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SYNTHESIS AND SOME CONVERSIONS OF PARTIALLY HYDROGENATED 1-AMINOPYRANO(THIOPYRANO)[4,3-*d*]-PYRAZOLO[3,4-*b*]PYRIDINES AND PYRAZOLO[3,4-*c*]ISOQUINOLINES

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We have synthesized derivatives of pyrano(thiopyrano)[4,3-d]pyrazolo[3,4-b]pyridine and pyrazolo-[3,4-c]isoquinoline, and we have also carried out some conversions with them.

Keywords: hydrazine, isoquinoline, pyrazole, pyran, pyridine, synthesis.

Compounds including novel heterocyclic systems of partially hydrogenated pyrano(thiopyrano)[4,3-*d*]-pyrazolo[3,4-*b*]pyridine and tetrahydropyrazolo[3,4-*c*]isoquinoline are of interest as potentially biologically active substances.

In this work, the indicated systems were constructed based on the 4-cyanopyridin-3-ones **1a-l** condensed with a cyclohexene or tetrahydropyran (thiopyran) ring that we obtained earlier [1, 2]. By chlorination of compounds **1a-l** with phosphorus oxychloride, we obtained condensed 3-chloro-4-cyanopyridines **2a-l**. Upon reaction of the latter with a strong 1,2-binucleophilic reagent (hydrazine), as a result of intramolecular cyclization we synthesized condensed 1-aminopyrazoles **3a-l**,* the structures of which are supported by IR and ^{1}H NMR spectra. Thus in the IR spectra of compounds **2a-l**, there is an absorption band from the nitrile group in the 2220 cm^{-1} region. After closure of the pyrazole ring and formation of products **3a-l**, the band in this region disappears and several absorption bands appear in the 3160-3420 cm^{-1} region which are characteristic for the NH_2 and NH groups. In the ^{1}H NMR spectra of compounds **3a-l**, there are signals from the NH_2 and NH groups in the 4.40-5.65 ppm and 11.2-11.7 ppm regions respectively.

The presence of NH_2 and NH groups allowed us to carry out some conversions of compounds **3**. Thus by treatment of amines **3j-k** with acid chlorides, we obtained the amides **4a,b**, and by condensation of pyrazole **3a** with malonic ester we obtained hexahydro-4H-pyrano[4",3":4',5']pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine **5**. Diazotization of aminopyrazole **3c** and further condensation of the diazo derivative with acetoacetic ester led to the condensed pyrazolo[5,1-*c*][1,2,4]triazine (**6**). Probably adduct **7** is formed as an intermediate, which undergoes ring closure when treated with acetic acid.

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TABLE 1. Characteristics of Compounds **2***

