Brief Communications

Synthesis and crystal structure of 2-nitroxyethyl nicotinate and its complex with $PdCl_2$

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The reaction of nicotinoyl chloride with ethylene glycol mononitrate yielded the previously unknown 2-nitroxyethyl nicotinate. The resulting ester was used as a ligand in the reaction with $PdCl_2$ for preparing a new complex, *trans*-bis(2-nitroxyethyl nicotinate-*N*)dichloropalladium(II). The structures of the ligand and the complex were established by X-ray structural analysis.

Key words: nicotinoyl chloride; ethylene glycol mononitrate; 2-nitroxyethyl nicotinate, reaction with palladium(II) chloride; *trans*-bis(2-nitroxyethyl nicotinate-*N*)dichloropalladium(II), crystal structure, X-ray structural analysis.

Presently, *N*-(2-nitroxyethyl)nicotinamide[1,2] (commercial name Nicorandil or Sigmart) is used in the treatment of stenocardia and cardiac insufficiency. The key feature of Nicorandil is that its molecule contains two biologically active fragments, namely, the nicotinecarboxamide and alkyl nitrate fragments.

With the aim of elucidating the effect of the amide group on the antianginal activity of Nicorandil, we synthesized its ester analog, 2-nitroxyethyl nicotinate (**1**), and determined its crystal structure. In addition, we prepared the complex of ester **1** with palladium(II) chloride (**2**), which is of interest as an object for studying its biological activity.

Synthesis and studies of the complexes of Pt and Pd with various ligands is a traditional line of investigations, one practical application of which is the design of antitumor drugs.[3,4] Complexes whith nitrate ions as anionic ligands are known.[5,6] The substantial drawbacks of these compounds are their high toxicity and their ability to readily undergo hydrolysis, which hinder their practical use. From this standpoint, the synthesis of complexes with $R—CH_2CH_2ONO_2$ ligands, where R contains fragments of various biologically active compounds (for example, such as aminosuccinic, aminoglutaric, and pyridinecarboxylic acids, their amides, *etc.*), is of obvious interest. However, this procedure has not yet been developed. Apparently, the behavior of the nitrate group in such complexes and in anionic nitrate ligands should be different. It is also known that nitrates of alcohols can serve as a source of nitrogen monoxide,[7] which is known to be an endogenic bioregulator[8—11] that affects the function of blood platelets and immune system.

Previously unknown 2-nitroxyethyl nicotinate was prepared by the reaction of nicotinoyl chloride with ethylene glycol mononitrate.

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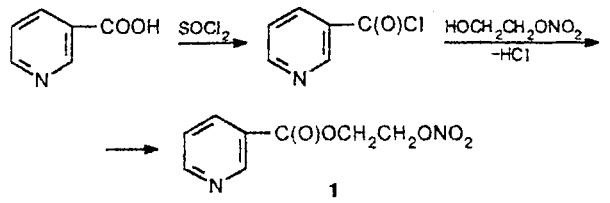


According to the data of X-ray diffraction analysis of compound **1** (Fig. 1), the O(3)C(1)O(5)C(2) plane forms angles of 4.1° and 2.0° with the C(7)O(5)C(1) and C(2)C(3)C(4)C(5)N(2)C(6) planes, respectively, *i.e.*, the three above-mentioned fragments are virtually in a single plane, which is due, apparently, to π-electron delocalization. The atoms of the nitrate fragment, including the C(8) atom, are also in a single plane. The angle between the O(1)O(2)N(1)O(4) and N(1)O(4)C(8) planes is 1.7°.

Therefore, molecule **1** consists of two virtually planar fragments, which are rotated about the C(7)—C(8) bond by 93.5°. This conformation of the molecule results in a mutually perpendicular arrangement of the lone electron pairs of the O(4) and O(5) atoms and their minimum repulsion energy.

The bond lengths have standard values. Thus, the C(1)—O(3) bond of the carbonyl group is 1.20(3) Å. The lengths of the bonds with the participation of the ester O atom, namely, O(5)—C(1) and O(5)—C(7), are 1.32(3) and 1.47(3) Å, respectively. The N(2)—C(5) and N(2)—C(6) bond lengths in the pyridine ring are 1.38(4) and 1.40(4) Å, respectively. The atomic coordinates in the structure of **1** are given in Table 1.

