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SYNTHESIS AND PROPERTIES OF NEW FUNCTIONALIZED 2-BENZAZEPINES*

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2-Aryl-4-hydroxy-2,3-dihydro-1H-2-benzazepine-5-carbonitriles were obtained by the cyclization of methyl esters of N-aryl-N-(2-cyanomethylbenzyl)aminoacetic acids by the action of sodium methylate. The keto–enol tautomerism of these compounds and their reactions with hydrazines were studied.

Keywords: 1-aminopyrazolo[3,4-*d*]benzazepine, 2-benzazepines, keto–enol tautomerism.

Intramolecular acylation in *o*-functionalized phenylacetonitriles has been used in our previous work [2-4] for the synthesis of dibenz[*b*,*f*]azocine derivatives. In a continuation of these studies and in light of the promising search for biological activity in 2-benzazepine derivatives [5], we studied this approach for the synthesis of previously unreported functionally substituted 2-benzazepines. The reaction of 2-bromomethylphenylacetonitrile **1** with methyl N-arylaminoacetate **2** in the presence of AcONa gave a series of methyl N-aryl-N-(2-cyanomethylbenzyl)-2-aminoacetates **3**. Heating of these products in methanolic sodium methylate for 1.5 h would be expected to give intramolecular cyclization involving the cyano group (according to Thorpe [6]), leading to iminobenzazepines **4** or the formation of cyanobenzazepines **5** due to ester condensation.

The lack of bands in the IR spectra of the cyclization products corresponding to ester, imino, or amino groups and the finding of a strong band in the vicinity of 2200 (conjugated C≡N), 3160 (broad, O–H), and 1610 cm^{-1} (C=C) indicate structure **5**. Nitriles **5** are capable of existing in two tautomeric forms, namely, ketonic ***K*-5** and enolic ***E*-5.** In DMSO-d_6 solution, **5** exists predominantly in enolic form ***E*-5**, as indicated by a broad band at 11.39-11.46 ppm (OH), which disappears in the presence of D_2O. On the other hand, both forms are found in $CDCl_3$.

Thus, the minor enolic form gives two methylene group singlets in the upfield portion of the spectrum at 4.43-4.49 (1-CH_2) and 4.34-4.42 ppm (3-CH_2). The ketonic form is seen as two AB-spin systems of diastereotopic protons of the same methylene groups at 4.94-5.00 (d) and 4.71-4.74 ppm (d, J = 16 Hz, $C_{(1)}$) and also 4.06-4.14 (d) and 4.22-4.24 ppm (d, J = 18 Hz, $C_{(3)}$). The methine proton at $C_{(5)}$ gives a singlet at 5.36-5.49 ppm. Integration of the intensities of the signals corresponding to each of these forms gives their ratio in the equilibrium mixture ***K*-5** ⇄ ***E*-5** equal to 1:0.7. The IR spectra of **5** show bands at 2200 (C≡N) and 3490 cm^{-1} for the enolic form and 2245 (C≡N) and 1735 cm^{-1} (C=O) for the ketonic form.

* Previous communication, see ref. [1].