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	R_f	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
		Cl	N				
2b	$C_{14}H_{17}ClN_2O$	13.17 / 13.39	10.44 / 10.58	139-141	0.62	0.95 (3H, t, *J* = 7.5, $\underline{CH_2}CH_3$); 1.25 (6H, s, $2CH_3$); 1.60-1.80 (2H, m, $\underline{CH_2}CH_3$); 2.60 (2H, t, *J* = 7.5, $\underline{CH_2}$–C_2H_5); 2.82 (2H, s, 4-CH_2); 5.65 (2H, s, CH_2O)	84.3
2c	$C_{14}H_{17}ClN_2O$	13.25 / 13.39	10.51 / 10.58	121-122	0.57	1.21 (6H, d, *J* =7, $CH(\underline{CH_3})_2$); 1.25 (6H, s, $2CH_3$); 2.82 (2H, s, 4-CH_2); 2.98 (1H, m, *J* = 7, CH); 4.65 (2H, s, CH_2O)	83.1
2d	$C_{18}H_{17}ClN_2O$	11.24 / 11.33	8.77 / 8.96	132-134	0.61	1.20 (6H, s, $2CH_3$); 2.85 (2H, s, 4-CH_2); 4.05 (2H, s, $\underline{CH_2}C_6H_5$); 4.65 (2H, s, CH_2O); 7.15-7.35 (5H, m, C_6H_5)	82.4
2e	$C_{15}H_{19}ClN_2O$	12.61 / 12.72	9.89 / 10.05	127-129	0.73	0.93 (6H, d, *J* = 6, $CH(\underline{CH_3})_2$); 1.25 (6H, s, $2CH_3$); 2.20-2.34 (1H, m, CH); 2.55 (2H, d, *J* = 8, CH_2CH); 2.85 (2H, s, 4-$\underline{CH_2}$); 4.75 (2H, s, CH_2O)	75.8
2f	$C_{13}H_{15}ClN_2S$	13.14 / 13.29	10.39 / 10.50	131-132	0.62	1.20 (3H, t, *J* = 7.5, $CH_2\underline{CH_3}$); 1.37 (6H, s, $2CH_3$); 2.80 (2H, q, *J* = 7.5, $\underline{CH_2}CH_3$); 2.97 (2H, s, 4-CH_2); 3.66 (2H, s, CH_2S)	79.9
2g	$C_{15}H_{19}ClN_2S$	11.94 / 12.02	9.38 / 9.50	77-78	0.57	0.90 (3H, t, *J* = 7, CH_3); 1.40–1.70 (4H, m, $2CH_2$); 2.92 (2H, t, *J* = 7.5, $\underline{CH_2}C_3H_7$); 3.05 (2H, s, 4-CH_2); 3.90 (2H, s, CH_2S)	80.6
2h	$C_{14}H_{17}ClN_2S$	12.52 / 12.63	9.74 / 9.98	125-126	0.63	1.27 (6H, d, *J* = 7, $CH(\underline{CH_3})_2$); 1.40 (6H, s, $2CH_3$); 3.05 (2H, s, 4-CH_2); 3.39 (1H, m, *J* = 7, CH); 3.85 (2H, s, CH_2S)	73.6
2i	$C_{15}H_{13}ClN_2OS$	11.51 / 11.63	9.04 / 9.19	180-181	0.59	1.45 (6H, s, $2CH_3$); 3.05 (2H, s, 4-CH_2); 4.25 (2H, s, CH_2S); 6.54 (1H, t, *J* = 1.8, CH); 7.30 (1H, d, *J* = 3.4, CH); 7.65 (1H, d, *J* = 1.8, CH)	75.8
2k	$C_{12}H_{13}ClN_2$	15.97 / 16.06	12.44 / 12.61	107-108	0.56	1.25 (3H, t, *J* = 7.5, CH_3); 1.85 (4H, m, $2CH_2$); 2.65 (2H, t, *J* = 6.6, 5-CH_2); 2.75 (2H, q, *J* = 7.5, $\underline{CH_2}CH_3$); 2.95 (2H, t, *J* = 6.6, 8-CH_2)	85.1
2l	$C_{16}H_{13}ClN_2$	12.94 / 13.19	10.31 / 10.42	156-157	0.59	1.75-1.95 (4H, m, $2CH_2$); 2.75 (2H, t, *J* = 6.6, 5-CH_2); 3.01 (2H, t, *J* = 6.6, 8-CH_2); 7.40-7.62 (5H, m, C_6H_5)	80.3

