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SHORT COMMUNICATIONS

Dedicated to Full Member of the Russian Academy of Sciences A.I. Konovalov on the 70th Anniversary of His Birth

A Convenient Synthesis of Bis(aminooxy)methane Dihydrochloride

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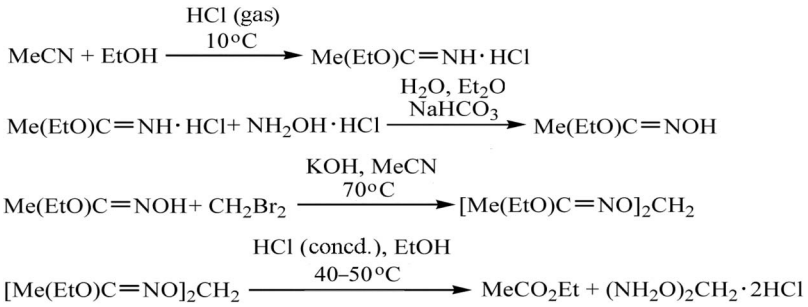
Bis(aminooxy)methane and its derivatives at the nitrogen atoms are energy-rich compounds [1, 2] which can be used in the synthesis of heterocycles of the dioxadiazine series [3–6]. Only one multistep procedure for the preparation of bis(aminooxy)methane dihydrochloride, starting from acetonitrile has been reported [1, 2] (Scheme 1).

Despite the initial compounds and reagents are fairly simple, the procedure is characterized by a number of substantial disadvantages, such as the use of gaseous hydrogen chloride and large volumes of dry solvents, etc. Moreover, the overall yield of the target product does not exceed 40%, and the reaction conditions should be strictly met to avoid sharp decrease in the product yield and purity. The goal of the present work was to develop a simple and convenient procedure for the preparation of bis(aminooxy)methane dihydrochloride (**III**) and create a library of potential biologically acive bis(methyleneaminooxy)methanes (**IIa**–**IIn**) [7, 8].

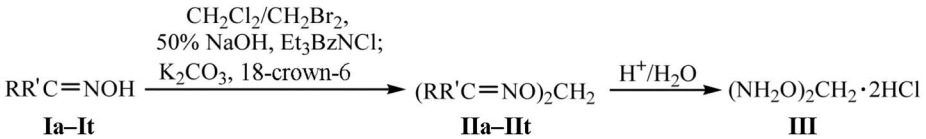
Theoretically, compounds **IIa–IIn**, which are available from the corresponding oximes **Ia**–**In**, may be direct precursors of compound **III**. Taking into account that procedures for the preparation of compounds **IIa–IIn** under various conditions have been explored to a sufficient extent [9, 10], the synthesis of bis(aminooxy)-methane dihydrochloride (**III**) may follow Scheme 2.

While optimizing the conditions for O-alkylation of oximes **Ia**–**It** with methylene halides, we have found that all the examined oximes are readily coupled through a methylene group under conditions of phase-transfer

Scheme 1.



Scheme 2.



I, **II**, R = R' = Me (**a**); R = Me, R' = Ph (**b**); R = R' = Ph (**c**); R = R' = COOEt (**d**); R = NH_2, R= Ph (**e**); R = Me, R' = 4-MeC_6H_4 (**f**), 4-ClC_6H_4 (**g**), 4-$MeOC_6H_4$ (**h**), 4-$O_2NC_6H_4$ (**i**), 4-BrC_6H_4 (**j**), 2-FC_6H_4 (**k**), 3-FC_6H_4 (**l**), 4-FC_6H_4 (**m**), 2,4-$F_2C_6H_3$ (**n**), 2-$MeOC_6H_4$ (**o**), 2-ClC_6H_4 (**p**), 2-F-4-$MeOC_6H_3$ (**q**), 3-F-4-MeC_6H_3 (**r**), 3,4-$(MeO)_2C_6H_3$ (**s**), 3,4,5-$(MeO)_3C_6H_2$ (**t**).

