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SYNTHESIS OF 6-AMINO-5-R^2-7-(6-R^1-4-OXO-3,4-DIHYDRO-2-QUINAZOLYL)-5H-PYRROLO[2,3-*b*]-PYRAZINE-2,3-DICARBONITRILES

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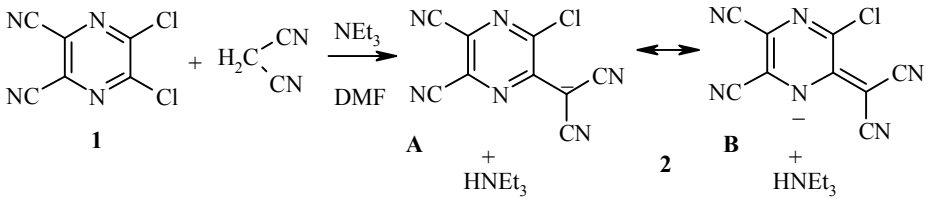
It has been found that malonodinitrile and 2-(6-R^1-oxo-3,4-dihydro-2-quinazolyl)acetonitrile in the presence of triethylamine undergo hetarylation by 5,6-dichloro-2,3-pyrazinedicarbonitrile at the active methylene group to give the triethylammonium salt of 2-(3-chloro-5,6-dicyano-2-pyrazinyl)malononitrile or 5-chloro-6-cyano(6-R^1-4-oxo-1,2,3,4-tetrahydro-2-quinazolylidene)methyl-2,3-pyrazinedicarbonitriles. Reaction of these with primary amines leads to annelation of the pyrrole ring at the pyrazine [b] edge to give 6-amino-5-R-5H-pyrrolo[2,3-b]pyrazine-2,3,7-tricarbonitriles and 6-amino-5-R^2-7-(6-R^1-4-oxo-3,4-dihydro-2-quinazolyl)-5H-pyrrolo[2,3-b]pyrazine-2,3-dicarbonitriles respectively.

Keywords: 6-amino-5-R-5H-pyrrolo[2,3-*b*]pyrazine-2,3,7-tricarbonitriles, 6-amino-5-R^2-7-(6-R^1-4-oxo-3,4-dihydro-2-quinazolyl)-5H-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles, 5,6-dichloro-2,3-pyrazinedicarbonitrile, hetarylation of 2-(6-R^1-4-oxo-3,4-dihydro-2-quinazolyl)acetonitriles.

Starting from the products of hetarylation of α-azahetarylacetonitriles by 5,6-dichloro-2,3-pyrazinedicarbonitrile (**1**) we have previously obtained a series of condensed and functionally substituted pyrrolo[*b*]pyrazines [1, 2].

By hetarylation of the methylene group of ethyl cyanoacetate and malonodinitrile by 2,3-dichloro-5-cyanopyrazine the authors of the patent [3] have obtained materials having anti-inflammatory and analgesic activity, comparable with aspirin and antipyrine.

5,6-Dichloro-2,3-pyrazinedicarbonitrile (**1**) reacts readily with malonodinitrile at room temperature in DMF in the presence of triethylamine to form the salt **2**:



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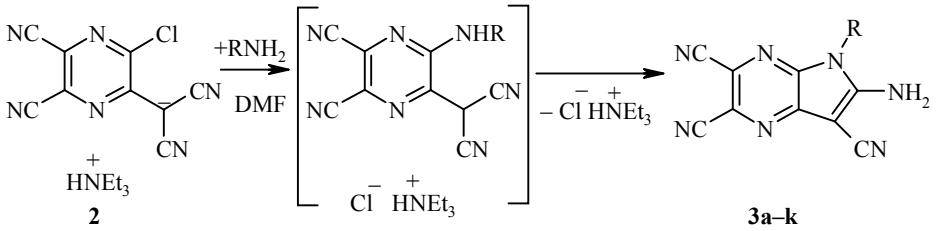
In the ^{1}H NMR spectrum of compound **2** taken in DMSO-d_6 solvent there are present signals from the protons of the triethylammonium cation, i.e. a methyl groups triplet in the region 1.18 ppm (9H, t, CH_3) and a methylene groups multiplet centred at 3.09 ppm (6H, m, CH_2). The form of this signal is due to additional splitting of the methylene groups by the N^+–H proton, the signal of which is observed in the spectrum at 8.83 ppm (1H, s, N^+–H) as a broadened singlet.

