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Dedicated to the Full Member of the Russian Academy of Sciences V.A.Tartakovsky on occasion of his 75th birthday

Synthesis of 1,2-Diols Ethers, Condensation Products of Glyoxal with Nitrogen-Containing Nucleophiles: I. Reaction of Cyclic Sulfites with Primary Alcohols and Glycols

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Abstract—In reactions of 4,5-diacetoxy-2-(dinitromethylene)imidazolidine, 4,5-diacetoxy-2-nitriminoimidazolidine, and 1,2-diacetoxy-1,2-bis(chloroacetylamino)ethane with thionyl chloride at room temperature the corresponding cyclic sulfites were obtained. Treating the sulfites with methanol, ethanol, and 2-chloroethanol at room temperature we prepared acyclic ethers in 80–90% yields. Similarly cyclic ethers were synthesized from ethylene glycol and 1,3-propanediol in 50–60% yields.

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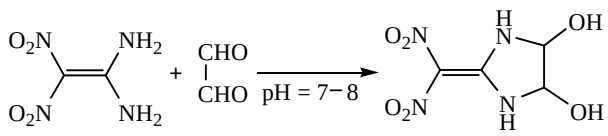
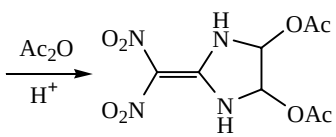
We showed formerly [1] that 2-(dinitromethylene)-imidazolidine-4,5-diol (**I**), a condensation product of 1,1-diamino-2,2-dinitroethylene with glyoxal reacted with various nitrogen-containing nucleophiles (acetonitrile, benzonitrile, urethane, and 3,4-diaminofurazan) in acid medium to form cyclic derivatives of 1,1,2,2-tetraaminoethane. In extension of the studies on new syntheses of polyfunctional 1,1-diamino-2,2-dinitroethylene derivatives we investigated a reaction of 4,5-diacetoxy-2-(dinitromethylene)imidazolidine (**II**) with thionyl chloride (Scheme 1).

Published data reveal that treating polyhydric alcohols with thionyl chloride provides alongside chlorides also cyclic sulfites [2–7]. As a rule five- and six-membered cyclic sulfites are obtained from 1,2-alkanediols [2, 3, 7] or 1,3-glycols [4–7] and thionyl chloride under milder conditions than those used to prepare the corresponding chlorides, namely, at room temperatire in the presence of a catalytic quantity of DMF.

Scheme 1.



