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Dedicated to the memory of Professor Margareta Avram on the remembrance of her 100th anniversary

SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NITRODERIVATIVES OF A DOPAMINE ANALOG

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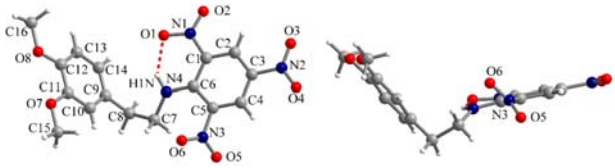
Starting from 3,4-dimetoxyphenethylamine and 1-fluoro-2.4-dinitrobenzene, 1-chloro-2,4,6-trinitrobenzene and 4-chloro-7-nitro-1,2,3-benzoxadiazole, the corresponding secondary amines **1–3** were obtained through classical nucleophilic substitution. These were characterized by UV-Vis, fluorescence, IR, ^{1}H- and ^{13}C-NMR. For compound **2** the X-ray structure was also obtained.



INTRODUCTION

Phenethyl amines are a class of natural occurring compounds that usually have a very good biological activity. We can mention dopamine and adrenaline (Fig. 1) as natural organic compounds that act as hormones and neurotransmitters; a similar compound, mescaline (Fig. 1), is a potent hallucinogenic alkaloid.[1–3]

3,4-Dimetoxyphenethylamine is a similar derivative that can be found in several species of cactus. However, it has no or very low biological effect and may act as an amino-oxidase inhibitor.[4]

Halogeno-polynitrobenzenes are known for their reactivity towards amines. This is due to the influence of the nitro-groups that make the halogen atom easily replaceable through a substitution mechanism. Moreover, polynitro-aromatic compounds are also known for their intense yellow color, and this behavior is commonly used for labeling of a large range of amines within biological systems, like amino-acids, peptides, proteins. A such compound, 1-fluoro-2,4-dinitrobenzene (Sanger's reagent) is widely used for structural analysis of N-terminal amino-acids encountered in protein-like structures (1958, Nobel prize for insulin structure).[5]

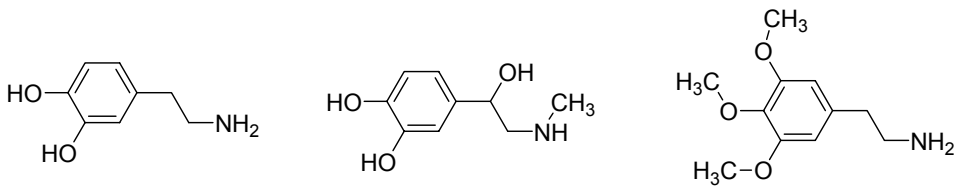


Fig. 1 – Structure of dopamine, adrenaline and mescaline.

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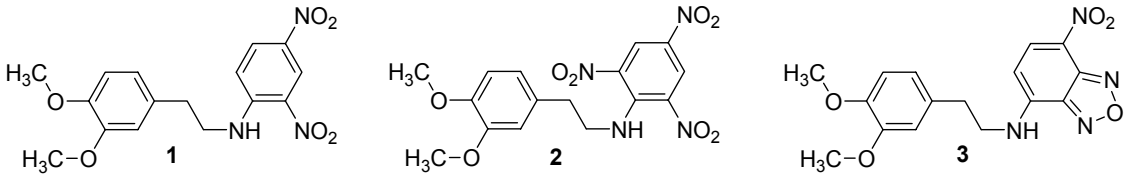

Fig. 2 – Structure of the synthesized compounds **1-3**.

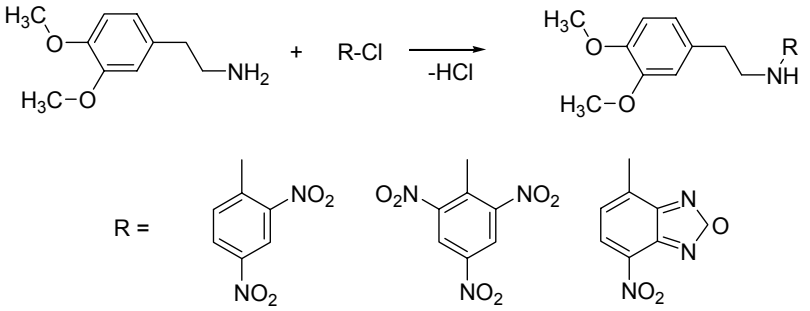

Fig. 3 – Synthesis of compounds **1–3**.

