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UNEXPECTED REARRANGEMENT OF PHENOXYPICRAMIDE TO 1,3-DINITRO-10*H*-PHENOXAZINE**

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The attempt to obtain phenoxypicramide from a classical nucleophilic substitution reaction using as reagents phenoxyamine and picryl chloride unexpectedly led to the formation of 1,3-dinitro-10*H*-phenoxazine. The possible mechanisms of formation, involving a molecular rearrangement with expelling of a nitro group, are discussed.

INTRODUCTION

Alkoxyl picramides are well-known as precursors for persistent (oxy)aminyl free radicals, *N*-methoxypicramide (*N*-methoxy-2,4,6-trinitroaniline) being one of the most known.[1] The stability of such free radicals is dependent on their chemical structure, the factors that mainly affect this behavior being the steric and electronic effects (push-pull, mero- or capto-dative stabilization).[2]

Although a lot of research was pursued over many decades regarding similar congeners derivatives, the literature data showed that *N*-phenoxy-2,4,6-trinitroaniline or the corresponding phenoxyaminyl free radical was not reported. This free radical (*N*-phenoxy-picrylaminyl) might possess some very interesting features, as the unpaired electron can be easily delocalized over the entire molecule (Scheme 1).

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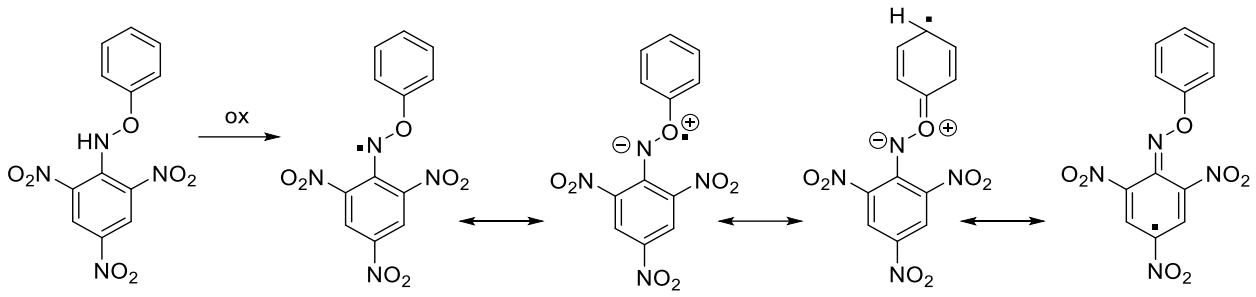
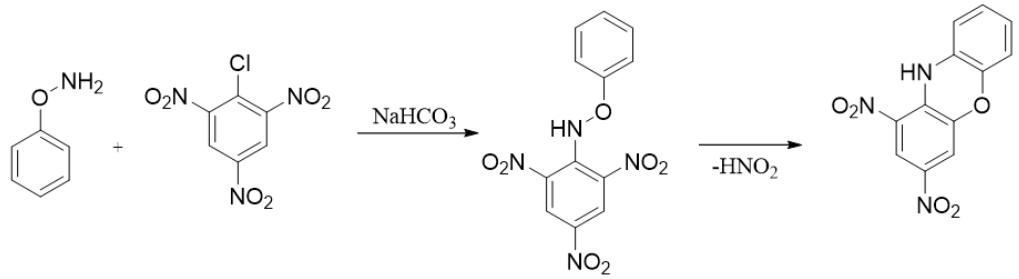


Scheme 1 – Oxidation of *N*-phenoxypicramide to the corresponding free radical and some of the possible resonance structures.

RESULTS AND DISCUSSION

N-Phenoxypicramide should be obtained straightforward from *N*-phenoxyamine and picryl chloride, in a similar manner with all other congeners.[1,2] However, following the procedure described in Scheme 2, the structure of the isolated compound was completely unexpected, all physical and chemical data demonstrating that is not the expected *N*-phenoxypicramide, but 1,3-dinitro-10*H*-phenoxazine. The same compound was previously prepared in literature from trinitrobenzene and 2-aminophenol[3] or from picryl chloride and 2-aminophenol.[4]



Scheme 2 – Unexpected synthesis of 1,3-dinitro-10*H*-phenoxazine.

