ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 1, pp. 108–111. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © T.N. Kaipnazarov, K.B. Abdireimov, N.S. Mukhamedov, R.Ya. Okmanov, B. Tashkhodjaev, G.E. Berdimbetova, Kh.M. Shakhidoyatov, 2013, published in Zhurnal Organicheskoi Khimii, 2013, Vol. 49, No. 1, pp. 113–116.

Benzazoles: I. Regioselective Arylsulfonylation of Benzimidazol-2-amine

T. N. Kaipnazarov[a], K. B. Abdireimov[b], N. S. Mukhamedov[c], R. Ya. Okmanov[c], B. Tashkhodjaev[c], G. E. Berdimbetova[a], and Kh. M. Shakhidoyatov[c]

[a] *Research Institute of Natural Sciences, Karakalpak Division, Academy of Sciences of Uzbekistan Republic, Nukus, Uzbekistan*

[b] *Berdakh Karakalpak State University, Nukus, Uzbekistan*

[c] *Yunusov Institute of Chemistry of Plant Substances, Academy of Sciences of Uzbekistan Republic, ul. M. Ulugbeka 77, Tashkent, 100170, Uzbekistan*
e-mail: nasirxon@rambler.ru

Received May 21, 2012

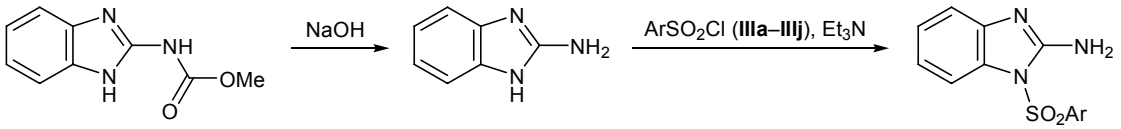
Abstract—Benzimidazol-2-amine reacted with arenesulfonyl chlorides in the presence of triethylamine in regioselective fashion at the endocyclic nitrogen atom, the exocyclic amino group remaining intact. The yields of 1-arylsulfonylbenzimidazol-2-amines depend on the electronic properties of substituents in the benzene ring of arenesulfonyl chlorides.

DOI: 10.1134/S1070428013010181

Increased interest in benzazoles, including benzimidazole derivatives, is determined by broad spectrum of their biological activity. Compounds exhibiting hypotensive, neuroleptic, antitumor, and antibacterial properties [1–5], as well as fungicidal and growth-regulating effects [6, 7] were found among 2-substituted benzimidazoles. Relatively recently, Foks et al. [8] reported on the synthesis of 2-aryl- and 2-cycloalkyl-1-alkylsulfonylbenzimidazoles by reaction of 2-substituted benzimidazoles with methane- and benzenesulfonyl chlorides, and the products were shown to exhibit tuberculostatic activity [8]. This reaction was later extended to 2-alkylbenzimidazoles and various arenesulfonyl chlorides [9], and a number of 2-alkyl-1-arylsulfonylbenzimidazoles were obtained. Analogous reactions of benzimidazol-2-amine were not studied. In the present work we synthesized benzimidazol-2-amine and examined its reactions with arenesulfonyl chlorides.

Benzimidazol-2-amine (**II**) was prepared by alkaline hydrolysis of methyl 1*H*-benzimidazol-2-ylcarbamate (**I**) [10]. The reactions of **II** with arenesulfonyl chlorides **IIIa**–**IIIj** (reactant molar ratio 1:1) in the presence of triethylamine regioselectively occurred at the endocyclic nitrogen atom without involving the exocyclic amino group to produce the corresponding 1-arenesulfonyl-1*H*-benzimidazol-2-amines **IVa**–**IVj** (Scheme 1). The yield of **IVa**–**IVj** depended on the substituent nature in the initial arenesulfonyl chloride. Electron-withdrawing substituents (such as NO_2, Cl, and NHCOMe) favored increased yield of sulfonylation products **IV**, whereas introduction of electron-donating groups reduced the yield. Presumably, electron-withdrawing effect of substituent in the benzene

Scheme 1.



