Chemistry of Heterocyclic Compounds, Vol. 40, No. 2, 2004

NOVEL APPROACHES TO SYNTHESIS OF 4-ALKYL-6-AMINO-5-CYANO-3-METHYL(PROPYL, PHENYL)-2H,4H-PYRANO[2,3-*c*]PYRAZOLES

V. D. Dyachenko[1] **and E. B. Rusanov**[2]

We have obtained 4-alkyl-6-amino-5-cyano-3-methyl(propyl, phenyl)-2H,4H-pyrano[2,3-c]pyrazoles by reaction of 4-alkylmethylene-3-substituted 5-pyrazolones with malononitrile or cyanothioacetamide. We have used X-ray diffraction to study the structure of 6-amino-5-cyano-4-isopropyl(hexyl)-3-phenyl-2H,4H-pyrano[2,3-c]pyrazoles.

Keywords: 4-alkylmethylene-3-substituted 5-pyrazolones, 4-alkyl-6-amino-5-cyano-3-methyl(propyl, phenyl)-2H,4H-pyrano[2,3-*c*]pyrazoles, malononitrile, cyanothioacetamide, Michael reaction.

4-Aryl(hetaryl)-substituted pyrano[2,3-*c*]pyrazoles have been obtained by reaction of aryl(hetaryl)-methylenemalononitriles with 5-pyrazolone [1-4]. We have proposed a modified method for synthesis of 4-alkyl-substituted pyrano[2,3-*c*]pyrazoles, involving three-component condensation of aliphatic aldehydes, malononitrile, and 3-methyl-5-pyrazolone [5] (Scheme 1).

In this paper, we consider novel variants of the synthesis of 4-alkyl-6-amino-5-cyano-3-methyl(propyl, phenyl)-2H,4H-pyrano[2,3-*c*]pyrazoles **1**, involving the reaction of 4-alkylidene-substituted 5-pyrazolones **2** with cyanothioacetamide **3** (method A) or malononitrile **4** (method B) in ethanol in the presence of morpholine. Both routes probably include formation of the corresponding Michael adducts **5** and **6**, regioselectively undergoing ring closure under the reaction conditions to form the substituted pyrano[2,3-*c*]pyrazoles **1**.

Condensation of 3-methyl-4-(3'-pentylmethylene)-5-pyrazolone (**7**) with cyanothioacetamide **3** leads to formation of substituted 1H,4H-pyrano[2,3-*c*]pyrazole (**8**) (Scheme 2). Physicochemical and spectral study methods support the structure of compound **8** (Tables 1, 2) specifically as a 1H,4H-pyranopyrazole structure.

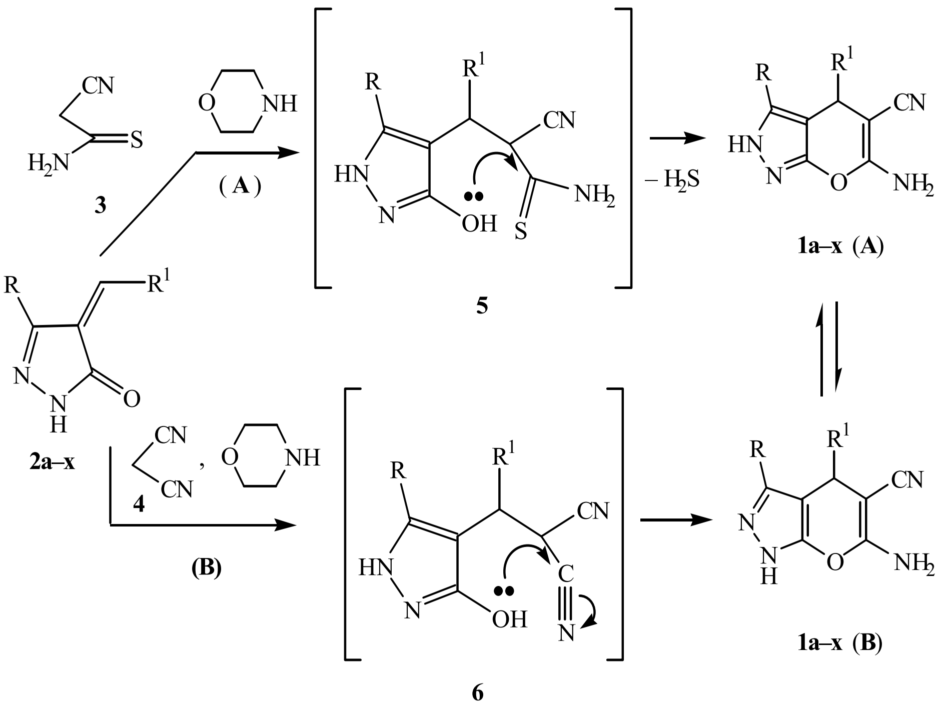
At the same time, these arguments are not convincing as evidence for the structure of systems **1**, because the ^{1}H NMR spectra obtained are not inconsistent with either structures **1A** or their prototropic isomers **1B**. We have discussed this problem earlier in [5].