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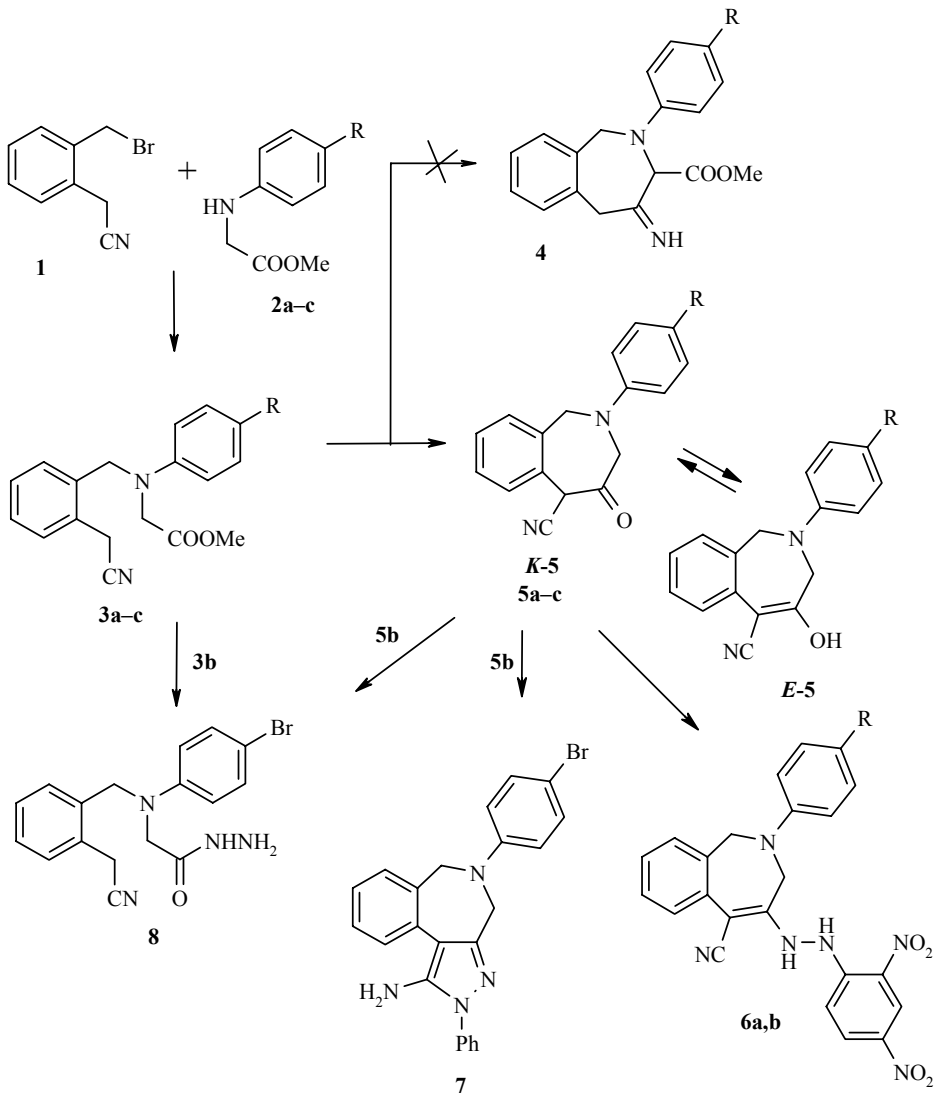

2, 3, 5 a R = H, **b** R = Br, **c** R = Me; **6 a** R = Br, **b** R = Me

The existence of a ketonic form for **5** provides for their reactivity in condensations with hydrazines. Thus, under standard conditions [7], **5** readily react with 2,4-dinitrophenylhydrazine but the condensation products **6** exist predominantly in the enehydrazine form, as indicated by the low-frequency position of the C≡N band (2190 cm^{-1}) in the IR spectrum and presence of two single proton singlets, which exchange in the presence of D_2O in the ^1H NMR spectra in DMSO-d_6. It is interesting that the condensation of phenylhydrazine with azepine **5b** does not stop upon formation of the corresponding enehydrazine (or hydrazone) and, as the result of subsequent reactions of the nitrile and β-NH groups, gives 1-amino-5-(4-bromophenyl)-2-phenyl-2,4,5,6-tetrahydropyrazolo[3,4-*d*]-2-benzazepine (**7**). The IR spectrum of **7** shows bands for the N–H group and lacks nitrile bands. We should note that pyrazoles fused at the [*d*] side of the 2-benzazepine system have an anxiolytic effect and have been described in several patents [8-11] but the nature of their fusion with the benzazepine system is different.

The reaction of azepine **5b** with 85% hydrazine hydrate proceeds unexpectedly with opening of the azepine ring and 2-[N-(4-bromophenyl)-N-(2-cyanomethylbenzyl)amino]acethydrazide **8** was obtained in high yield. The ^1H NMR spectrum of **8** shows three two-proton singlets for methylene group protons and signals for