I **II** **IVa–IVj**

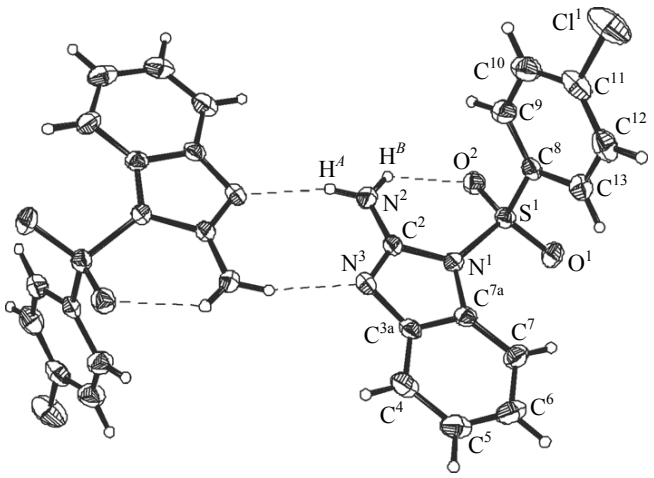
Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 3-$O_2NC_6H_4$ (**e**), 4-*t*-BuC_6H_4 (**f**), 4-$MeCONHC_6H_4$ (**g**), 2,4-$Me_2C_6H_3$ (**h**), 3,4-$Me_2C_6H_3$ (**i**), 2,4,6-$Me_3C_6H_2$ (**j**).

ring of **III** weakens the S–Cl bond, thus making the chlorine atom more labile.

The structure of compounds **IVa**–**IVj** was confirmed by their elemental compositions, IR, ^{1}H NMR, and mass spectra, and X-ray diffraction data for compound **IVd**. The IR spectra of **IVa**–**IVj** contained absorption bands typical of antisymmetric (1360–1390 cm^{-1}) and symmetric (1160–1190 cm^{-1}) stretching vibrations of the sulfonyl group (see Experimental). Compounds **IVa**–**IVj** showed in the mass spectra the molecular ion peaks and peaks from fragment ions corresponding to the assumed structure. Regardless of the substituent nature in the arylsulfonyl group, fragmentation of **IVa**–**IVj** under electron impact involved cleavage of the S–N bond to produce $[M - ArSO_2]^+$ and $[M - Ht]^+$ ions. Like 1-arylsulfonyl-2-alkylbenzimidazoles [9], the $[M - ArSO_2]^+$ ion was the most abundant.

In the ^{1}H NMR spectra of **IVa**–**IVj** we observed signals at δ 6.92–7.97 ppm from the 4-H, 5-H, 6-H, and 7-H protons in the benzimidazole fragment (multiplets, doublet of doublets, and a doublet), a broadened signal from the primary amino group (δ 6.06–6.92 ppm), and signals from aromatic protons (δ 6.86–7.61 ppm) and alkyl substituents in the arenesulfonyl fragment (δ 1.12–3.75 ppm). The only exception was 1-(3-nitrobenzenesulfonyl)-1*H*-benzimidazol-2-amine (**IVe**) whose ^{1}H NMR spectrum contained more downfield signals at δ 8.78, 8.22, and 8.43 ppm (*o*-H, *o*′-H, and *p*-H, respectively) due to electron-withdrawing effect of the nitro group.