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catalysis. However, a proper choice of both alkylating agent and the system base–phase-transfer catalyst is necessary to achieve a good preparative yield of dimeric products **IIa**–**IIt** [7, 8]. For example, oxime **Ib** was quantitatively converted into compound **IIb** by the action of methylene chloride in the system potassium carbonate–rown ether, whereas complete transformation of oxime **Ie** into compound **IIe** was effected with the use of methylene bromide and the system alkali–quaternary ammonium salt. Also, success in the acid hydrolysis of compounds **IIa**–**IIt** strongly depended on the R and R' substituents. We failed to obtain product **III** by hydrolysis of compounds **IIc** and **IId** despite wide variation of the reaction conditions. On the other hand, the simplest derivatives **IIa** and **IIb** were readily hydrolyzed in aceto-nitrile by the action of concentrated hydrochloric acid; here, the yield and purity of compound **III** were better in the reaction with **IIb**. Bis(aminooxy)methane dihydrochloride (**III**) can readily be converted into *N*,*N*,*N*',*N*'-tetraacetyl derivative **IV** (which is more convenient to handle with) by heating in boiling acetic anhydride.

The NMR spectra were recorded on a Varian XL-100 spectrometer. The mass spectra were run on a Finnigan MAT-113 instrument with direct sample admission into the ion source. The properties of previously known compounds were in a good agreement with published data [1, 2, 7, 8].

Bis[bis(ethoxycarbonyl)methyleneaminooxy]-methane (IId). Yield 85%. Colorless crystals, mp 100–102°C (from CCl_4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.92 s (2H, CH_2), 4.43 q (8H, OC**H**$_2$CH$_3$), 1.31 t (12H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %) : 390 (2) M^+, 202 (3) [*M*–NC(CO$_2$Et)$_2$]$^+$, 172 (100) [*M* – OCH$_2$ONC(CO$_2$Et)$_2$]$^+$, 73 (30) [CO$_2$Et]. Found, %: C 47.00; H 5.60; N 7.00. $C_{15}H_{22}N_2O_{10}$. Calculated, %: C 47.15; H 5.68; N 7.18.

Bis(α-aminobenzylideneaminooxy)-methane (IIe). Yield 80%. Colorless crystals, mp 185–187°C (from $CHCl_3$). 1H NMR spectrum (CD_3OD), δ, ppm: 7.30–7.80 m (10H, Ph), 5.50 s (2H, CH_2), 4.70 s (4H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 284 (3) M^+, 165 (3) [*M* – NC(NH$_2$)Ph]$^+$, 119 (100) [*M*–OCH$_2$ONC(NH$_2$)Ph]$^+$, 77 (35) [Ph]+. Found, %: C 63.20; H 5.54; N 19.65. $C_{15}H_{16}N_4O_2$. Calculated, %: C 63.40; H 5.70; N 19.90.

Bis(2-fluoro-α-methylbenzylideneaminooxy)-methane (IIk). Yield 92%. Colorless crystals, mp 89–90°C (from CCl_4). 1H NMR spectrum ($CDCl_3$), δ, ppm: 7.51–7.56 m (2H, *o*-H), 7.33–7.40 m (2H, *p*-H), 7.10–7.18 m (4H, *m*-H), 5.86 s (2H, CH_2), 2.30 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 318 (2) M^+, 166 (2) [*M* –NC(CH$_3$)C$_6$H$_4$F]$^+$, 136 (100) [*M*–OCH$_2$ONC(CH$_3$)CC$_6$H$_4$F]$^+$, 95 (31) [C$_6$H$_4$F]$^+$. Found, %: C 64.14; H 5.07; F 11.85; N 8.70. $C_{17}H_{16}F_2N_2O_2$. Calculated, %: C 64.15; H 5.10; F 11.94; N 8.72.