The presence at 2160 cm^{-1} in the IR spectrum of the salt **2** of an intense absorption band for the nitrile groups of the malonodinitrile fragment points to their efficient conjugation with the pyrazine ring and this is apparent in the structure of the mesomer **2B**. In the region 3130 cm^{-1} there is observed a strong band for the absorption of the N^+–H bond of the triethylammonium cation. With the inclusion of the long wavelength maximum in the UV spectrum of compound **2** at 378 nm (ε 2.7 x 10^4), all of the spectroscopic data confirm its salt like structure. Formation of this salt is possible thanks to the high acidity of the proton at the carbon atom which has three electron acceptor substituents. In order to calculate the pK_a of the C–H acid the UV spectra of the corresponding salt **2** were recorded in the presence of a series of acids. The UV spectra, taken in acetic and in 0.1 N hydrochloric acid, showed only a maximum for the salt at 378 nm. The absorption band for the protonated molecule (at 310 nm) appeared only with an excess of hydrochloric acid (about 4000 equivalents) or in 0.2 N sulfuric acid. The pK_a value of the acid (about 0.84), which forms the salt **2**, is comparable with the pK_a of hydrochloric acid. The high yield of the salt **2** (87%) is achieved only when carrying out the reaction in the presence of 2 equivalents of triethylamine. With one equivalent the reaction only proceeds half way and the starting pyrazine **1** is produced along with the salt **2** since the C–H acid formed protonates the triethylamine. Attempts to isolate the C–H acid in the free state were unsuccessful due to tarring of the salt **2** in a strongly acidic medium.

It is known that the reaction of 5-chloro-6-cyano(2,3-dihydro-1-R-benzo[*d*]azol-2-yl)methyl-2,3-pyrazinedicarbonitriles with primary amines gives products where the chlorine atom is substituted by an amino group and the secondary amino group so formed then adds to the nitrile function to yield 6-amino-7-hetaryl-5-R-5-H-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles [2]. Evidently, in the reaction of the salt **2** with primary amines, substitution of the chlorine atom by the amino group also occurs at the first stage and this is followed by annelation of a pyrrole ring at the [*b*] edge of the pyrazine to give the 6-amino-5H-pyrrolo[2,3-*b*]pyrazine-2,3,7-tricarbonitriles (**3a-k**):



a R = $PhCH_2$; **b** R = $PhCH_2CH_2$; **c** R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$; **d** R = Me_2N–CH_2CH_2; **e** R = $MeOCH_2CH_2$; **f** R = morpholino-CH_2CH_2; **g** R = morpholino-$CH_2CH_2CH_2$; **h** R = CH_2=CH–CH_2; **i** R = THF–CH_2; **j** R = 3-$MeOC_6H_4$; **k** R = 2-furyl-CH_2

In the ^{1}H NMR spectra of compounds **3a-k**, recorded in DMSO-d_6, the signal for the amino group protons is observed in the range 8.90-9.38 ppm (2H, s, NH_2), along with the proton signals for the substituent on the pyrrole ring nitrogen atom (Table 1). The IR spectra show absorption bands for the three nitrile groups in the range 2210-2190 cm^{-1}. Two absorption bands for the stretching of the primary group are seen at 3350-3200 cm^{-1}. Bands for the scissoring vibrations of the amino group are seen at 1595-1570 cm^{-1}.