Figure shows the structure of 1-(4-chlorobenzenesulfonyl)-1*H*-benzimidazol-2-amine (**IVd**) determined by X-ray analysis. Molecule **IVd** consists of planar benzimidazole (±0.0204 Å) and benzene fragments (±0.0059 Å) which form a dihedral angle of 89.7(1)° with each other. The bond lengths in molecule **IVd** differ from those found previously for benzimidazol-2-amine [11]. The C^{7a}–N^1 and N^1–C^2 bonds in **IVd** [1.420(4) and 1.414(4) Å, respectively] are longer, while the C^2–N^3 and C^2–N^2 bonds are shorter [1.291(4) and 1.338(4) Å, respectively] than the corresponding bonds in benzimidazol-2-amine [1.383(2), 1.352(2), 1.321(2), and 1.349(2) Å, respectively]. In addition, the sum of bond angles at N^2 in **IVd** suggests its sp^2 hybridization in contrast to sp^3 hybridization of N^2 in benzimidazol-2-amine. This indicates π-electron conjugation system in the N^3=C^2–N^2 fragment of molecule **IVd** (benzimidazol-2-amine molecule is characterized by conjugation in the N^3=C^2–N^1 fragment).



Structure of centrosymmetric dimer formed by molecules of 1-(4-chlorobenzenesulfonyl)-1*H*-benzimidazol-2-amine (**IVd**) in crystal according to the X-ray diffraction data. Inter- and intramolecular hydrogen bonds are shown with dashed lines.

Molecules **IVd** in crystal are linked to centrosymmetric dimers via face-to-face intermolecular hydrogen bonds N^2–$H^A\cdots N^3$ with the following parameters $N^2\cdots N^3$ 2.967(4), $H\cdots N^3$ 2.13 Å, $\angle N^2HN^3$ 163° (1 – *x*, 1 – *y*, 1 – *z*). In addition, the N^2 atom is involved in intramolecular hydrogen bond N^2–$H^B\cdots O^2$ [$N^2\cdots O^2$ 2.804(4), $H^B\cdots O^2$ 2.15 Å, $\angle N^2H^BO^2$ 133°].

EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer 2000 spectrometer with Fourier transform from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Unity 400 Plus spectrometer at 400 MHz using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS-30 instrument with direct sample admission into the ion source. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene–acetone (10 : 1) as eluent; spots were detected by treatment with iodine vapor or with a solution of 1 g of potassium permanganate in a mixture of 96 ml of water and 4 ml of sulfuric acid.

Benzimidazol-2-amine (II). A solution of 1 g (25 mmol) of sodium hydroxide in 3 ml of water was added to a suspension of 1.91 g (10 mmol) of methyl 1*H*-benzimidazol-2-ylcarbamate (**I**) in 10 ml of water. The mixture was heated for 2 h under reflux, 0.2 g of activated charcoal was added, and the mixture was heated for 30 min at the boiling point. The mixture was filtered while hot, the charcoal was washed on a filter

with hot water (4×5 ml), the filtrate was cooled and carefully acidified with 0.8 ml of concentrated hydrochloric acid, and the precipitate was filtered off and recrystallized from 10 ml of water. Yield 0.86 g (65%), mp 229–230°C [10].

1-Arenesulfonyl-1*H*-benzimidazol-2-amines IVa–IVj (*general procedure*). A solution of 1.33 g (10 mmol) of benzimidazol-2-amine (**II**) and 1.01 g (10 mmol) of triethylamine in 30 ml of acetone was added dropwise to a solution of 10 mmol of arenesulfonyl chloride **IIIa**–**IIIj** in 20 ml of acetone. The mixture was stirred for 4 h at room temperature, the solvent was distilled off, the residue was treated with 50 ml of water, and the precipitate was filtered off and recrystallized from appropriate solvent.

1-Benzenesulfonyl-1*H*-benzimidazol-2-amine (IVa). Yield 2.18 g (80%), mp 204–206°C. IR spectrum, ν, cm^{-1}: 3430 s (NH_2), 1369 s (SO_2, asym.), 1183 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.92 m (2H, 4-H, 5-H), 7.61 m (4H, 6-H, 7-H, *o*-H), 7.04 m (2H, *m*-H), 6.91 m (3H, *p*-H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 273 (52) $[M]^+$, 141 (100), 132 (39). Found, %: C 57.40; H 4.34; N 15.51. $C_{13}H_{11}N_3O_2S$. Calculated, %: C 57.14; H 4.02; N 15.38.

