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First synthesis of 1,10-phenanthroline-2,9-diamine dioxides, a novel family of phenanthroline-based ligands

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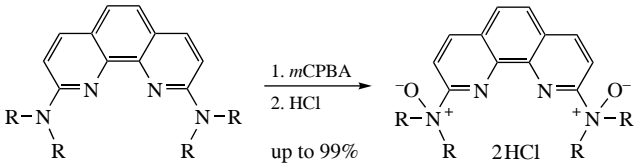
Oxidation of 2,9-dialkylamino-1,10-phenanthrolines with *m*CPBA affords the corresponding *N*,*N*′-dioxides at the aliphatic amino substituents in up to 99% yield. The stability of these compounds can be improved by their conversion into dihydrochlorides at the remaining aromatic nitrogen atoms. The mercury-assisted Meisenheimer rearrangement of the prepared compounds is described.



Keywords: 1,10-phenanthrolines, amines, oxidation, *N*-oxides, ligands, Meisenheimer rearrangement.

Molecules with *N*-oxide moieties belong to the interesting organic compounds which have drawn a lot of attention in recent years. High polarization of the N–O bond in *N*-oxides leads to their zwitterionic structure and ability to form hydrogen bonds through the oxide ion. As a consequence, these compounds are highly soluble in water, and *N*-oxide groups can be used to increase solubility and decrease membrane permeability of drugs.[1] Several *N*-oxides are marketed drugs (Figure 1) used as sedative, antihypertensive and lipid-lowering agents. In 2024, FDA approved Arimoclomol for treatment of a rare genetic disease so called 'Childhood Alzheimer's'.

Installation of the *N*-oxide structural motif into molecules enables 'turn-on' and opens a pathway for applications of *N*-oxide fluorophores in hypoxic cell lines, Fe^{II} detection, and bioimaging.[2] *N*-Methylmorpholine *N*-oxide is used as an oxidant[3] for example in Upjohn[4] or Ley–Griffith oxidations[5] as well as in TPAP-catalyzed direct oxidation of alcohols to carboxylic acids.[6] *N*-Methylmorpholine *N*-oxide is also utilized as a solvent in the manufacturing of cellulose fibers in the Lyocell process.[7] *N*-Lauryl-*N*,*N*-dimethylamine oxide is a widely used zwitterionic surfactant.[8] Additionally, an application of six-membered heterocyclic *N*-oxide scaffolds for the design of novel energetic materials is a recently emerged trend.[9]

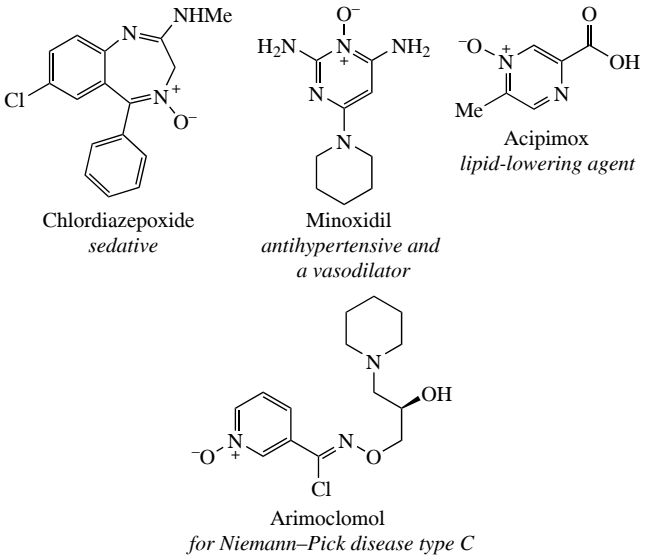
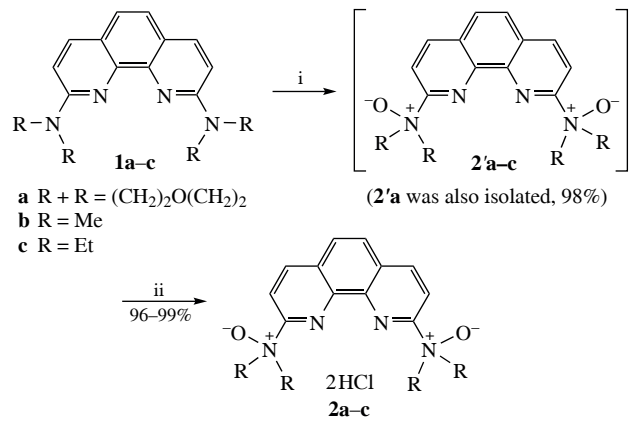


Figure 1 Some marketed drugs containing *N*-oxide moieties.

