Na^+) salts.[25] Dinitrourea was obtained in 85% yield by nitration of urea with a H_2SO_4—HNO_3 mixture according to the published procedure[26] with subsequent washing with trifluoroacetic acid.

Synthesis of dinitrosemicarbazones 2—8 (general procedure). An aldehyde (1.2 mmol) (2 mmol of the aldehyde were in the case of bis-nitrosemicarbazones **4** and **7**) was slowly added to a solution of 4-nitrosemicarbazide (1 mmol) in the corresponding solvent with vigorous stirring. Reaction conditions are given in Table 1. After cooling, a precipitate formed was collected by filtration and recrystallized from water or ethanol.

Vanillal nitrosemicarbazone (2). M.p. 184 °C. UV (H_2O), λ_{max}/nm: 328, 211. IR (KBr), ν/cm^{-1}: 3466 (OH); 3308 (NH); 3042, 2947, 2787 (CH_{ring}); 1704 (C=O); 1602 (C=N); 1543 (N—NO_2); 1513, 1430, 1346, 1295, 1270 (N—NO_2); 1194, 1120 (C—N); 1067 (N—N); 1018, 943. ^1H NMR (500.13 MHz, acetone-d_6), δ: 3.86 (s, 1 H, OCH_3); 6.86 (d, 1 H, ArH, ^3J = 8.0 Hz); 7.15 (d, 1 H, ArH, ^3J = 8.0 Hz); 7.46 (s, 1 H, ArH); 8.14 (br.s, 2 H, OH, CH=N); 10.74 and 10.27 (both br.s, 1 H each, NH); 12.50 (br.s, 1 H, $NHNO_2$). ^{13}C NMR (125.75 MHz, acetone-d_6), δ: 56.2, 110.0, 115.8, 123.4, 126.6, 145.9, 148.0; 148.7, 150.0, 150.6). Found (%): C, 42.11; H, 4.23; N, 22.37. $C_9H_{10}N_4O_5$. Calculated (%): C, 42.52; H, 3.93; N, 22.05.

Salicylaldehyde nitrosemicarbazone (3). M.p. 172 °C. UV (H_2O), λ_{max}/nm: 302, 284, 211. IR (KBr), ν/cm^{-1}: 3236 (NH); 3050, 2970, 2785 (CH_{ring}); 1693 (C=O); 1603 (C=N); 1575 (δ(NH)); 1524 (N—NO_2); 1489, 1390, 1335 1263 (N—NO_2); 1187 (C—N); 1128 (C—N); 1109, 1067 (N—N); 970. ^1H NMR (500.13 MHz, acetone-d_6), δ: 6.93 (dd, 1 H, ArH, ^3J = 8.5 Hz, ^4J = 1.2 Hz); 6.93 (ddd, 1 H, ArH, ^3J = 7.3 Hz, ^3J = 7.3 Hz, ^4J = = 1.2 Hz); 7.33 (ddd, 1 H, ArH, ^3J = 7.3 Hz, ^3J = 8.6 Hz, ^4J =

= 1.6 Hz); 7.40 (dd, 1 H, ArH, ^3J = 7.3 Hz, ^4J = 1.6 Hz); 8.65 (br.s, 1 H, CH=N); 11.08 (br.s, 2 H, NH, OH); 13.06 (br.s, 1 H, $NHNO_2$). ^{13}C NMR (125.75 MHz, acetone-d_6), δ: 116.7, 117.8, 119.3, 131.0, 131.8, 146.6, 151.9, 158.3. Found (%): C, 43.23; H, 3.21; N, 24.58. $C_8H_8N_4O_4$. Calculated (%): C, 42.86; H, 3.57; N, 25.00.

Glyoxal bis(nitrosemicarbazone) (4). M.p. 251 °C. UV (H_2O), λ_{max}/nm: 331.7, 258, 214. IR (KBr), ν/cm^{-1}: 3297 (NH); 3182, 2940 (CH); 1750, 1740 (C=O); 1583 (C=N, NNO_2, δ(NH)); 1473, 1417, 1316 (NNO_2); 1219, 1116 (C—N); 1043 (N—N); 967, 941. ^1H NMR (400.13 MHz, DMSO-d_6), δ: 7.82 (br.s, 1 H, CH); 11.69 (s, 1 H, NH). ^{13}C NMR (100.62 MHz, DMSO-d_6), δ: 147.98, 144.86. Found (%): C, 18.36; H, 2.41; N, 42.85. $C_4H_6N_8O_6$. Calculated (%): C, 18.32; H, 2.29; N, 42.75.