1-(4-Methylbenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVb). Yield 2.03 g (71%), mp 200–201°C. IR spectrum, ν, cm^{-1}: 3453 s (NH_2), 1375 s (SO_2, asym.), 1187 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.81 m (2H, 4-H, 7-H), 7.57 d.d (1H, 6-H, $J_{6,4}$ = 2.1, $J_{6,5}$ = 7.5 Hz), 7.26 m (2H, *o*-H), 7.02 m (2H, *m*-H), 6.92 m (3H, 7-H, NH_2), 2.31 s (3H, Me). Mass spectrum, *m*/*z* (I_{rel}, %): 287 (48) $[M]^+$, 155 (100), 132 (42). Found, %: C 58.25; H 4.65; N 14.38. $C_{14}H_{13}N_3O_3S$. Calculated, %: C 58.53; H 4.52; N 14.63.

1-(4-Methoxybenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVc). Yield 2.24 g (74%), mp 210–212°C. IR spectrum, ν, cm^{-1}: 3454 s (NH_2), 1368 s (SO_2, asym.), 1172 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.85 m (2H, 4-H, 5-H), 7.65 d.d (1H, 6-H, $J_{6,4}$ = 2.1, $J_{6,5}$ = 7.9 Hz), 7.22 d (1H, 7-H, $J_{7,6}$ = 7.6 Hz), 7.07 m (2H, *o*-H), 6.86 m (2H, *m*-H), 6.06 br.s (2H, NH_2), 3.75 s (3H, OMe). Mass spectrum, *m*/*z* (I_{rel}, %): 303 (43) $[M]^+$, 171 (100), 132 (45). Found, %: C 55.64; H 4.38; N 14.14. $C_{14}H_{13}N_3O_2S$. Calculated, %: C 55.44; H 4.29; N 13.86.

1-(4-Chlorobenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVd). Yield 2.76 g (90%), mp 197–198°C. IR spectrum, ν, cm^{-1}: 3440 s (NH_2), 1377 s (SO_2, asym.), 1173 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.84 m (2H, 4-H, 5-H), 7.64 d.d (1H, 6-H, $J_{6,4}$ = 2.1, $J_{6,5}$ = 7.5 Hz), 7.38 m (2H, *o*-H), 7.24 d (1H, 7-H, $J_{7,6}$ = 7.5 Hz), 7.11 m (2H, *m*-H), 6.09 br.s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 307 (34 for ^{35}Cl) $[M]^+$, 175 (100), 132 (45). Found, %: C 51.02; H 3.38; Cl 11.78; N 13.87. $C_{13}H_{10}ClN_3O_2S$. Calculated, %: C 50.81; H 3.25; Cl 11.56; N 13.65.

1-(3-Nitrobenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVe). Yield 3.02 g (95%), mp 235–236°C. IR spectrum, ν, cm^{-1}: 3460 s (NH_2), 1372 s (SO_2, asym.), 1183 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 8.78 m (1H, o′-H), 8.43 m (1H, *p*-H), 8.22 m (1H, *o*-H), 7.69 m (2H, 4-H, 5-H), 7.21 m (3H, 6-H, 7-H, *m*-H), 6.07 br.s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 318 (27) $[M]^+$, 186 (100), 132 (40). Found, %: C 49.23; H 3.25; N 17.32. $C_{13}H_{10}N_4O_4S$. Calculated, %: C 49.05; H 3.14; N 17.61.

1-(4-*tert*-Butylbenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVf). Yield 2.46 g (75%), mp 197–199°C. IR spectrum, ν, cm^{-1}: 3445 s (NH_2), 1374 s (SO_2, asym.), 1174 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.84 m (2H, 4-H, 5-H), 7.69 d.d (1H, 6-H, $J_{6,4}$ = 2.0, $J_{6,5}$ = 7.8 Hz), 7.42 m (2H, *o*-H), 7.23 d (1H, 7-H, $J_{7,6}$ = 7.8 Hz), 7.11 m (2H, *m*-H), 6.27 br.s (2H, NH_2), 1.12 s (9H, *t*-Bu). Mass spectrum, *m*/*z* (I_{rel}, %): 329 (38) $[M]^+$, 197 (100), 132 (36). Found, %: C 61.77; H 6.01; N 13.01. $C_{17}H_{19}N_3O_2S$. Calculated, %: C 62.00; H 5.77; N 12.76.