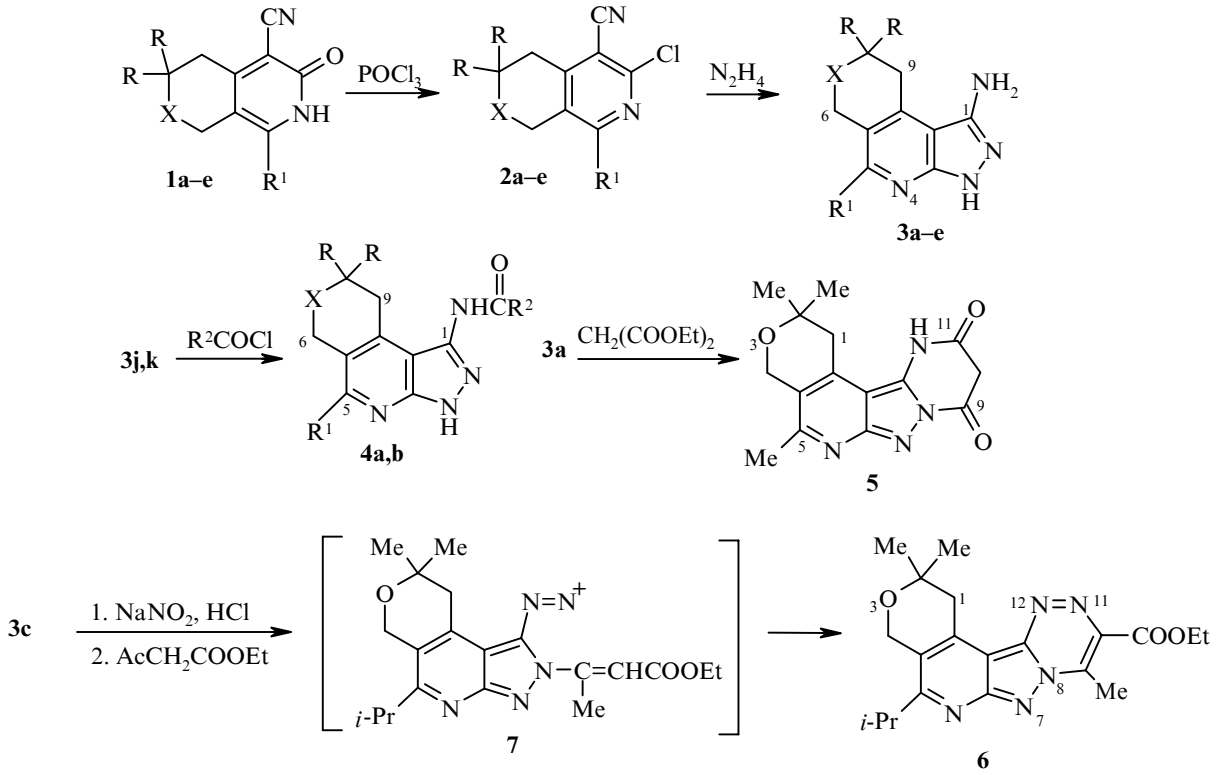
* IR spectrum of compounds **2b-i,k,l** (thin film), ν, cm^{-1}: 2220 (CN), 1580-1600 (C=C arom.).