Furfural nitrosemicarbazone (5). M.p. 135 °C. UV (H_2O), λ_{max}/nm: 315, 257, 204. IR (KBr), ν/cm^{-1}: 3287 (NH); 3146, 3117, 3084 (CH); 2979—2801 ($CH_{fur.ring}$); 1703 (C=O); 1630, 1601 (C=N); 1580 (δ(NH)); 1537 (N—NO_2); 1476, 1410, 1335 (N—NO_2); 1192, 1164 (C—N); 1111, 1060 (N—N); 1017, 942. ^1H NMR (400.13 MHz, DMSO-d_6), δ: 6.61 (dd, 1 H, ArH, ^3J = = 3.40 Hz, ^3J = 1.78 Hz); 6.93 (d, 1 H, ArH, ^4J = 3.40 Hz); 7.82 (d, 1 H, ArH, ^3J = 1.78 Hz); 8.09 (br.s, 1 H, ArH); 11.47 (s, 1 H, NH); 13.34 (br.s, 1 H, $NHNO_2$). ^{13}C NMR (100.62 MHz, DMSO-d_6), δ: 112.3, 114.2, 138.1, 145.4, 147.7, 149.9. Found (%): C, 36.66; H, 2.61; N, 27.86. $C_6H_6N_4O_4$. Calculated (%): C, 36.36; H, 3.03; N, 28.28.

Nitrofurfural nitrosemicarbazone (6). M.p. 226 °C. UV (H_2O), λ_{max}/nm: 350, 284, 250. 201. IR (KBr), ν/cm^{-1}: 3330 (NH); 3251, 3152, 3118, 3011 (CH); 2873 ($CH_{fur.ring}$); 1741, 1703 (C=O); 1626, 1604 (C=N, δ(NH)); 1545 (N—NO_2, NO_2); 1476, 1395, 1347 (NO_2); 1316, 1254 (N—NO_2); 1221, 1167 (C—N); 1068 (N—N); 1017, 963. ^1H NMR (500.13 MHz, acetone-d_6), δ: 7.23 (d, 1 H, ArH, ^3J = 3.8 Hz); 7.61 (d, 1 H, ArH, ^3J = 3.8 Hz); 8.25 (br.s, 1 H, CH=N); 11.01 (br.s, 1 H, NH=N); 13.00 (br.s, 1 H, $NHNO_2$). ^{13}C NMR (125.75 MHz, acetone-d_6), δ: 113.3, 114.0, 146.8, 151.1, 151.2, 152.1. Found (%): C, 29.56; H, 2.28; N, 28.80. $C_6H_5N_5O_6$. Calculated (%): C, 29.63; H, 2.06; N, 28.81.

Diacetyl bis(nitrosemicarbazone) (7). M.p. 258 °C. UV (H_2O), λ_{max}/nm: 324, 257, 208. IR (KBr), ν/cm^{-1}: 3356, 3323 (NH); 3143, 3075, 2977, 2798 (CH_3); 1709 (C=O); 1597 (C=N, N—NO_2, δ(NH)); 1524, 1343 (N—NO_2); 1412, 1245, 1205 (C—N); 1143, 1049 (N—N); 981, 960. ^1H NMR (400.13 MHz, DMSO-d_6), δ: 2.11 (s, 6 H, CH_3); 10.57 (s, 2 H, NHN=); the signal for the proton of the $NHNO_2$ group was not found because of exchange with water. ^{13}C NMR (100.62 MHz, DMSO-d_6), δ: 11.3, 147.9, 151.5. Found (%): C, 24.63; H, 3.34; N, 38.85. $C_6H_{10}N_8O_6$. Calculated (%): C, 24.83; H, 3.45; N, 38.62.

Phenylacetaldehyde nitrosemicarbazone (8). M.p. 118 °C. UV (H_2O), λ_{max}/nm: 273, 207. IR (KBr), ν/cm^{-1}: 3256, 3128 (NH); 3060, 3027, 2973, 2802 (CH_{ring}); 1676 (C=O); 1639, 1612, 1538 (C=N, N—NO_2, δ(NH)); 1493, 1375, 1333 (N—NO_2); 1417, 1221 (C—N); 1088, 1056 (N—N); 987. Found (%): C, 48.63; H, 4.34; N, 25.45. $C_9H_{10}N_4O_3$. Calculated (%): C, 48.87; H, 4.07; N, 25.34.