In this study we used three polynitro-derivatives, namely 1-fluoro-2.4-dinitrobenzene, 1-chloro-2,4,6-trinitrobenzene and 4-chloro-7-nitro-1,2,3-benzoxadiazole (NBD-chloride), in the reaction with 3,4-dimetoxyphenethylamine, yielding thus the compounds denoted as **1–3** (Fig. 2).

RESULTS AND DISCUSSION

The synthesis of compounds **1–3** occurs in a single step, by simply mixing the reactants dissolved in dichloromethane (DCM) in presence of triethylamine as base, required to neutralize the acid evolved during the reaction (Fig. 3). The syntheses are fast at room temperature (reaction times around 1–2 h) and proceed in very high yields (around 95% for **1** and **2** and 80% for **3**). Isolation of pure samples was achieved by extracting the unreacted amine and the base with acidulated water; removal of DCM affords the desired compounds (as crystals for **2**). Compound **1** is encountered in the literature, while compounds **2** and **3** are newly synthesized.[6,7]

^{1}H- and ^{13}C-NMR spectra confirmed the expected structures. Thus, in ^{1}H-NMR the corresponding signals for C*H*$_3$-O- are noticed at about 3.8–3.9 ppm as singlet, Ar-C*H*$_2$- at 2.9–3 ppm as triplet, -C*H*$_2$-NH- at about 3.3–3.7 ppm as a superposed quartet, aromatic protons from the phenetyl moiety appear at 6.8–7 ppm, while the other aromatic protons from the nitrophenyl ring appear between 6.2–9 ppm, depending on the structure (for exact values see Experimental part). Regarding the ^{13}C-NMR, the signals for *C*H$_3$- are observed at about 55 ppm, Ar-*C*H$_2$- at 35 ppm, -*C*H$_2$-NH- at about 45–48 ppm, while for the aromatic carbons appear between 110–150 ppm, depending as well on the structure (see also Experimental part for individual values).

IR spectra showed the expected -NH- band around 3300 cm^{-1}, whereas nitro groups are present at ~ 1240 cm^{-1}and 1500 cm^{-1}. Aliphatic C-H bonds appear between 2900–3000 cm^{-1}, while aromatic C-H between 3000–3100 cm^{-1}. C-O bonds are also present at 1020 cm^{-1}.

UV-Vis spectra of the compounds **1–3** recorded in methanol showed absorption bands at 350 nm, 346 nm, and 468 nm, respectively. Bands around 350 nm are due to the presence of nitro groups, while the band at ~470 nm is due to the nitrofurazan moiety.

Compound **3** has fluorescent properties, well known for oxadiazoles or NBD-derivatives.[8–10] Excitation of a solution of **3** in methanol (0.3 mM) at λ_{exc}= 470 nm yielded an emission maximum at λ_{em}= 550 nm (Fig. 4), which is in agreement with the emission of NBD-containing compounds.

The X-ray structure of compound **2,** *N*-(3,4-dimethoxyphenethyl)-2,4,6-trinitrobenzenamine, determined by X-ray diffraction on single crystal is depicted in Fig. 5 along with the atoms labelling scheme. It crystallizes in the monoclinic *P2$_1$/c* space group with one molecule in the asymmetric unit. In solid-state, the molecules present a 'V' conformation with the dihedral angle between the mean plans of the two benzene rings of 59.8 º. The two methoxy groups lie in the plan of the (C9···C14) benzene ring, while

in the 2,4,6-trinitrophenyl fragments only two nitro groups are nearly coplanar with the (C1···C6) benzene ring. The dihedral angles between the plans of (O1-N1-O2), (O3-N2-O4), (O5-N3-O6) nitro groups and the mean plan of (C1···C6) benzene ring are 9.7, 4.8 and 55.5 º respectively. The (O1-N1-O2) nitro group is involved in intramolecular hydrogen interaction with the amino group, N4-H1N···O1 = 1.89 Å. Selected bond lengths are gathered in the Table 1.

