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Dedicated to the 90th Anniversary of Academician M.G. Voronkov

Methylglyoxal Bis-(*N*,*N*-dimethylhydrazone): Synthesis and Some Reactions

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Abstract—Methods were proposed for the synthesis of the methylglyoxal 1,2-bis-(*N*,*N*-dimethylhydrazone). A possibility was shown for the first time of its participation in the Diels–Alder reaction with maleic anhydride as an electron-rich diene. The second reaction of these reagents, which is observed in a wet media, is the formation of the hydrazinium salt of the initial diene with maleic acid. The most probable structure of the protonated diene among the four possible forms was revealed by the quantum-chemical calculations of the energy of the molecules and by the analysis of the ^{13}C NMR chemical shifts.

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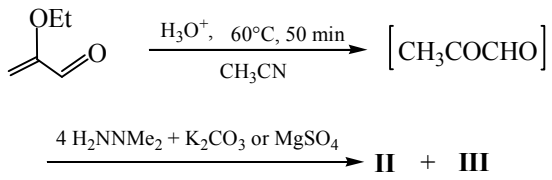
The methylglyoxal bishydrazones, in particular, substituted bisguanylhydrazones and bisthiosemicarbazones, show pronounced biological activity, and some of them are used as drugs [1–5]. Earlier [6] by the reaction of 2-ethoxypropenal with equimolar amount of 1,1-dimethylhydrazine we obtained in a yield of 8% the previously poorly studied methylglyoxal bis-(*N*,*N*-dimethylhydrazone) (**II**) potentially possessing a pharmacological action.

The aim of this work was an optimization of the methods for the synthesis of this compound in diverse ways and the study its properties.

By the reaction of 50% aqueous solution of methylglyoxal (**I**) (commercial reagent) with dimethylhydrazine (molar ratio 1:4) the methylglyoxal bis-(*N*,*N*-dimethylhydrazone) (**II**) was produced. Depending on the experimental conditions and the method of binding water, the yield of bishydrazone **II** before distillation (according to ^1H NMR spectra) was 37–54%. A by-product of the reaction is methylglyoxal mono-*N*,*N*-dimethylhydrazone (**III**). Molar content of this compound in the reaction mixture was 13–22% depending on the experimental conditions.

The formation of monohydrazone **III** is due to the reversible equilibrium in the water medium of the bishydrazone **II** and the related product of the hydrolysis at the ketone imine group.

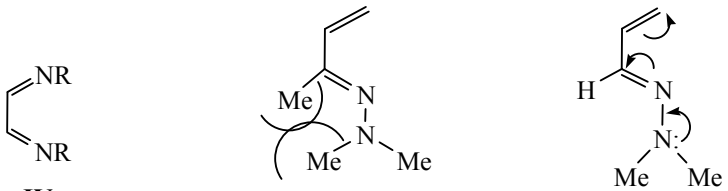
To eliminate the water medium we performed the synthesis of methylglyoxal from 2-ethoxypropenal in acetonitrile by the method of [7]. In the subsequent reaction of methylglyoxal with dimethylhydrazine $MgSO_4$ or molecular sieves 4 Å were used for binding the water formed at the condensation.



But even at twofold excess of *N*,*N*-dimethylhydrazine over the stoichiometric amount the bishydrazone **II** yield was no more than 65% (according to ^{1}H NMR data). The monohydrazone **III** was formed in 18–25% yield.

A surprising feature of the methylglyoxal bis-*N*,*N*-dimethylhydrazone **II** is the ability to exist as two stereoisomers, major **IIa** and minor **IIb,** in a ratio of 1.9–4: 1, as we judged from the ^{1}H NMR spectra and GC-MS. At heating the mixture with the isomers ratio 1.9:1 for 15 min at 50°C in the NMR ampule the ratio changed to 2.7:1. In gas chromatography-mass spectrum of the authentic sample of methylglyoxal bisdimethylhydrazone also two geometric isomers were observed with molecular weight 156, with the retention time of 8.801 and 9.164 min. The ratio of the isomers cannot be estimated from the GC-MS data due to their mutual transformations. The configurational assignment of the isomers was carried out on the basis of experimental measurements and *ab initio* calculations of the spin–spin coupling constants $^1J_{CC}$ and $^1J_{CH}$ [8]. The calculations showed that bishydrazone methylglyoxal exists as a mixture of *EE* and *ZE* isomers [8].

