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Synthesis of Nitroso- and Amino Derivatives of *N*-Arylaminoalkyladamantanes

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Abstract—By amination of 4-nitrosophenol and 1-nitroso-2-naphthol the corresponding *N*-arylaminoalkyladamantanes were obtained whose reduction provided 1,4-phenylenediamines and 1,2-naphthylenediamines.

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Many amines with adamantyl fragments in the structure exhibit biological activity and are widely used as drugs [1]. The presence of N-aryl group in the structure of alkyladamantane amino derivatives should presumably strengthen the influence on the central dopamine- and noradrenergic mediator systems [2] important for preparation of drugs with stimulating psychotropic action.

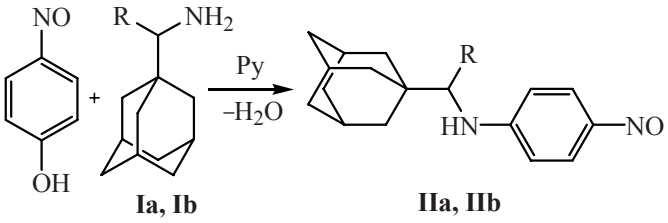
N-Alkyl- and N-aryl derivatives of adamantanamine are prepared by amination of adamantine haloderivatives [3], by alkylation or arylation of adamantanamine [4], or by reductive amination of carbonyl compounds [5, 6]. Up till now the synthesis of N-aryl-substituted adamantan- and adamantylalkanamines was not performed by amination of nitrosophenols with sterically hindered amines, although the 4-nitrosophenols unlike the other phenols are known to undergo amination with aliphatic (butyl-, methyl-, benzyl-) amines, cyclohexylamine, and anilines in the presence of acid catalysts (hydrogen chloride, boron trifluoride, *p*-toluenesulfonic acid) or without catalyst [7].

We investigated the amination of 4-nitrosophenol and 1-nitroso-2-naphthol with sterically hindered amines: (1-adamantyl)methanamine (**Ia**), 1-(1-adamantyl)ethanamine (**Ib**), and 1-adamantanamine.

Amination of 4-nitrosophenol was carried out by treating with a double excess of amines **Ia** and **Ib** in pyridine at 20°C. After the dilution of the reaction mixture with water and the extraction of reaction products into ethyl ether followed by chromatographic purification we obtained previously unknown *N*-[(1-adamantyl)methyl-4-nitrosoaniline (**IIa**) and *N*-[1-(1-adamantyl)ethyl]-4-nitrosoaniline (**IIb**) in 56 and 45% yield respectively (Scheme 1).

The amination of 1-nitroso-2-naphthol with amines **Ia** and **Ib** under similar conditions led to the formation of the corresponding *N*-[(1-adamantyl)methyl]-1-nitrosonaphthalene-2-amine (**IIIa**) and *N*-[1-(1-adamantyl)-ethyl]-1-nitrosonaphthalene-2-amine (**IIIb**) in 41 and 48% yield respectively (Scheme 2).

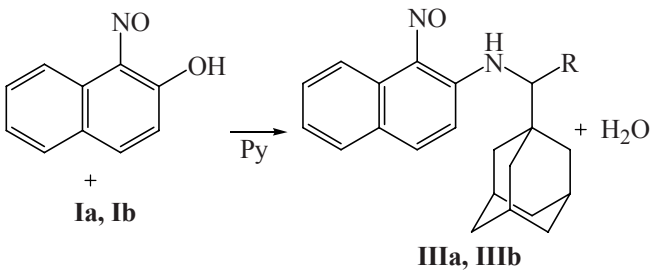
Scheme 1.



Ia, Ib **IIa, IIb**

R = H (**a**), Me (**b**).

Scheme 2.