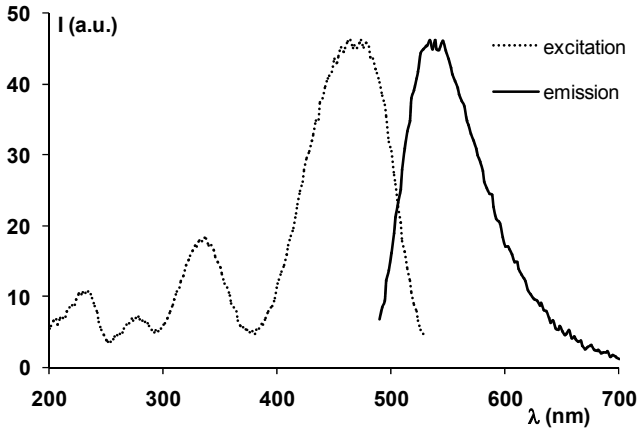

Fig. 4 – Fluorescence spectrum of compound **3**.

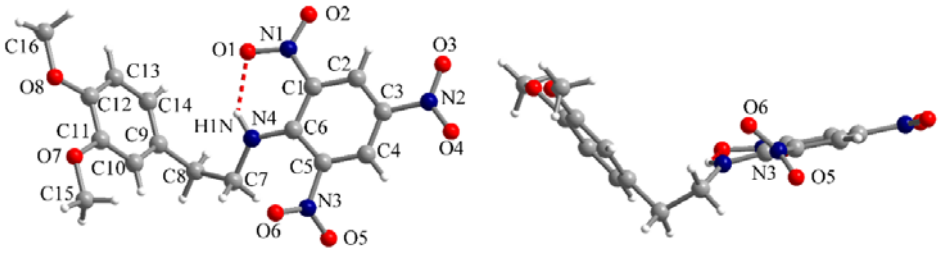

Fig. 5 – Perspective (left) and side (right) views of the asymmetric unit in the crystal structure of compound **2** along with the atoms labelling scheme (for clarity, only the H atom involved in the intramolecular hydrogen interaction was labelled).

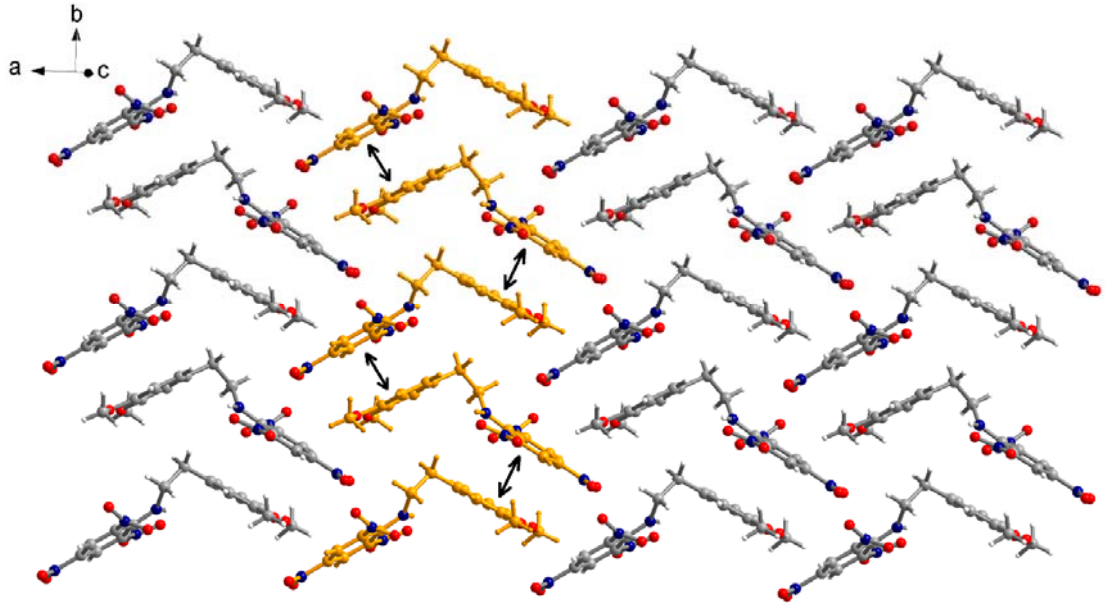

Fig. 6 – Packing diagram showing the supramolecular columns generated by π–π interactions in crystal **2**.