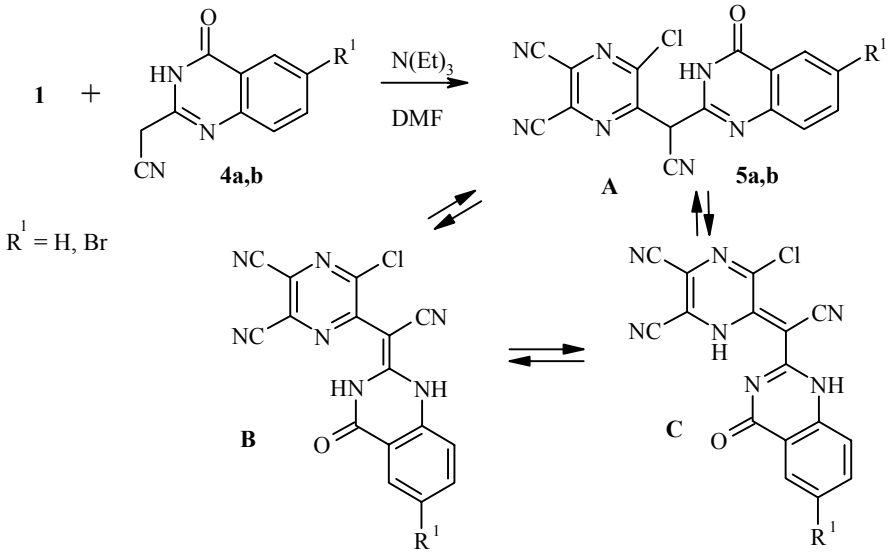
TABLE 1. Characteristics for Compounds **2** and **3a-k**

Com-pound	R	Empirical formula	Found, % / Calculated, % N	^{1}H NMR spectrum, δ, ppm, DMSO-d_6, *J* (Hz)	Yield, %
2*		$C_{15}H_{16}ClN_7$	29.65 / 29.73	1.18 (9H, t, CH_3); 3.09 (6H, m, CH_2); 8.83 (1H, s, N^+–H)	87
3a*[2]	Benzyl	$C_{16}H_9N_7$	32.45 / 32.76	5.40 (2H, s, CH_2); 7.22-7.34 (5H, m, Ph–H); 9.18 (2H, s, NH_2)	75
3b	Phenethyl	$C_{17}H_{11}N_7$	31.14 / 31.29	2.96 (2H, t, CH_2); 4.38 (2H, t, N–CH_2); 7.19-7.28 (5H, m, Ph–H); 9.09 (2H, s, NH_2)	80
3c	3,4-Dimethoxyphenethyl	$C_{19}H_{15}N_7O_2$	26.36 / 26.26	2.83 (2H, t, CH_2); 3.72 (6H, s, O–CH_3); 4.35 (2H, t, N–CH_2); 6.62 (1H, d, *J* = 8, 6-H_{Ph}); 6.75 (1H, s, 2-H_{Ph}); 6.78 (1H, d, *J* = 8.3, 5-H_{Ph}); 9.17 (2H, s, NH_2)	92
3d	2-Dimethylaminoethyl	$C_{13}H_{12}N_8$	39.87 / 39.98	2.22 (6H, s, CH_3); 2.59 (2H, t, CH_2); 4.24 (2H, t, CH_2); 9.03 (2H, s, NH_2)	70
3e	2-Methoxyethyl	$C_{12}H_9N_7O$	36.43 / 36.69	1.87 (2H, t, CH_2); 3.16 (3H, s, OCH_3); 4.18 (2H, t, N–CH_2); 9.13 (2H, s, NH_2)	74
3f	2-Morpholinoethyl	$C_{15}H_{14}N_8O$	34.84 / 34.76	2.45 (4H, m, –CH_2–N–CH_2–); 2.61 (2H, t, CH_2); 3.46 (4H, m, –CH_2–O–CH_2–); 4.26 (2H, t, CH_2); 9.33 (2H, s, NH_2)	96
3g	3-Morpholinopropyl	$C_{16}H_{16}N_8O$	33.46 / 33.31	1.85 (2H, t, CH_2); 2.25-2.30 (6H, m, –CH_2–N–CH_2– + –CH_2–CH_2–CH_2–); 3.46 (4H, m, –CH_2–O–CH_2–); 4.17 (2H, t, CH_2); 9.32 (2H, s, NH_2)	88
3h	Allyl	$C_{12}H_7N_7$	39.28 / 39.34	4.76 (2H, d, *J* = 3.7, CH_2); 4.98 (1H, d, *J* = 17.1, –CH=CH_2 *trans*); 5.17 (1H, d, *J* = 10.8, –CH=CH_2 *cis*); 5.90 (1H, m, –CH_2–CH=CH_2); 9.14 (2H, s, NH_2)	77
3i	Tetrahydro-2-furanylmethyl	$C_{14}H_{11}N_7O$	33.71 / 33.43	1.65-2.02 (4H, m, 3-,4-CH_2 in THF); 3.60-3.75 (2H, m, 5-CH_2 in THF); 4.20-4.30 (3H, m, N–CH_2+ 2-CH in THF); 9.10 (2H, s, NH_2)	83
3j	3-Methoxyphenyl	$C_{16}H_9N_7O$	31.17 / 31.10	3.81 (3H, s, CH_3); 7.06-7.23 (3H, m, 4-, 5-, 6-H_{Ph}); 7.56 (1H, t, 2-H_{Ph}); 8.90 (2H, s, NH_2)	69
3k	2-Furylmethyl	$C_{14}H_7N_7O$	34.09 / 33.90	5.43 (2H, s, N–CH_2); 6.43 (1H, dd, 4-H_{Het}); 6.54 (1H, d, *J* = 3.5, 3-H_{Het}); 7.65 (1H, d, *J* = 1.7, 5-H_{Het}); 9.38 (2H, s, NH_2)	86