The structure of the 1,3-dinitro-10*H*-phenoxazine was firstly confirmed by ^{1}H- and ^{13}C-NMR, IR, and ESI-MS (see Electronic Supporting Information (ESI)). Thus, in the ^{1}H-NMR spectrum, the hydrogen nucleus from the amino group appears at highest δ value, 9.36 ppm, as a broad singlet; all other H-nuclei are present with the corresponding integrals; besides, in the ^{13}C-NMR spectrum all twelve carbons can be found (ESI Figs. S1a and S1b). IR spectrum confirm also the presence of the amino group around 3400 cm^{-1}, while the nitro groups are present with the highest intensities at 1525 and 1323 cm^{-1} (ESI Fig. S1c). The ESI-MS spectrum showed the molecular peak with an intensity of 85%, while the base peak appears at 227 *m*/*z*, representing the molecular mass after losing a nitro group (ESI Fig. S1d). The presence of the nitro-groups is responsible for the very intense red color, due to the *n*–π* transition; thus, the UV-Vis spectrum of the 1,3-dinitro-10*H*-phenoxazine showed two intense bands, at 290 and 449 nm (ESI Fig. S2).

Additionally, the final confirmation of the structure was obtained from X-ray diffraction on single crystal. The compound crystallizes in trigonal system, space group P-1 (#2). The crystal structure (Fig. 1) consists of an oxazine fused to two benzene rings, one bearing two nitro groups. The molecule is almost planar, although the benzene rings planes form a 3.92° dihedral angle between them. One nitro group is in the same plane with the connected benzene ring, while the other one is twisted away forming a 11.49° dihedral angle (ESI Figs. S3a and S3b). Different C-C bond lengths in the substituted benzene ring (ESI Table S1) could indicate conjugation of the N1 lone pair electrons with the ring. Similar characteristics were observed in the recently reported crystal structure of the 2,3-dinitro-10*H*-phenoxazine.[5] The crystal network (Fig. 1) present short contacts between twisted nitro group of neighboring molecules and it is stabilized by hydrogen bonds (between N−H···(O,O) atoms in the nitro group) and the π-π stacking interactions (between benzene rings from neighboring molecules).

The details of the crystal parameters, data collection and refinement for the compound are listed in Table 1 (CCDC 2323909).

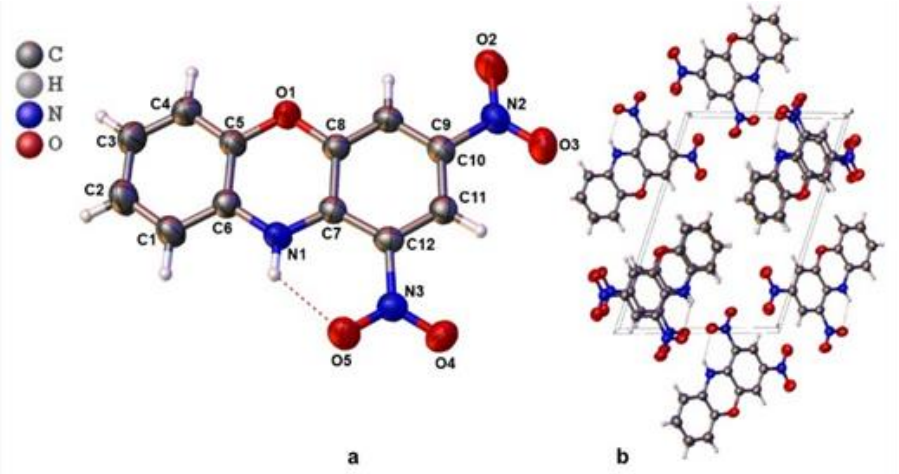


Fig. 1 – (a) X-ray molecular structure of compound with atoms numbering scheme. Thermal ellipsoids representation with 50% probability. (b) Crystal packing along *a* axis (Olex2 and POV-Ray representation).

Table 1

Summary of crystallographic data.