I

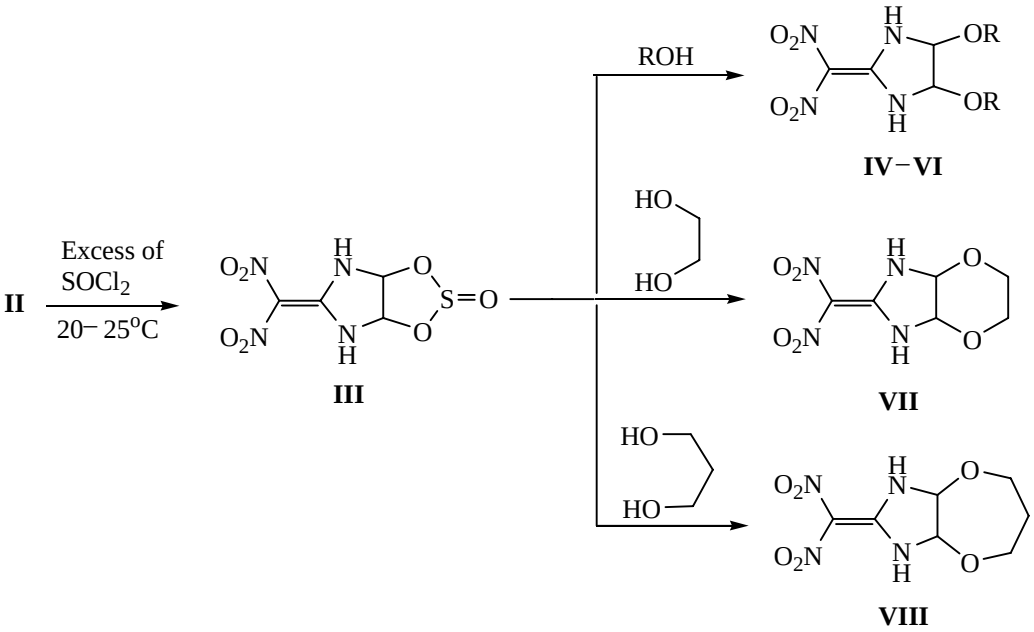


II

We stated in the previous publication [1] that diol **I**, like its diacetoxy derivative **II**, suffered a fast decomposition at heating to 80–90°C in nonaqueous acid media. To avoid hydrogen chloride liberation in the course of the reaction with thionyl chloride we applied instead of diol **I** 4,5-diacetoxy-2-(dinitromethylene)-imidazolidine (**II**). However on heating the latter in excess thionyl chloride fast tarring occurred. The reaction carried out under milder conditions (at room temperature) made it possible to obtain cyclic sulfite **III** in 65% yield (Scheme 2). Compound **III** is unstable at storage under common conditions and decomposes at room temperature with sulfur dioxide evolution within 2–3 days. Its IR spectrum contains a wide absorption band in the region 1234 cm^{-1} (S=O). We failed to register a plausible ^1H NMR spectrum of compound **III** because of its low stability is weakly basic polar solvents (DMSO, DMF, acetone).

Commonly 5–7% excess of thionyl chloride is sufficient for preparation of cyclic sulfites [4–7]. The

Scheme 2.



R = Me (**IV**), Et (**V**), CH_2CH_2Cl (**VI**).

use of thionyl chloride as solvent in our experiments was due to the low solubility of diacetoxy derivative **II** in inert solvents. We also succeeded in isolating sulfite **III** on carrying out the reaction in chloroform with 5–7% excess of the thionyl chloride. However under these conditions the 65% yield of compound **III** as expected was obtained in a 3 times longer reaction.

Treating cyclic sulfite **III** with excess methanol, ethanol, and 2-chloroethanol at room temperature gave rise to acyclic ethers **IV–VI** in 87–92% yields. Cyclic ethers **VII** and **VIII** were similarly obtained in 50% yield (Scheme 2). The lower yields of cyclic ethers **VII** and **VIII** are caused by their high solubility in glycols.

We formerly [1] synthesized dimethoxy and diethoxy derivatives **IV** and **V** by heating diol **I** in mixtures MeOH–H_2SO_4, 2:1, and EtOH–H_2SO_4, 2:1, respectively, in 70–88% yield.

We believe that the synthesis of ethers of 1,2-diols, products of glyoxal condensation with nitrogen-containing nucleophiles, through an intermediate preparation of cyclic sulfites possesses considerable advantages as compared with the standard procedure [8, 9] consisting in heating the 1,2-diols in alcohol or glycol under the conditions of acid catalysis. The synthesis via sulfites permits performing the alcoholysis in a neutral medium at room temperature. Here the reaction equilibrium shifts to the final products due to the liberation of gaseous sulfur dioxide from the reaction medium. Evidently the mild conditions of etherification are preferable for preparation of ethers from hydrolytically and thermally unstable 1,2-diols, for instance, like some *N*-(α-oxyalkyl)amide.

By an example of 4,5-diacetoxy-2-nitriminoimidazolidine (**IX**) and 1,2-diacetoxy-1,2-bis(chloroacetylamino)ethane (**X**) we showed that the developed procedure of ethers synthesis had a general character.