Bis(3-fluoro-α-methylbenzylideneaminooxy)-methane (IIl). Yield 89%. Colorless crystals, mp 88– 90°C (from CCl_4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.54–7.58 m (2H, *p*-H), 7.41–7.51 m (4H, *o*-H), 7.14–7.21 m (2H, *m*-H), 5.87 s (2H, CH_2), 2.26 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 318 (3) M^+, 166 (2) [*M*–NC(CH$_3$)C$_6$H$_4$F]$^+$, 136 (100) [*M*–OCH$_2$ONC(CH$_3$)C$_6$H$_4$F]$^+$, 95 (33) [C$_6$H$_4$F]$^+$. Found, %: C 64.12; H 5.08; F 11. 87; N 8.76. $C_{17}H_{16}F_2N_2O_2$. Calculated, %: C 64.15; H 5.10; F 11.94; N 8.72.

Bis(4-fluoro-α-methylbenzylideneaminooxy)methane (IIm). Yield 96%. Colorless crystals, mp 104–106°C (from CCl_4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.62–7.69 m (4H, *o*-H), 7.00–7.19 m (4H, *m*-H), 5.82 s (2H, CH_2), 2.25 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 318 (2) M^+, 166 (3) [*M* –NC(CH$_3$)C$_6$H$_4$F]$^+$, 136 (100) [*M* – OCH$_2$ONC(CH$_3$)C$_6$H$_4$F]$^+$, 95 (30) [C$_6$H$_4$F]$^+$. Found, %: C 64.11; H 5.12; F 11. 83; N 8.68. $C_{17}H_{16}F_2N_2O_2$. Calculated, %: C 64.15; H 5.10; F 11.94; N 8.72.

Bis(2,4-difluoro-α-methylbenzylideneaminooxy)methane (IIn). Yield 83%. Colorless crystals, mp 127–129°C (from CCl_4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.50–7.57 m (2H, *m*-H), 6.82–6.93 m (4H, *o*-H, *m*-H), 5.83 s (2H, CH_2), 2.28 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 354 M^+, 200 (3) [*M* – NC(CH$_3$)C$_6$H$_3$F$_2$]$^+$, 154 (100) [*M* – OCH$_2$ONC(CH$_3$)C$_6$H$_3$F$_2$]$^+$, 114 (35) [C$_6$H$_3$F$_2$]. Found, %: C 64.14; H 5.07; F 21.12; N 8.80. $C_{17}H_{14}F_4N_2O_2$. Calculated, %: C 57.63; H 3.98; F 21.45; N 7.91.

Bis(2-fluoro-4-methoxy-α-methylbenzylideneaminooxy)methane (IIq). Yield 90%. Colorless crystals, mp 128–130°C (from CCl_4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.45–7.51 m (2H, *m*-H), 6.61–6.73 m (4H, *o*-H, *m*-H), 5.82 s (2H, CH_2), 3.77 s (6H, CH_3O), 2.30 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 378 (3) M^+, 212 (2) [*M* – NC(CH$_3$)C$_6$H$_3$FOCH$_3$]$^+$, 166 (100) [*M* – OCH$_2$ONC(CH$_3$) C$_6$H$_3$FOCH$_3$]$^+$, 126 (38) [C$_6$H$_3$FOCH$_3$Ar]$^+$. Found, %: C 60.25; H 5.28; F 10.00; N 7.36. $C_{19}H_{20}F_2N_2O_4$. Calculated, %: C 60.31; H 5.33; F 10.04; N 7.40.