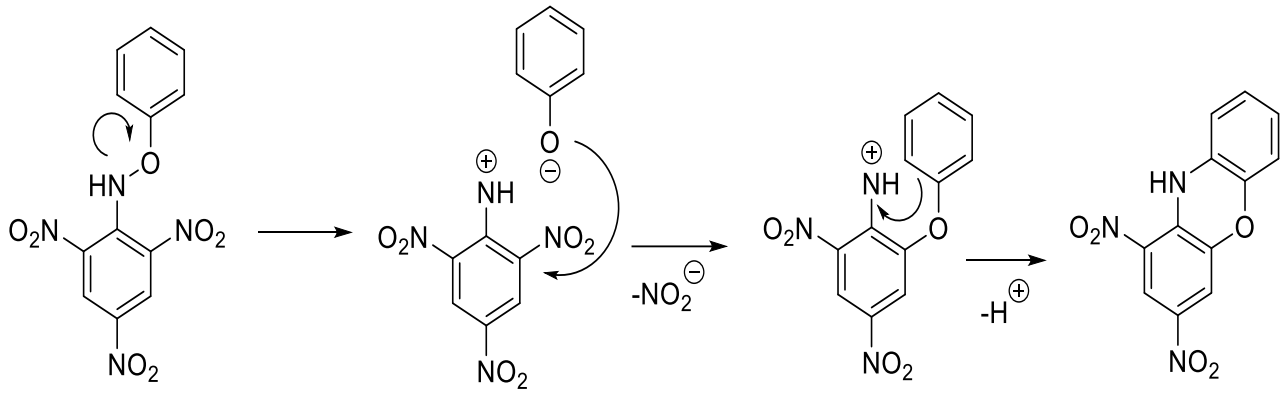
Crystal data	
Empirical formula	$C_{12}H_7N_3O_5$
Formula weight	273.20
Crystal size (mm)	0.900 × 0.350 × 0.020
Crystal system	triclinic
Space group	P-1 (#2)
a (Å)	4.2535(4)
b (Å)	10.2816(9)
c (Å)	13.5069(15)
α (°)	70.640(5)
β (°)	88.549(6)
γ (°)	84.576(6)
Volume (Å^3)	554.79(10)
Z	2
Dcalc.(g/cm^3)	1.635
F(000)	280.00
μMoK$_\alpha$ (cm^{-1})	1.309
Temperature (K)	293
Range of h, k, l	5,13,17
θ min/max	3.039/27.480
Reflections collected/unique/observed	9056/2545/1568
Data/restraints/parameters	2545/0/181
Goodness of fit on F^2	1.148
Final *R* indices [I > 2σ(I)]	R_1 = 0.0453, wR_2 = 0.1319
R indices (all data)	R_1 = 0.0742, wR_2 = 0.1592

Regarding of the mechanism of formation, we can suppose that in the first step the *N*-phenoxypicramide is formed (Scheme 2 and 3). Our supposition is based on similar reactions that occurs smoothly (a classical nucleophilic substitution) if *N*-methoxyamine is used instead of *N*-phenoxyamine, often with (almost) quantitative yields.[1,2] TLC monitoring of the reaction showed the formation of an intermediate that appears at the beginning of reaction; attempts to isolate it were unsuccessful, because, during the isolation procedure, this compound (although impure) is decomposing with the formation of a mixture of many other compounds, from which the derivative (*N*-phenoxypicramide) cannot be isolated and identified.

The unexpected rearrangement of the *N*-phenoxypicramide to 1,3-dinitro-10*H*-phenoxazine can be explained *via* two mechanisms, that involve in the first instance the dissociation of the *O-NH* bond, either following an ionic (heterolytic) or a radical (homolytic) mechanism. Scheme 3 shows a such proposed mechanism (heterolytic ionic version, for the homolytic radical one all charges

should be replaced with unpaired electrons). In order to differentiate between them, the same synthesis reaction was done in the presence of an excess of TEMPO stable free radical, that should act as a scavenger of the radical intermediates. Results showed a lowering in the final yields of 1,3-dinitro-10*H*-phenoxazine, from about 30 % to 20%. Although this result can be a strong indication of a radical mechanism, the ionic one cannot be excluded, as there are many literature data pointing towards it (see below).

The formation of the nitrenium ion is well documented in literature and it is often encountered in several types of rearrangements.[6] Nitrenium ions are isoelectric with carbenes, therefore can exist in two forms, a singlet or a triplet one, and each form might undergo different chemical routes. As triplet, the nitrenium ion has unpaired electrons, therefore is quite probably to favor radical processes. Preparative chemistry using nitrenium ion showed that *N*-methoxy-nitrenium ions easily undergo intra-molecular cyclization reactions.[7] Besides, the replacement of a nitro-group with a phenoxy one, under alkaline conditions, is also well established.[3,8]



Scheme 3 – Proposed mechanism of the rearrangement of *N*-phenoxypicramide to 1,3-dinitro-10*H*-phenoxazine; a parallel reaction can be written replacing both negative and positive charges with an unpaired electron.