Ia, Ib

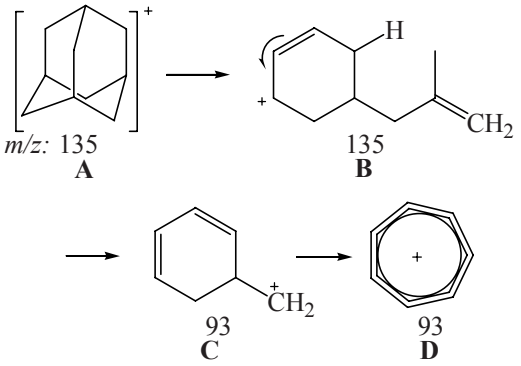
IIIa, IIIb
41–48%

R = H (**a**), Me (**b**).

1-Adamantanamine was not involved in reaction with 4-nitrosophenol and 1-nitroso-2-naphthol under the given conditions. It is evidently due to the steric hindrances from the bulky adamantyl framework in agreement with the data on the growing reactivity of amino derivatives of adamantane with the growing distance of the NH_2 group from the adamantine skeleton [8].

In the amination of 4-nitrosophenol with amine **Ib** in alcohol in the presence of *p*-toluenesulfonic acid the conversion into 4-nitrosoaniline **IIb** was close to that in pyridine, 94%. The conversion into nitrosoaniline **IIb** was estimated spectrophotometrically at the absorption maximum in the region 410 nm corresponding to the π–π* transition in the nitrosoanilines.

The composition of compounds **IIa, IIb**, and **IIIb** was established by elemental analysis, of compounds **IIb** and **IIIa**, by mass spectrometry. The mass spectra of compounds **IIb** and **IIIa** contain molecular ion peaks corresponding to the calculated values, *m/z* 284 and 320 respectively. The maximum abundant (100%) peak in the mass spectra of compounds **IIb** and **IIIa** is the fragment ion, *m/z* 135, corresponding to the adamantyl-cation **A**. Further fragmentation of the adamantyl-cation results im ions **B**–**D**.



This fragmentation is characteristic of 1-alkyl-substituted adamantanes and is weakly affected by the structure of the alkyl group [9].

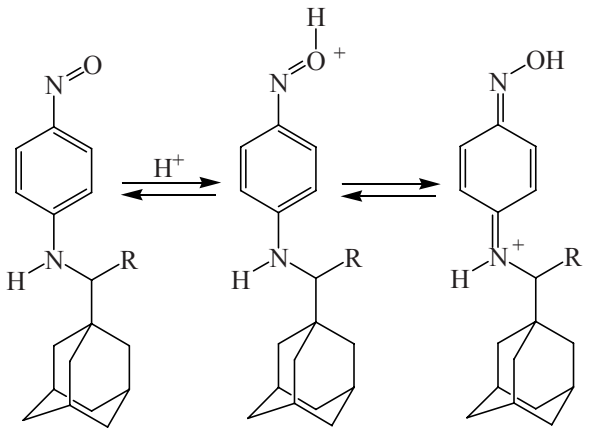
The structure of amines **IIa, IIb** and **IIIa, IIIb** was established based on the complex of analytical and spectral data. In the electronic spectra of ethanol solutions of nitrosoanilines **IIa** and **IIb** and nitrosonaphthylamines **IIIa** and **IIIb** absorption band is observed in the region 650–700 nm (π–π* transition of aromatic NO group). In the short-wave region the *p*-nitrosoanilines **IIa** and **IIb** have an absorption band at 410-430 nm (π–π* transition of nitrosoaniline). This finding is in agreement with the published data for *p*-nitrosoanilines [10, 11]. The protonation of compounds **IIa** and **IIb** in 0.1 N HCl resulted in a blue shift of the short-wave peak to 340 nm.

The IR spectrum of nitrosoaniline **IIb** contains the absorption bands of the stretching vibrations of N–H bond in the secondary amino group at 3232 cm^{-1}, aromatic C–H bonds at 3030 cm^{-1}, methyl group at 2921 cm^{-1} and methylene groups at 2845 cm^{-1}, and bond $C=C_{arom}$ at 1606, 1543 cm^{-1}; in the IR spectrum of nitrosonaphthylamine **IIIb** appear the absorption bands of the stretching vibrations of N–H bond in the secondary amino group at 3329–3650 cm^{-1}, aromatic C–H bonds at 3030 cm^{-1}, methyl group at 2903 cm^{-1} and methylene groups at 2846 cm^{-1}, and bond $C=C_{arom}$ at 1620, 1565 cm^{-1}.