Camphor nitrosemicarbazone potassium salt [9]K$^+$. Potassium hydroxide (0.56 g, 0.01 mol) was gradually added to a solution of nitrosemicarbazide (1.2 g, 0.01 mol) in 50% aqueous dioxane (160 mL). The reaction mixture was allowed to stand for 10 min at room temperature. Then, a solution of camphor (1.52 g, 0.01 mol) in dioxane (10 mL) was added with vigorous stirring, keeping temperature below 25 °C. Then the reaction mixture was allowed to stand for 17 h at 20 °C and concentrated dry. The salt was washed with diethyl ether (3×20 mL) from traces of camphor. Then, the precipitate was dissolved in water (10 mL) and reprecipitated with ethanol (30 mL), an impurity of nitrosemicarbazide potassium salt was filtered off, the filtrate was concentrated dry to obtain a pure camphor nitrosemicarbazone potassium salt. The yield was 0.76 g (30%), m.p. 118—120 °C. IR (KBr), ν/cm^{-1}: 3327, 3050, 1665, 1600, 1532, 1346, 1261, 1186; 1118, 1085, 1045, 957, 784, 684. Found (%): C, 45.52; H, 5.65; N, 20.06. $C_{11}H_{17}N_4O_3K$. Calculated (%): C, 45.20; H, 5.82; N, 19.18.

Glyoxal bis(nitrosemicarbazone) dipotassium salt [4]$^+$. ***A.*** A 40% aqueous glyoxal (4.4 mL, 0.037 mol) was added to a solution of nitrosemicarbazide potassium salt (11.85 g, 0.075 mol) in water (200 mL) with stirring. The mixture was allowed to stand for 8 h at room temperature. A precipitate formed was collected by filtration and recrystallized from water. The yield was 11.6 g (92%).

B. A mixture of compound **4** (1.31 g, 0.005 mol) and KOH (0.56 g, 0.01 mol) in distilled water (150 mL) was allowed to stand for 30 min at room temperature. A yellow precipitate formed was collected by filtration and recrystallized from water. The yield was 1.2 g (71%). T.decomp. 235 °C. UV (H_2O), λ_{max}/nm: 334, 256, 203. IR (KBr), ν/cm^{-1}: 3480, 3403 (NH); 3193, 3034 (CH); 1687 (C=O); 1660 (C=N); 1580 (δ(NH)); 1541, 1369, 1336 (N—NO_2); 1231, 1144 (C—N); 1072 (N—N); 978. ^1H NMR (500.13 MHz, DMSO-d_6), δ: 7.66 (s, 1 H, CH); 10.59 (s, 1 H, NH). ^{13}C NMR (100.62 MHz, DMSO-d_6), δ: 140.86, 157.8. Found (%): C, 12.98; H, 1.69; N, 29.58. $C_4H_4N_8O_6K_2$. Calculated (%): C, 12.83; H, 2.17; N, 29.94.

Synthesis of salts 10—14 (general procedure). An amine (0.03 mol) was added in portions to a suspension of compound **4** (2.62 g, 0.01 mol) in distilled water (200 mL) with stirring and cooling to 0—5 °C. The mixture was allowed to stand for 1 h. A precipitate formed was collected by filtration and recrystallized from water. To isolate compound **12**, the reaction mixture was concentrated dry on a rotary evaporator, a precipitate was recrystallized from 50% aqueous ethanol. The yields of salts **10—14** are given in Table 2.

Glyoxal bis(nitrosemicarbazone) diammonium salt (10). T.decomp. 255 °C. UV (H_2O), λ_{max}/nm: 334; 258, 205. IR (KBr), ν/cm^{-1}: 3435, 3190, 3034, 1616, 1578, 1540, 1388, 1328, 1308, 1234, 1154, 1068, 914. Found (%): C, 16.3; H, 4.04; N, 47.14. $C_4H_{12}N_{10}O_6$. Calculated (%): C, 16.22; H, 4.05; N, 47.30.

Glyoxal bis(nitrosemicarbazone) hydrazinium salt (11). M.p. 180 °C. UV (H_2O), λ_{max}/nm: 330, 258.4, 213. IR (KBr), ν/cm^{-1}: 3433, 3338, 3188, 3032, 1658, 1612, 1575, 1538, 1383, 1315, 1253, 1152, 1097, 1068, 929, 871, 780, 692. Found (%): C, 16.08; H, 2.91; N, 47.46. $C_4H_{10}N_{10}O_6$. Calculated (%): C, 16.33; H, 3.40; N, 47.62.