In order to establish the regioselectivity of the condensation of 4-alkylmethylidene-3-methyl(propyl, phenyl)-5-pyrazolones **2** with CH-acids **3** and **4** and to unambiguously resolve the question concerning the structure of its products **1**, we used X-ray diffraction to study 6-amino-5-cyano-4-hexyl-3-phenyl-2H,4H-pyrano[2,3-*c*]pyrazole (**1a**) and 6-amino-5-cyano-4-isopropyl-3-phenyl-2H,4H-pyrano[2,3-*c*]pyrazole (**1k**).

---

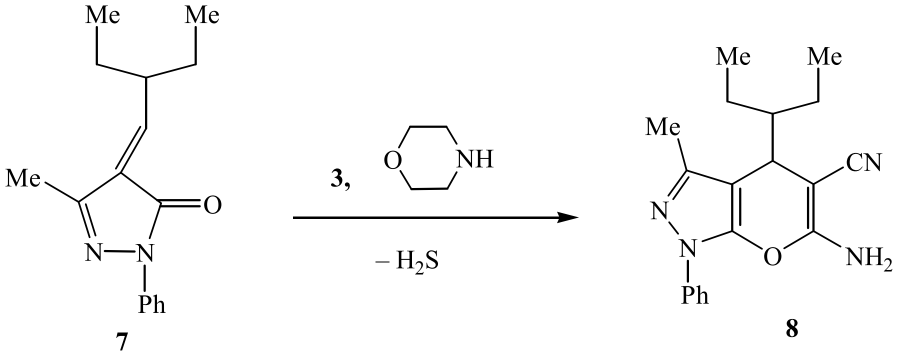
[1] Taras Shevchenko Lugansk State Pedagogical University, Lugansk 91011, Ukraine; e-mail: dvd_lug@online.lg.ua. [2] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02094; e-mail: iochkiev@ukrpak.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 270-281, February, 2004. Original article submitted June 13, 2001; revision submitted February 20, 2003.

Scheme 1



1, **2 a, b, k–q**,**u**,**v** R = Ph, **c–h**,**t**,**w**, **x** R = Me, **i**, **j**, **r** R = Pr; **a** R^1 = Me(CH$_2$)$_5$, **b** R^1 = Me$_2$CHCH$_2$,
c R^1 = cyclohexyl, **d** R^1 = 2-butyl, **e** R^1 = 2-pentyl, **f** R^1 = Me(CH$_2$)$_8$, **g** R^1 = Ph(CH$_2$)$_2$,
h R^1 = Me(CH$_2$)$_{10}$, **i** R^1 = Me$_2$CH, **j** R^1 = cyclohexyl, **k** R^1 = Me$_2$CH, **l** R^1 = MeCHPh,
m R^1 = Me(CH$_2$)$_8$, **n** R^1 = Et$_2$CH, **o** R^1 = cyclohexyl, **p** R^1 = 3-cyclohexyl, **q** R^1 = PhCH$_2$,
r R^1 = 3-cyclohexyl, **s** R^1 = Ph(CH$_2$)$_2$, **t** R^1 = 3-cyclohexyl, **u** R^1 = 2-pentyl, **v** R^1 = 2-butyl, **w** R^1 = MeCHPh, **x** R^1 = PhCH$_2$

Scheme 2



A general view of molecules **1a** and **1k** is shown in Figs. 1 and 2; the basic geometric parameters are given in Tables 3 and 4.

The central bicyclic system $O_{(1)}N_{(3)}N_{(4)}C_{(1-5,7)}$ for both compounds is practically flat: the deviations of the atoms from the mean-square plane are no greater than 0.123(3) Å, the dihedral angle between the five-membered heterocycle $N_{(3)}N_{(4)}C_{(4)}C_{(5)}C_{(7)}$ and the six-membered ring $O_{(1)}C_{(1-5)}$ is only 5.8° for **1a** and 3.5° for **1k**. The $N_{(1)}$, $C_{(6)}$, $C_{(8)}$, and $C_{(14)}$, $C_{(10)}$ atoms deviate from the central plane respectively by -0.067 Å, -0.290 Å, 1.462 Å, and -0.048 Å for **1a**, and by 0.051 Å, -0.483 Å, 1.434 Å, and 0.073 Å for **1k**.