Table 1

Selected bond lengths (Å) for the compound **2**

C1-C2 = 1.379(2)	C10-C11 = 1.374(2)
C1-C6 = 1.423(2)	C11-O7 = 1.363(2)
C1-N1 = 1.450(2)	C11-C12 = 1.400(2)
C2-C3 = 1.361(2)	C12-O8 = 1.368(2)
C3-C4 = 1.375(2)	C12-C13 = 1.369(3)
C3-N2 = 1.451(2)	C13-C14 = 1.386(3)
C4-C5 = 1.366(2)	C15-O7 = 1.415(2)
C5-C6 = 1.421(2)	C16-O8 = 1.420(2)
C5-N3 = 1.465(2)	N1-O2 = 1.2157(18)
C6-N4 = 1.335(2)	N1-O1 = 1.2304(18)
C7-N4 = 1.459(2)	N2-O3 = 1.218(2)
C7-C8 = 1.515(3)	N2-O4 = 1.225(2)
C8-C9 = 1.513(2)	N3-O5 = 1.214(2)
C9-C14 = 1.366(3)	N3-O6 = 1.215(2)
C9-C10 = 1.392(2)	N4-H1N = 0.890(19)

Table 2

Crystallographic data, details of data collection and structure refinement parameters for compound **2**

Compound	**2**
Chemical formula	$C_{16}H_{16}N_4O_8$
M (g mol^{-1})	392.33
Temperature, (K)	293(2)
Wavelength, (Å)	0.71073
Crystal system	*Monoclinic*
Space group	$P2_1/c$
a(Å)	11.7245(6)
b(Å)	9.8530(6)
c(Å)	16.3858(6)
α(°)	90
β(°)	109.254(4)
γ(°)	90
V(Å^3)	1787.03(16)
Z	4
D_c (g cm^{-3})	1.458
μ (mm^{-1})	0.119
F(000)	816
Goodness-of-fit on F^2	0.994
Final $R1$,wR_2 [$I>2\sigma(I)$]	0.0439, 0.1002
$R1$, wR_2(all data)	0.0816, 0.1152
Largest diff. peak and hole (eÅ^{-3})	0.156, -0.201

In the crystal, the V-shape molecules stack along the crystallographic *b* axis generating columns. In these supramolecular columns, the dimethoxybenzene and trinitrobenzene fragments of neighboring molecules establish strong π–π interactions (Fig. 6). The separation between the aromatic fragments is 3.32-3.61 Å. Supramolecular columns with the same orientation of the molecules form layers in the *ab* plane. In the neighboring layers the orientation of the V-shape molecules is alternating.

EXPERIMENTAL

Materials and apparatus. All materials, chemicals and solvents were purchased from Sigma-Aldrich, Merck or Chimopar and used as received. Picryl chloride (1-chloro-2,4,6-trinitrobenzene) was obtained from picric acid and thionyl chloride.[11] UV-Vis spectra were recorded in methanol on a UVD-3500 spectrometer. IR spectra were recorded on an FT-IR Bruker Vertex 70 spectrometer. The solution fluorescence spectra were performed on a Thermo Scientific Varioskan Flash spectral scanning multimode reader. NMR spectra were recorded on a Bruker Fourier 300 or 500 MHz instruments, using the solvent signals for calibration.

Crystallography. X-ray diffraction measurements were performed on a STOE IPDS II diffractometer, operating with Mo-K_α (λ = 0.71073 Å) X-ray tube with graphite monochromator. The structure was solved by direct methods (using SHELXS-2013 crystallographic software) and refined by full-matrix least squares techniques based on F^2. The non-H atoms were refined with anisotropic displacement parameters. Calculations were performed using SHELXL-2018 crystallographic software package. A summary of the crystallographic data and the structure refinement for crystal **2** are given in Table 2. CCDC reference number: 1918868.

