EXPERIMENTAL

The IR spectra of solutions of IIa-g in chloroform were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Spectromom-202 spectrophotometer. The ionization constants in the sulfuric acid–water system were determined by spectrophotometry with the same spectrophotometer for $2 \cdot 10^{-5}$ M solutions at 20 ±1°C. The analytical wavelength corresponded to the maximum at 374-392 nm. The equation $pK_R^+ = H_R + \log([IV]/[III])$ was used to find the pK_R^+ values. The pK_R^+ value was found from seven points with a predesignated reliability of 0.98. The results were treated by the method of least squares.

2-R-3-Methyl-8-R'-10-phenyl-10-hydroxy-10H-pyrido[2,3-b]chromenes (IIa-g). A 20-ml sample of concentrated sulfuric acid was added to a solution of 3.5 mmole of Ia-g in 10 ml of acetic acid, and the mixture was heated on a water bath for 1-6 h. It was then poured into water, and the aqueous mixture was neutralized with sodium carbonate. The precipitate was removed by filtration and crystallized from ethanol. This method was used to obtain IIa-g.

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6-AMINO-5-CYANO-1H,4H-PYRAZOLO[3,4-b]PYRANS

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The reaction of 3-methyl-1-phenyl-5-pyrazolene with arylideneamino nitriles in alcohol leads to the formation of 3-methyl-4(1-aryl-2,2-dicyanoethyl)-5-pyrazolones, which are readily cyclized in the presence of bases to the corresponding 6-amino-5-cyano-3-methyl-4-aryl-1H,4H-pyrazolo[3,4-b]pyrans. The structures of the intermediate and final products were confirmed by the IR, UV, PMR, and mass spectra.

Some derivatives of 2-aminopyrans [1], as well as condensed 2-amino-3-cyanopyrans [2], are pharmacologically active compounds. They have been tested as pesticides [3] and have been proposed as medicinal preparations that have antiallergenic and antiasthmatic activity [2]. 2-Aminopyrans obtained on the basis of 1,3-dicarbonyl compounds and unsaturated nitriles with an active double bond are known [4]. However, very little study has thus far been devoted to 6-aminopyrazolo[3,4-b]pyrans. A single representative of this series, viz., 6-amino-1-phenyl-4,4,5-tricyano-1H,4H-pyrazolo[3,4-b]pyran, which was obtained by the reaction of 3-methyl-1-phenyl-5-pyrazolone with tetracyanoethylene by heating the components in alcohol, has been described in the literature [5]. However, the method does not make it possible to vary the substituents in various positions of the pyran ring. The scope of the method have been extended substantially by a recently published paper [3] in which the addition of malononitrile to 4-arylidene-3-methyl-1-phenyl-5-pyrazolines was studied.

We have developed a simple convenient method for the preparation of 6-amino-5-cyano-3-methyl-1H,4H-pyrazolo[3,4-b]pyrans that consists in the reaction of 3-methyl-1-phenyl-5-pyrazolone with arylidene-malononitriles (method A). It can be recommended for preparative purposes.

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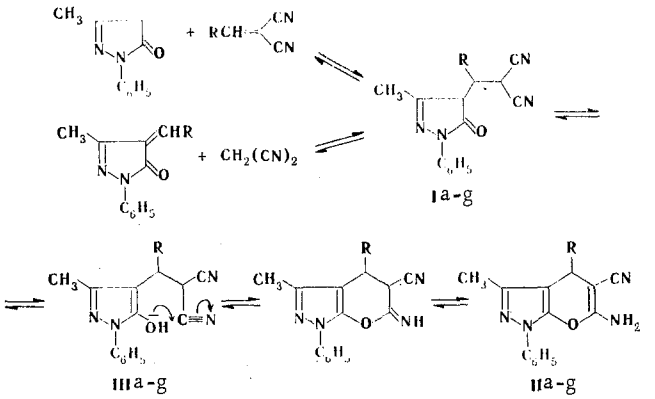
Scheme 1



a R = C_6H_5; b R = 4-FC_6H_4; c R = 4-ClC_6H_4; d R = 4-BrC_6H_4; e R = 2-ClC_6H_4;
f R = 4-$CH_3O$$C_6H_4$; g R = 3-$O_2N$$C_6H_4$

It is expedient to carry out the reaction of 5-pyrazolones with arylidenemalononitriles with an equimolar ratio of the starting components in methanol (preferably absolute) in the presence of catalytic amounts of an organic base (morpholine, diethylamine, piperidine, etc.) at 30-40°C. Under these conditions the final products were isolated in high yields that approached quantitative values. The reaction proceeds through a step involving the formation of 3-methyl-1-phenyl-4-(1-aryl-2,2-dicyanoethyl)-5-pyrazolones (I), which were isolated in the reaction of the reagents in a neutral medium.