In the ^1H NMR spectra of nitrosoanilines **IIa** and **IIb** the signals of aromatic protons are observed in the region 6.5–8.0 ppm. The aromatic protons of naphthylamines **IIIa** and **IIIb** give rise to signals in the ^1H NMR spectra in the region 7.05–9.06 ppm. The proton signals of the methylene groups of the adamantyl fragment of compounds **IIa, IIb** and **IIIa, IIIb** appear as a multiplet in the region 1.38–1.80 ppm, the resonances of methine groups protons, at 1.9–2.1 ppm. These findings are consistent with the known data on the chemical shifts of β-, γ-, and δ-protons of the adamantyl framework of 1-monosubstituted alkyladamantanes [12]. The broadened signal of the NH group proton in the spectrum of nitrosoanilines **IIa** and **IIb** is observed in the region 4.8–5.3 ppm.

One of the most important properties of nitroso compounds are acid-catalyzed conversions, therefore we One of the protonation sites is the oxygen of the nitroso group [10, 11] (Scheme 3), for in the acid environment the electronic spectra of amines **IIa** and **IIb** lack the

Scheme 3.



absorption at 650–750 nm corresponding to the π–π* transition of the nitroso group.

The evaluation of pK of compounds **IIa** and **IIb** was performed in buffer solutions spectrophotometrically. Nitrosoanilines **IIa** and **IIb** are insufficiently soluble in weak acid medium, therefore the pK_{BH^+} was measured in 50% alcohol.

The pK_{BH^+} values of compounds **IIa** and **IIb** (3.62 and 3.44 respectively) are less than the pK_{BH^+} of unsubstituted *p*-nitrosoaniline (3.90). This decrease in basicity may be due to the use 50% aqueous ethanol as solvent [13], and also probably because of the distortion of the conjugation of the amino group with the aromatic ring effected by the presence of a spatially bulky substituent resulting in decreased contribution of the resonance structure stabilizing the protonated form.

The reduction of nitrosoaniline **IIa** and nitrosonaphthylamine **IIIa** with hydrazine hydrate on a catalyst Pd/C gave rise respectively to *N*-[(1-adamantyl)methyl]-1,4-phenylenediamine (**IV**) and *N*²-[(1-adamantyl)-methyl]-1,2-naphthylenediamine (**V**) (Scheme 4).

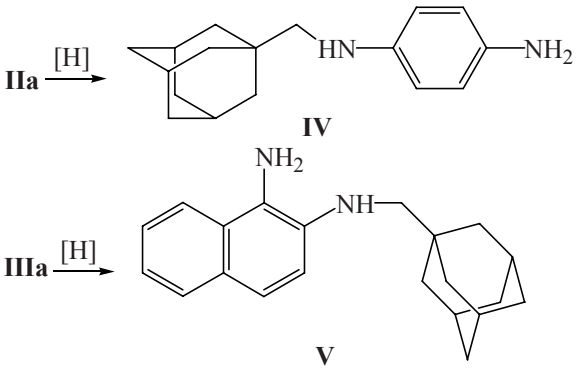
The composition and structure of diamines **IV** and **V** were established from elemental analyses and ^{1}H NMR spectra. In the ^{1}H NMR spectrum of phenylenediamine **IV** two doublet signals at 6.48 and 6.58 ppm belong to the aromatic protons. The value $J_{A,B}$ 8 Hz coincides with the typical value of coupling constant $J_{A,B}$ in benzene derivatives [14]. In the ^{1}H NMR spectrum of naphthylenediamine **V** the aromatic protons give rise to a multiplet in the region 7.11–7.75 ppm.

The proton signals of the methylene groups of the adamantyl framework of compounds **IV** and **V** appear in their spectra as a multiplet in the region 1.5–1.79 ppm, protons of methine groups, at 1.96–2.01 ppm. The broadened signal of the protons of NH and NH_2 groups of diamines **IV** and **V** is observed in the region 2.69–3.40 ppm. In compounds **IV** and **V** the protons of methylene groups not included into the adamantyl skeletone give signals at 2.69 and 2.86 ppm respectively.