Bis(3-fluoro-4-methoxy-α-methylbenzylideneaminooxy)methane (IIr). Yield 81%. Colorless crystals, mp 148–150°C (from CCl_4). 1H NMR spectrum ($CDCl_3$), δ, ppm: 7.47–7.56 m (4H, *o*-H, *m*-H), 7.12–

7.17 m (2H, *m*-H), 5.80 s (2H, CH_2), 4.00 s (6H, CH_3O), 2.80 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 378 (3) M^+, 212 (3) [*M*–$NC(CH_3)C_6H_3FOCH_3$]$^+$, 166 (100) [*M*–$OCH_2ONC(CH_3)$ $C_6H_3FOCH_3$]$^+$, 126 (40) [$C_6H_3FOCH_3Ar$]$^+$. Found, %: C 60.23; H 5.29; F 10.01; N 7.35. $C_{19}H_{20}F_2N_2O_4$. Calculated, %: C 60.31; H 5.33; F 10.04; N 7.40.

Bis(3,4-dimethoxy-α-methylbenzylideneamino-oxy)methane (IIs). Yield 85%. Colorless crystals, mp 110–112°C (from $CHCl_3$). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 7.35–7.38 m (2H, *o*-H), 7.22–7.26 m (2H, *m*-H), 6.45–6.65 m (2H, *o*-H), 5.81 s (2H, CH_2), 3.78 s (6H, *m*-OCH_3), 3.82 s (6H, *p*-OCH_3), 2.85 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 402 M^+, 224 (4) [*M*–$NC(CH_3)C_6H_3(OCH_3)_2]^+$, 178 (100) [*M*–$OCH_2ONC(CH_3)C_6H_3(OCH_3)_2]^+$, 138 (42) [$C_6H_3(OCH_3)_2]^+$. Found, %: C 62.56; H 6.45; N 6.88. $C_{21}H_{26}N_2O_6$. Calculated, %: C 62.67; H 6.51; N 6.96.

Bis(3,4,5-trimethoxy-α-methylbenzylidene-amino-oxy)methane (IIt). Yield 75%. Colorless crystals, mp 113–115°C (from $CHCl_3$). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 7.00 s (4H, *o*-H), 83 s (2H, CH_2), 3.80 s (12H, *m*-OCH_3), 3.72 s (6H, *p*-OCH_3), 2.25 s (6H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 462 (2) M^+, 254 (3) [*M* – $NC(CH_3)C_6H_2(OCH_3)_3]^+$, 208 (100) [*M* – $OCH_2ONC(CH_3)C_6H_2(OCH_3)_3]^+$, 168 (39) [$C_6H_2(OCH_3)_3]^+$. Found, %: C 59.65; H 6.45; N 6.00. $C_{23}H_{30}N_2O_8$. Calculated, %: C 59.73; H 6.54; N 6.06.

Bis(aminooxy)methane dihydrochloride (III). Compound **IIc**, 28.23 g (0.1 mol), was dissolved in 300 ml of anhydrous acetonitrile at 40°C, and 25 ml of concentrated hydrochloric acid was added dropwise with stirring, maintaining the temperature below 50°C. The mixture was stirred for 6 h at 40–50°C and cooled to 18–20°C, and the precipitate was filtered off, washed with acetone and ether, and dried in air. Yield 8.3–9.0 g (55–60%). mp 154–155°C; published data [1]: mp 152–153°C. ^{1}H NMR spectrum (DMSO-d_6, 50°C), δ, ppm: 5.63 s (2H, CH_2), 8.00 s (6H, NH_3^+). Mass spectrum (150°C), *m*/*z* (I_{rel}, %): 78 (100) [*M* – 2HCl]$^+$. Found, %: C 8.18; H 15.54; Cl 46.91; N 18.57. $CH_8Cl_2N_2O_2$. Calculated, %: C 7.95; H 15.30; Cl 46.96; N 18.54.

***N*,*N*,*N*',*N*'-Tetraacetylbis(aminooxy)methane (IV).** Yield 85%. Colorless crystals, mp 68–71°C, bp 158–161°C (5 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.38 s (12H, CH_3), 5.32 s (2H, CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 204 (100) [M^+ H – $CH_3CO]^+$. Found, %: C 43.68; H 5.65; N 11.17. $C_9H_{14}N_2O_6$. Calculated, %: C 43.90; H 5.73; N 11.38.

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