In contrast to the UV spectra of cyclic pyrazolopyrans II, the UV spectra of I contain three absorption maxima. Thus 3-methyl-1-phenyl-4-(1-phenyl-2,2-dicyanoethyl)-5-pyrazolone (Ia) absorbs at 207 (log ε 4.43), 245 (log ε 4.19), and 273 nm (log ε 4.13). The UV spectra of Ib and Ig contain absorption maxima at, respectively, 208 (4.46), 246 (4.27), and 270 (4.23) and 207 (4.44), 247 (4.24), and 269 nm (4.24). Substantial differences are observed in the IR spectra of I and II. The IR spectra of pyrazolones Ia-g contain a weak absorption band of stretching vibrations of a cyano group at 2257-2260 cm^{-1}; this is characteristic for unconjugated nitriles. To confirm the structures of the cyclic and noncyclic compounds we recorded their PMR spectra, which showed that pyrazolones Ia-g exist [at least in solution in dimethyl sulfoxide (DMSO)] in equilibrium with the tautomeric 5-hydroxy-3-methyl-1-phenyl-4-(1-aryl-2,2-dicyanoethyl)pyrazole form (III). The ratio of these forms in the investigated examples ranges from 4:1 to 6:1. The PMR spectra of IIa-g contain two doublets of methylidyne protons [$(CN)_2CH$ and Ar_2CH] at 5.8-6.1 (d) and 4.7-5.1 (d) ppm with $J \approx 7.6$ Hz. The signal of the protons of the $(CN)_2CH$ group is complicated by superimposition of the signal of the methylidyne group of pyrazolone, the intensity of which, as noted above, is low. In addition, the PMR spectra of these compounds contain signals of protons of a methyl group at 2.1-2.3 ppm (s, 3H) and of a benzene ring at 7.2-8.2 ppm (m, 4H). Moreover, the spectrum of 3-methyl-1-phenyl-4-[1-(3-nitrophenyl)-2,2-dicyanoethyl]-5-pyrazolone contains a signal at 8.58 ppm, which confirms the Ig $\rightleftarrows$ IIIg equilibrium. However, a signal of a hydroxy proton is not observed in the PMR spectra of Ia-f, evidently as a consequence of rapid exchange with the protons of the water that is present in the solvent. For a clearer interpretation of the PMR spectra we synthesized 3-methyl-4[1-(4-tolyl)-2,2-dicyanoethyl]-5-pyrazolone. Signals of protons at 2.02 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 4.50 (doublet of a dicyanomethyl group), 5.43 (d, 1H, $J = 6.9$ Hz, Ar_2CH), 7.08 (d, 2H, aromatic CH), and 7.27 ppm (d, 2H, $J =$ 5.1 Hz, aromatic CH) are observed in the PMR spectrum of this compound.

The isolated 4-(2,2-dicyanoethyl)-5-pyrazolones Ia-g undergo cyclization smoothly to give the corresponding 6-amino-5-cyano-1-phenyl-4-aryl-1H,4H-pyrazolo[3,4-b]pyrans II (method B) in virtually quantitative yields under identifal conditions under the influence of organic bases.

Compounds II can also be obtained by three-component condensation of equimolar amounts of 3-methyl-1-phenyl-5-pyrazolone, an aromatic aldehyde, and malononitrile in methanol in the presence of morpholine (method C). In this case the aldehyde condenses with malononitrile in the first step of the reaction with subsequent Michael addition of the 5-pyrazolone to the resulting unsaturated nitrile in complete conformity with method A. The first step of the reaction may also be Knoevenagel reaction of the 5-pyrazolone with the aromatic aldehyde and subsequent addition of malononitrile to the resulting 4-arylidene-5-pyrazolone [3] to give the corresponding pyrans. The reaction may take place in both directions simultaneously. It is presently impossible to choose between these pathways. However, it can be emphasized with complete confidence that the intermediates in all of the examined cases are pyrazolones I. Enolization (I $\rightleftarrows$ III) evidently plays an important role in this case. The possibility of the isolation of pyrazolones I is excluded in [3], since the reaction is

TABLE 1. Relative Intensities of the Peaks of the Characteristic Ions in the Mass Spectra of Pyrazolopyrans IIa, c, g (in percent of the maximum peak)