Glyoxal bis(nitrosemicarbazone) methydammonium salt (12). M.p. 218—220 °C. UV (H_2O), λ_{max}/nm: 330, 258, 212. IR (KBr), ν/cm^{-1}: 3436, 3190, 3050, 1658, 1642, 1572, 1530, 1502, 1401, 1222, 1132, 1066, 967, 862, 760. ^1H NMR (600.30 MHz, D_2O), δ: 2.56 (s, 6 H, CH_3); 7.77 (s, 2 H, CH=N). ^{13}C NMR (150.95 MHz, D_2O), δ: 24.01, 143.93, 158.86. Found (%): C, 21.89; H, 4.67; N, 43.42. $C_6H_{16}N_{10}O_6$. Calculated (%): C, 22.22; H, 4.94; N, 43.21.

Glyoxal bis(nitrosemicarbazone) dimethydammonium salt (13). M.p. 92—96 °C. UV (H_2O), λ_{max}/nm: 334, 257, 214. IR (KBr), ν/cm^{-1}: 3467, 3204, 3022, 2964, 2850, 2779, 2438, 1650, 1581, 1539, 1429, 1302, 1237, 1146, 1017, 928, 871. Found (%): C, 27.53; H, 5.94; N, 39.89. $C_8H_{20}N_{10}O_6$. Calculated (%): C, 27.27; H, 5.68; N, 39.77.

Glyoxal bis(nitrosemicarbazone) diethydammonium salt (14). M.p. 224—225 °C. UV (H_2O), λ_{max}/nm: 334, 258, 213. IR (KBr), ν/cm^{-1}: 3466, 3198, 3032, 2974, 2936, 2800, 2738, 2677, 2490, 1649, 1581, 1539, 1475, 1430, 1398, 1330, 1304, 1226, 1146, 1067, 1035, 927, 780. Found (%): C, 35.09; H, 6.55; N, 34.65. $C_{12}H_{28}N_{10}O_6$. Calculated (%): C, 35.29; H, 6.86; N, 34.31.

Synthesis of salts 15 and 16 (general procedure). Compound **1** (2.4 g, 0.02 mol) was dissolved in distilled water (100 mL) with stirring, then diimine **25** or **26** (0.01 mol) was gradually added. The mixture was allowed to stand for 1 h at room temperature. A precipitate formed was collected by filtration and recrystallized from water.

Glyoxal bis(nitrosemicarbazone) isopropydammonium salt (15). The yield was 88%, m.p. 225—227 °C. UV (H_2O), λ_{max}/nm: 334, 256, 203. IR (KBr), ν/cm^{-1}: 3478, 3094, 3032, 2985, 2544, 1649, 1582, 1511, 1408, 1307, 1226, 1125, 1061, 1034, 932. ^{1}H NMR (600.30 MHz, D_2O), δ: 1.25 (d, 6 H, CH_3, ^3J = 6.5 Hz); 3.45 (septet, 1 H, C<u>H</u>$(CH_3)_2$, ^3J = 6.5 Hz); 7.76 (s, 1 H, CH=N). ^{13}C NMR (150.95 MHz, D_2O), δ: 19.74, 43.96, 144.40, 159.37. Found (%): C, 46.69; H, 7.53; N, 32.48. $C_{10}H_{24}N_{10}O_6$. Calculated (%): C, 46.88; H, 7.81; N, 32.81.

Glyoxal bis(nitrosemicarbazone) *tert*-butylammonium salt (16). The yield was 78%, m.p. 266—268 °C. UV (H_2O), λ_{max}/nm: 335, 254, 210. IR (KBr), ν/cm^{-1}: 3429, 3100, 3040, 2982, 2893, 2825, 2725, 2618, 2585, 1643, 1588, 1523, 1403, 1381, 1325, 1240, 1133, 1052, 967. ^{1}H NMR (500.13 MHz, D_2O), δ: 1.43 (s, 9 H, CH_3); 7.86 (s, 1 H, CH=N). ^{13}C NMR (125.75 MHz, D_2O), δ: 23.3, 51.6, 144.0, 159.0. Found (%): C, 35.42; H, 6.67; N, 34.03. $C_{12}H_{22}N_{10}O_6$. Calculated (%): C, 35.29; H, 6.86; N, 34.31. Compounds **15** and **16** were obtained in 48 and 70% yields by the reaction of glyoxal bis(nitrosemicarbazone) **4** with the corresponding amines (see Scheme 6 and Table 2).