The bishydrazone **II** is a poorly studied [9] representative of a class of diaza-1,3-dienes used in the diene synthesis [10]. Among them, 1,4-diaza-1,3-butadienes have been used as potential intermediates in the study of transformations of methylglyoxal in the body [11] or as ligands in metallocomplex catalysts [12, 13]. But they only seldom have been studied in the reactions of [4+2]-cycloaddition as the dienes [14–17]. The possible Diels–Alder reaction for 1.4-diamino-substituted 1.4-diaza-1,3-dienes **IV**, having at positions 1 and 4 electron-donor and electron-acceptor substituents, with dienophiles with an electron-deficient double bond, in particular, with acrolein was calculated in [14]. It is known that the introduction of the NMe_2 substituent in the imino group of azadiene leads to an increase in its reactivity with respect to electrophilic dienophiles [18]. However, it was shown in [19] that the steric repulsion of methyl groups in the $Me_2NN{=}C(Me)$ fragment does not activate the molecule of vinylmethylketone hydrazone **V** to participate in the diene synthesis, as was in the case of the acrolein hydrazone **VI**, but hinders by violating the coplanarity of the diene fragment.



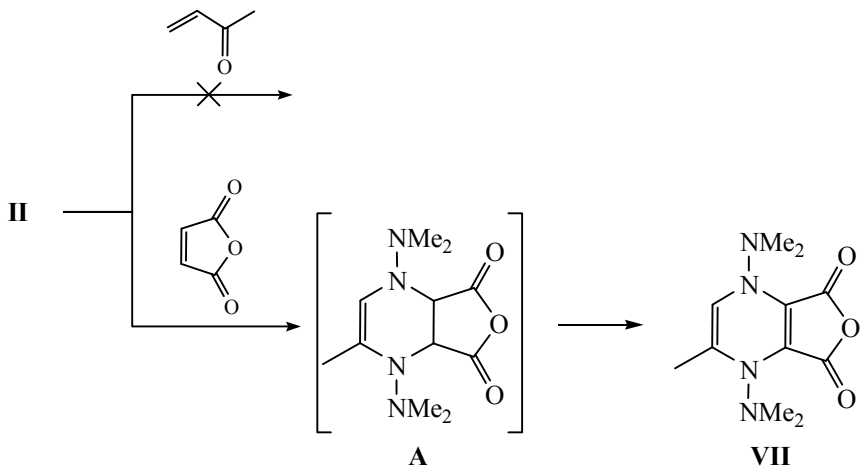
IV **V** **VI**

R = NH_2, OH, CH_3, OCH_3, H, Cl, CN, NO_2.

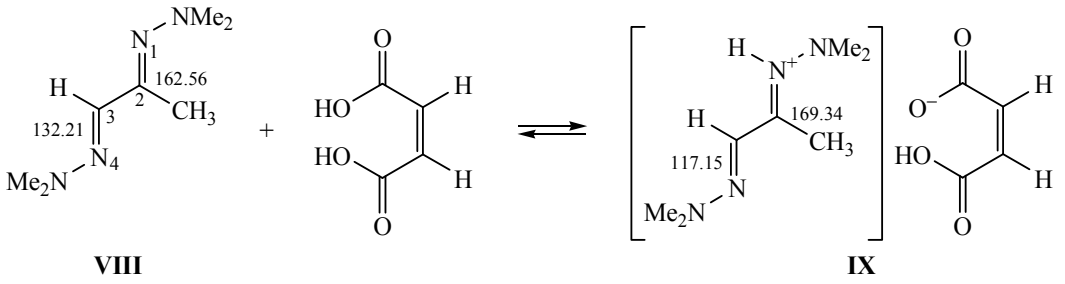
Thus, the presence of two dimethylamino groups in studied diazadiene **II** activates the diene not explicitly (not proportional to the number of groups), so the ease of diene synthesis is not obvious *a priori*. It should be borne in mind that molecule **II** should participate in the diene synthesis in the *s-cis* form, which in this case is energetically less favorable [8].