TABLE 1. Physicochemical Characteristics of Compounds **3-8**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Br		
3a	$C_{18}H_{18}N_2O_2$	73.61 / 73.45	6.22 / 6.16	9.72 / 9.52		107	70
3b	$C_{18}H_{17}BrN_2O_2$	58.11 / 57.92	4.63 / 4.59	7.62 / 7.51	21.67 / 21.41	96	84
3c	$C_{19}H_{20}N_2O_2$	74.15 / 74.00	6.70 / 6.54	9.31 / 9.08		112	71
5a	$C_{17}H_{14}N_2O$	77.90 / 77.84	5.48 / 5.38	10.86 / 10.68		163	88
5b	$C_{17}H_{13}BrN_2O$	60.00 / 59.84	3.98 / 3.84	8.35 / 8.21	23.54 / 23.42	163	68
5c	$C_{18}H_{16}N_2O$	78.30 / 78.24	5.90 / 5.84	10.24 / 10.14		145	82
6a	$C_{23}H_{17}BrN_6O_4$	53.05 / 52.99	3.33 / 3.29	16.24 / 16.12	15.52 / 15.33	216	69
6b	$C_{24}H_{20}N_6O_4$	63.21 / 63.15	4.48 / 4.42	18.54 / 18.41		264	67
7	$C_{23}H_{19}BrN_4$	64.10 / 64.05	4.49 / 4.44	13.09 / 12.99	18.60 / 18.52	195	83
8	$C_{17}H_{17}BrN_4O$	54.74 / 54.70	4.63 / 4.59	15.20 / 15.01	21.58 / 21.41	158	82

the protons of NH protons, which exchange with D_2O, while its IR spectra show bands for NH and amide C=O groups. The structure of this compound was demonstrated by showing that it is identical to the sample obtained by an independent synthesis involving hydrazinolysis of aminoester **3b**.

EXPERIMENTAL

The IR spectra were taken on a Pye–Unicam SP3-300 spectrometer using KBr pellets. The ^{1}H NMR spectra were taken on Bruker WP-100SY (100 MHz) and Varian VXR-300 spectrometers (300 MHz) with TMS as the internal standard. Benzazepine **6b** was recrystallized from ethanol and the other products were recrystallized from 2-propanol. The melting points of the products were taken on a Boetius block and not corrected. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates.

The physicochemical and spectral characteristics of the products are given in Tables 1 and 2.

Methyl N-Aryl-N-(2-cyanomethylbenzyl)-2-aminoacetates 3a-c (General Method). A mixture of (2-bromomethylphenyl)acetonitrile **1** (60 mmol), methyl N-arylglycidine **2** (14.6 g, 60 mmol), and sodium acetate (24.6 g, 300 mmol) in 2-propanol (160 ml) was heated at reflux with stirring for 6 h. The reaction mixture was cooled and filtered. The solvent was removed from the filtrate at reduced pressure. The residue was triturated with cold water. The solid was filtered off, washed with water, and crystallized from 2-propanol.

2-Aryl-4-hydroxy-1,3-dihydro-1H-(2)-benzazepine-5-carbonitriles 5a-c (General Method). The corresponding acetate **3** (10.54 g, 33 mmol) was added to a solution of sodium methylate obtained by dissolving metallic sodium (1.15 g, 50 mmol) in methanol (80 ml). The reaction mixture was heated at reflux for 1.5 h and cooled. Then, 150 ml water was added with stirring and the mixture was neutralized by adding acetic acid. The precipitate formed was filtered off, washed with water, and crystallized from 2-propanol.