* For compound **2**. Found, %: Cl 10.85; calculated, %: Cl 10.75. Mp 159-160°C.

*[2] The prepared compounds **3a-k** melt above 300°C.

The polyfunctional nature of the 2-(4-oxo-3,4-dihydro-2-quinazolyl)acetonitrile (**4**) is of interest in synthetic organic chemistry. We have previously shown that acylation of the 2-quinazolylacetonitrile **4** occurs at the methylene group [4]. The reaction of the 2-quinazolylacetonitriles **4a, b** with dichloropyrazine **1** takes place with arylation of the methylene group to give compounds **5a, b**, the structure of which may be represented in the three tautomeric forms **A**, **B**, and **C**:



In the IR spectra of compounds **5a, b** the conjugated nitrile groups absorb strongly at 2195-2190 cm^{-1} and the carbonyl group of the quinazolone ring at 1675 (**5a**) and 1690 cm^{-1} (**5b**). A broad absorption band for a chelated type N–H bond is observed at 3200-3060 cm^{-1}. In the ^{1}H NMR spectra of compounds **5a, b** recorded in DMSO-d_6 the signal for the methylene group protons is absent and the signals for the aromatic protons are shifted to low field when compared with the spectrum of the starting quinazolinone **4** (Table 2). Due to rapid exchange with water the signal for the N–H proton is absent. The spectroscopic data indicate that compounds **5a,b** can exist principally in the two tautomeric forms: **B** and **C**.

The structure of the hetarylation products **5a,b** is characterized by the presence of two nucleophilic centers (i.e. the nitrogen atoms in positions 1 and 3 of the quinazoline ring) and an electrophilic carbon atom bearing the chlorine atom. Refluxing solutions of compounds **5a,b** in pyridine causes an intramolecular arylation. On the basis of the ^{1}H NMR spectrum this product is a mixture of the isomers **6a,b** and **7a,b** in the ratio 1: 1.