Carrying out the reactions of diene synthesis of α,β-unsaturated *N*,*N*-dimethylhydrazones with methylvinylketone or methacrylate often requires prolonged heating at high temperature [18]. We failed to carry out the reaction of diene synthesis of bishydrazone **II** with methyl vinyl ketone at heating (140°C, 2 h). However, we first showed that this electoron-rich bisdimethylamino-1,4-diazadiene **II** can enter the diene synthesis with the electron-deficient maleic anhydride. The reaction takes place at the temperature –15 to –20°C within 20 minutes with full conversion of initial reagents. In the reaction mixture the expected anhydride of 1,4-bis(dimethylamino)-1,4-dihydropyrazine-2,3-dicarboxylic acid **VII** formed in a yield of up to 77% (according to ^{1}H NMR data).

The dehydrogenation of the primary adduct **A** with the air oxygen, accompanying the diene synthesis, is not unexpected [6]. Unfortunately, we failed to isolate the anhydride **VII** in pure form, since it is readily hydrolyzed like other anhydrides [20] at the chromatography on silica gel and decomposes at the vacuum distillation. However, in the reaction mixtures, it is stored for several weeks, as confirmed by ^{1}H and ^{13}C NMR spectra.

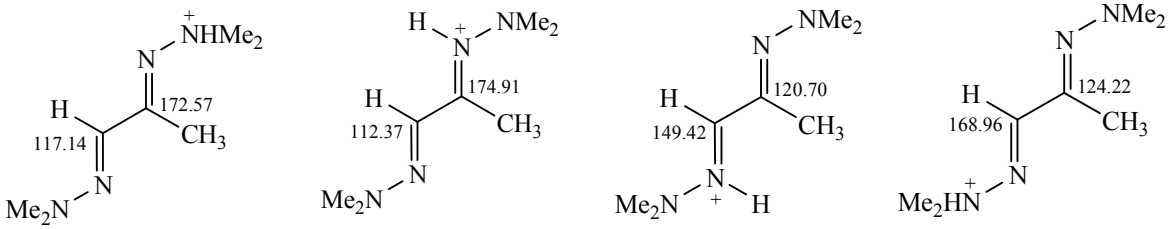


The second product in the reaction of compound **II** with maleic anhydride was a crystalline substance containing (according to ^{1}H NMR spectrum) the fragments similar in structure to the parent compounds. But the ^{13}C NMR resonance signals are shifted compared with compound **II**, which may be a consequence of protonation of the main stereoisomer **VIII** of the parent compound **II** [8] by a proton of the maleic acid formed from the original anhydride *in situ* in the presence of some water in the reaction mixture. The scheme below shows the experimental values of the ^{13}C NMR chemical shifts (ppm) of carbon atoms C^2 and C^3.



VIII **IX**

To prove the structure of the hydrazinium salt **IX** we calculated the energy characteristics and the ^{13}C NMR chemical shifts of four possible protonated forms of the bishydrazone **VIIIa–VIIId**. The geometry optimization was performed within the B3LYP/6-311G(d,p) method using the PCM model to account for the medium effects, in this case chloroform. The chemical shifts were calculated also accounting for the GIAO-B3LYP/DZP field of the solvent. The results of the calculations [relative energies (kcal mol^{-1}) and theoretical values of the δ_C, ppm] for the four forms of compound **VIII** are shown below.