TABLE 2. Spectral Data for **3-8**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
	C≡N	Other bands	
3a	2240	1745 (C=O); 1200 (C–O)	3.67 (3H, s, OC<u>H</u>$_3$); 4.00 (2H, s, C<u>H</u>$_2$CN); 4.12 (2H, s, N–C<u>H</u>$_2$CO); 4.61 (2H, s, ArC<u>H</u>$_2$N); 6.57 (2H, d, *J* = 8, Ar<u>H</u>); 6.66 (1H, t, *J* = 8, Ar<u>H</u>); 7.12 (2H, t, *J* = 8, Ar<u>H</u>); 7.21–7.29 (3H, m, Ar<u>H</u>); 7.42 (1H, d, *J* = 7, Ar<u>H</u>)
3b	2240	1745 (C=O); 1200 (C–O)	3.67 (3H, s, OC<u>H</u>$_3$); 3.99 (2H, s, C<u>H</u>$_2$CN); 4.14 (2H, s, N–C<u>H</u>$_2$CO); 4.59 (2H, s, ArC<u>H</u>$_2$N,); 6.53 (2H, d, *J* = 8, Ar<u>H</u>); 7.17-7.30 (5H, m, Ar<u>H</u>); 7.43 (1H, d, *J* = 8, Ar<u>H</u>)
3c	2240	1740 (C=O); 1200 (C–O)	2.19 (3H, s, ArC<u>H</u>$_3$); 3.65 (3H, s, OC<u>H</u>$_3$); 3.98 (2H, s, C<u>H</u>$_2$CN); 4.06 (2H, s, N–C<u>H</u>$_2$CO); 4.57 (2H, s, ArC<u>H</u>$_2$N); 6.50 (2H, d, *J* = 8, Ar<u>H</u>); 6.92 (2H, d, *J* = 8, Ar<u>H</u>); 7.22–7.29 (3H, m, Ar<u>H</u>); 7.41 (1H, d, *J* = 8, Ar<u>H</u>)
5a	2200	1610 (C=C); 3160 (OH)	4.43 (2H, s, C$_{(3)}$<u>H</u>$_2$); 4.51 (2H, s, C$_{(1)}$<u>H</u>$_2$); 6.61 (1H, t, *J* = 8, Ar<u>H</u>); 6.73 (2H, d, *J* = 8, Ar<u>H</u>); 7.08 (3H, t, *J* = 8, Ar<u>H</u>); 7.20 (1H, t, *J* = 8, Ar<u>H</u>); 7.32 (1H, d, *J* = 8, Ar<u>H</u>); 7.42 (1H, d, *J* = 8, Ar<u>H</u>); 11.39 (1H, s, O<u>H</u>)
5b	2210	1590 (C=C); 3150 (OH)	4.43 (2H, s, C$_{(3)}$ <u>H</u>$_2$); 4.52 (2H, s, C $_{(1)}$<u>H</u>$_2$); 6.69 (2H, d, *J* = 8, Ar<u>H</u>); 7.09 (1H, t, *J* = 8, Ar<u>H</u>); 7.17-7.23 (3H, m, Ar<u>H</u>); 7.33 (1H, d, *J* = 8, Ar<u>H</u>); 7.42 (1H, d, *J* = 8, Ar<u>H</u>); 11.46 (1H, s, O<u>H</u>)
5c	2200	1590 (C=C); 3120 (OH)	2.14 (3H, s, ArC<u>H</u>$_3$); 4.38 (2H, s, C$_{(3)}$<u>H</u>$_2$); 4.48 (2H, s, C$_{(1)}$<u>H</u>$_2$); 6.62 (1H, d, *J* = 7, Ar<u>H</u>); 6.88 (1H, d, *J* = 7, Ar<u>H</u>); 7.06-7.20 (4H, m, Ar<u>H</u>); 7.28 (1H, d, *J* = 7, Ar<u>H</u>); 7.40 (1H, d, *J* = 7, Ar<u>H</u>); 11.40 (1H, s, O<u>H</u>)
6a	2200	1600 (C=C); 3300 (NH)	3.87 (2H, s, C$_{(3)}$<u>H</u>$_2$); 4.16 (2H, s, C$_{(1)}$<u>H</u>$_2$); 6.91-6.93 (2H, m, Ar<u>H</u>); 7.01 (1H, d, *J* = 8, Ar<u>H</u>); 7.19–7.37 (6H, m, Ar<u>H</u>); 8.16 (1H, d, *J* = 8, Ar<u>H</u>); 8.90 (1H, s, Ar<u>H</u>); 9.72 (1H, s, N<u>H</u>); 10.56 (1H, s, N<u>H</u>)
6b	2200	1600 (C=C); 3300 (NH)	2.20 (3H, s, ArC<u>H</u>$_3$); 3.83 (2H, s, C$_{(3)}$<u>H</u>$_2$); 4.12 (2H, s, C$_{(1)}$<u>H</u>$_2$); 6.88-6.99 (5H, m, Ar<u>H</u>); 7.17–7.23 (1H, m, Ar<u>H</u>); 7.30–7.35 (3H, m, Ar<u>H</u>); 8.10-8.13 (1H, m, Ar<u>H</u>); 8.87 (1H, s, Ar<u>H</u>); 9.70 (1H, s, N<u>H</u>); 10.55 (1H, s, N<u>H</u>)
7		1590 (C=C); 3320, 3420 (NH)	4.47 (4H, s, C$_{(4)}$<u>H</u>$_2$, C$_{(6)}$ <u>H</u>$_2$); 5.46 (2H, s, N<u>H</u>$_2$); 6.88 (2H, d, *J* = 7, Ar<u>H</u>); 7.13 (1H, t, *J* = 7, Ar<u>H</u>); 7.26-7.32 (3H, m, Ar<u>H</u>); 7.39 (1H, t, *J* = 7, Ar<u>H</u>); 7.52-7.64 (6H, m, Ar<u>H</u>)
8	2240	1650 (C=O); 3300*, 3520 NH	3.89 (2H, s, C<u>H</u>$_2$CN); 4.01 (2H, s, NC<u>H</u>$_2$CO); 4.16 (2H, s, N<u>H</u>$_2$); 4.62 (2H, s, ArC<u>H</u>$_2$N); 6.52 (2H, d, *J* = 7, Ar<u>H</u>); 7.08 (1H, d, *J* = 7, Ar<u>H</u>); 7.18-7.27 (4H, m, Ar<u>H</u>); 7.42 (1H, d, *J* = 7, ArH); 9.18 (1H, s, N<u>H</u>)