Ions	Compound					
	IIa		IIc		IIg	
	m/z	I	m/z	I	m/z	I
M^+	3,2	326	2,5	362	2,8	373
F_1	100,0	262	100,0	296[a]	100,0	307
$[F_1-H]^+$	29,7	261	14,0	295	8,2	306
$[M-R]^+$	6,8	251	3,0	251	16,2	251
F_4	91,8	185	88,0	185	96,2	185
F_2	20,2	174	17,2	174	30,0	174
$[F_2-C_2H_2O]$	5,6	132	3,6	132	5,0	132
F_3	16,2	129	16,3	163	6,1	173
$[F_3-H]^+$	22,0	128	7,0	162	3,0	172
$[F_3-CN]^+$	14,8	103	6,0	137	2,5	147
$[F_3-HCN]^+$	7,0	102	5,8	136	2,5	146
$C_6H_5N_2^+$	10,8	105	8,6	105	16,2	105
$C_6H_5N^+$	32,4	91	29,1	91	42,5	91
$C_6H_5^+$	60,7	77	62,3	77	80,0	77

[a]The mass of the ion containing the principal isotope is given.

carried out in the presence of bases. One should also take into account the fact that an equilibrium between 5-pyrazolone I and aminopyrazolone II, which is shifted to favor the formation of cyclic product II when the temperature is raised, may be established in a neutral medium.

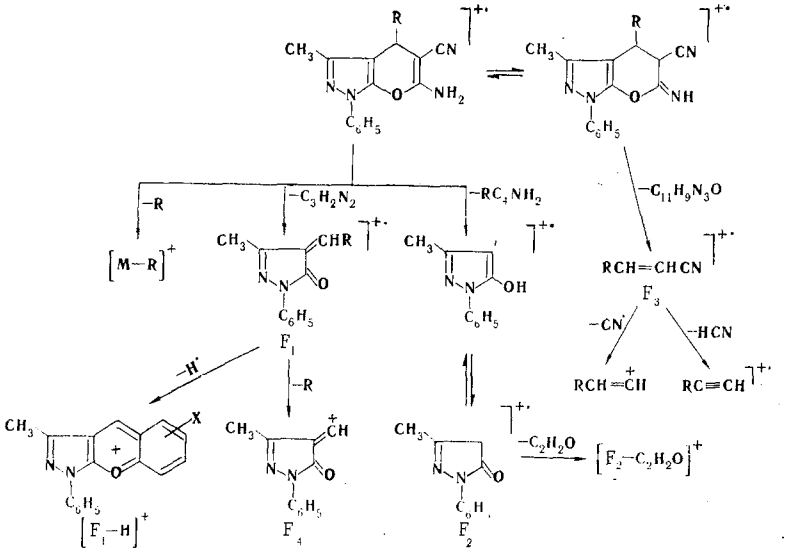
The 6-aminopyrazolo[3,4-b]pyrans IIa-g obtained by methods A-C and by the method in [3] are completely identical. Their structures were confirmed by various spectroscopic data. The UV spectra of pyrans IIb, g contain only two absorption maxima. For example, 6-amino-5-cyano-3-methyl-1-phenyl-4-(4-fluorophenyl)pyrazolo[3,4-b]pyran (IIb) absorbs at 209 (log ε 4.39) and 253 nm (log ε 4.31). 6-Amino-5-cyano-3-methyl-1-phenyl-4-(3-nitrophenyl)-1H,4H-pyrazolo[3,4-b]pyran (IIg) has corresponding maxima at 209 (log ε 4.02) and 252 nm (log ε 3.94). Characteristic absorption bands are present in the IR spectra of IIb, g. The position and high intensity of the absorption band of stretching vibrations of a nitrile group at 2190-2200 cm^{-1} make it possible to speak of the presence of a conjugated nitrile group in the molecule. In addition, as compared with the spectra of noncyclic products Ia-g, absorption bands of stretching vibrations of free and associated amino groups at 3170-3450 cm^{-1}, deformation vibrations of an amino group at 1650-1660 cm^{-1}, and stretching vibrations of the C–O–C group of the pyran ring at 1130-1150 cm^{-1} appear in the IR spectra. The PMR spectra of pyrazolopyrans IIa-g contain signals of aromatic protons at 7.2-7.8 ppm, a broad signal of protons of an amino group at 5.8-6.9 ppm, a singlet of a 4H proton at 4.3-4.9, and a singlet of protons of a methyl group at 2.2-2.4 ppm. The integral curve gives a ratio between the intensities of these forms of protons of 10(9) : 2 : 1 : 3, respectively.