1,10-Phenanthroline is a versatile building block for the design of ligands whose complexes with metals have a wide range of applications.[10–14] In recent years, we have been deeply engaged with the design of phenatroline-based ligands for extraction and separation of spent nuclear fuels.[15–19] Recently, we elaborated a convenient approach to 2,9-diamino-1,10-phenanthrolines as new bidentate ligands with d-elements.[20] Conversion of such diamines to *N*-oxides could open a pathway to a novel class of tetradentate N–O ligands. Having in mind stability of *N*-methylmorpholine *N*-oxide, we chose dimorpholino phenanthroline **1a** as a model substrate for oxidation (Scheme 1). We found that compound **1a** could be easily transformed into *N*,*N*′-dioxide **2′a** by treatment with *m*CPBA in chloroform for 20–30 min. Product **2′a** could be isolated by column chromatography, however its partial decomposition was observed to form 5–10% of admixtures. Relatively low stability of such *N*-oxides may be due to their



Scheme 1 *Reagents and conditions*: i, *m*CPBA, $CHCl_3$, room temperature, ~18 h (30 min for the preparation of **2′a**); ii, HCl (2 N aq.).

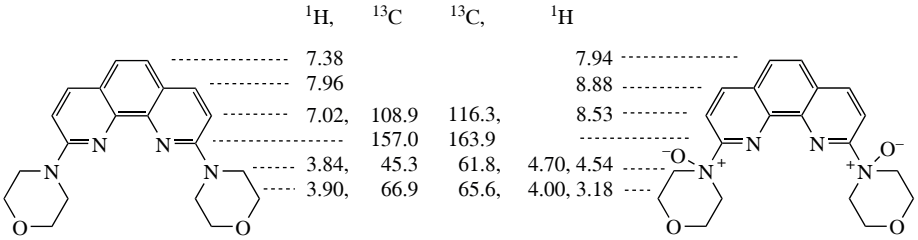


Figure 2 Comparison of ^{1}H and ^{13}C NMR spectra of compounds **1a** and **2a**.

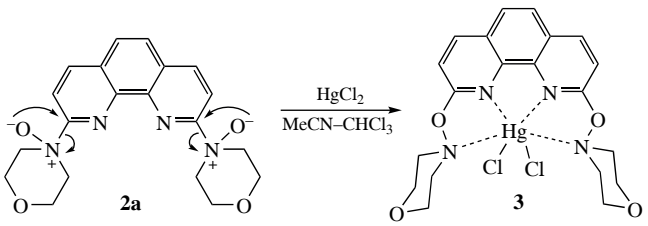
participation in a number of characteristic reactions, *e.g.*, the Meisenheimer rearrangements,[21] the Cope eliminations[22] as well as the Polonovski reactions.[23]

Alternatively, **2a** can be transformed to the more stable dihydrochloride easily separable from admixtures (see Scheme 1). Apparently, the HCl molecules would protonate the remaining aromatic nitrogen atoms which were not oxidized with *m*CPBA. Using this procedure, we synthesized *N*,*N*′-dioxide dihydrochlorides **2a–c** in high yields. Such hydrochlorides are more stable and can be stored both in solution and solid form for weeks without decomposition.

The structures of compounds **2** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. Comparing to starting diamine **1a**, signals for both protons and carbons of **2a** are shifted downfield due to the electron-withdrawing nature of *N*-oxide moiety. The loss of symmetry in the morpholine fragment in **2a** leads to non-equivalence of all protons, which appear as four signals instead of two in **1a** (Figure 2).

Next, we decided to obtain complex of **2a** with $HgCl_2$. To our surprise, compound **3** was formed as the result of the Meisenheimer rearrangement of **2a** followed by complexation with the rearranged ligand (Scheme 2). Note that it is a first example of such rearrangements for phenanthroline derived *N*-oxides.

X-ray diffraction examination of complex **3** (Figure 3) revealed that the $HgCl_2$ fragment in **3** is perpendicular to the phenanthroline plane and is coordinated by two nitrogen atoms N(1) and N(2).† It should be noted that the Hg–Cl bonds are shorter [2.388(1) Å] than the Hg–N [2.470(3)–2.481(3) Å] ones. The latter bonds are markedly longer than those for four-coordinated mercury bonded with the phenanthroline part (2.31–2.36 Å) according to analysis of CSD. The plane of the morpholine ring coincides with the phenanthroline ring, and as a result, the N(3) and N(4) atoms form shortened contacts [2.785(3) and 2.829(3) Å] with mercury. Taking into account the additional coordination, Hg(1) is characterized by a coordination number equal to 6 and its coordination polyhedron is a highly distorted trigonal prism.