TABLE 2. Characteristics of Compounds **3a-l***

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
		C	H	N				
3a*[2]	$C_{12}H_{16}N_4O$	61.92 / 62.05	6.71 / 6.94	24.13 / 24.12	289-290	0.59	1.24 (6H, s, $2CH_3$); 2.41 (3H, s, CH_3); 3.36 (2H, s, 9-CH_2); 4.77 (2H, s, CH_2O); 5.12 (2H, s, NH_2); 11.23 (1H, s, NH)	92.4
3b	$C_{14}H_{20}N_4O$	64.31 / 64.59	7.63 / 7.74	21.41 / 21.52	242-244	0.64	1.10 (3H, t, *J* = 7.5, CH_2–CH_3); 1.25 (6H, $2CH_3$); 1.75 (2H, m, *J* = 7.5, CH_2–CH_3); 2.6 (2H, t, *J* = 7.5, CH_2–C_2H_5); 3.05 (2H, s, 9-CH_2); 4.65 (2H, s, CH_2O); 4.90 (2H, s, NH_2); 11.60 (1H, s, NH)	93.9
3c	$C_{14}H_{20}N_4O$	64.46 / 64.59	7.51 / 7.74	21.44 / 21.52	256-257	0.68	1.30 (6H, s, $2CH_3$); 1.41 (6H, d, *J* = 7, $CH(CH_3)_2$); 2.88 (1H, m, *J* = 7, CH); 3.33 (2H, s, 9-CH_2); 4.92 (2H, s, CH_2O); 5.63 (2H, s, NH_2); 11.37 (1H, s, NH)	84.6
3d	$C_{18}H_{20}N_4O$	69.89 / 70.11	6.46 / 6.54	18.02 / 18.17	232-233	0.76	1.23 (6H, s, $2CH_3$); 3.05 (2H, s, 9-CH_2); 4.00 (2H, s, $CH_2C_6H_5$); 4.65 (2H, s, CH_2O); 5.01 (2H, s, NH_2); 7.05-7.30 (5H, m, C_6H_5); 11.80 (1H, s, NH)	75.9
3e	$C_{15}H_{22}N_4O$	65.51 / 65.67	8.14 / 8.08	20.29 / 20.42	241-242	0.61	0.95 (6H, d, *J* = 6, $CH(CH_3)_2$); 1.22 (6H, s, $2CH_3$); 2.15 (1H, m, *J* = 6, CH); 2.50 (2H, d, *J* = 8, CH–CH_2); 3.05 (2H, s, 9-CH_2); 4.71 (2H, s, CH_2O); 4.95 (2H, s, NH_2); 11.70 (1H, s, NH)	73.8
3f	$C_{13}H_{18}N_4S$	59.37 / 59.51	6.78 / 6.91	21.22 / 21.35	257-258	0.72	1.21 (3H, t, *J* = 7, CH_2CH_3); 1.30 (6H, s, $2CH_3$); 2.82 (2H, q, *J* = 7.5, CH_2CH_3); 3.55 (2H, s, 9-CH_2); 3.95 (2H, s, CH_2S); 5.65 (2H, s, NH_2); 11.4 (1H, s, NH)	85.1
3g	$C_{15}H_{22}N_4S$	61.94 / 62.03	7.54 / 7.63	19.11 / 19.29	253-254	0.59	0.86 (3H, t, *J* = 7, CH_2CH_3); 1.35 (6H, s, $2CH_3$); 1.38-2.05 (4H, m, $2CH_2$); 2.86 (2H, t, *J* = 7, $CH_2C_3H_7$); 3.57 (2H, s, 9-CH_2); 3.93 (2H, s, CH_2S); 5.62 (2H, s, NH_2); 11.2 (1H, s, NH)	65.1
3h	$C_{14}H_{20}N_4S$	60.75 / 60.84	7.14 / 7.29	20.09 / 20.27	268-269	0.74	1.28 (6H, t, *J* = 7, $CH(CH_3)_2$); 1.40 (6H, s, $2CH_3$); 3.25 (2H, s, 9-CH_2); 3.35 (1H, m, *J* = 7, CH); 3.85 (2H, s, CH_2S); 4.80 (2H, s, NH_2); 11.6 (1H, s, NH)	89.2
3i	$C_{15}H_{16}N_4OS$	59.77 / 59.98	5.26 / 5.37	18.48 / 18.65	236-237	0.69	1.30 (6H, s, $2CH_3$); 3.55 (2H, s, 9-CH_2); 4.25 (2H, s, CH_2S); 5.65 (2H, s, NH_2); 6.49 (1H, t, *J* = 3.4, CH); 7.10 (1H, d, *J* = 3.4, CH); 7.65 (1H, d, *J* = 3.4); 11.20 (1H, s, CH)	92.1
3j	$C_{17}H_{18}N_4S$	65.69 / 65.78	5.73 / 5.84	17.94 / 18.05	213-214	0.63	1.35 (6H, s, $2CH_3$); 3.40 (2H, s, 9-CH_2); 3.78 (2H, s, CH_2S); 5.10 (2H, s, NH_2); 7.45-7.52 (5H, m, C_6H_5); 11.33 (1H, s, NH)	87.0
3k	$C_{12}H_{16}N_4$	66.57 / 66.64	7.37 / 7.46	25.71 / 25.90	240-241	0.71	1.25 (3H, t, *J* = 7, CH_2CH_3); 1.76-1.85 (4H, m, $2CH_2$); 2.60-2.80 (4H, m, 6-CH_2, CH_2CH_3); 3.14 (2H, t, *J* = 6.6, 9-CH_2); 4.60 (2H, s, NH_2); 11.50 (1H, s, NH)	93.4
3l	$C_{16}H_{16}N_4$	72.51 / 72.70	6.03 / 6.10	21.04 / 21.20	240-242	0.62	1.60-1.95 (4H, m, $2CH_2$); 2.65 (2H, *J* = 6.6, 6-CH_2); 3.25 (2H, t, *J* = 6.6, 9-CH_2); 4.40 (2H, s, NH_2); 7.35-7.42 (5H, m, C_6H_5); 11.42 (1H, s, NH)	83.7

* IR spectrum of compounds **3a-l** (thin film), ν, cm^{-1}: 3160-3420 (NH, NH_2), 1610-1630 (NH bend), 1580-1600 (C=C arom.).