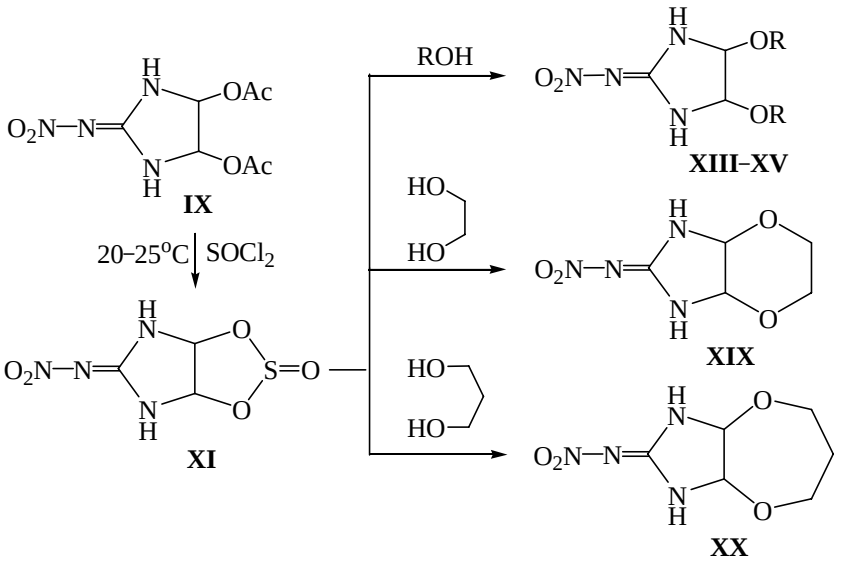
On stirring diacetoxy derivatives **IX** and **X** in excess thionyl chloride at room temperature the corresponding cyclic sulfites **XI** and **XII** were obtained in approximately 80% yield (Schemes 3 and 4).

Isolated compounds **XI** and **XII** are also unstable substances that decompose at room temperature with sulfur dioxide liberation: nitroguanidine derivative **XI** in 3–4 h, chloroacetamide derivative **XII** in 2–3 days. Sulfites obtained **III**, **XI**, and **XII** can be stored without decomposition at –20°C for two weeks.

By reactions of sulfites **XI** and **XII** with excess methanol, ethanol, and 2-chloroethanol at room temperature acyclic ethers **XIII–XVIII** were obtained in 70–90% yields. Cyclic ethers **XIX–XXII** were synthesized in a similar way in about 50% yield (Schemes 3 and 4).

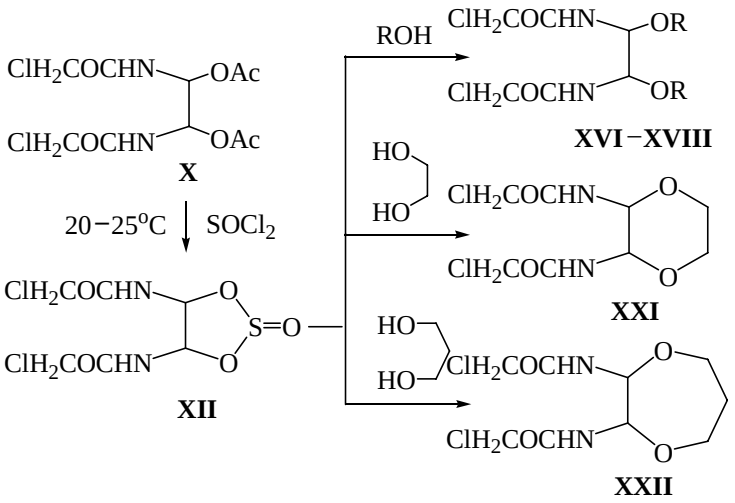
Thus we demonstrated that the synthesis of acyclic

Scheme 3.



R = Me (**XVI**), Et (**XVII**), CH_2CH_2Cl (**XVIII**).

Scheme 4.



R = Me (**XIII**), Et (**XIV**), CH_2CH_2Cl (**XV**).

and cyclic ethers of 1,2-diols obtained by condensation of glyoxal with amides and low-basic amines carried out via intermediate formation of cyclic sulfites was of general character and made it possible to prepare the target compounds in good yields (from 50 to 90%).