TABLE 1. Characteristics of Compounds **1a-x, 8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method A, B)
		C	H	N		
1a	$C_{19}H_{22}N_4O$	70.59 70.78	6.98 6.88	17.47 17.38	153-155	88 (A), 79 (B)
1b	$C_{17}H_{18}N_4O$	69.45 69.37	6.10 6.16	18.87 19.03	194-196	95 (A), 84 (B)
1c	$C_{14}H_{18}N_4O$	65.22 65.09	6.88 7.02	21.54 21.69	191-192	91 (A), 88 (B)
1d	$C_{12}H_{16}N_4O$	61.87 62.05	7.15 6.94	23.96 24.12	193-195	78 (A), 81 (B)
1e	$C_{13}H_{18}N_4O$	63.28 63.39	7.41 7.37	22.58 22.75	178-180	70 (A), 73 (B)
1f	$C_{17}H_{26}N_4O$	67.63 67.52	8.60 8.67	18.44 18.53	155-157	91 (A), 83 (B)
1g	$C_{16}H_{16}N_4O$	68.49 68.55	5.64 5.75	20.14 19.99	177-179	84 (A), 70 (B)
1h	$C_{19}H_{30}N_4O$	68.87 69.05	8.96 9.15	17.14 16.95	148-149	76 (A), 89 (B)
1i	$C_{13}H_{18}N_4O$	63.42 63.39	7.50 7.37	22.59 22.75	183-185	92 (A), 76 (B)
1j	$C_{16}H_{22}N_4O$	66.90 67.11	7.82 7.74	19.48 19.56	202-203	75 (A), 83 (B)
1k	$C_{16}H_{16}N_4O$	68.41 68.55	5.80 5.75	20.04 19.99	228-230	74 (A), 80 (B)
1l	$C_{21}H_{18}N_4O$	73.54 73.67	5.19 5.30	16.48 16.36	170-172	79 (A), 74 (B)
1m	$C_{22}H_{28}N_4O$	72.41 72.50	7.82 7.74	15.25 15.37	144-145	90 (A), 88 (B)
1n	$C_{18}H_{20}N_4O$	69.88 70.11	6.60 6.54	18.02 18.17	228-230	81 (A), 84 (B)
1o	$C_{19}H_{20}N_4O$	71.29 71.23	6.15 6.29	17.32 17.49	223-225	88 (A), 90 (B)
1p	$C_{19}H_{18}N_4O$	71.54 71.68	5.69 5.70	17.63 17.60	218-220	68 (A), 72 (B)
1q	$C_{20}H_{16}N_4O$	73.22 73.15	5.06 4.91	15.87 17.06	182-183	70 (A), 74 (B)
1r	$C_{16}H_{20}N_4O$	67.42 67.58	6.94 7.09	19.82 19.70	201-203	92 (A), 88 (B)
1s	$C_{21}H_{18}N_4O$	73.58 73.67	5.34 5.30	16.29 16.36	193-195	95 (A), 81 (B)
1t	$C_{14}H_{16}N_4O$	65.54 65.61	6.31 6.29	21.70 21.86	207-209	72 (A), 73 (B)
1u	$C_{18}H_{20}N_4O$	69.95 70.11	6.63 6.54	17.98 18.17	203-205	84 (A), 81 (B)
1v	$C_{17}H_{18}N_4O$	69.20 69.37	5.95 6.16	19.24 19.03	228-230	79 (A), 85 (B)
1w	$C_{16}H_{16}N_4O$	68.63 68.55	5.61 5.75	20.14 19.99	188-190	94 (A), 95 (B)
1x	$C_{15}H_{14}N_4O$	67.49 67.65	5.44 5.30	20.96 21.04	171-173	70 (A), 64 (B)
8	$C_{19}H_{22}N_4O$	70.87 70.78	7.01 6.88	17.18 17.38	188-190	70 (A)

The geometric characteristics of molecule **1k** are rather close to those found for molecule **1a**. In particular, in these molecules the corresponding bond lengths for the central bicyclic system match within experimental error limits, and the conformations of these molecules are only slightly different.