***N*-[4-(2-Amino-1*H*-benzimidazole-1-sulfonyl)-phenyl]acetamide (IVg).** Yield 2.87 g (87%), mp 235–237°C. IR spectrum, ν, cm^{-1}: 3439 s (NH_2), 1369 s (SO_2, asym.), 1189 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.93 m (2H, 4-H, 5-H), 7.64 m (4H, 6-H, 7-H, *o*-H), 7.07 m (2H, *m*-H), 6.88 br.s (2H, NH_2), 3.65 (COMe). Mass spectrum, *m*/*z* (I_{rel}, %): 330 (41) $[M]^+$, 198 (100), 132 (47). Found, %: C 54.68; H 4.43; N 17.16. $C_{15}H_{14}N_4O_3S$. Calculated, %: C 54.54; H 4.24; N 16.96.

1-(2,4-Dimethylbenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVh). Yield 2.22 g (74%), mp 230–232°C. IR spectrum, ν, cm^{-1}: 3435 s (NH_2), 1353 s (SO_2, asym.), 1174 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.91 d.d (1H, 4-H, $J_{4,6}$ = 2.0, $J_{4,5}$ = 8.5 Hz), 7.68 m (2H, 5-H, 6-H), 7.46 d.d (1H, 7-H, $J_{7,5}$ = 2.0, $J_{7,6}$ = 8.5 Hz), 7.37 m (1H, *o*-H), 7.29 m (2H, *m*-H), 6.09 br.s (2H, NH_2), 2.45 s (3H, 2-Me), 2.38 s (3H, 4-Me). Mass spectrum, *m*/*z* (I_{rel}, %): 301 (42) $[M]^+$, 169 (100), 132 (38). Found, %: C 60.04;

H 5.21; N 13.74. $C_{15}H_{15}N_3O_2S$. Calculated, %: C 59.80; H 4.98; N 13.95.

1-(3,4-Dimethylbenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVi). Yield 2.16 g (72%), mp 216–218°C. IR spectrum, ν, cm^{-1}: 3453 s (NH_2), 1372 s (SO_2, asym.), 1165 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.97 d.d (1H, 4-H, $J_{4,6}$ = 2.1, $J_{4,5}$ = 8.4 Hz), 7.63 m (3H, 5-H, 6-H, 7-H), 7.38 m (3H, C_6H_3), 6.08 br.s (2H, NH_2), 2.34 s (6H, Me). Mass spectrum, *m*/*z* (I_{rel}, %): 301 (39) $[M]^+$, 169 (100), 132 (44). Found, %: C 59.51; H 4.74; N 14.23. $C_{15}H_{15}N_3O_2S$. Calculated, %: C 59.80; H 4.98; N 13.95.

1-(2,4,6-Trimethylbenzenesulfonyl)-1*H*-benzimidazol-2-amine (IVj). Yield 2.20 g (70%), mp 196–198°C. IR spectrum, ν, cm^{-1}: 3461 s (NH_2), 1384 s (SO_2, asym.), 1188 s (SO_2, sym.). ^1H NMR spectrum (CD_3OD), δ, ppm: 7.67 m (2H, 4-H, 5-H), 7.39 m (2H, 6-H, 7-H), 7.23 s (2H, C_6H_2), 6.12 br.s (2H, NH_2), 2.44 s (6H, 2′-Me, 6′-Me), 2.35 s (3H, 4′-Me). Mass spectrum, *m*/*z* (I_{rel}, %): 315 (51) $[M]^+$, 183 (100), 132 (36). Found, %: C 61.27; H 5.67; N 13.07. $C_{16}H_{17}N_3O_2S$. Calculated, %: C 60.95; H 5.39; N 13.33.

