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SYNTHESIS OF CONDENSED PYRROLO[*b*]PYRAZINES

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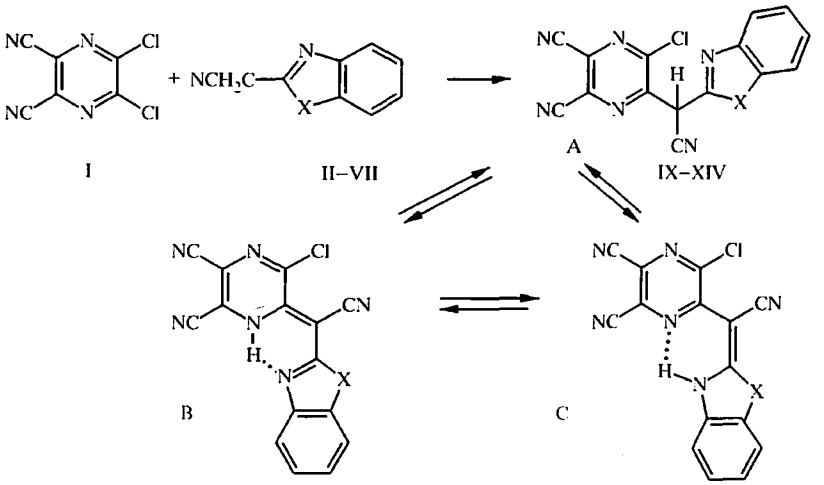
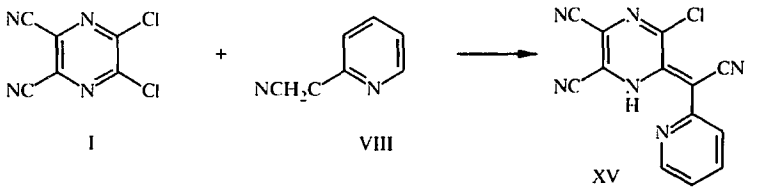
Reaction of 2,3-dichloro-5,6-dicyanopyrazine with α-azahetarylacetonitriles gives α-(3-chloro-5,6-dicyanopyrazin-2-yl)-α-(2-azahetaryl)acetonitriles. Subsequent heating in pyridine causes an intramolecular cyclization to yield condensed pyrrolo[b]pyrazines.

The reaction of α-azahetarylacetonitriles with 2,3-dichloroquinoxaline has been studied before. It was found that, under nucleophilic substitution conditions, annelation of the pyrrole ring occurs along the [*b*] edge of the quinoxaline [1]. The mobility of the halogen atoms in 2,3-dichloropyrazine is significantly less [2] than in 2,3-dichloroquinoxaline [3]. Introduction into the 2,3-dichloropyrazine molecule of two electron acceptor nitrile groups increases the nucleophilic reactivity of the chlorine atoms [4].

We have studied the reaction of 2,3-dichloro-5,6-dicyanopyrazine (I) with 2-cyanomethylbenzothiazole (II), 2-cyanomethylbenzimidazole (III), 1-alkyl-2-cyanomethylbenzimidazoles (IV-VI), 2-cyanomethylquinoline (VII), and 2-cyanomethylpyridine (VIII). In mild conditions (3-4 h in DMF at 30-40°C) substitution of one of the chlorine atoms occurs to give the dihetarylacetonitriles IX-XV. As might be expected, the greater basicity of the