EXPERIMENTAL

Electronic spectra were recorded on a spectrophotometer SF-26 in a cell 1 cm thick at solution concentration 5×10^{-5} mol l^{-1} in the region 200–500 nm, 10^{-2} mol l^{-1} in the region 600–800 nm. ^{1}H NMR spectra were registered on a spectrometer Bruker Avance DRX-200 (operating frequency 200 Hz) from solutions in $CDCl_3$. The column chromatography was performed

Scheme 4.



on silica gel of the grade Silicagel L 100/400 (Chemapol). Analytic TLC was carried out on the plates Sorbfil of the grade PTSKh-AF-V (Krasnodar) with a UV indicator. Mass spectra were measured on a mass spectrometer MAT-8200 Finnigan. IR spectra were taken on Vector 22 instrument from pellets with KBr.

***N*-[1-(1-Adamantyl)alkyl]-4-nitrosoanilines IIa and IIb.** *a*. A mixture of 0.02 mol of amine **Ia** or **Ib** and 1.23 g (0.01 mol) of 4-nitrosophenol in 45 ml of pyridine was maintained at 20°C for 96 h, then it was poured into 250 ml of ice water and extracted with ethyl ether (3 × 15 ml). The extract was washed with 5% HCl (2 × 15 ml), 5% NaOH (2 × 15 ml), and then with water (50 ml). The ether was evaporated, and the oily residue was washed with petroleum ether till it turned into green crystals. The analytically pure sample was obtained by column chromatography (2 × 100 cm, 100 g of silica gel, eluent ethyl acetate).

***N*-[1-(1-Adamantyl)methyl]-4-nitrosoaniline (IIa).** Yield 1.5 g (56%), mp 191°C (ethyl acetate). UV spectrum, λ_{max}, nm (e), alcohol: 270 (4400), 420 (27000), 650 (119); 0.1 N HCl: 360 (11600). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.58–1.80 m (12H, CH_2), 2.00–2.05 m (3H, CH), 2.97 (*J* 6.4 Hz), (2H, CH_2), 4.88 br.m (1H, NH), 6.60 d (*J* 8.2 Hz), ($2H_{arom}$), 7.5–8.0 br.m ($2H_{arom}$). Found, %: C 75.80; H 8.76; N 9.85. $C_{17}H_{22}N_2O$. Calculated, %: C 75.52; H 8.20; N 10.36.

***N*-[1-(1-Adamantyl)ethyl]-4-nitrosoaniline (IIb).** Yield 37%, mp 179°C. Electronic spectrum, λ_{max}, nm (e), alcohol: 285 (5700), 420 (30000), 660 (88); 0.1 N HCl: 340 (20000). IR spectrum, ν, cm^{-1}: 3232 (NH), 3030 (CH_{arom}), 2921 (CH_3), 2845 (CH_2), 1606, 1543 ($C{=}C_{arom}$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 d (3H, CH_3, *J* 6.4 Hz), 1.38–1.67 m (12H, CH_2), 1.89–1.95 m (3H, CH), 3.26 m (1H, CH), 5.24 br.d (1H, NH, *J* 6.6 Hz), 6.54 d ($2H_{arom}$, *J* 8 Hz), 7.6–8.2 br.m ($2H_{arom}$). Mass

spectrum, *m/z* (I_{rel}, %): 284 (55) $[M]^+$, 270 (19), 149 (79), 135 (100), 119 (44), 107 (10), 93 (14), 77 (13). Found, %: C 75.80; H 8.76; N 9.15 $C_{18}H_{24}N_2O$. Calculated, %: C 76.02; H 8.51; N 9.85.

b. A mixture of 0.0896 g (0.5 mmol) of amine **Ib** and 0.0307 g (0.25 mmol) of 4-nitrosophenol in 4 ml of pyridine was maintained at 20°C for 96 h. Then the reaction mixture was diluted with alcohol to 10 ml, an aliquot of 0.5 ml was transferred into a volumetric flask of 25 ml capacity, filled to the mark with alcohol, and the solution was used to register the electronic spectrum. The conversion of amine **Ib** into 4-nitrosoaniline **IIb** was 96% (λ 420 nm, e 30000).

