

## Synthesis and Properties of Substituted 2-Amino-5-nitrosobenzylamines

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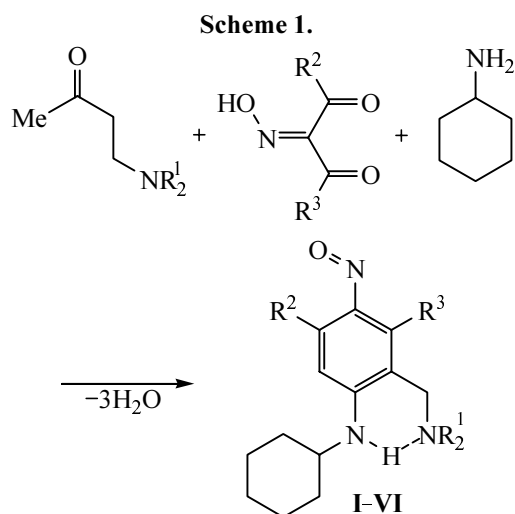
**Abstract**—Substituted nitrosobenzylamines were synthesized by cyclocondensation of hydroxyimino- $\beta$ -diketones with 4-dialkylamino-2-butanones.

Amino-substituted benzylamines are difunctional compounds which have found application in manufacture of drugs. For example, 2-aminobenzylamines (including 2-amino-4,6-dibromo-*N,N*-diethylbenzylamine known as Bromhexin) and their salts possess secretolytic activity and low toxicity, soothe cough [1], and can be used for treatment of alveole atelectasis [2]. Up to now, methods for preparation of only the simplest 2-amino-benzylamine derivatives from aromatic compounds have been reported [2, 3]. We previously studied cycloaromatization of hydroxyimino- $\beta$ -diketones with ketones and amines which leads to formation of substituted *p*-nitroso-anilines. We presumed that cyclocondensation of hydroxyimino- $\beta$ -dicarbonyl compounds with  $\beta$ -amino-ketones and amines

should give rise to hitherto unknown 2-amino-5-nitrosobenzylamines [4].

In fact, substituted 2-amino-5-nitrosobenzylamines were formed in 8–11% yield by cyclocondensation of hydroxyimino- $\beta$ -dicarbonyl compounds with 4-dialkylamino-2-butanones and cyclohexylamine. The yields were determined by spectrophotometry from the absorption intensity in the region  $\lambda$  650–750 nm which corresponds to  $n,\pi^*$  transition involving the nitroso group in aromatic C-nitroso compounds. Taking into account that the condensation of hydroxyimino- $\beta$ -dicarbonyl compounds with ketones and amines is accompanied by elimination of water, we presumed that the reaction equilibrium may be displaced toward formation of the target products by removal of water using zeolites (molecular sieves). Preliminary experiments showed that the conversion increased 2–4-fold in the presence of NaX, NaA, CaX, and CaA zeolites. Here, the most efficient were CaX and CaA. The use of the latter allowed us to synthesize previously unknown *N,N*-dialkyl-2-cyclohexylamino-5-nitrosobenzylamines **I–VI** having alkyl and aryl substituents in the benzene ring (Scheme 1).

The structure of amines **I–VI** was confirmed by their elemental compositions and electron absorption and IR spectra. The electron spectra of amines **I–VI** contain absorption bands in the region 690–740 nm ( $n,\pi^*$  transition of the aromatic nitroso group) and 410–430 nm ( $\pi,\pi^*$  transition typical of nitrosoanilines). In the IR spectra of **I–VI** we observed characteristic absorption bands due to stretching vibrations of the nitroso group (1490–1550  $\text{cm}^{-1}$ ), C–N bond (1250–1360  $\text{cm}^{-1}$ ), and aromatic C–H and C–C bonds (3000 and 1600  $\text{cm}^{-1}$ , respectively), as well as bending vibrations of the benzene ring (900  $\text{cm}^{-1}$ ).



**I**,  $R^1 = \text{Me}$ ,  $R^2 = R^3 = \text{Me}$ ; **II**,  $R^1 = \text{Et}$ ,  $R^2 = R^3 = \text{Me}$ ; **III**,  $\text{NR}_2^1 = \text{piperidino}$ ,  $R^2 = R^3 = \text{Me}$ ; **IV**,  $\text{NR}_2^1 = \text{piperidino}$ ,  $R^2 = R^3 = \text{Ph}$ ; **V**,  $\text{NR}_2^1 = \text{morpholino}$ ,  $R^2 = R^3 = \text{Ph}$ ; **VI**,  $\text{NR}_2^1 = \text{piperidino}$ ,  $R^2 = \text{Me}$  (Ph),  $R^3 = \text{Ph}$  (Me).