VIIIa, 7.1 **VIIIb**, 0.0 **VIIIc**, 12.0 **VIIId**, 12.2

According to the calculations of the ^{13}C NMR chemical shifts, the best agreement with experiment is found for the forms **VIIIa** and **VIIIb**, for which the difference between calculated and experimental values does not exceed 5 ppm. In contrast, for **VIIIc** and **VIIId** the agreement with experiment is much worse: the difference is 50 ppm, which clearly favors the structures **VIIIa** and **VIIIb**. In addition, the data on the relative energies of four possible forms **VIIIa–VIIId** show clearly that the protonation proceeds with the formation of cation **VIIIb**. The relative energies of the other forms are higher than 7 kcal mol^{-1}, which indicates their complete absence in the reaction mixture. Thus, our calculations allow us an unequivocal establishment of the structure of compound **IX**, existing as a salt of maleic acid anion and the imine with the protonated nitrogen at the C^2 atom of methylglyoxal bisdimethylhydrazone. The yield is varied in the range of 30–90% depending on water content in the solvents (CH_2Cl_2, $CHCl_3$, CH_3CN).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer, at the resonance frequency 400.13 and 100.61 MHz, respectively, solvents $CDCl_3$, CD_3CN, and DMSO-d_6, internal reference HMDS. The IR spectra were obtained on an IR spectrometer Specord IR-75. Chromatography-mass spectrometry analysis was performed on a gas chromatograph-mass spectrometer Hewlett-Packard HP 5971A (EI, 70 eV, mass-selective detector) with a HP-5890 gas chromatograph, column Ultra-2 (5% phenylmethylsilicone), evaporator temperature 250°C , oven temperature 70–280°C, the rate of heating 20 deg min^{-1}. The melting points were determined on a Micro-Hot-Stage Poly Term A instrument (Warner and Muzn). The geometry optimization of compounds **VIIIa–VIIIg** was performed using the GAMESS software package [21], calculations of shielding constants was carried out with the ADF software package [22].

Reaction of methylglyoxal with dimethylhydrazine. To a solution of 0.5 g (1 ml) of 50% aqueous methylglyoxal in 50 ml of ether was added 0.002 g of hydroquinone and 1.67 g of dimethyl hydrazine. The solution was stirred for 8 h at 18°C and left overnight. The top layer of the reaction mixture was separated and dried over $CaCl_2$, and then ether was removed in a vacuum. The remaining reaction product (1.47 g) containing mainly (according to ^1H NMR data) hydrazones **II** and **III** was distilled in a vacuum. The distillation provided 0.7 g (32.2%) of substance with bp 70–76°C (4 mm Hg), n_D^{20} 1.5248. According to ^1H NMR, the fraction contains isomers of methylglyoxal bis-(*N*,*N*-dimethylhydrazone) **II** in a ratio of 2.35: 1 and 13.15 mol % of methylglyoxal *N*,*N*-dimethylhydrazone **III** described in [23]. The ^1H NMR spectrum of major isomer **IIa** ($CDCl_3$), δ, ppm: 2.12 s (3H, CH_3), 2.53 s (6H, NMe_2), 2.93 s (6H, NMe_2), 6.91 s (1H, =CH). The ^1H NMR spectrum of minor isomer **IIb** ($CDCl_3$), δ, ppm: 2.08 s (3H, CH_3), 2.47 s (6H, NMe_2), 3.01 s (6H, NMe_2), 7.39 s (1H, =CH). ^{13}C NMR spectrum major isomer **IIa** ($CDCl_3$), δ, ppm: 12.90 (CH_3), 42.53 (C=$NNMe_2$), 47.34 (CH=$NNMe_2$), 132.85 (CH=N), 163.40 (C=N). ^{13}C NMR spectrum of minor isomer **IIb** ($CDCl_3$), δ, ppm: 19.34 (CH_3), 42.37 (C=$NNMe_2$), 47.88 (CH=$NNMe_2$), 128.40 (CH=N), 162.15 (C=N). The assignment of the signals is made on the basis of two-dimensional spectra ^1H–^{13}C HMBC-GP. The mass spectrum of major isomer **IIa**, *m/z* (I_{rel}, %): 156(56) $[M]^+$, 112(11) $[M - NMe_2]^+$, 97 (8) $[M - NMe_2–CH_3]^+$, 83(10) $[CCHNNMe_2]^+$, 70(22) $[C=NNMe_2]^+$, 58(7) $[NNMe_2]^+$, 44(100) $[NMe_2]^+$, 28 (53), 18(17). The mass spectrum of minor isomer **IIb**, *m/z* (I_{rel},%): 156(49) $[M]^+$, 112(10) $[M - NMe_2]^+$, 97 (10) $[M - NMe_2 - CH_3]^+$, 83(10) $[CCHNNMe_2]^+$, 70 (20) $[C=NNMe_2]^+$, 58(7) $[NNMe_2]^+$, 44(100) $[NMe_2]^+$, 28(28), 18(12). IR spectrum, ν, cm^{-1}: 1590 and 1525 (C = N).