EXPERIMENTAL

IR spectra of compounds synthesized were recorded on a spectrophotometer Shimadzu FTIR 8400 (from films or pellets with KBr). ^{1}H NMR spectra were registered from solutions of compounds in DMSO-d_6 on a spectrometer Bruker WM-400 (400 MHz), internal reference HMDS. Elemental analysis was carried out on an analyzer Hewlett Packard 185B.

Initial 4,5-diacetoxy-2-(dinitromethylene)-imidazolidine (**II**) [1], 4,5-diacetoxy-2-nitrimino-imidazolidine (**IX**) [10], and 1,2-diacetoxy-1,2-bis(chloroacetylamino)-ethane (**X**) [11] were prepared by published procedures.

Cyclic sulfites III, XI, and XII. *General procedure.* To 20 ml (0.280 mol) of thionyl chloride was added 0.035 mol of compound **II, IX**, or **X**, the mixture was stirred for 24 h at room temperature, the precipitate was

filtered off, thoroughly washed with chloroform, and dried in air for 3 h. Synthesized sulfites **III, XI**, and **XII** are unstable and decompose at room temperature in 1–3 days. Compounds **III, XI**, and **XII** are unstable in weakly basic polar solvents (DMSO, DMF, acetonitrile, acetone) and also in water.

5-(Dinitromethylene)tetrahydro-3a*H*-[1,3,2]-dioxathiolo[4,5-*d*]imidazole 2-oxide (III). Yield 65%, light-yellow powder, mp 98°C (decomp.). IR spectrum, cm^{-1}: 3336 (NH), 1558 (C=C), 1527 (NO_2), 1454, 1354 (NO_2), 1258 (C–O), 1234 (S=O), 1061, 1003, 960, 817, 756 (NH).

***N*-Nitrotetrahydro-5*H*-[1,3,2]dioxathiolo[4,5-*d*]-imidazol-5-imine 2-oxide (XI).** Yield 85%, light-yellow powder, mp 85–86°C (decomp.). IR spectrum, cm^{-1}: 3263 (NH), 1604 (C=N), 1524 (NO_2), 1474, 1338 (NO_2), 1280 (C–O), 1238 (S=O), 1115, 1053 (N–N), 960, 833, 725 (NH), 656 (NNO_2).

***N*,*N*'-(1,3,2-Dioxathiolane-2-oxide)-4,5-bis(2-chloroacetamide) (XII).** Yield 81%, colorless powder, mp 148–150°C (decomp.). IR spectrum, cm^{-1}: 3294 (NH), 3024 (CN), 1670 (C=O), 1527 (CN, NH), 1404 (CH_2Cl), 1326 (CH), 1275 (CH_2Cl), 1253 (CNH, S=O), 1199 (C–O), 1169, 1130, 1045, 964, 779 (NH).

Acyclic ethers IV–VI, XIII–XVIII. General procedure. To 7 ml of alcohol (methanol, ethanol, 2-chloroethanol) was added 4 mmol of sulfite **III, XI**, or **XII**, the mixture was stirred for 6 h at room temperature, the precipitate was filtered off, washed with 2-propanol and ether, and dried in air.

2-(Dinitromethylene)-4,5-dimethoxyimidazolidine (IV). Yield 90%, yellow crystals, mp 107–109°C (methanol) (106–108°C [1]).

2-(Dinitromethylene)-4,5-diethoxyimidazolidine (V). Yield 87%, light-yellow crystals, mp 142–145°C (ethanol) (143–145°C [1]). ^{1}H NMR spectra of compounds **IV** and **V** are identical to those published [1].

2-(Dinitromethylene)-4,5-bis(2-chloroethoxy)-imidazolidine (VI). Yield 92%, light-yellow crystals, mp 143–145°C (decomp.). IR spectrum, cm^{-1}: 3325 (NH), 2939, 2881 (CH_2), 1566 (C=C), 1512 (NO_2), 1454, 1415, 1339 (NO_2), 1219 (CH_2Cl), 1137 (COC), 1114, 1087, 987, 752 (NH). ^{1}H NMR spectrum, δ, ppm: 3.50–3.80 m (4H, CH_2), 3.80–4.00 m (4H, CH_2), 5.15 s (2H, CH), 10.10 s (2H, NH). Found, %: C 29.48; H 3.81; N 16.40. $C_8H_{12}Cl_2N_4O_6$. Calculated, %: C 29.02; H 3.65; N 16.92.