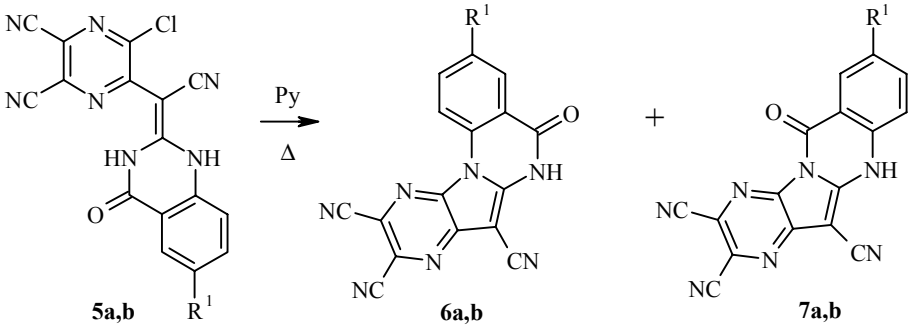


TABLE 2. Characteristics for Compounds **5a,b** and **8a-g**

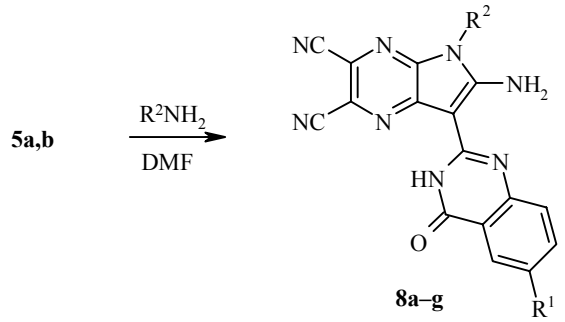
Com-pound*	Empirical formula	Found, % / Calculated, %			^{1}H NMR spectrum, δ, ppm, *J* (Hz)	Yield, %
		N	Br	Cl		
5a	$C_{16}H_6ClN_7O$	28.50 / 28.20		10.36 / 10.20	DMSO-d_6: 7.95 (1H, t, 6'-H*[2]); 8.11 (1H, t, 7'-H); 8.29 (1H, d, J_{1-3} = 9, 5'-H); 9.13 (1H, d, J_{1-3} = 9, 8'-H)	88
5b	$C_{16}H_5BrClN_7O$	23.18 / 22.98	18.97 / 18.73	8.36 / 8.31	DMSO-d_6: 8.26 (1H, dd, J_{1-3} = 9, J_{1-4}=2.4, 7'-H); 8.31 (1H, d, J_{1-4} = 2.4, 5'-H); 9.03 (1H, d, J_{1-3} = 9, 8'-H)	91
8a	$C_{23}H_{14}N_8O$	26.84 / 26.78			CF_3CO_2D: 5.64 (2H, s, CH_2); 7.37-7.44 (5H, m, Ph–H); 7.87 (1H, t, 7'-H); 7.97 (1H, d, *J* = 7, 8'-H); 8.21 (1H, t, 6'-H); 8.48 (1H, d, *J* = 7.6, 5'-H) DMSO-d_6: 5.54 (2H, s, CH_2); 7.30-7.40 (5H, m, Ph–H); 7.44 (2H, m, 8-',7'-H); 7.84 (1H, t, 6'-H); 8.31 (1H, d, *J* = 8, 5'-H); 9.4 (2H, s, NH_2); 10.8 (1H, s, N–H)	86
8b	$C_{21}H_{16}N_8O_2$	27.46 / 27.17			CF_3CO_2D: 1.99-2.44 (4H, m, 3-, 4-CH_2 in THF); 4.2 (2H, m, 5'-CH_2); 4.63-4.75 (3H, m, 2'-H+ N–CH_2); 7.87-8.01 (2H, m, 8-', 7'-$H_{quinazolone}$); 8.22 (1H, t, 6'-H); 8.49 (1H, d, *J* = 7, 5'-H)	77
8c	$C_{26}H_{20}N_8O_3$	23.05 / 22.75			CF_3CO_2D: 3.24 (2H, t, CH_2); 3.93 (6H, s, CH_3); 4.68 (2H, t, CH_2); 6.80-6.90 (3H, m, Ph–H); 7.85 (1H, t, 7'-H); 7.96 (1H, d, *J* = 8, 8'-H); 8.21 (1H, t, 6'-H); 8.49 (1H, d, *J* = 8.6, 5'-H)	96
8d	$C_{23}H_{13}BrN_8O$	22.48 / 22.53	16.29 / 16.07		CF_3CO_2D: 5.63 (2H, s, CH_2); 7.35-7.43 (5H, m, Ph–H); 7.87 (1H, d, *J* = 8.7, 8'-H); 8.27 (1H, dd, J_{1-3} = 8.4, J_{1-4} = 2.5, 7'-H); 8.59 (1H, d, J_{1-4} = 2.5, 5'-H)	93
8e	$C_{21}H_{15}BrN_8O_2$	22.90 / 22.81	16.33 / 16.26		CF_3CO_2D: 1.97-2.45 (4H, m, 3-, 4-CH_2 in THF); 4.17 (2H, m, 5'-CH_2); 4.63-4.70 (3H, m, 2'-H+ N–CH_2); 7.89 (1H, d, *J* = 8.4, 8'-$H_{quinazolone}$); 8.28 (1H, d, *J* = 9, 7'-H), 8.61 (1H, s, 5'-H)	82
8f	$C_{26}H_{19}BrN_8O_3$	19.83 / 19.61	13.87 / 13.98		CF_3CO_2D: 3.25 (2H, t, CH_2); 3.92 (6H, s, CH_3); 4.71 (2H, t, CH_2); 6.80-6.90 (3H, m, Ph–H); 7.86 (1H, d, *J* = 9.6, 8'-H); 8.26 (1H, d, *J* = 9.6, 7'-H); 8.61 (1H, s, 5'-H)	94
8g	$C_{24}H_{15}BrN_8O$	21.90 / 21.91	15.73 / 15.63		CF_3CO_2D: 2.49 (6H, s, CH_3); 7.12 (2H, s, 2-, 6-H_{Ph}); 7.45 (1H, s, 4-H_{Ph}); 7.91 (1H, d, *J* = 8.7, 8'-H); 8.3 (1H, dd, J_{1-3} = 9.3, J_{1-4} = 2.5, 7'-H); 8.62 (1H, d, J_{1-4} = 2.5, 5'-H)	79