According to the results of studies of cardiological activity (carried out at the All-Russian Research Center of Safety of Biologically Active Compounds) and high toxicity (performed at the Department of the Kinetics of Chemical and Biological Processes of the Institute of Chemical Physics in Chernogolovka of the Russian Academy of Sciences), compound **1** does not exhibit

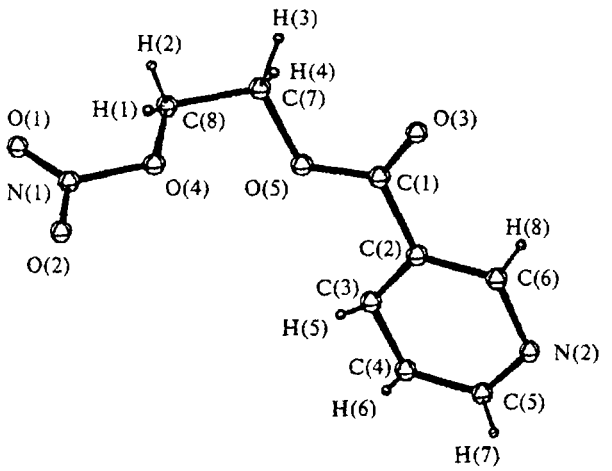


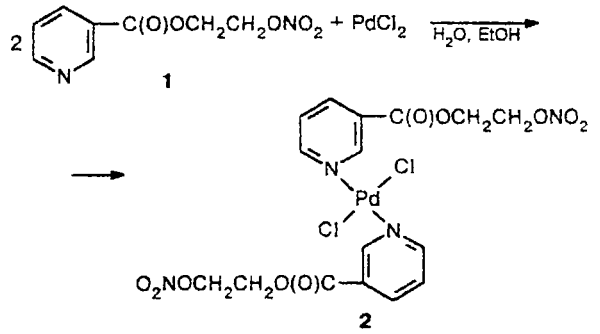
Fig. 1. Overall view of molecule **1**.

Table 1. Atomic coordinates ($\times 10^3$) in the structure of **1**

Atom	*x*	*y*	*z*
O(1)	−245(3)	84(2)	682(1)
O(2)	54(3)	−34(2)	650(1)
O(3)	506(3)	649(2)	677(1)
O(4)	66(3)	235(2)	671(1)
O(5)	177(3)	573(2)	634(1)
N(1)	−58(3)	84(2)	667(1)
N(2)	697(3)	808(2)	489(1)
C(1)	381(4)	637(3)	632(2)
C(2)	440(4)	692(3)	565(2)
C(3)	281(4)	679(3)	516(2)
C(4)	329(4)	734(3)	455(2)
C(5)	530(4)	794(3)	443(2)
C(6)	647(4)	756(3)	552(2)
C(7)	94(4)	526(3)	698(2)
C(8)	−65(4)	382(3)	690(2)
H(1)	−171(9)	404(8)	676(7)
H(2)	−73(9)	355(8)	646(7)
H(3)	43(9)	616(8)	722(7)
H(4)	190(9)	487(8)	721(7)
H(5)	171(9)	668(8)	500(7)
H(6)	301(9)	775(8)	410(7)
H(7)	549(9)	876(8)	412(7)
H(8)	770(9)	736(8)	588(7)

antianginal activity and belongs to nontoxic compounds. Therefore, it can be stated that the antianginal activity of $RC(O)NHCH_2CH_2ONO_2$ compounds is determined by a combination of all three fragments, namely, the residue of an organic acid (R), the carbamide group, and the 2-nitroxyethyl fragment. In this case, the amide group plays a very significant role in imparting physiological activity to the Nicorandil molecule. The replacement of the amide nitrogen atom (—NH—) in the Nicorandil molecule by the ester oxygen atom (—O—) leads to a loss of antianginal activity.

We synthesized *trans*-bis(2-nitroxyethyl nicotinate-*N*)dichloropalladium(II) (**2**) by the reaction of an aqueous solution of $PdCl_2$ with an aqueous-alcoholic solution of compound **1**.



Molecules of distorted planar-square complex **2** occupy special positions (Fig. 2). Both pairs of ligand are

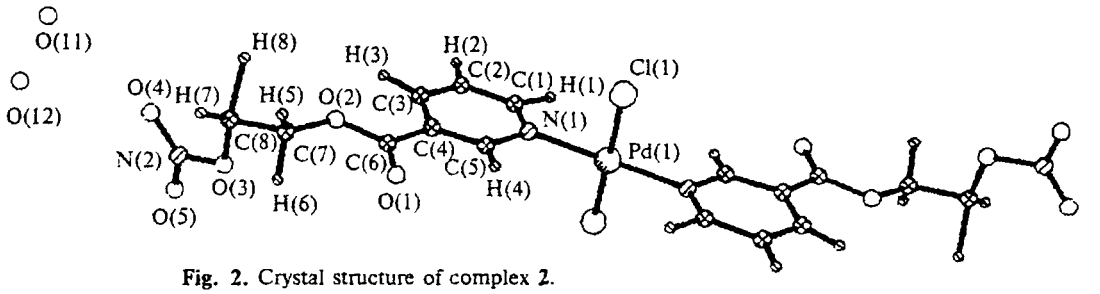


Fig. 2. Crystal structure of complex **2**.