Synthesis of glyoxal semicarbazones 17—22 (general procedure). An amine (0.04 mol) was gradually added to a suspension of compound **4** (2.62 g, 0.01 mol) in distilled water (50 mL) with stirring. The mixture was refluxed for 1—3 h. The reaction progress was monitored by UV spectroscopy. After disappearance of absorption maximum at 258 nm, the reaction mixture was cooled, a precipitate formed was collected by filtration and recrystallized from water. The yields of compounds **17—22** are given in Table 2.

Glyoxal bis(methylsemicarbazone) (18). M.p. 255—256 °C. UV (H_2O), λ_{max}/nm: 294, 200. IR (KBr), ν/cm^{-1}: 3352, 3186, 3117, 2965, 1666, 1547, 1416, 1314, 1274, 1151, 1117, 928. ^{1}H NMR (400.13 MHz, DMSO-d_6), δ: 2.64 (d, 6 H, CH_3, ^3J = 4.5 Hz); 6.81 (q, 2 H, NHCH, ^3J = 4.5 Hz); 7.51 (s, 2 H, CH=N); 10.54 (s, 2 H, NHN=). ^{13}C NMR (100.62, DMSO-d_6), δ: 26.1, 138.2, 155.6. Found (%): C, 36.5; H, 5.9; N, 41.8. $C_6H_{12}N_6O_2$. Calculated (%): C, 36.00; H, 6.00; N, 42.00.

Glyoxal bis(dimethylsemicarbazone) (19). M.p. 235—237 °C. UV (H_2O), λ_{max}/nm: 298, 195. IR (KBr), ν/cm^{-1}: 3247, 2870, 2810, 1728, 1659, 1544, 1491, 1409, 1304, 1217, 1164, 1093, 1017, 920, 888, 822, 731. Found (%): C, 42.52; H, 7.9; N, 36.80. $C_8H_{16}N_6O_2$. Calculated (%): C, 42.11; H, 7.02; N, 36.84.

Glyoxal bis(diethylsemicarbazone) (20). M.p. 230—232 °C. UV (H_2O), λ_{max}/nm: 300, 200. IR (KBr), ν/cm^{-1}: 3237, 3060, 2970, 2932, 1651, 1537, 1488, 1457, 1408, 1374, 1314, 1266, 1178, 1078, 1099, 1083, 1043, 986, 936. Found (%): C, 50.51; H, 8.9; N, 29.82. $C_{12}H_{24}N_6O_2$. Calculated (%): C, 50.70; H, 8.45; N, 29.58.

Glyoxal bis(isopropylsemicarbazone) (21). M.p. 244—245 °C. UV (H_2O), λ_{max}/nm: 296, 200. IR (KBr), ν/cm^{-1}: 3372, 3192, 3100, 2967, 2873, 1660, 1547, 1468, 1358, 1325, 1263, 1181, 1140, 1061, 929. ^{1}H NMR (600.30 MHz, DMSO-d_6), δ: 1.10 (d, 12 H, CH_3, ^3J = 6.6 Hz); 3.83 (d.septet, 2 H, C<u>H</u>$(CH_3)_2$ ^3J = 6.6 Hz, ^3J = 8.3 Hz); 6.49 (d, 2 H, NHCH, ^3J = 8.3 Hz); 7.51 (s, 2 H, CH=N); 10.50 (s, 2 H, NHN=). ^{13}C NMR (150.95, DMSO-d_6), δ: 22.76, 40.94, 138.35, 154.25. ^{15}N NMR (60.84, DMSO-d_6), δ: 100 (NHCH); 158 (<u>N</u>HN=); 330 (NH<u>N</u>=). Found (%): C, 46.60; H, 7.9; N, 33.09. $C_{10}H_{20}N_6O_2$. Calculated (%): C, 46.88; H, 7.81; N, 32.81.

Glyoxal bis(*tert*-butylsemicarbazone) (22). M.p. 236—238 °C. UV (H_2O), λ_{max}/nm: 297, 200. IR (KBr), ν/cm^{-1}: 3415, 3197, 3090, 2970, 2950, 1670, 1525, 1460, 1394, 1365, 1322, 1285, 1228, 1209, 1144, 1057, 926. ^{1}H NMR (600.30 MHz, DMSO-d_6), δ: 1.30 (s, 18 H, CH_3); 6.05 (s, 2 H, NHCH); 7.48 (s, 2 H, CH=N); 10.38 (s, 2 H, NHN=). ^{13}C NMR (150.95, DMSO-d_6), δ: 28.96, 49.62, 138.05, 154.76. Found (%): C, 46.39; H, 9.41; N, 32.60. $C_{10}H_{24}N_6O_2$. Calculated (%): C, 46.15; H, 9.23; N, 32.31.