A similar cyclization reaction with a leaving nitro group was noticed in the synthesis of substituted 1,2-benzoxazines.[9] Moreover, nitrenium ion is known for *ipso*-addition and *ortho*-cyclization of arenes, and the proposed mechanism was a radical one.[10] The formation of a new *C–N* bond *via* a reaction involving antiaromatic endocyclic nitrenium ions is also presented in literature.[11]

Thus, based on these facts, we consider that in the first step the *O-NH* bond is heterolytically broken to form the nitrenium ion as a triplet rather than a singlet (as the energetic gap between singlet- and triplet state is low). A homolytic scission of the *O-N* bond should imply in the first step the formation of the persistent phenoxyaminyl radical *via* oxidation of the *N-H* bond (the energy of bond dissociation (BDE) for *N-H* in similar derivatives is in the domain of 75–78 kcal/mol),[12] followed by the homolytic dissociation of the *O-N* bond (calculated BDE for similar alcoxyamines is around 30–40 kcal/mol),[13] with the formation of the phenoxy-radical and picryl-nitrene, which looks improbable. It is known that alcoxyamidyl radicals undergo cyclization,[14] as well hydroxylamine derivatives are known for their sigmatropic rearrangements.[15] Literature data showed that radical intermediate mechanism was proved by ESR in an aberrant $S_{NR}1$ reaction;[16] our test experiments showed that no ESR signals were obtained.

By oxidation, phenoxazines can conduct to the corresponding phenoxazinyl cation-radicals (by removing one electron) or to the neutral phenoxazinyl radicals (by removing a hydrogen atom, as one electron and one proton).[17] Phenoxazine *N-H* bond dissociation is about 77 kcal/mol.[18] In our case, we consider that the oxidation of 1,3-dinitro-10*H*-phenoxazine with lead dioxide in DCM lead to the neutral radical (Fig. 2). Simulation of the ESR spectrum with the following hyperfine coupling constants (a_N = 6.8 Gauss; a_H = 3.6, 2.5, 1.2, 1.1, 0.7, and 0.5 Gauss, respectively) gave good results (SI Fig. S4); however, these values should be taken into consideration with some reserves, because of the large linewidths values (around 1 Gauss).

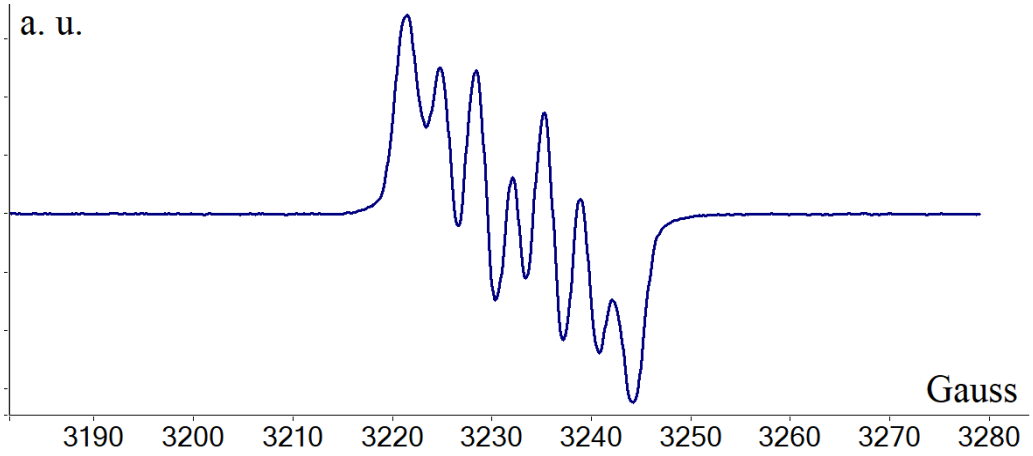


Fig. 2 – ESR spectrum of 1,3-dinitro-10*H*-phenoxazinyl free radical.