4,5-Dimethoxy-*N*-nitrimidazolidine 2-imine (XIII). Yield 86%, colorless crystals, mp 171–172°C (decomp.). IR spectrum, cm^{-1}: 3205 (NH), 2943 (OCH_3), 2842 (OCH_3), 1612 (C=N), 1535 (NO_2), 1489 (OCH_3), 1365 (NO_2), 1288, 1234, 1110 (COC), 1076 (N–N), 1003, 937, 821, 783 (NNO_2), 752 (NH), 683, 609 (NNO_2). ^{1}H NMR spectrum, δ, ppm: 3.40 s (6H, CH_3), 4.75 s (2H, CH), 9.55 s (2H, NH). Found, %: C 31.72; H 5.50; N 29.89. $C_5H_{10}N_4O_4$. Calculated, %: C 31.58; H 5.30; N 29.46.

***N*-Nitro-4,5-diethoxyimidazolidine 2-imine (XIV).** Yield 68%, colorless crystals, mp 161–162°C (decomp.). IR spectrum, cm^{-1}: 3209 (NH), 2977 (CH_3), 2896 (CH_2), 1581 (C=N), 1542 (NO_2), 1476 (CH_3, CH_2), 1373 (CH_3), 1350 (NO_2), 1265, 1226, 1110 (COC), 1080 (N–N), 1022, 964, 829, 752 (NH), 632 (NNO_2). ^{1}H NMR spectrum, δ, ppm: 1.20 t (6H, CH_3, *J* 5.6 Hz), 3.45–3.65 m (4H, CH_2), 4.80 s (2H, CH), 9.55 s (2H, NH). Found, %: C 38.44; H 6.62; N 25.71. $C_7H_{14}N_4O_4$. Calculated, %: C 38.53; H 6.47; N 25.68.

***N*-Nitro-4,5-bis(2-chloroethoxy)imidazolidine 2-imine (XV).** Yield 90%, colorless crystals, mp 141–143°C (decomp.). IR spectrum, cm^{-1}: 3395, 3194 (NH), 2931 (CH_2), 2877 (CH_2), 1585 (C=N), 1546 (NO_2), 1474 (CH_2), 1458 (CH_2Cl), 1357 (NO_2), 1296 (CH_2Cl), 1226, 1118 (COC), 1034 (N–N), 1010, 964, 825, 783, 756 (NH), 629 (NNO_2). ^{1}H NMR spectrum, δ, ppm: 3.50–3.90 m (8H, CH_2), 5.00 s (2H, CH), 9.70 s (2H, NH). Found, %: C 29.35; H 4.54; N 19.31. $C_7H_{12}Cl_2N_4O_4$. Calculated, %: C 29.28; H 4.21; N 19.51.

***N*,*N*'-(1,2-Dimethoxyethan-1,2-diyl)bis(2-chloroacetamide) (XVI).** Yield 89%, colorless crystals, mp 172–174°C (decomp.). IR spectrum, cm^{-1}: 3271 (NH), 3059 (CN), 2950 (OCH_3), 2835 (CH, OCH_3), 1670 (C=O), 1551 (CN, NH), 1462 (CH_2Cl, OCH_3), 1396, 1346 (CH), 1277 (CH_2Cl), 1219 (CO, CNH), 1107 (COC), 1072, 964, 934, 794 (NH). ^{1}H NMR spectrum, δ, ppm: 3.25 d (6H, CH_3, *J* 4.8 Hz), 4.00–4.15 m (4H, CH_2), 4.95 t (2H, CH, *J* 3.2 Hz), 8.50 q (2H, NH, *J* 3.2 Hz). Found, %: C 35.42; H 5.28; N 10.01. $C_8H_{14}Cl_2N_2O_4$. Calculated, %: C 35.18; H 5.17; N 10.26.