symmetrically equivalent. The angles between the plane of the square, which passes through the coordination unit, and the planes of the pyridine rings are 72.4°. This arrangement of the ligands in the complex is conformationally favorable for orbital interactions between the d_{xy}-orbital of Pd^{II} and the π^*-orbital systems of the pyridine rings. However, these interactions affect only slightly the bond lengths. Actually, the Pd(1)—N(1) bond is slightly shortened (2.003(12) Å) compared to the sum of the covalent radii (2.070 Å), and, correspondingly, the bonds in the pyridine rings are slightly elongated. Probably, the pyridine ligands are in the mutually *trans* arrangement because this conformation is energetically favorable due to the d_{xy}—π^*-orbital interaction. The pyridine ring, the carbonyl group, and the O atom of the ester group are virtually in a single plane (the Pd(1)N(1)C(1)C(2)C(3)C(4)C(5) plane is inclined to the C(4)C(6)O(1)O(2) and C(6)O(2)C(7) planes at angles of 4.4° and 2.9°, respectively; the angle between the two last-mentioned planes is 2.9°). The Pd(1)—Cl(1) bond length is 2.305(4) Å. In the crystal, statistically disordered water molecules are found (Table 2, the O(11) and O(12) atoms).

In going from free ester **1** to the ligand in complex **2**, the spatial arrangement of the planar fragments remains virtually unchanged, and the corresponding bond lengths differ only slightly.

In the molecule of Nicorandil,[12] the C=O bond and the C—O bond of the CH_2—ONO_2 fragment are directed toward the N atom of the pyridine ring. In molecule **1** and complex **2**, the C=O bond is also directed toward the pyridine ring, whereas the CH_2—ONO_2 fragment points in the opposite direction. The above-mentioned difference is attributable to the fact that in the Nicorandil molecule, the CH_2—ONO_2 fragment is bonded to the asymmetrical portion of the molecule in the *cis* position, whereas in the molecule of 2-nitroxyethyl nicotinate, this fragment is in the *trans* position.

Experimental

The IR spectra were recorded on a Specord M-80 spectrophotometer as KBr pellets.

2-Nitroxyethyl nicotinate (1) was synthesized by the reaction of ethylene glycol mononitrate with nicotinoyl chloride (prepared *in situ* from the acid and $SOCl_2$) in dichloroethane (the yield was 70.5%) or in water (60%), m.p. 46—48 °C (from a CCl_4—*n*-C_7H_{16} mixture). Found (%): C, 45.12; H, 3.64; N, 13.11. $C_8H_8N_2O_5$. Calculated (%): C, 45.28; H, 3.77; N, 13.20. IR, ν/cm^{-1}: 860 (O—NO_2); 1274, 1637 (ONO_2); 1733 (C=O); 701, 740, 1421, 1592 (C—H and C—C in Py).

2-Nitroxyethyl nicotinate hydrochloride (1 · HCl). Gaseous HCl was bubbled with intense stirring through a solution of 2-nitroxyethyl nicotinate (2.12 g, 9.992 mmol) in methanol or ethanol (30 mL) at 15—20 °C until evolution of heat ceased. Ether (40 mL) was added to the reaction mixture. The precipitate that formed was filtered off, washed with ether, and dried in air. Salt **1** · HCl was obtained in a yield of 2.42 g (97.4%), m.p. 96—97 °C. Found (%): C, 38.58; H, 3.60; N, 11.21; Cl, 14.18. $C_8H_9ClN_2O_5$. Calculated (%): C, 38.65; H, 3.62; N, 11.27; Cl, 14.26.

***trans*-Bis(2-nitroxyethyl nicotinate-*N*)dichloropalladium(II) (2).** A solution of 2-nitroxyethyl nicotinate (0.283 g, 1.335 mmol) in a mixture of water (20 mL) and alcohol (20 mL) was added with stirring to an aqueous solution (3 mL)