A low-intensity molecular-ion (M^+) peak is recorded in the mass spectra of the synthesized 6-aminopyrazolo[3,4-b]pyrans. The principal pathway of its fragmentation involves retrodiene fragmentation of the γ-pyran ring, as a result of which a stable ion radical with a pyrazole structure with an exocyclic bound in the 4 position is formed (Scheme 1, F_1 ion). The intensity of the F_1 ion peaks is maximal in the mass spectra (Table 1). A similar fragmentation pathway is characteristic for dihydropyrans [6, 7]. It proves the presence and position of the amino and nitrile groupings in the γ-pyran ring. Characteristic (in the case of a tetrahedral carbon atom in the molecule [8, 9]) detachment of R from M^+ makes a less significant contribution to the total ion current.

Two other pathways of fragmentation of the γ-pyran ring occur simultaneoulsy with the indicated processes involving the fragmentation of M^+. The first of them involves cleavage of the pyran ring at the C_2-C_3 and C_4-C_5 bonds with the formation of a stable $RCH=CHCN^{+\cdot}$ cation radical. This pathway suggests isomerization of the starting M^+ with the formation of the imine form. The second process, viz. cleavage of the C_2-O and C_4-C_5 bonds, leads to the formation of a 3-methyl-1-phenyl-5-pyrazolone pseudomolecular ion (F_2). The subsequent fragmentation of this rearranged ion is known, and there are therefore no complications in the interpretation of the daughter fragment ion with m/z 132, 105, 91, and 77 [10, 11].

Thus the character of the fusion of the γ-pyran ring and the pyrazolone ring in the molecule is confirmed by the presence of F_1 and F_2 ion peaks in the mass spectra.

Scheme 2



The compositions of the ions indicated in the scheme were confirmed by their high-resolution mass spectra.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with UR-20 and Perkin–Elmer spectrometers. The UV spectra were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in deuterodimethyl sulfoxide–carbon tetrachloride (5 : 1) were recorded with a Tesla BS-487C spectrometer (80 MHz) with tetramethylsilane as the internal standard. The high-resolution mass spectra were recorded with a Varian MAT-112 spectrometer under standard conditions, viz. an ionizing voltage of 70 V and an ion-source temperature of 170-190°C. The individuality of the synthesized compounds was monitored by chromatography on Silufol UV-254 plates [elution with hexane–acetone (5 : 3)].

3-Methyl-1-phenyl-4-(1-aryl-2,2-dicyanoethyl)-5-pyrazolones (I). A 0.01-mole sample of the arylidenemalononitrile was added to a suspension of 0.01 mole of 3-methyl-1-phenyl-5-pyrazolone in 60-85 ml of absolute methanol, and the reaction mixture was stirred until the solid material dissolved (in the case of slightly soluble products with heating at no higher than 35-40°C), after which it was allowed to stand for crystallization. The precipitate was removed by filtration, washed with methanol, and dried. The substances obtained by this method were analytically pure (Table 2). We were able to recrystallize them from nitromethane. However, this was not required in the case of sufficiently pure starting reagents, especially since they underwent cyclization to the corresponding pyrazolopyrans II under the influence of heat.

TABLE 2. 3-Methyl-1-phenyl-4-(1-aryl-2,2-dicyanoethyl)-5-pyrazolones (I) and 6-Amino-5-cyano-3-methyl-4-aryl-1H,4H-pyrazolo-[3,4-b]pyrans (II)

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Hal	N		C	H	Hal	N	
Ia	173—174	73,4	5,0		17,0	$C_{20}H_{16}N_4O$	73,1	4,9		17,1	96
Ib	169—170	69,0	4,2	5,4	16,0	$C_{20}H_{15}FN_4O$	69,3	4,4	5,5	16,2	93
Ic	192—193	66,0	4,0	9,5	15,8	$C_{20}H_{15}ClN_4O$	66,2	4,2	9,8	15,5	90
Id	187—188	58,6	3,9	19,2	13,9	$C_{20}H_{15}BrN_4O$	59,0	3,7	19,6	13,8	95
Ie	164—165	66,1	4,3	9,6	15,6	$C_{20}H_{15}ClN_4O$	66,2	4,2	9,8	15,5	94
If	161—162	73,6	5,1		16,4	$C_{21}H_{18}N_4O_2$	73,6	5,3		16,4	92
Ig	192—193	64,5	4,2		18,9	$C_{20}H_{15}N_5O_3$	64,3	4,0		18,8	94
IIa	167—168[a]	73,0	4,8		17,3	$C_{20}H_{16}N_4O$	73,1	4,9		17,1	93
IIb	176—177	69,1	4,4	5,3	16,3	$C_{20}H_{15}FN_4O$	69,3	4,4	5,5	16,2	94
IIc	186—187[b]	66,3	4,2	9,6	15,6	$C_{20}H_{15}ClN_4O$	66,2	4,2	9,8	15,5	90
IId	184—185	58,8	3,6	19,3	13,7	$C_{20}H_{15}BrN_4O$	59,0	3,7	19,6	13,8	98
IIe	159—160	66,4	4,3	9,7	15,7	$C_{20}H_{15}ClN_4O$	66,2	4,2	9,8	15,5	85
IIf	177—178	73,4	5,0		16,5	$C_{21}H_{18}N_4O_2$	73,6	5,3		16,4	88
IIg	178—179	64,2	3,8		18,6	$C_{20}H_{15}N_5O_3$	64,3	4,0		18,8	91