***N*,*N*'-(1,2-Diethoxyethan-1,2-diyl)bis(2-chloroacetamide) (XVII).** Yield 91%, colorless crystals, mp 150–152°C (decomp.). IR spectrum, cm^{-1}: 3283 (NH), 3070 (CN), 2978 (CH_3, OCH_2), 2885 (CH), 1670 (C=O), 1551 (CN, NH), 1450 (CH_3, CH_2Cl), 1400, 1346 (CH, CH_3), 1269 (CH_2Cl), 1215 (CO, CNH), 1110 (COC), 1064, 956, 794 (NH). ^{1}H NMR spectrum, δ, ppm: 1.05–1.15 m (6H, CH_3), 3.35–3.65 m (4H, CH_2), 3.95–4.15 m (4H, CH_2), 4.95–5.05 m (2H, CH), 8.35–8.50 m (2H, NH). Found, %: C 40.03; H 6.30; N 9.28. $C_{10}H_{18}Cl_2N_2O_4$. Calculated, %: C 39.88; H 6.02; N 9.30.

***N,N'*-[1,2-Bis(2-chloroethoxy)ethan-1,2-diyl]bis-(2-chloroacetamide) (XVIII).** Yield 85%, colorless crystals, mp 167–169°C (decomp.). IR spectrum, cm^{-1}: 3283 (NH), 3055 (CN), 2923 (CH_2), 2881 (CH), 1658 (C=O), 1531 (CN, NH), 1435 (CH_2Cl), 1404, 1361 (CH), 1296 (CH_2Cl), 1265 (CNH), 1200, 1099 (COC), 1053, 1022, 960, 779 (NH). ^1H NMR spectrum, δ, ppm: 3.65 m (8H, CH_2), 4.05 q (4H, CH_2, *J* 15.4 Hz), 5.10 d (2H, CH, *J* 7.7 Hz), 8.65 d.d (2H, NH, *J* 46.2 and 7.7 Hz). Found, %: C 32.55; H 4.76; N 7.39. $C_{10}H_{16}Cl_4N_2O_4$. Calculated, %: C 32.46; H 4.36; N 7.57.

Cyclic ethers VII, VIII, XIX–XXII. *General procedure.* To 7 ml of glycol (ethylene glycol, 1,3-propanediol) was added 4 mmol of sulfite **III, XI**, or **XII**, the mixture was stirred for 24 h at room temperature, the precipitate was filtered off, thoroughly washed with water, boiling ethanol, and ether, and dried in air.

2-(Dinitromethylene)hexahydro-1*H*-[1,4]dioxino-[2,3-*d*]imidazole (VII). Yield 53%, light-yellow powder, mp 219–221°C (decomp.). IR spectrum, cm^{-1}: 3337 (NH), 2977 (OCH_2), 1604 (C=C), 1527 (NO_2), 1496, 1365 (NO_2), 1319, 1203 (COC), 1172, 1060, 1018, 995, 756 (NH). ^1H NMR spectrum, δ, ppm: 3.65–3.85 m (4H, CH_2), 5.45 s (2H, CH), 9.65 s (2H, NH). Found, %: C 31.27; H 3.62; N 24.01. $C_6H_8N_4O_6$. Calculated, %: C 31.04; H 3.47; N 24.13.

2-(Dinitromethylene)hexahydro-1*H*,5*H*-[1,4]dioxepino[2,3-*d*]imidazole (VIII). Yield 51%, light-yellow powder, mp 167–170°C (ethanol, decomp.). IR spectrum, cm^{-1}: 3341 (NH), 2907 (OCH_2), 1574 (C=C), 1524 (NO_2), 1446 (CH_2), 1358 (NO_2), 1207 (COC), 1172, 1107, 1057, 853, 752 (NH). ^1H NMR spectrum, δ, ppm: 1.20 d.d (3H, CH_2, *J* 24.1 and 4.2 Hz), 3.60–4.05 m (3H, CH_2), 5.20–5.55 m (2H, CH), 9.55 q (2H, NH, *J* 32.2 Hz). Found, %: C 34.49; H 4.40; N 23.02. $C_7H_{10}N_4O_6$. Calculated, %: C 34.15; H 4.09; N 22.76.