Monohydrazone III. The ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.27 s (3H, CH_3CO), 3.12 s (6H, NMe_2), 6.57 s (1H, =CH). The spectrum coincides with the spectrum of this compound given in [23]. The ^1H NMR spectrum (CD_3CN), δ, ppm: 2.16 s (3H, CH_3 CO), 3.07 s (6H, NMe_2), 6.51 s (1H, =CH). The ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.91 (CH_3), 67.90 (NMe_2), 124.21 (CH=N), 197.52 (C=O).

Methylglyoxal bis-(*N*,*N*-dimethyl)hydrazone II from α-ethoxyacrolein. To the solution of 0.07 g of preliminary prepared catalyst (0.5 ml of concentrated HCl was dissolved in 1 ml of acetonitrile) was added 0.002 g of hydroquinone in 0.38 g of water, at 55°C was added 2.9 g of α-ethoxyacrolein, and the mixture was heated for 50 min. After cooling to 25°C was added 3 g of $MgSO_4$, the mixture was stirred for 30 min, and 6.7 g of dimethylhydrazine was added dropwise. The mixture was stirred for 4 h and left overnight. The filtered reaction mixture was evaporated and distilled under nitrogen. Yield of compound **II** 1.72 g (53%), bp 81–82°C (1 mm Hg).

Found, %: C 53.88, H 10.40; N 35.69. $C_7H_{16}N_4$. Calculated, %: C 53.84, H 10.25; N 35.89. The spectra correspond to the above listed.

1,4-Bis(dimethylamino)-1,4-dihydro-2-methylfuropyrazin-5,7-dione (VII). To 0.29 g of maleic anhydride in 2 ml of methylene chloride (dried over 4A sieves) at a temperature –15 to –20°C was added 0.46 g of compound **II,** and the mixture was stirred until the temperature reaches the room temperature. The yield of crude product 77% (^{1}H NMR). Yellow-brown oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.24 s (3H, CH_3), 2.70 s (6H, $NNMe_2$), 3.21 s (6H, $NNMe_2$), 7.90 s (H, CH) . ^{1}H NMR spectrum (CD_3CN), δ, ppm: 2.35 s (3H, CH_3), 2.64 s (6H, $NNMe_2$), 3.20 s (6H, $NNMe_2$), 7.10 s (1H, CH .) ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.18 s (3H, CH_3), 2.54 s (6H, $NNMe_2$), 7.3 s (6H, $NNMe_2$), 6.84 s (1H, CH). The ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.7 (CH_3), 46.0 and 46.3 (NMe_2), 116.9 (C=NN), 121.4 (C^{4a}, C^{7a}), 131.4 (C^2), 171.7 (C^5, C^7).

1-{(*E*)-2-[(*E*)-2',2'-Dimethylhydrazino]-1-methylethylidene}-2,2-dimethylhydrazinium maleate (IX). To 0.242 g of maleic anhydride in 1.5 ml of methylene chloride was added 0.385 g of compound **II,** and the mixture was stirred at room temperature for 1 h and left overnight. A day later, according to ^{1}H NMR spectrum, the reaction mixture contained compounds **VII** and **IX**. The salt **IX** was isolated by recrystallization from methylene chloride. Yield 0.566 g (84.5%). Pale yellow needles, mp 102°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.49 s (3H, CH_3), 2.70 s (6H, $NNMe_2$), 3.31 s (6H, N^+NMe_2), 6.26 s (2H, CH=CH), 7.31 s (1H, N=CH). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 2.32 s (3H, CH_3), 2.64 s (6H, $NNMe_2$), 3.34 s (6H, N^+NMe_2), 6.16 s (2H , CH=CH), 7.27 s (1H, N= CH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.27 s (3H, CH_3), 2.61 s (6H, $NNMe_2$), 3.37 s (6H, N^+NMe_2), 6.08 s (2H, CH=CH), 7.21 s (1H, N=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.8 (CH_3), 46.3 and 46.7 (NMe_2), 117.2 (N =CH), 136 (CH=CH), 169.4 (C=O). Found, %: C 48.77, H 7.8; N 20.44. $C_{11}H_{20}N_4O_4$. Calculated, %: C 48.53, H 7.35; N 20.59.

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