II. IX X = S; III. X X = NH; IV. XI X = NMe;
V. XII X = NEt; VI. XIII X = NCH_2Ph; VII. XIV X = HC=CH



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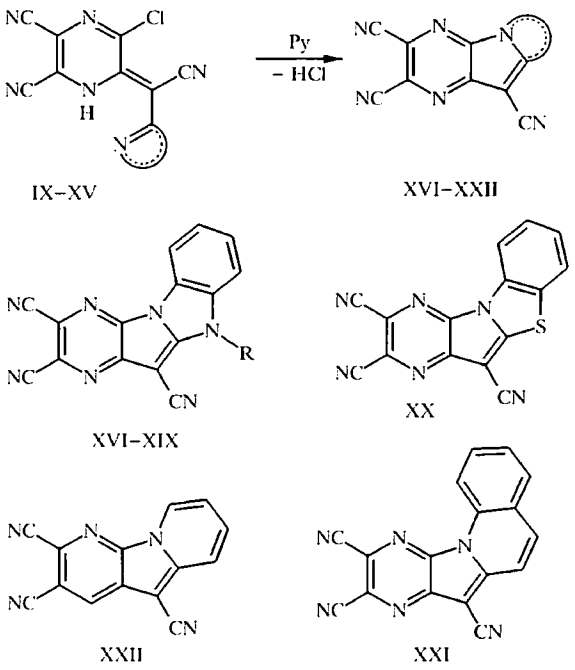
starting heterocycle leads to the more rapid and complete substitution and the deeper color of the final products. The slowest reaction occurs with benzothiazolylacetonitrile II having the lowest basicity (pK_a 1.2). Addition of an equivalent amount of triethylamine to the reaction mixture increases significantly the speed of the reaction. In dioxane at room temperature in the presence of the triethylamine the reaction does not reach completion, which lowers the yields and purity of the final products. The compounds obtained XI-XV can exist in the three tautomeric forms (A, B, and C).

The IR spectra of these compounds show characteristic absorption bands for the conjugated nitrile group at 2185-2195 cm^{-1} and a low intensity absorption band for the nitrile groups of the pyrazine ring at 2215-2225 cm^{-1}, which is typical of the starting compound I [4]. The PMR spectra (DMSO-d_6) of the dihetarylacetonitriles IX-XV show a chelate type NH proton signal in the region 9.91-14.53 ppm and the absence of a signal for the C–H proton of tautomer A. On the basis of the spectral data it can be concluded that the obtained compounds IX-XV exist principally in the tautomeric forms B and C. In the case of compound XV an unambiguous choice between tautomers B and C can be made. Hence, in the PMR spectrum of compound XV a pyridine ring α-proton can be observed at 8.5 ppm (1H, d, J = 6 Hz). If compound XV were to exist in the tautomeric form C then the signal of this pyridine ring α-proton should exist as a double doublet due to its coupling to the imine proton [5]. On this basis we propose that, in compound XV, the exchanging proton is found on the nitrogen of the pyrazine ring and this can only be realized in the tautomeric form B. In the PMR spectrum of the hetarylation product X of 2-cyanomethylbenzimidazole the N–H proton is combined as a broad two proton singlet at 13.03 ppm together with the four aromatic protons of the benzimidazole ring as two symmetrical signals at 7.35 and 7.66 ppm. This is possible for a symmetrical benzimidazole fragment structure of tautomeric form C in which both nitrogen atoms of the benzimidazole bear protons.



The structure of the hetarylation products IX-XV is characterized by the presence of two reactive centers, *viz.* nucleophilic at the nitrogen atom of the heterocycle and electrophilic at the carbon atom bonded to chlorine. On this basis we propose that the possibility exists for cyclization to occur *via* intramolecular arylation.

Attempts to carry out the cyclization of these compounds in dioxane in the presence of triethylamine or in DMF with potash were unsuccessful. The best results were obtained by refluxing their pyridine solutions.