Scheme 2

† *Crystal data for* **3**. $C_{20}H_{21}Cl_2HgN_4O_4$, M = 652.90, triclinic, space group $P\bar{1}$, Z = 2, T = 120 K, a = 7.9686(5), b = 9.0321(5) and c = 15.6606(10) Å, α = 101.653(2), β = 92.491(3) and γ = 103.599(2)°, V = 1068.05(11) Å^3. A total of 10548 ($2\theta_{max}$ = 58°, R_{int} = 0.0436) reflections were collected and 5598 independent reflections were used for the structure solution and refinement, which converged to R_1 = 0.0347 (for 3690 observed reflections), wR_2 = 0.0747, GOF = 1.000.

CCDC 2431139 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

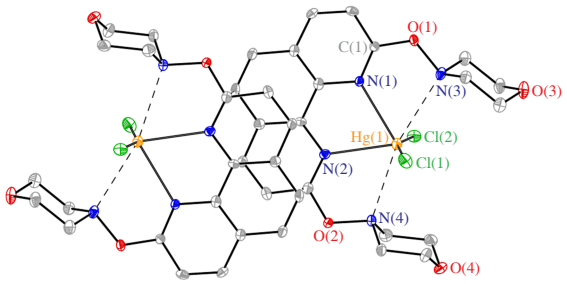


Figure 3 The general view of stacking assembled Hg complex **3** in representation of atoms by atomic displacement parameters (p = 50%). Selected bond lengths (Å): Hg(1)–Cl(2) 2.389(1), Hg(1)–Cl(1) 2.388(1), Hg(1)–N(2) 2.470(4), Hg(1)–N(1) 2.481(3), O(1)–N(3) 1.481(5), O(1)–C(1) 1.362(5), O(2)–N(4) 1.465(4), O(2)–C(12) 1.360(5); bond angles (°): Cl(2)–Hg(1)–N(2) 98.36(9), Cl(2)–Hg(1)–N(1) 98.35(9), Cl(1)–Hg(1)–Cl(2) 157.82(4), Cl(1)–Hg(1)–N(2) 101.23(9), Cl(1)–Hg(1)–N(1) 98.42(9), N(2)–Hg(1)–N(1) 68.50(11).

To get additional evidence for the presence of interactions between mercury and the nitrogen atoms of morpholine, we carried out a topological analysis of the electron density distribution function obtained for the experimental geometry on the basis of the PBE1PBE/def2TZVP calculation,[24–26] which showed the presence of critical points (3,–1) for the above bonds.‡ All bonds formed by Hg are characterized by positive values of $\nabla^2\rho(r)$ and electron energy density in critical points (3,–1) and thus correspond to intermediate type of interatomic interactions, and their energies can be estimated with the Espinosa correlation.[27,28] The binding energies of Hg–N with phenanthroline and morpholine are 15.6 and 6 kcal mol^{-1}, respectively, and thus the total energy or the ligand is *ca.* 43 kcal mol^{-1}. This allows one to suppose that the supramolecular organization of molecules in crystal is their assembling into dimers by means of stacking interaction with high area of overlap and 3.37 Å interplane separation.

In conclusion, we explored oxidation of 2,9-dialkylamino-1,10-phenanthrolines with *m*CPBA, which affords previously unknown 1,10-phenanthroline-2,9-diamine dioxides in up to 99% yield. An effort to prepare complex of *N*-oxide containing morpholine moiety with $HgCl_2$ led to the first example of Meisenheimer rearrangement of phenanthroline-derived *N*-oxide.

The study was performed under the state assignment of The Lomonosov Moscow State University (project no. AAAA-A21-121012290046-4). The X-ray diffraction investigation was conducted under the state assignment of the Lomonosov Moscow State University (project no. 121031300090-2).

‡ All quantum chemistry computations were performed with the Gaussian 09, Revision D.01 program[24] using the density functional theory (PBE0)[25] and the def-2-TZVP basis set. Topological analysis of the $\rho(r)$ functions was performed using the AIMAll program.[26] All expected critical points were found and the whole set of critical points in each system satisfies the Poincaré–Hopf rule.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7802.

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