* Strong band.

4-Hydroxy-2-phenyl-2,3-dihydro-1H-2-benzazepine-5-carbonitrile (5a). ^{1}H NMR spectrum ($CDCl_3$)*, δ, ppm (*J*, Hz): 4.14 (1H, d, *J* = 18, $C_{(3)}\underline{H}_B$) (***K***); 4.23 (1H, d, *J* = 18, $C_{(3)}\underline{H}_A$) (***K***); 4.42 (1.4H, s, $C_{(3)}\underline{H}_2$) (***E***); 4.49 (1.4H, s, $C_{(1)}\underline{H}_2$) (***E***); 4.74 (1H, d, *J* = 16, $C_{(1)}\underline{H}_B$) (***K***); 5.04 (1H, d, *J* = 16, $C_{(1)}\underline{H}_A$) (***K***); 5.46 (1H, s, $C_{(5)}\underline{H}$) (***K***); 6.75-6.82 (5.1H, m, ArH); 6.90 (1.7H, t, *J* = 7, ArH); 7.16-7.53 (6.8H, m, ArH); 7.64 (1.7H, d, *J* = 7, Ar$\underline{H}$).

2-Bromophenyl)-4-hydroxy-2,3-dihydro-1H-2-benzazepine-5-carbonitrile (5b). ^{1}H NMR spectrum ($CDCl_3$),* δ, ppm (*J*, Hz): 4.06 (1H, d, *J* = 18, $C_{(3)}\underline{H}_B$) (***K***); 4.24 (1H, d, *J* = 18, $C_{(3)}\underline{H}_A$) (***K***); 4.39 (1.4H, s, $C_{(3)}\underline{H}_2$) (***E***); 4.47 (1.4H, s, $C_{(1)}\underline{H}_2$) (***E***); 4.74 (1H, d, *J* = 16, $C_{(1)}\underline{H}_B$) (***K***); 4.95 (1H, d, *J* = 16, $C_{(1)}\underline{H}_A$) (***K***); 5.36 (1H,s, $C_{(5)}\underline{H}$) (***K***); 6.64-6.70 (3.4H, m, Ar$\underline{H}$); 7.19-7.29 (3.4H, m, Ar$\underline{H}$); 7.33-7.43 (5.1H, m, Ar$\underline{H}$); 7.52-7.64 (1.7H, m, Ar$\underline{H}$).