The aromatic amino group in molecules **I–VI** is located in the *ortho* position with respect to the dialkylamino-methyl group; therefore, formation of an intramolecular hydrogen bond between the aromatic and aliphatic amino groups is possible. In fact, compounds **I–VI** displayed in the IR spectra a broad band in the region 3200–3000  $\text{cm}^{-1}$ ; the shape and intensity of this band remained unchanged in solutions in carbon tetrachloride with different concentrations.

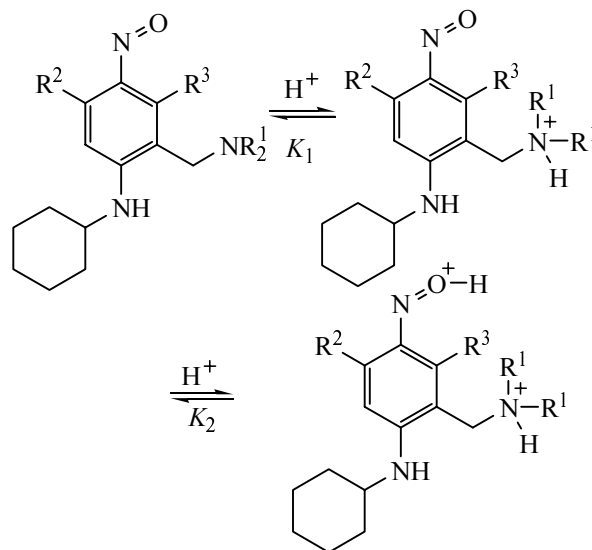
It is known that nitroso compounds are capable of undergoing acid-catalyzed transformations. We examined the basicity of amines **II–IV** and **VI** by potentiometric titration. We found that compound **III** in aqueous medium is a two-hydric base characterized by a two-step ionization process. One protonation center is the oxygen atom in the nitroso group [5, 6], for the electron absorption spectra of amines **II–IV** and **VI** lack absorption corresponding to  $n,\pi^*$  transition of the nitroso group at  $\lambda$  650–750 nm. The other possible protonation center in **II–IV** and **VI** is the side-chain amino group. Scheme 2 illustrates acid–base equilibria of 2-amino-5-nitrosobenzylamines.

The basicity factors ( $pK$ ) of amines **II–IV** and **VI** were determined in buffer solutions by the spectrophotometric technique. Compounds **II–IV** and **VI** are sparingly soluble in weakly acidic aqueous medium; therefore, their  $pK_1$  values were determined in 50% ethanol, and  $pK_2$ , in aqueous solution. Proton-acceptor properties of the side-chain amino group in compounds **II–IV** and **VI** were found to be characterized by  $pK_1$  values of 5.46–4.61; these values are lower than those typical of unsubstituted benzylamines ( $pK_a = 8.23–9.48$ ) [7]. The reduced basicity is likely to originate from the effect of hydrogen bonding and from the use of 50% aqueous ethanol as solvent. Replacement of the methyl group in the *ortho*-position with respect to the nitroso group in **II** ( $pK_1 = 5.46$ ) and **III** ( $pK_1 = 5.57$ ) by aryl (**VI**,  $pK_1 = 5.09$ ; **IV**,  $pK_1 = 4.61$ ) decreases  $pK_1$  values, presumably due to inductive effect of the substituent.

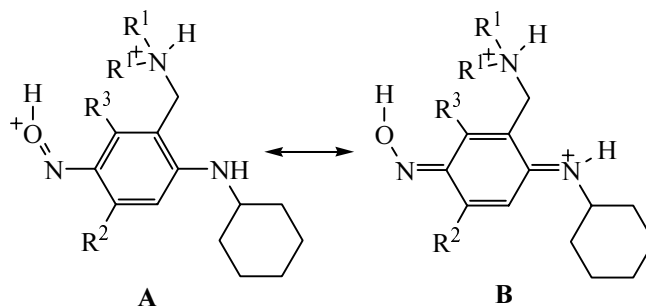
The  $pK_2$  values of amines **II–IV** and **VI**, 2.9–3.8, are lower than the corresponding values reported for 3,5-dialkyl-4-nitrosoanilines ( $pK_a = 4.7–5.69$ ) [8]. A probable reason is interaction between the unshared electron [pair on the nitrogen atom in the cyclohexylamino group and the ammonium group. Such interaction reduces the contribution of canonical structure **B** as compared to **A** (Scheme 3), and protonation of the nitroso group becomes less favorable. In addition, the presence of a cationic center (formed by first protonation) reduces the basicity of the second potential protonation center.