As phenoxazine derivatives are widely used as dyes,[19,20] radical-trapping antioxidants,[21] medicines,[22] and so on, while some *O*-aralkylhydroxylamines are also known for their biological effects, like decarboxylase inhibitors and mild antidepressants,[23] we tried to extend the scope of this reaction, using similar chemical derivatives. Thus, the reaction between *O*-(2,4-dinitrophenyl)hydroxylamine[24] and picryl chloride or 1-fluoro-2,4-dinitrobenzene led to a mixture of many compounds, from which the expected (or another major) product cannot be isolated; similar (unsuccessful) results were obtained employing *O*-phenoxyamine and 1-fluoro-2,4-dinitrobenzene. Although at this moment the scope of such reaction seems limited, future developments are for sure possible.

EXPERIMENTAL

All chemicals, solvents and materials were purchased from Sigma-Aldrich, Merck, and Chimopar and used as received. UV-Vis spectra were recorded in methanol on an UVD-3500 double-beam spectrophotometer, using 1 cm cells. IR spectra were measured using a Bruker Tensor 27 FT-IR spectrometer. NMR spectra were measured in chloroform-d1 using a Bruker Advance spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C, and the chemical shifts are reported in δ values as ppm; the residual solvent peaks was used as an internal reference. A Varian 310-MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI) was used for MS-spectra. ESR spectra were measured on a Jeol JES-FA spectrometer, operating in the X-band. X-ray diffraction measurements were performed on a Rigaku R-AXIS RAPID II diffractometer using graphite monochromated Mo-Ka radiation (λ = 0.71075 A). An orange-red plate crystal was mounted on a glass fiber. The ω-ϕ scan technique was used. Non-hydrogen atoms were refined anisotropically. The structure was solved by direct methods and expanded using Fourier techniques. Hydrogen atoms were refined using the riding model. Hydrogen atoms were refined by a riding model. All calculation were performed using the Crystal Structure crystallographic software package, except for refinement, which was performed using SHELXL program. A summary of selected bond lengths (Å) and angles (°) are given in ESI Table S1.

Synthesis. 1 Mmol of *O*-phenoxylamine hydrochloride (145 mg) was reacted with 1 mmol of reactive halogeno-derivative in 30 mL methanol, in the presence of 3–5 mmol of sodium hydrogen carbonate. The mixture was heated at reflux for 1 h and allowed to stand till next day. After addition of about 100 mL of water and 50 mL of diluted (1 N) hydrochloric acid (beware of the effervescence!) the mixture was extracted with DCM (3 × 100 mL). The separated organic phase was dried over anhydrous sodium sulfate, filtered off and the solvent removed using a rotavap. The residue was chromatographed using silica gel as stationary phase and a mixture of DCM/hexane 4/1 *v/v* as eluent. Yields ~ 30 %.

1,3-dinitro-10H-phenoxazine. Red crystals. $C_{12}H_7N_3O_5$ M. W. 273. -ESI-MS (*m/z*) 272 (M-H$^+$). ^{1}H-NMR (500 MHz, $CDCl_3$, δ ppm, J Hz): 9.36 (bs, 1H, N*H*), 8.59 (d, 1H, H_{Ar}, 2.5 Hz), 7.55 (d, 1H, H_{Ar}, 2.5 Hz), 6.92-6.89 (m, 2H, H_{Ar}), 6.75 (dd, 1H, H_{Ar}, 2.1 Hz, 7.4 Hz), 6.67 (dd, 1H, H_{Ar}, 2.2 Hz, 7.3 Hz) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$, δ ppm): 145.7, 143.1, 142.7, 138.7, 136.3, 129.6, 125.9, 125.4, 125.0, 116.0, 115.8, 113.0 ppm. IR (cm^{-1}): 3455; 3441; 3100; 1635; 1583; 1525; 1496; 1323; 1282; 1159; 1075; 882; 746; 597; 528; 441.

CONCLUSION

A novel synthesis reaction type affords the obtaining of a heterocyclic compound, namely 1,3-dinitro-10*H*-phenoxazine. Possible mechanisms of formation are discussed, emphasizing the rearrangement of phenoxypicramide to the named compound. X-ray crystal structure of the title compound is also presented.

Electronic Supporting Information. ^{1}H-NMR, ^{13}C-NMR, IR, ESI-MS, and UV-Vis spectra; X-ray molecular structure details, and selected bond length and angles.

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