Typical synthesis of compounds 1–3. To 1.1 mmol 3,4-dimetoxyphenethylamine dissolved in 25 mL DCM was added 1 mmol of 1-fluoro-2.4-dinitrobenzene (or 1 mmol of 1-

chloro-2,4,6-trinitrobenzene or 1 mmol of 4-chloro-7-nitro-1,2,3-benzoxadiazole) dissolved in 25 mL of DCM and the mixture stirred at room temperature for a couple of hours, in the presence of 0.5 mL of triethylamine. The mixture was extracted twice with 50 mL of aqueous diluted hydrochloric acid and the organic phase dried over anhydrous sodium sulfate, filtered off and the solvent removed using a rotavap. No further purification was requested.

Compound 1. *N*-(3,4-dimethoxyphenethyl)-2,4-dinitrobenzenamine. R_f 0.64 (silica gel/ DCM).^{1}H-NMR (δ ppm, *J* Hz, $CDCl_3$): 9.02 (d, 3 Hz, 1H, C*H* ArNO2); 8.56 (t, 3 Hz, 1H, C*H* ArNO2); 8.19 (dd, 3 Hz, 6 Hz, 1H, C*H* $ArNO_2$); 6.77-6.90 (m, 3H, C_6H_3O); 3.87 (s, 3H, CH_3O); 3.83 (s, 3H, CH_3O); 3.63 (dt, 6 Hz, 6 Hz, 2H, CH_2N); 3.00 (t, 6 Hz, 2H, CH_2Ar). ^{13}C-NMR (δ ppm, $CDCl_3$):149.13; 148.03; 135.78; 130.07; 124.04; 120.61; 113.85; 111.45; 55.74; 44.98; 34.35. IR (cm^{-1}): 3367, 3117, 3070, 2957, 2904, 2835, 1615, 1584, 1515, 1414, 1331, 1255, 1235, 1124, 1076, 1025, 919, 802, 744, 632, 500, 438.

Compound 2. *N*-(3,4-dimethoxyphenethyl)-2,4,6-trinitrobenzenamine. R_f 0.72 (silica gel/ DCM).^{1}H-NMR (δ ppm, *J* Hz, $CDCl_3$): 8.99 (s, 2H, C*H* ArNO2); 6.73-6.86 (m, 3H, C_6H_3O); 3.90 (s, 3H, CH_3O); 3.87 (s, 3H, CH_3O); 3.34 (dt, 6 Hz, 6 Hz, 2H, CH_2N); 2.94 (t, 6 Hz, 2H, CH_2Ar). ^{13}C-NMR (δ ppm, $CDCl_3$): 149.45; 148.49; 142.49; 136.21; 133.63; 128.51; 127.21; 120.92; 111.58; 55.87; 48.34; 35.35. IR (cm^{-1}): 3325, 3073, 2933, 2833, 1623, 1513, 1437, 1329, 1240, 1150, 1024, 923, 789, 722, 646, 545, 433.

Compound 3. *N*-(3,4-dimethoxyphenethyl)-7-nitrobenzofurazan-4-amine. R_f 0.27 (silica gel/ DCM).). ^{1}H-NMR (δ ppm, *J* Hz, $CDCl_3$): 8.46 (d, 6 Hz, 1H, C*H* ArNO2); 6.75-6.86 (m, 3H, C_6H_3O); 6.18 (d, 6 Hz, 1H, C*H* ArNO2); 3.87 (s, 6H, CH_3O); 3.75 (dt, 6 Hz, 6 Hz, 2H, CH_2N); 3.04 (t, 6 Hz, 2H, CH_2Ar). ^{13}C-NMR (δ ppm, $CDCl_3$): 149.40; 148.30; 143.80; 136.36; 120.68; 111.62; 98.70; 55.93; 45.01; 34.25. IR (cm^{-1}): 3397, 3159, 3068, 2921, 1586, 1487, 1230, 1117, 1022, 905, 809, 756, 594, 513, 450.

CONCLUSIONS

Two new compounds, **2** and **3**, derivatives of 3,4-dimetoxyphenethylamine, were synthesized and characterized by IR, NMR, and UV-Vis spectroscopy. Their spectral and structural properties were compared with the known compound **1**. For compound **2** the crystal X-ray structure has been obtained, whereas compound **3** has fluorescence properties.

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