4-Hydroxy-2-(4-methylphenyl)-2,3-dihydro-1H-2-benzazepine-5-carbonitrile (5c). IR spectrum, ν, cm^{-1}: 2200 (s) (***E***), 2245 (w) (***K***) (C≡N), 1735 (C=O) (***K***), 3490 (OH) (***E***). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.18 (2.1H, s, $C\underline{H}_3$) (***E***); 2.28 (3H, s, $C\underline{H}_3$) (***K***); 4.07 (1H, d, *J* = 18, $C_{(3)}\underline{H}_B$) (***K***); 4.22 (1H, d, *J* = 18, $C_{(3)}\underline{H}_A$) (***K***); 4.34 (2H, s, $C_{(3)}\underline{H}_2$) (***E***); 4.43 (2H, s, $C_{(1)}\underline{H}_2$) (***E***); 4.71 (1H, d, *J* = 15, $C_{(1)}\underline{H}_B$) (***K***); 5.00 (1H, d, *J* = 16, $C_{(1)}\underline{H}_A$) (***K***); 5.49 (1H, s, $C_{(5)}\underline{H}$) (***K***); 6.68-6.73 (3.4H, m, Ar$\underline{H}$); 6.95-6.97 (3.4H, m, Ar$\underline{H}$); 7.10-7.42 (5.1H, m, Ar$\underline{H}$); 7.50-7.64 (1.7H, m, Ar$\underline{H}$).

2-(4-Bromophenyl)-4-(2,4-dinitrophenylhydrazino)-1,3-dihydro-1H-2-benzazepine-5-carbonitrile (6a). Water (1.5 ml) and, then, ethanol (5 ml) were added with stirring consecutively to a mixture of 2,4-dinitrophenylhydrazine (0.26 g, 1.3 mmol) and concentrated sulfuric acid (1 ml). A solution of 2-benzazepine **5b** (0.34 g, 1 mmol) in a minimal amount of ethanol was added to the prepared mixture. The precipitate formed was filtered off, washed with water, and recrystallized from ethanol.

4-[2-(2,4-Dinitrophenyl)hydrazino]-2-(4-methylphenyl)-2,3-dihydro-1H-2-benzazepine-5-carbonitrile (6b) was obtained analogously to **5c**.

1-Amino-5-(4-bromophenyl)-2-phenyl-2,4,5,6-tetrahydropyrazolo[3,4-*d*]-2-benzazepine (7). Phenylhydrazine (0.11 ml, 1 mmol) was added to a solution of 2-benzazepine **5b** (0.34 g, 1 mmol) in 2-propanol (10 ml). The mixture was heated at reflux for 2 h and cooled. The precipitate formed was filtered off and crystallized from 2-propanol.

N-4-Bromophenyl-N-(2-cyanomethylbenzylamino)acethydrazide (8). A sample of 85% hydrazine hydrate (1 ml, 17 mmol) was added to a solution of benzazepine **5b** (0.34 g, 1 mmol) in 2-propanol (10 ml). The reaction mixture was heated at reflux for 4 h and cooled. Then, ice water was added. The precipitate formed was filtered off and crystallized from 2-propanol.

The same compound was obtained under the same conditions from ester **3b**.

REFERENCES

1. V. M. Kysil, E. O. Kostyrko, and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.*, 999 (1999) [*Chem. Heterocycl. Comp.*, **35**, 878 (1999)].
2. V. A. Kovtunenko, V. M. Kysil, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 1000 (1988) [*Chem. Heterocycl. Comp.*, **24**, 826 (1988)].
3. V. M. Kysil, V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 109 (1991) [*Chem. Heterocycl. Comp.*, **27**, 92 (1991)].
4. V. M. Kysil, V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, *Ukr. Khim. Zh.*, **56**, 749 (1990).
5. S. Kasparek, *Adv. Heterocycl. Chem.*, **17**, 45 (1974).

* The integral intensities of the signals are given relative to proton absorption of the ketonic form ***K***.

6. F. S. Babichev, Yu. A. Sharanin, V. P. Litvinov, V. K. Promonenko, and Yu. M. Volovenko, *Intramolecular Reactions of the Nitrile with C–H, O-H and S–H Groups* [in Russian], Naukova Dumka, Kiev (1985), p. 53.
7. R. Shriner, R. Fuson, D. Curtin, and T. Morrill, *Identification of Organic Compounds* [Russian translation], Mir, Moscow (1983), p. 185.
8. W. Gschwend, US Patent 3939271; *Chem. Abstr.*, **84**, 150623 (1976).
9. W. Gschwend, Ger. Patent 2543382; *Chem. Abstr.*, **84**, 135650 (1976).
10. W. Gschwend, Ger. Patent 2524048; *Chem. Abstr.*, **84**, 121822 (1976).
11. W. Gschwend, US Patent 4028381; *Chem. Abstr.*, **87**, 117854 (1977).