Substituents in the *ortho* position with respect to the nitroso group slightly affect the basicity of amines **II–IV**

Scheme 2.



Scheme 3.



and **VI**. The  $pK_2$  values tend to decrease in going from *o*-alkyl (**II**,  $pK_2 = 3.7$ ; **III**,  $pK_2 = 3.8$ ) to *o*-aryl derivatives (**IV**,  $pK_2 = 2.51$ ; **VI**,  $pK_2 = 2.9$ ).

## EXPERIMENTAL

The electron absorption spectra were recorded on SF-26 and SF-46 spectrophotometers in ethanol; layer thickness 1 cm; amine concentration  $5 \times 10^{-5}$  M ( $\lambda$  200–500 nm) or  $10^{-2}$  M ( $\lambda$  600–800 nm). The IR spectra were obtained on Nicolet Impact 400 and Bruker Vector-22 instruments.

4-Dialkylamino-2-butanones were synthesized by the Mannich reaction [9, 10, 11], 4-morpholino-2-butanone was obtained via Michael addition [12], and hydroxyimino- $\beta$ -diketones were prepared by the procedure described in [13].

**N,N-Dialkyl-2-cyclohexylamino-5-nitrosobenzylamines I–VI.** A mixture of 0.01 mol of the corresponding hydroxyimino- $\beta$ -diketone, 0.07 mol of 4-dialkylamino-2-butanone, 0.009 mol of cyclohexylamine,

and 2–2.5 g of CaX zeolite was kept at 20°C, poured into 250 ml of an ice–water mixture, and extracted with diethyl ether (2 × 15 ml). The extract was washed with two 15-ml portions of a 5% solution of sodium hydroxide and with 50 ml of water, the solvent was evaporated, and the oily residue was treated with petroleum ether until it crystallized to give a green solid.

**2-Cyclohexylamino-4,6,*N,N*-tetramethyl-5-nitrosobenzylamine (I).** Reaction time 24 h. Yield 14%, mp 87°C. Electron absorption spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 410 (27 200), 690 (68). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1521 (N=O); 1324 (C–N); 2966, 1596, 838, 684 (arom.); 2924, 1445 ( $\text{CH}_2$ ). Found, %: C 70.87; H 9.77; N 14.38.  $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}$ . Calculated, %: C 70.55; H 9.40; N 14.52.

**2-Cyclohexylamino-*N,N*-diethyl-4,6-dimethyl-5-nitrosobenzylamine (II).** Reaction time 72 h. Yield 15%, mp 85°C. Electron absorption spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 410 (35 100), 690 (72). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1526 (N=O); 1323 (C–N); 1599, 985, 782, 686 (arom.); 2890, 1439 ( $\text{CH}_2$ ). Found, %: C 72.35; H 9.65; N 13.46.  $\text{C}_{19}\text{H}_{31}\text{N}_3\text{O}$ . Calculated, %: C 71.88; H 9.84; N 13.24.

***N*-Cyclohexyl-3,5-dimethyl-4-nitroso-2-piperidinomethylaniline (III).** Reaction time 72 h. Yield 19%, mp 110°C. Electron absorption spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 410 (43 200), 690 (85). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1520 (N=O); 1321 (C–N); 1596, 862, 782, 660 (arom.); 2850, 1439 ( $\text{CH}_2$ ). Found, %: C 72.65; H 9.65; N 12.33.  $\text{C}_{20}\text{H}_{31}\text{N}_3\text{O}$ . Calculated, %: C 72.91; H 9.48; N 12.75.