* The prepared compounds **5a,b, 8a-g** melt above 300°C.

*[2] 5',6,7',8'-H indicate the aromatic protons of the quinazolone nucleus.

Elemental analytical analysis and IR spectroscopy also support the formation of a mixture of isomers in this reaction. In the IR spectra of the isomers **6a,b** and **7a,b** the nitrile group vibrations are observed as one band at 2200 cm^{-1} and at 1710 cm^{-1} a carbonyl group absorption is seen. It did not prove possible to separate each of the isomers into their individual forms.

As in the case of compound **2**, the reaction of compounds **5a,b** with primary amines occurred *via* annelation of a pyrrole ring at the [*b*] edge of the pyrazine to give the 6-amino-5H-pyrrolo[2,3-*b*]pyrazines **8a-g**.



a-c R^1 = H; **d-g** R^1 = Br; **a,d** R^2 = $PhCH_2$; **b,e** R^2 = THF–CH_2;
c,f R^2 = 3,4-$(MeO)_2C_6H_3CH_2CH_2$; **g** R^2 = 3,5-$Me_2C_6H_3$

Due the limiting solubility of compounds **8a-g** in DMSO-d_6 their ^{1}H NMR spectra were measured in deuterotrifluoroacetic acid, i.e. the measurement is actually made on the compounds **8a-g** which are protonated at the amino group (Table 2). The IR spectra of these compounds show a weak absorption band for the nitrile groups of the pyrazine ring at 2220-2210 cm^{-1}. Two absorption bands are seen for the amino group at 3450-3150 cm^{-1} together with the absorption band for the NH bond of the quinazolone ring. The scissoring deformations of the amino group are observed at 1590-1580 cm^{-1} and absorption bands for the carbonyl group at 1700-1675 cm^{-1}.

EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the synthesized compounds were carried out chromatographically on Silufol UV-254 plates using chloroform–methanol eluent (9:1). IR spectra were taken for KBr tablets recorded on UR-20, Specord IR-75, and Pye Unicam instruments in the range 4000-400 cm^{-1}. ^{1}H NMR spectra were taken on a Varian (300 MHz) instrument using DMSO-d_6 or CF_3CO_2D solvent and TMS internal standard. Chemical shift values were measured with an accuracy of 0.001 ppm.

The starting dichloropyrazine **1** was synthesized using the method reported in [5].