Table 2. Atomic coordinates ($\times 10^4$) in the structure of complex **2**

Atom	*x*	*y*	*z*
Pd(1)	0	5000	0
Cl(1)	557(2)	6241(3)	2744(11)
O(1)	2058(5)	4561(10)	−5860(26)
O(2)	2512(5)	3033(9)	−4204(25)
O(3)	3046(6)	1564(10)	−8387(33)
O(4)	3700(13)	302(16)	−7277(87)
O(5)	3037(15)	−82(18)	−10243(74)
O(11)	5000	0	−5000
O(12)	4999(78)	166(140)	−8802(261)
N(1)	664(5)	3924(11)	−177(34)
N(2)	3270(13)	481(15)	−8726(76)
C(1)	639(7)	2949(12)	1319(41)
C(2)	1101(7)	2187(13)	1218(47)
C(3)	1576(7)	2405(12)	−570(43)
C(4)	1588(6)	3425(10)	−2261(40)
C(5)	1109(6)	4134(12)	−2071(39)
C(6)	2070(7)	3751(13)	−4308(37)
C(7)	3010(6)	3310(13)	−6048(43)
C(8)	3371(7)	2283(14)	−6401(54)
H(1)	299(35)	2768(75)	2481(95)
H(2)	1085(35)	1513(75)	2403(95)
H(3)	1892(35)	1884(75)	−683(95)
H(4)	1098(35)	4791(75)	−3331(95)
H(5)	3229(35)	3885(75)	−5058(95)
H(6)	2889(35)	3577(75)	−8032(95)
H(7)	3738(35)	2457(75)	−7305(95)
H(8)	3435(35)	1935(75)	−4439(95)

of $PdCl_2$ (40 mg mL^{-1}, 0.665 mmol) at 20—30 °C. The reaction mixture was stirred for 30 min. The precipitate that formed was filtered off, washed with water, and dried in air. Compound **2** was obtained in a yield of 0.3 g (75%). Recrystallization from Me_2CO gave coffee-colored crystals, m.p. 167—168 °C. Found (%): C, 31.67; H, 2.45; Cl, 11.64; N, 9.09. $C_{16}H_{16}Cl_2N_4O_{10}Pd$. Calculated (%): C, 31.94; H, 2.68; Cl, 11.78; N, 9.31. IR, ν/cm^{-1}: 690, 745 (CH in Py); 860 (O—NO_2); 1040, 1145 (C—O); 1270, 1620 (ONO_2); 1365, 1435, 2296, 2931, 2944, (CH_2); 1530, 1580, 1605 (C—C and C—N in Py); 1730 (C=O); 3075 (CH).

X-ray diffraction analysis of compounds 1 and 2. Crystals of **1** are monoclinic, M = 212.16, a = 5.997(4) Å, b = 7.782(2) Å, c = 20.771(10) Å, β = 90.66(5)°, V = 969.3(5) Å^3, d_{calc} = 1.453(5) g cm^{-3}, λ = 1.5418 Å, space group $P2_1/n$, Z = 4.

Crystals of complex **2**, $[PdCl_2(N_2O_5C_8H_8)_2]$, are monoclinic, M = 601.65, a = 23.112(25) Å, b = 12.003(3) Å, c = 4.341(6) Å, β = 89.72°, V = 1204.2(9) Å^3, d = 1.659(3) g cm^{-3}, λ = 0.70926 Å, space group $P2_1/a$, Z = 2.

Intensities of 464 (for **1**) and 2131 (for **2**) observed unique reflections were measured on a four-circle KM-4 diffractometer (KUMA-Diffraction, Poland) in the range $0.02 < \sin\theta/\lambda < 0.50$ using the $\omega/2\theta$ scanning technique. The structures were solved by direct methods using the SHELX-86 program package on a PC computer. The atomic coordinates in the structure of **1** (see Table 1) were refined by full-matrix least squares to R = 0.11. Temperature factors of the nonhydrogen atoms were refined anisotropically. The high value of the R factor is attributable to the fact that the X-ray diffraction data were collected from layered crystals prepared by low-temperature crystallization. We failed to improve the quality of the crystals by using other solvents and temperature conditions of crystallization. The atomic coordinates in the structure of **2** (see Table 2) were refined by full-matrix least squares using the SHELX-93 program to R = 0.10. The nonhydrogen atoms were refined anisotropically, and the H atoms were refined isotropically. When absorption correction was applied using the DIFABS program, the refinement converged to the R factor of 0.079.

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Glycosylation of betulin acetates with glycals

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Betulin 2-deoxy-α-D-, 2-deoxy-α-L-, and 2,6-dideoxy-α-L-*arabino*-hexopyranosides were synthesized by acid-catalyzed glycosylation (cationite in the H^+ form, LiBr) of betulin 3- and 28-monoacetates with glycal acetates.

Key words: 3-*O*-acetylbetulin, 28-*O*-acetylbetulin, glycal acetates, stereoselective glycosylation, acid catalysis, betulin 2-deoxy-α-D-, 2-deoxy-α-L, and 2,6-dideoxy-α-L-*arabino*-hexopyranosides.

The birch bark is rich in pentacyclic triterpenoids. The content of betulin (**1**) in it reaches 35—40%, depending on the species.[1] Derivatives of betulin and betulinic acid have a broad range of biological activity, including antiviral[2] and antitumor[3] action.

We carried out the glycosylation of betulin monoacetates (**2, 3**) with acetylated glycals (**4—6**) under acid catalysis conditions, using the KU-2-8 cationite (H^+ form) in combination with LiBr as the activator (Scheme 1). We have used this method of glycosylation[4]

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