*[2] Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ 232 (91), 217 (19), 203 (17), 174 (100), 160 (24).



1–3 a–e X = O, **f–j** X = S, **k**, **l** X = CH_2; **a–j** R = Me, **k**, **l** R = H; **a** R^1 = Me, **b** R^1 = Pr, **c, h** R^1 = *i*-Pr, **d** R^1 = CH_2Ph, **e** R^1 = *i*-Bu, **f**, **k** R^1 = Et, **g** R^1 = Bu, **i** R^1 = 2-C_4H_3O, **j**, **l** R^1 = Ph,
4 a X = S, R = Me, R^1 = Ph, R^2 = 2-C_4H_3O, **b** X = CH_2, R = H, R^1 = Et, R^2 = Ph

EXPERIMENTAL

The IR spectra were taken on a Specord UR-20 (in vaseline oil); the ^1H spectra were obtained on a Mercury-300 (300 MHz) in DMSO-d_6. The mass spectra were measured on an MX-1303 mass spectrometer with direct sample injection. The purity of the compounds was monitored by TLC on Silufol UV-254 plates using the system: ethanol–ether, 1:3 (**2b-e,k,l)**; chloroform–ether, 1:2 (**2f-i**); pyridine–ethanol, 1:3 (**3a-e**); pyridine–hexane–ethanol, 1:2:3 (**3f-j**); chloroform–acetone-hexane, 1:1:2 (**3k,l)**; chloroform–ethanol, 2:1 (**4a,b**); butanol–acetic acid–water, 4;2:5 (**5,6**).

Synthesis of compounds **2a,j** is described in [3,4]. Compounds **2b-i,k,l** were obtained similarly (Table 1).

10,10-R^2-1-Amino-8,9-dihydro-6H-pyrano(thiopyrano)[4,3-*d*]pyrazolo[3,4-*b*]pyridines (3a-j) and 6,7,8,9-Tetrahydropyrazolo[3,4-*c*]isoquinolines (3k,l). A mixture of chloronitrile **2a-l** (0.01 mol), hydrazine hydrate (10 ml), and ethanol (50 ml) were refluxed for 6 h. Then the ethanol and excess hydrazine hydrate were distilled off and water (50 ml) was added to the residue; the precipitated crystals of product **3** were filtered out, washed with water, dried, and recrystallized from ethanol (Table 2).

1-Furoylamino-8,8-dimethyl-5-phenylthio-8,9-dihydro-6H-pyrano[4,3-*d*]pyrazolo[3,4-*b*]pyridine (4a) and 1-Benzoylamino-5-ethyl-6,7,8,9-tetrahydropyrazolo[3,4-*c*]isoquinoline (4b). A solution of compound **3j,k** (0.01 mol), the corresponding acid chloride (0.01 mol), and triethylamine (3 ml) in benzene (50 ml) was refluxed for 8 h. The benzene was distilled off, water was added to the residue, the precipitated crystals of product **4** were filtered out, washed with water, dried, and recrystallized from ethanol.

Compound 4a. Yield 75.4%; mp 195-196°C (ethanol), R_f 0.71. IR spectrum (thin film), ν, cm-1: 3350, 3410 (NH), 1670 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.5 (6H, s, $2CH_3$); 3.21 (2H, s, 9-CH_2); 2.65 (2H, s, SCH_2); 6.63 (1H, t, *J* = 3.4, CH); 6.8 (1H, s, NH); 7.48-7.53 (5H, m, C_6H_5); 7.8 (1H, d, *J* = 3.4, CH); 8.6 (1H, d, *J* = 3.4, CH); 11.22 (1H, s, NH). Found, %: C 65.23; H 5.03; N 13.76; S 8.06. $C_{22}H_{20}N_4O_2S$. Calculated, %: C 65.32; H 4.98; N 13.85; S 7.92.

Compound 4b. Yield 80.2%; mp 212-214°C. R_f 0.64. IR spectrum (thin film), ν, cm^{-1}: 3330, 3410 (NH), 1670 (CO). Found, %: C 71.32; H 6.13; N 17.37. $C_{19}H_{20}N_4O$. Calculated, %: C 71.22; H 6.29; N 17.48.