c. A mixture of 0.0896 g (0.5 mmol) of amine **Ib**, 0.0307 g (0.25 mmol) of *p*-nitrosophenol, and 0.006 g (0.035 mmol) of 4-toluenesulfonic acid in 4 ml of alcohol was maintained at 20°C for 96 h. Then the reaction mixture was subjected to workup described for procedure *a*. Amine **Ib** conversion 94%.

***N*-[1-(1-Adamantyl)alkyl]-1-nitrosonaphthalene-2-amines IIIa and IIIb.** A mixture of 3.3 g (0.02 mol) of amine **Ia** and 1.73 g (0.01 mol) of 1-nitroso-2-naphthol in 75 ml of pyridine was maintained at 20°C for 96 h, then it was poured into 250 ml of ice water and extracted with ethyl ether (3×15 ml). The extract was washed with 5% HCl (2 × 15 ml), 5% NaOH (2 × 15 ml), and then with water (50 ml). The ether was evaporated, and the oily residue was washed with petroleum ether till it turned into green crystals.

***N*-[(1-Adamantyl)methyl]-1-nitrosonaphthalene-2-amine (IIIa).** Yield 1.3 g (41%), mp 175–176°C (hexane–chloroform, 1:1). UV spectrum ($CHCl_3$), λ_{max}, nm (e): 295 sh (5600), 370 (6600), 450 (7900), 660 (84). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.65–1.83 m (12H, CH_2), 1.95–2.10 m (3H, CH), 3.14 d (2H, CH_2, *J* 6 Hz), 7.04 d ($1H_{arom}$, *J* 9.6 Hz) , 7.48–7.40 m ($1H_{arom}$), 7.63–7.59 m ($2H_{arom}$), 7.73 d ($1H_{arom}$, *J* 9.6 Hz), 9.01–9.13 m ($1H_{arom}$). Mass spectrum, *m/z* (I_{rel}, %): 320 (3) $[M]^+$, 164 (5), 135 (100), 107 (10), 93 (20), 79 (23), 67 (10), 55 (5).

***N*-[1-(1-Adamantyl)ethyl]-1-nitrosonaphthalene-2-amine (IIIb).** Yield 1.6 g (48%), mp 172єC (hexane–chloroform, 1:1). UV spectrum ($CHCl_3$), λ_{max}, nm (e): 295 sh (5760), 370 (5400), 450 (5900), 660 (72). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 d (3H, CH_3, *J* 6.6 Hz), 1.64–1.70 m (12H, CH_2), 2.04 s (3H, CH), 3.58 m (1H, CH), 7.05 d ($1H_{arom}$, *J* 9.6 Hz), 7.48–7.40 m ($1H_{arom}$), 7.57–7.65 m ($2H_{arom}$), 7.70 d ($1H_{arom}$, *J* 9.6 Hz), 9.06 m ($1H_{arom}$). Found, %: C 79.03; H 8.85; N 8.90. $C_{22}H_{26}N_2O$. Calculated, %: C 79.00; H 7.84; N 8.38.

Reduction of compounds IIa and IIIa. To 1.8 mmol of nitroso compound **IIa** or **IIIa** and 0.5 g of 0.5% Pd/C in 120 ml of alcohol was added 0.4 ml (8 mmol) of 96% hydrazine hydrate. After 1 h the catalyst was filtered off, the colorless solution was evaporated on a rotary evaporator in a vacuum of a water-jet pump.

***N*-[(1-Adamantyl)methyl]-1,4-phenylenediamine (IV).** Yield 0.43 g (90%), mp 110єC. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.54–1.75 m (12H, CH_2), 1.96 m (3H, CH), 2.69 s (2H, CH_2), 2.69–2.96 br.s (3H, NH, NH_2), 6.58 d ($2H_{arom}$, $J_{A,B}$ 8.7 Hz), 6.48 d ($2H_{arom}$, $J_{A,B}$ 8.7 Hz). Found, %: C 79.13; H 9.06; N 10.70. $C_{17}H_{24}N_2$. Calculated, %: C 79.64; H 9.44; N 10.93.