[a]According to the data in [3], this compound had mp 175-177°C. [b]According to the data in [3], this compound had mp 182-184°C.

6-Amino-5-cyano-1-phenyl-4-aryl-1H,4H-pyrazolo[3,4-b]pyrans (II). A) A 0.1-0.3 ml sample of morpholine was added to a suspension of 0.1 mole of 3-methyl-1-phenyl-5-pyrazolone and 0.01 mole of the arylidenemalononitrile in 50-60 ml of methanol, and the mixture was heated until the starting reagents dissolved (possibly up to the boiling point) and allowed to stand at 20°C overnight. The precipitate was removed by filtration and washed with methanol. Recrystallization from nitromethane or ethyl acetate–alcohol gave 6-aminopyrazolo[3,4-b]pyrans II (Table 2).

6-Amino-5-cyanopyrazolo[3,4-b]pyrans II were obtained under similar conditions by method B by cyclization of 3-methyl-1-phenyl-4-(1-aryl-2,2-dicyanoethyl)-5-pyrazolones I and by method C from 5-pyrazolone, aromatic aldehydes, and malononitrile. Pyrazolopyrans IIc and IIg were obtained by the method in [3] by alternative synthesis under identical conditions from 3-methyl-1-phenyl-4-arylidene-5-pyrazolones.

The yields of pyrazolo[3,4-b]pyrans obtained by these methods differ only slightly, and the data for method A are therefore presented in Table 2.

3-Methyl-4-[1-(4-tolyl)-2,2-dicyanoethyl]-5-pyrazolone. A mixture of 0.01 mole of 3-methyl-5-pyrazolone and 0.01 mole of 4-methylbenzylidenemalononitrile in 50 ml of methanol was stirred with heating to 40°C until the starting reagents dissolved completely. The reaction mixture was then allowed to stand at room temperature for 4 h. The precipitate was removed by filtration, washed with methanol, and dried to give colorless crystals with mp 208-209°C and R_f 0.18 in 73% yield. IR spectrum: 3400 (NH) and 2255 cm^{-1} (CN). Found: C 67.5; H 5.1; N 20.8%. $C_{15}H_{14}N_4O$. Calculated: C 67.7; H 5.3; N 21.0%.

6-Amino-5-cyano-3-methyl-4-(4-tolyl)-1H,4H-pyrazolo[3,4-b]pyran. A 0.2-ml sample of morpholine was added to a mixture of 0.01 mole of 3-methyl-4-[1-(4-tosyl)-2,2-dicyanoethyl]-5-pyrazolone or 0.01 mole of 3-methyl-5-pyrazolone and 0.01 mole of 4-methylbenzylidenemalononitrile in 50 ml of methanol, and the mixture was heated to the boiling point and allowed to stand for crystallization. After 3 h, the precipitate was removed by filtration, washed with alcohol, and dried to give a product with mp 197°C and R_f 0.28 in 82% yield. IR spectrum: 3150-3410 (NH and NH_2), 2200 (shoulder), 2182 (conjugated CN), 1640 (NH_2), and 1148 cm^{-1} (COC). PMR spectrum: 11.90 (s, 1H, NH), 7.28 (d, 2H, aromatic CH), 7.07 (d, 2H, aromatic CH), 6.60 (s, 2H, NH_2), 4.58 (s, 1H, 4-H), 2.15 (s, 3H, CH_3), and 1.81 ppm (s, 3H, CH_3). Found: C 67.7; H 5.3; N 20.9%. $C_{15}H_{14}N_4O$. Calculated: C 67.7; H 5.3; N 21.0%.

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