2,2,5-Trimethyl-1,2,9,10,11,12-hexahydro-4H-pyrano[4'',3'':4',5']pyrido[2',3':3,4]pyrazolo[1,5-*a*]-pyrimidine-9,11-dione (5). A mixture of compound **3a** (2.3 g, 0.01 mol), diethyl ester of malonic acid (1.6 g, 0.01 mol), and butanol (30 ml) was refluxed for 10 h. The butanol was distilled off, the residue was dissolved in an aqueous 2N sodium hydroxide solution (50 ml), and filtered; the filtrate was acidified with 10% hydrochloric acid. The precipitated crystals of product **5** were filtered out, washed with water, and dried. Yield 1.6 g (53.3%); mp >360°C (nitromethane). R_f 0.64. IR spectrum (thin film), ν, cm^{-1}: 3400-3430 (NH), 1700, 1660 (CO). ^{1}H NMR spectrum, δ, ppm: 1.20 (6H, s, $2CH_3$); 2.62 (3H, s, CH_3); 3.49 (2H, s, 1-CH_2); 3.95 (2H, s, CH_2CO); 4.75 (2H, s, 4-CH_2); 8.54 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ 300 (28), 242 (11), 232 (36), 218 (87), 203 (72), 175 (17), 161 (58), 160 (100). Found, %: C 6.04; H 5.30; N 18.53. $C_{15}H_{16}N_4O_3$. Calculated, %: C 59.99; H 5.37; N 18.66.

Ethyl Ester of 5-Isopropyl-2,2,9-trimethyl-1,4-dihydro-2H-pyrano[4'',3'':4',5']pyrido[2',3':3,4]-pyrazolo[5,1-*c*][1,2,4]triazine-10-carboxylic Acid (6). A solution of sodium nitrite (0.7 g, 0.01 mol) in water (5 ml) was added to a mixture of compound **3c** (2.6 g, 0.01 mol) and 6N hydrochloric acid (6 ml) that had been cooled down to 0°C. The mixture was stirred for 30 min and acetoacetic ester (1.3 g, 0.01 mol) in ethanol (40 ml) and water (10 ml) containing sodium acetate (5 g) were added gradually to the solution. This was stirred for 3 h at 20°C and then filtered, and the filtrate was refluxed for 2 h in acetic acid (40 ml). After cooling, the crystals of product **6** formed were filtered out. Yield 49.6%; mp 229-230°C (acetic acid). R_f 0.57. IR spectrum (thin film), ν, cm^{-1}: 1700 (CO), 1590 (C=C arom.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20-1.32 (15H, m, $5CH_3$); 2.41 (1H, m, *J* = 7, CH); 2.69 (3H, s, CH_3); 2.80 (2H, s, 1-CH_2); 4.31 (2H, q, *J* = 7.5, $\underline{CH_2}CH_3$); 4.70 (2H, s, OCH_2). Mass spectrum, *m*/*z* (I_{rel}, %): M^+ 383 (56), 368 (11), 354 (19), 313 (16), 299 (6), 280 (10). Found, %: C 62.57; H 6.42; N 18.40. $C_{20}H_{25}N_5O_3$. Calculated, %: C 62.64; H 6.57; N 18.26.

REFERENCES

1. E. G. Paronikyan, S. N. Sirakanyan, S. V. Lindeman, M. S. Aleksanyan, A. A. Karapetyan, A. S. Noravyan, and Yu. T. Struchkov, *Khim. Geterotsikl. Soedin.*, 1137 (1989).
2. E. G. Paronikyan, S. N. Sirakanyan, G. Kh. Grigoryan, and A. S. Noravyan, *Arm. Khim. Zh.*, 505 (1989).
3. E. G. Paronikyan, S. N. Sirakanyan, A. S. Noravyan, and R. G. Paronikyan, *Arm. Khim. Zh.*, 766 (1989).
4. E. G. Paronikyan, S. N. Sirakanyan, A. S. Noravyan, and Dzh. A. Melkonyan, *Arm. Khim. Zh.*, 250 (1991).