***N*-Nitrohexahydro-2*H*-[1,4]dioxino[2,3-*d*]-imid-azole 2-imine (XIX).** Yield 68%, colorless powder, mp 205°C (decomp.). IR spectrum, cm^{-1}: 3352, 3201 (NH), 2947 (CH_2), 1604 (C=N), 1531 (NO_2), 1481 (CH_2), 1354 (NO_2), 1292, 1234 (COC), 1161, 1118, 1064 (N–N), 1018, 968, 906, 875, 798 (NH), 636 (NNO_2). ^1H NMR spectrum, δ, ppm: 3.65–3.80 m (4H, CH_2), 5.30 s (2H, CH), 9.15 s (2H, NH). Found, %: C 32.01; H 4.44; N 29.60. $C_5H_8N_4O_4$. Calculated, %: C 31.92; H 4.29; N 29.78.

***N*-Nitrohexahydro-2*H*,5*H*-[1,4]dioxepino[2,3-*d*]imidazole 2-imine (XX).** Yield 52%, colorless powder, mp 184–185°C (decomp.). IR spectrum, cm^{-1}: 3390, 3151 (NH), 2943 (CH_2), 1620 (C=N), 1535 (NO_2), 1481 (CH_2), 1377, 1346 (NO_2), 1288, 1230 (COC), 1164, 1115, 1053 (N–N), 968, 856, 783 (NH), 682 (NNO_2). ^1H NMR spectrum, δ, ppm: 1.00–1.15 m (3H, CH_2), 3.20–4.00 m (3H, CH_2), 5.05–5.45 m (2H, CH), 9.15 d (2H, NH, *J* 30.8 Hz). Found, %: C 35.73; H 5.10; N 27.79. $C_6H_{10}N_4O_4$. Calculated, %: C 35.65; H 4.99; N 27.71.

***N,N'*-(1,4-Dioxan-2,3-diyl)bis(2-chloroacetamide) (XXI).** Yield 57%, colorless powder, mp 205–207°C (decomp.). IR spectrum, cm^{-1}: 3302 (NH), 3066 (CN), 2858 (CH, OCH_2), 1670 (C=O), 1535 (CN, NH), 1427 (CH_2Cl), 1365, 1323 (CH), 1257 (CH_2Cl), 1207 (CO, CNH), 1169 (COC), 1122, 1103, 1022, 987, 956, 779 (NH). ^1H NMR spectrum, δ, ppm: 3.65 d.d (4H, CH_2, *J* 57.1 and 5.7 Hz), 4.00 s (4H, CH_2), 4.85 d (4H, CH, *J* 4.2 Hz), 8.95 d (2H, NH, *J* 4.2 Hz). Found, %: C 35.67; H 4.69; N 10.10. $C_8H_{12}Cl_2N_2O_4$. Calculated, %: C 35.44; H 4.46; N 10.33.

***N,N'*-1,4-Dioxepan-2,2-diylbis(2-chloroacetamide) (XXII).** Yield 48%, colorless powder, mp 189–192°C (decomp.). IR spectrum, cm^{-1}: 3294 (NH), 3032 (CN), 1654 (C=O), 1535 (CN, NH), 1446 (CH_2Cl), 1326 (CH), 1265 (CH_2Cl), 1250 (CO, CNH), 1134 (COC), 1060, 1007, 875, 829, 792 (NH). ^1H NMR spectrum, δ, ppm: 1.1 m (3H, CH_2), 3.50–4.05 m (3H, CH_2), 4.15 d (4H, CH_2, *J* 5.4 Hz), 4.75–5.15 m (2H, CH), 8.80–9.35 m (2H, NH). Found, %: C 38.03; H 5.11; N 9.72. $C_9H_{14}Cl_2N_2O_4$. Calculated, %: C 37.91; H 4.95; N 9.82.

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