***N*-Cyclohexyl-4-nitroso-3,5-diphenyl-2-piperidinomethylaniline (IV).** Reaction time 120 h. Yield 15%, mp 115°C. Electron absorption spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 430 (26 700), 740 (92). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1489 (N=O); 1331 (C–N); 1582, 891, 755, 660 (arom.); 2850, 1415 ( $\text{CH}_2$ ). Found, %: C 79.88; H 8.02; N 9.49.  $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}$ . Calculated, %: C 79.43; H 7.78; N 9.26.

***N*-Cyclohexyl-2-morpholinomethyl-4-nitroso-3,5-diphenylaniline (V).** Reaction time 240 h. Yield 12%, mp 137°C. Electron absorption spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 430 (13 000), 740 (55). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1491 (N=O); 1330 (C–N); 1582, 865, 752, 696 (arom.); 2850, 1443 ( $\text{CH}_2$ ). Found, %: C 76.90; H 7.55; N 9.39.  $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_2$ . Calculated, %: C 76.45; H 7.30; N 9.22.

***N*-Cyclohexyl-5(3)-methyl-4-nitroso-3(5)-phenyl-2-piperidinomethylaniline (VI).** Reaction time 72 h. Yield 15%, mp 120°C. Electron absorption spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 420 (28 800), 700 (87.5). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1470 (N=O); 1330 (C–N); 1591, 865, 761, 699 (arom.); 2848, 1442 ( $\text{CH}_2$ ). Found, %: C 76.97; H 8.24; N 10.87.  $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}$ . Calculated, %: C 76.69; H 8.49; N 10.73.

Spectrophotometric determination of the  $pK_1$  and  $pK_2$  values of amines **II–IV** and **VI** was performed according to the procedure described in [14]. The electron absorption spectra were measured on an SF-26 instrument; layer thickness 1 cm, concentration  $2.5 \times 10^{-5}$  M, temperature 25°C. Potentiometric titration of amine **I** was performed using an EV-74 Ionomer at 25°C; concentration  $5 \times 10^{-3}$  M.

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## REFERENCES

- Keck, J., Piper, H., Kruger, G., Puschmann, S., and Noll, K.-R., FRG Patent no. 2 318 636, 1974; *Ref. Zh., Khim.*, 1975, no. 14 O 52 P.
- Ruckdeschel, G., Stransky, D., and Schonenberger, H., *Pharmazie*, 1976, vol. 31, p. 374.
- Yamaguti, K., Sugimoto, K., Tanabe, I., Yamadzaki, M., and Yamaguti, A., JPN Patent no. 61-189 251, 1986; *Ref. Zh., Khim.*, 1987, no. 18 N 105 P.
- Belyaev, E.Yu. and Gidasov, B.V., *Aromaticheskie nitrosoedineniya* (Aromatic Nitroso Compounds), St. Petersburg: Teza, 1996, p. 120.
- Popp, C.J. and Ragsdall, R.O., *Inorg. Chem.*, 1969, vol. 7, p. 1845.
- Nertel, E. and Lebok, F., *Z. Phys. Chem.*, 1940, vol. 47, p. 315.
- Teitel'baum, A.B., Derstuganova, K.A., Shishkina, N.A., Kudryavtseva, L.A., Bel'skii, V.E., and Ivanov, B.E., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, no. 4, p. 803.
- Suboch, G. A., *Cand. Sci. (Chem.) Dissertation*, Leningrad, 1979.
- Kost, A.N. and Ershov, V.V., *Zh. Obshch. Khim.*, 1957, vol. 27, p. 1722.
- Wilds, A.L., Novak, R.M., and McCaleb, K.E., *Org. Synth.*, 1963, collect. vol. 4, p. 281.
- Hahn, W.E. and Bartnik, R., *Roczn. Chem.*, 1974, vol. 48, p. 475.
- Golovin, E.T., Peredreeva, M.A., and Bystrov, V.M., *Izv. Vyssh. Uchebn. Zaved., Ser. Khim. Khim. Tekhnol.*, 1967, vol. 10, p. 663.
- Weygand, C., *Organisch-chemische Experimentierkunst*, Leipzig, Johann Ambrosius Barth, 1938. Translated under the title *Metody eksperimenta v organicheskoi khimii*, Moscow: Khimiya, 1952, vol. 2, p. 293.
- Albert, A. and Serjeant, E., *Ionization Constants of Acids and Bases*, London: Methuen, 1962. Translated under the title *Konstanty ionizatsii kislot i osnovanii*, Moscow: Khimiya, 1964, p. 180.