TABLE 1. Characteristics for Compounds IX-XV*

Compound	Empirical formula	Found, % / Calculated, % C	Found, % / Calculated, % N	PMR Spectrum, δ, ppm, DMSO-d_6	Yield, %
IX*[2]	$C_{15}H_5ClN_6S$	10.15 / 10.53	25.13 / 24.96	10.22 (1H, s, N–H); 8.2-7.5 (4H, m, Ar–H)	95
X	$C_{15}H_6ClN_7$	10.82 / 11.08	30.25 / 30.67	13.03 (2H, s, N–H) 7.66 (2H, m, 4,7-H benzimidazole) 7.35 (2H, m, 5,6-H benzimidazole)	75
XI	$C_{16}H_8ClN_7$	10.48 / 10.62	29.08 / 29.38	14.2 (1H, s, N–H); 8.1-7.5 (4H, m, Ar–H) 3.75 (3H, s, CH_3)	91
XII	$C_{17}H_{10}ClN_7$	10.08 / 10.19	28.33 / 28.20	14.2 (1H, s, N–H); 8.1-7.5 (4H, m, Ar–H) 4.42 (2H, q, CH_2); 1.43 (3H, t, CH_3)	70
XIII	$C_{22}H_{12}ClN_7$	8.56 / 8.65	23.84 / 23.93	13.3 (1H, s, N–H); 7.8-7.2 (9H, m, Ar–H) 5.64 (2H, s, CH_2)	87
XIV	$C_{17}H_7ClN_6$	10.58 / 10.72	24.99 / 25.41	9.91 (1H, s, N–H); 9.43 (1H, d, 8-H quinoline) 8.3-7.5 (5H, m, Ar–H) 3.75 (3H, s, CH_3)	82
XV	$C_{13}H_5ClN_6$	12.24 / 12.63	30.70 / 29.94	8.5 (1H, d, 6-H pyridine); 8.5-8.3 (1H, m, 5-H) 8.2-8.1 (1H, m, 4-H); 7.5 (1H, d, 3-H)	79

* Mp for compounds IX-XIV presumably >300°C, XV 278-280°C.
*[2] Found, %: S 9.61. Calculated, %: S 9.52.

In this way we obtained high yields of the cyclization products XVI-XXII which occur as yellow substances, fluorescing in solution. A weakening of the color was noted when compared with the starting materials on account of the decrease in the conjugative chain. The cyclizations were particularly easy in the case of the benzimidazole derivatives XI-XIII. In the PMR spectra (DMSO-d_6) of the obtained cyclization products XVI-XXII

TABLE 2. Characteristics for Compounds XVI-XXII*

Compound	Substituent R	Empirical formula	Found, % / Calculated, % N	PMR Spectrum, δ, ppm, DMSO-d_6	Yield, %
XVI	H	$C_{15}H_5N_7$	34.25 / 34.62	10.1 (1H, s, N–H); 8.15 (1H, dd, 10-H); 7.7-7.5 (3H, m, 7,8,9-H)	62
XVII	CH_3	$C_{16}H_7N_7$	33.19 / 32.98	8.2 (1H, m, 10-H); 7.95 (1H, m, 7-H); 7.7-7.5 (2H, m, 8,9-H) 4.07 (3H, s, CH_3);	90
XVIII	C_2H_5	$C_{17}H_9N_7$	31.87 / 31.50	8.25 (1H, m, 10-H); 8.0 (1H, m, 7-H); 7.7-7.5 (2H, m, 8,9-H) 4.59 (2H, q, CH_2); 1.55 (3H, t, CH_3)	95
XIX	CH_2Ph	$C_{22}H_{11}N_7$	26.74 / 26.26	5.79 (2H, s, CH_2); 7.9 (1H, dd, 7-H) 8.25 (1H, dd, 10-H); 7.7-7.3 (7H, m, 8,9-H, Ph)	80
XX*[2]		$C_{15}H_4N_6S$	27.95 / 27.99	8.6 (1H, dd, 10-H); 8.32 (1H, dd, 7-H); 7.85 (1H, t, 9-H) 7.7 (1H, t, 8-H)	83
XXI		$C_{17}H_6N_6$	28.56 / 28.56	9.5 (1H, d, 1-H) 8.4-7.7 (5H, m, Ar-H)	79
XXII		$C_{13}H_4N_6$	34.62 / 34.41	9.4 (1H, d, 6-H); 8.1 (2H, m, 7,8-H) 7.48 (1H, m, 9-H)	71

* Mp for compounds XVI-XXII presumably >300°C, recrystallized from DMF.
*[2] Found, %: S 10.78. Calculated, %: S 10.68.

the exchangeable proton signal was absent and the signals of the aromatic protons were shifted to low field. Cyclization results in a rigid heterocyclic structure, as a result of which some of the heterocyclic protons fall in the region of deshielding by the nitrogen atom of the pyrazine ring.

The signal for the proton at position 6 in the compounds XVI-XIX was found at 8.1-8.3 ppm as a doublet or poorly resolved double doublet and, in the case of compound XX, at 8.6 ppm. A still larger chemical shift for this proton is observed in the case of other compounds, *viz.* XXI 9.5 ppm (1H, d, 1-H, J = 8 Hz), XXII 9.4 ppm (1H, d, 6-H, J = 7 Hz). The IR spectra of the obtained substances XVI-XXII showed absorption bands for the nitrile groups falling together as a single band of moderate intensity at 2200-2210 cm^{-1}.