Triethylamine Salt of 2-(3-Chloro-5,6-dicyano-2-pyrazinyl)malononitrile (2). Triethylamine (10.1 g, 0.1 mol) was added to a solution of the dichloropyrazine **1** (9.95 g, 50 mmol) and malonodinitrile (3.3 g, 50 mmol) in DMF (20 ml) at 10-15°C and the reaction mixture was stirred for 5 h at 30-40°C. With cooling, it was poured into water (200 ml) and the precipitate was filtered off and purified by boiling with chloroform. The yield and characteristics for the salt **2** are given in Table 1.

6-Amino-5-R-5H-pyrrolo[2,3-*b*]pyrazine-2,3,7-tricarbonitriles (3a-k). The corresponding primary amine (6 mmol) was added to a solution of the salt **2** (1 g, 3 mmol) in DMF (6 ml) and the mixture was stirred for 5 h at 50-60°C. It was then cooled, acidified with acetic acid (0.5 ml), the precipitate filtered off, and recrystallized from dioxane. The yields and characteristics for the compounds **3a-k** are given in Table 1.

5-Chloro-6-cyano(4-oxo-1,2,3,4-tetrahydro-2-quinazolylidene)methyl-2,3-pyrazinedicarbonitrile (5a) and 5-[6-Bromo-4-oxo-1,2,3,4-tetrahydro-2-quinazolylidene(cyano)methyl]-6-chloro-2,3-pyrazinedicarbonitrile (5b). Triethylamine (3.04 g, 30 mmol) was added to a solution of the dichloropyrazine **1** (5.97 g,

30 mmol) and the corresponding cyanomethylquinazolone **4a,b** (30 mmol) and the mixture was stirred for 8 h at 30-40°C (monitored by TLC). After 12 h the precipitate formed was filtered off and washed with a small amount of DMF and then water. The products **5a,b** obtained were chromatographically pure. An additional amount of material was separated from the filtrate and was purified by refluxing in dioxane. The yield and characteristics for the compounds **5a,b** are given in Table 2.

Isomeric Mixtures of 3-R^1-5-Oxo-5,6-dihydropyrazino[2',3':4,5]pyrrolo[1,2-a]quinazoline-7,9,10-tricarbonitrile (6a,b) and 8-R^1-6-Oxo-6,11-dihydropyrazino[2',3':4,5]pyrrolo[2,1-*b*]quinazoline-2,3,12-tricarbonitrile (7a,b). The corresponding compound **5a,b** (3 mmol) was refluxed in pyridine (15 ml), cooled, and the precipitate produced was filtered off, washed with water, and recrystallized from DMF. The reaction products obtained in 74% (R^1 = H) and 81% (R^1 = Br) yields were mixtures of isomers of **6** and **7**. For **6a, 7a** (R^1 = H). Found, %: N 31.25. $C_{16}H_5N_7O$. Calculated, %: N 31.50. For **6b, 7b** (R^1 = Br). Found, %: Br 20.66; N 25.21. $C_{16}H_4BrN_7O$. Calculated, %: Br 20.48; N 25.13.

6-Amino-5-R^2-7-(6-R^1-4-oxo-3,4-dihydro-2-quinazolyl)-5H-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles (8a-g). The corresponding primary amine (4 mmol) was added to a solution of compound **5a,b** (2 mmol) in DMF (6 ml) and the product was stirred for 5 h at 50-60°C and then left overnight. The precipitate formed was filtered off, washed with a small amount of DMF, then water, and recrystallized from DMF. The yields and characteristics for the heterocycles **8a-g** are given in Table 2.

REFERENCES

1. Yu. M. Volovenko and G. G. Dubinina, *Khim. Geterotsikl. Soedin.*, 1234 (1999).
2. Yu. M. Volovenko and G. G. Dubinina, *Khim. Geterotsikl. Soedin.*, in press.
3. B. Pilarski and H. Foks, Polish Patent 135250; *Chem. Abstr.*, **113**, 172054 (1990).
4. Yu. M. Volovenko, G. G. Dubinina, T. V. Shokol, and F. S. Babichev, *Dokl. Akad. Nauk Ukraine*, No. 10, 126 (1994).
5. T. Suzuki, Y. Nagae, and K. Mitsuhashi, *J. Heterocycl. Chem.*, **23**, 1419 (1986).