X-Ray analysis of compound IVd. Single crystals of 1-(4-chlorobenzenesulfonyl)-1*H*-benzimidazol-2-amine (**IVd**) were obtained by slow evaporation of its solution in ethanol at room temperature. The unit cell parameters were determined and refined using a Stoe Stadi-4 diffractometer (CuK_α irradiation, graphite monochromator, 300 K). Monoclinic crystal system, space group $P2_1/c$; unit cell parameters: a = 16.391(3), b = 5.1797(10), c = 15.677(3) Å; β = 95.43(3)°; V = 1325.0(5) $Å^3$; M 307.75; Z = 4; d_{calc} = 1.543 g/cm^3; μ = 4.079. Scan range $2.71 \le \theta \le 59.9°$; crystal dimensions 0.60×0.25×0.20 mm. A three-dimensional set consisting of 2558 reflection intensities (1955 independent reflections) was acquired. A correction for absorption was introduced using the Psi-scan method. The structure was solved by the direct method using SHELXS-97 software and was refined using SHELXL-97. The positions of all non-hydrogen atoms were refined against F^2 by the least-squares procedure in full-matrix anisotropic approximation to R = 0.0456, R_W = 0.1110 for 1955 reflections; goodness of fit S = 1.092. Hydrogen atoms were placed into positions calculated on the basis of geometry considerations and were refined with fixed isotropic displacement factors $U_{iso} = n U_{eq}$, where n = 1.2 for methylene groups and aromatic carbon atoms, and U_{eq} is the equivalent isotropic displacement factor of the corresponding carbon atom. The set of crystallographic parameters for compound **IVd** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 831010).

REFERENCES

1. Negwer, M. and Scharnow, H.-G., *Organic-Chemical Drugs and Their Synonyms*, Weinheim: Wiley, 2001.
2. Klimesova, V., Koci, J., Waisser, K., and Kaustova, K., *Farmaco*, 2002, vol. 57, p. 259.
3. Koci, J., Klimesova, V., Waisser, K., Kaustova, J., Danse, H.M., and Möllman, U., *Bioorg. Med. Chem. Lett*., 2002, vol. 12, p. 3275.
4. Guardiola-Diaz, H.M., Foster, L.A., Mushrush, D., and Vaz, A.D., *Biochem. Pharmacol*., 2001, vol. 61, p. 1463.
5. Shahar, Y.M., Mustaqeen, A.M., and Jaseela, M., *World Acad. Sci. Eng. Technol*., 2009, vol. 55, p. 593.
6. Umarov, A.A., Loi, N.P., Kadirov, Ch.Sh., and Ayupova, A.T., *Agrokhimiya*, 1973, no. 7, p. 123.
7. Umarov, A.A., *Benzimidazoly, ikh regulyatornye svoistva i funktsii* (Benzimidazoles. Their Regulatory Properties and Functions), Tashkent: Fan, 1990.
8. Foks, H., Pancechowska-Ksepko, D., Kuzmierkiewicz, W., Zwolska, Z., Augustynowicz-Kopec, E., and Janowiec, M., *Chem. Heterocycl. Compd*., 2006, vol. 42, p. 611.
9. Abdireimov, K.B., Mukhamedov, N.S., Aiymbetov, M.Zh., and Shakhidoyatov, Kh.M., *Khim. Geterotsikl. Soedin*., 2010, p. 1165.
10. Yunusov, S.Yu., Kadyrov, Ch.Sh., Khasanov, S.A., Shakirov, T.T., Atakuziev, A.A., Osmanov, U., and Arifov, Zh.M., USSR Inventor's Certificate no. 453405, 1974; *Byull. Izobret*., 1974, no. 46.
11. Wulff-Molder, D. and Meisel, M., Private communication, 1999.