The obtained 2,3,5-tricyanobenzothiazolo[3',2':1,2]pyrrolo[2,3-*b*]pyrazine system XX is a representative of a novel class of heterocyclic system.

EXPERIMENTAL

Monitoring of the reaction course and the purity of the synthesized compounds was carried out chromatographically on Silufol UV-254 plates in the system chloroform-methanol (9:1). IR spectra were recorded on a Pye Unicam instrument in the region 4000-400 cm^{-1} in KBr tablets. PMR spectra were taken for DMSO-d_6 solutions on a WP 100 instrument (frequency 100 MHz) relative to TMS internal standard. Chemical shift values were measured with an accuracy of 0.01 ppm.

The starting 2,3-dichloro-5,6-dicyanopyrazine was prepared according to method [4].

α-(3-Chloro-5,6-dicyanopyrazin-2-yl)-α-(2-azahetaryl)acetonitriles (IX-XV). A solution of the dichlorodicyanopyrazine I (1 g, 5.25 mmol) and the corresponding hetarylacetonitrile (III-VIII, 5.25 mmol) in DMF (7 ml) was stirred at 30-40°C for 3-4 h, the reaction being monitored by TLC. After 12 h the precipitate formed was filtered off and washed with a small amount of DMF and water. Chromatographically pure materials IX-XIII were obtained in 51-81% yield. Upon dilution of the filtrate with water, an additional amount of the material was isolated and it was purified by refluxing in dioxane. The overall yield 70-91%.

α-(3-Chloro-5,6-dicyanopyrazin-2-yl)-α-(benzothiazol-2-yl)acetonitrile (IX) was synthesized by the method described above but in the presence of an equimolar amount of triethylamine. The parameters and yields for compound IX-XV are given in Table 1.

Intramolecular Cyclization of α-(3-Chloro-5,6-dicyanopyrazin-2-yl)-α-(2-azahetaryl)acetonitriles (IX-XV), 2,3,5-Tricyano-6-R-6-H-benzimidazo[1',2':1,2]pyrrolo[2,3-*b*]pyrazines (XVII-XIX), and 2,3,12-Tricyanopyrazino[2',3':4,5]pyrrolo[1,2-*a*]quinoline (XXI). A solution of the corresponding compound XI-XIV (0.575 mmol) was refluxed for 3 h in pyridine (4 ml), cooled, filtered, and the precipitate was washed with a small amount of pyridine, water, and hydrochloric acid (3%). The gathered pyridine filtrate was evaporated in vacuo, water (15 ml) added, acidified with hydrochloric acid (1 ml), and an additional amount of the cyclization product was filtered off. After recrystallization from DMF the overall yield 80-95%.

2,3,5-Tricyano-6-H-benzimidazo[1',2':1,2]pyrrolo[2,3-*b*]pyrazine (XVI). A suspension of compound X (0.64 g, 2 mmol) was refluxed for 30 min in pyridine (10 ml) and then heated for 5 h on a boiling water bath. The pyridine was evaporated in vacuo, water was added to the residue, and it was acidified with hydrochloric acid (2 ml). The precipitated compound XVI was filtered off.

2,3,5-Tricyanobenzothiazolo[3',2':1,2]pyrrolo[2,3-*b*]pyrazine (XX). A suspension of substance IX (0.84 g, 2.5 mmol) in pyridine (15 ml) was heated for 4 h on a boiling water bath. The reaction product (XX) was separated as for compound XVI. After recrystallization from DMF the yield 83%.

Pyrazino[2,3-*b*]indolizine-2,3,10-tricarbonitrile (XXII). A suspension of compound XV (0.73 g, 3 mmol) in dry pyridine (10 ml) was refluxed for 3 h, triethylamine (0.45 ml, 3.3 mmol) was added, and the product was refluxed for a further 3 h. Separation of the reaction product was similar to the above.

The characteristics and yields for compound XVI-XXII are given in Table 2.

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