***N*²-[(1-Adamantyl)methyl]-1,2-naphthylenediamine (V).** Yield 0.31 g (65%), mp 130єC. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.64–1.79 m (12H, CH_2), 2.01 s (3H, CH), 2.86 (2H, CH_2), 3.1–3.4 br.s (3H, NH, NH_2), 7.11–7.42 m ($4H_{arom}$), 7.75–7.65 m ($2H_{arom}$). Found, %: C 82.03; H 8.13; N 9.83. $C_{21}H_{26}N_2$. Calculated, %: C 82.31; H 8.55; N 9.14.

The pK_{BH^+} values were estimated by spectrophotometric procedure [13]. Electronic spectra were taken of SF-26 instrument at the layer thickness 1 cm and concentration 2.5×10^{-5} mol l^{-1}, at 25єC.

NMR measurements were carried out on the equipment of the Krasnoyarsk Center of Joint Use of Siberian Division, Russian Academy of Sciences.

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REFERENCES

1. Bagrii, E.I., *Adamantany: poluchenie, svoistva, primenenie* (Adamantanes: Preparation, Properties, Application), Moscow: Nauka, 1989, p. 264.
2. Morozov, I.S., Klimova, N.V., Lavrova, L.N., Avdyunina, N.I., Pyatin, B.M., Troitskaya, V.S., and Bykov, N.P., *Khim.-Farm. Zh.,* 1998, no. 1, p. 3.
3. Krumkalns, E.V. and Pfeifer, W., *J. Med. Chem.,* 1968, vol. 5, p. 1103.
4. Lilly Inds Ltd., UK Patent 1299172, 1972; *Ref. Zh. Khim.,* 1973, 18N 248 P.
5. Voloboev, S.N., Butenko, L.N., and Novakov, I.A., *Khimiya i tekhnologiya elementoorganicheskikh*

monomerov i polimernykh materialov. Sbornik nauchnykh trudov (Chemistry and Technology of Organic Elemental Monomers and Polymeres. Collection of Works), Volgograd: Izd. Volgograd. Gos. Tekh. Univ., 1999, p. 3.

6. Paulshock, M. and Watts, J.C., Swiss Patent 318871, 1969; *Ref. Zh. Khim*., 1970, 23N330P7. Belyaev, E.Yu. and Gidaspov, B.V., *Aromaticheskie nitrozosoedineniya* (Aromatic Nitroso Compounds), St. Petersburg: Teza, 1996, p. 208.
7. Belyaev, E.Yu. and Gidaspov, B.V., *Aromaticheskie nitrozosoedineniya* (Aromatic Nitroso Compounds), 1996, St. Petersburg: Thesa.
8. Novakov, I.A. Orlinson, B.S., Sabirov, Z.M., Urazbaev, V.N., and Monakov, Yu.B., *Vysokomol. Soed. B,* 1993, vol. 12, p. 2053.
9. Dolejsek, Z., Halo, S., Hanus, V., and Lande, S., *Coll. Czech. Chem. Commun*., 1966, vol. 2, p. 435.
10. Rorr, S.J. and Ragsdall, R.O., *Inorg. Chem.,* 1969, vol. 7, p. 1845.
11. Hertel, E. and Lebok, F.Z., *Phys. Chem*., 1940, vol. 47, p. 315.
12. Warren, R.W., Schneider, A., and Janovski, E.J., *Appl. Spectr.,* 1968, vol. 2, p. 115.
13. Albert, A. and Serjeant, E., *Ionization Constants of Acids and Bases*, London: Methuen, New York: Wiley, 1962.
14. Brown, D.W., Floyd, A.J., and Sainsbury, M., *Organic Spectroscopy*, Chichester: Wiley, 1988. Translated under the *title Spektroskopiya organicheskikh veshchestv*, Moscow: Mir, 1992, p. 66.