Glyoxal bis(dimethylsemicarbazone) (19). Compound **1** (12.0 g, 0.1 mol) was added to a 33% aqueous dimethylamine (30.6 mL, 0.2 mol) with stirring. The mixture was heated for 4 h at 75—85 °C. The solvent was evaporated *in vacuo*, the resulting dimethylsemicarbazide **23** was dissolved in water (100 mL), followed by the addition of a 40% aqueous solution of glyoxal (5.5 mL, 0.046 mol) with stirring. The mixture was allowed to stand for 3 h at room temperature. A precipitate of compound **19** was collected by filtration and recrystallized from water. The yield was 7.0 g (67%). Physicochemical characteristics of the samples of compound **19** obtained by alternative methods (see above) are similar.

Glyoxal bis(diethylsemicarbazone) (20). 4-Nitrosemicarbazide **1** (12 g, 0.1 mol) was added to a solution of diethylamine (31.2 mL, 0.3 mol) in water (15 mL) with stirring. The mixture was heated for 4 h at 75—85 °C. The solvent was evaporated *in vacuo*, diethylsemicarbazide **24** was dissolved in water (100 mL), followed by the addition of a 40% aqueous solution of glyoxal (5.4 mL, 0.045 mol) with stirring. The mixture was allowed to stand for 3 h at room temperature. A precipitate of compound **20** was collected by filtration and recrystallized from water. The yield was 10.9 g (85%). Physicochemical characteristics of the samples of compound **20** obtained by alternative methods (see above) are similar.

Biological activity of synthesized compounds was studied in the Laboratory of Pharmacological Studies of the N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences according to the guidance on laboratory practice (GLP)[27] and the corresponding manuals.[28,29] The studies were carried out on 190—210-g Vistar rats obtained from vivarium of the Institute of Cytology and Genetics of the Siberian Branch of the RAS. The experimental animals were kept under constant access to food and water: a full diet of the extruded briquetted food (Chara, Russia, GOST (State Standard) for food R 50258-92) and drinking water were used. Animals were kept in a vivarium in plastic cages with stainless steel barred lids and with litter of wood shavings at 20—22 °C and 12-hour light regime (12 h of light, 12 h of darkness) with five—six rats in a cage. All the manipulations were carried out according to the rules and principles of humane treatment of animals. Experiments were carried out at the same time, from 9^{00} to 12^{00} h.

"Accute" toxicity was determined by the Kerber's method,[30] using a single intragastric administration of compounds **2—6**.

Standard models of calcium chloride and adrenalin arrhytmia were used for the assessment of antiarrhythmic effect. The

arrhytmia was caused by a single injection into the femoral vein of a lethal dose of a 10% solution of $CaCl_2$ in the dose 250 mg kg^{-1} (calcium chloride arrhytmia) or adrenalin hydrochloride (AH) in the dose 0.2 mg kg^{-1} (adrenalin arrhytmia). These doses of $CaCl_2$ and AH are lethal for rats in 100% of cases. To carry out the studies, the rats were separated into groups with eight animals in each. Aqueous solutions of test compounds **2** and [**9**]K^+ were administered to animals intravenously in the doses 5, 0.5, and 0.05 mg kg^{-1}. After 1 min, calcium chloride or AH were injected and the extent of ECG recovery was assessed. A criterion of the antiarrhythmic effect was the recovery of the ECG parameters after injection of compounds causing arrhytmia. Activity parameters were recorded on a LabLink V polyfunctional electrophysiological complex (USA). Electrocardiograms were recorded during 10 min. Electrocardiograms were recorded in the second standard lead on a LabLinK V model v75-11 instrument. Antiarrhythmic effect was evaluated by the length of RR, PQ, QRS, QT intervals, P wave; P, T, R wave amplitudes upon injection of compounds causing arrhytmia against the background of test compounds.

Statistical processing of obtained data was carried out by the method of variation statistics using Student's *t*-test (see STATISTICA-6 software package). Pressure was measured during the acute experiment by introducing a cannula in the carotid artery. Figures were recorded using a Coulbourn instruments appliance (USA). The data were processed using the Statistica 6.0 program by the averaging of basic readings of systolic and diastolic blood pressure. An average statistical error was used as the deviation from the average value, the Student's *t*-test was used as the reliability criterion.

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