The benzene ring $C_{(14-19)}$ in compound **1a** is rotated by only 8.2° relative to the central plane, while in compound **1k** the corresponding dihedral angle is 22.8°. The $(CH_2)_5CH_3$ group in **1a** in fact is orthogonal to this plane: the vector $C_{(3)}$–CEN (where CEN is the center of gravity of the system of $C_{(8-13)}$ atoms) makes an 84.4° angle with it. The shortened intramolecular contact $N_{(1)}\cdots C_{(6)}$ of 2.828(5) Å (the sum of the van der Waals radii

TABLE 2. Spectral Characteristics of Compounds **1a-x, 8**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm			
	C≡N	NH, NH$_2$	NH (br. s)	C$_{(4)}$H	NH$_2$ (br. s)	Other protons
1a	2165	3300, 3342, 3440	12.65	4.07, t	6.79	7.59 (2H, d, Ph); 7.45 (2H, t, Ph); 7.37 (1H, t, Ph); 1.50 (2H, m, CH$_2$); 1.00 (8H, m, (CH$_2$)$_4$); 0.73 (3H, t, CH$_3$)
1b	2174	3212, 3333, 3466	12.64	4.00, t	6.73	7.51 (2H, d, Ph); 7.49 (2H, t, Ph); 7.38 (1H, t, Ph); 1.65 (1H, m, CH); 1.32 (2H, m, CH$_2$); 0.88 (3H, t, CH$_3$); 0.59 (3H, t, CH$_3$)
1c	2170	3315, 3364, 3458	11.83	3.28, d	6.52	2.19 (3H, s, CH$_3$); 0.91-1.80 (11H, m, cyclohexyl)
1d	2185	3331, 3372, 3465	11.82	3.42, d	6.44	2.17 (3H, s, CH$_3$); 1.18 (1H, m, CH); 1.15 (2H, m, CH$_2$); 0.92 (3H, t, CH$_3$); 0.79 (3H, d, CH$_3$)
1e	2189	3272, 3310, 3476	11.99	3.40, d	6.68	2.18 (3H, s, CH$_3$); 1.62 (1H, m, CH); 0.63-1.42 (10H, m, (CH$_2$)$_2$ and (CH$_3$)$_2$)
1f	2190	3254, 3311, 3483	11.90	3.52, t	6.58	2.15 (3H, s, CH$_3$); 1.60 (2H, m, CH$_2$); 1.22 (14H, m, (CH$_2$)$_7$); 0.84 (3H, t, CH$_3$)
1g	2184	3297, 3384 3455	12.02	3.68, t	6.77	7.04-7.32 (5H, m, Ph); 2.24 (2H, m, CH$_2$); 2.19 (3H, s, CH$_3$); 1.90 (2H, m, CH$_2$)
1h	2187	3318, 3389, 3476	11.89	3.55, t	6.48	2.12 (3H, s, CH$_3$); 1.16 (2H, m, CH$_2$); 1.20 (18H, m, (CH$_2$)$_9$); 0.86 (3H, t, CH$_3$)
1i	2184	3240, 3325, 3472	11.98	3.37, d	6.55	1.83 (1H, m, CH); 1.60 (2H, m, CH$_2$); 0.91 (8H, m, (CH$_3$)$_2$ and CH$_2$); 0.72 (3H, d, CH$_3$)
1j	2188	3242, 3300, 3486	11.99	3.38, d	6.74	1.02-1.83 (15H, m, (CH$_2$)$_2$ and cyclohexyl); 0.85 (3H, t, CH$_3$)
1k	2195	3173, 3210, 3488	12.69	3.89, d	6.81	7.33-7.54 (5H, m, Ph); 1.72 (1H, m, CH); 0.86 (3H, d, CH$_3$); 0.50 (3H, d, CH$_3$)
1k	2195	3173, 3210, 3488	12.69	3.89, d	6.81	7.33-7.54 (5H, m, Ph); 1.72 (1H, m, CH); 0.86 (3H, d, CH$_3$); 0.50 (3H, d, CH$_3$)
1l	2174	3150, 3300, 3451	12.58	4.17, d	6.60	6.91-7.72 (10H, m, Ph$_2$); 2.88 (1H, m, CH); 0.89 (3H, d, CH$_3$)
1m	2202	3148, 3217, 3495	12.63	4.03, t	6.67	7.36-7.58 (5H, m, Ph); 1.49 (2H, m, CH$_2$); 1.11 (14H, m, (CH$_2$)$_7$); 0.93 (3H, t, CH$_3$)
1n	2188	3192, 3284, 3490	12.64	4.11, d	6.72	7.37-7.70 (5H, m, Ph); 1.42 (1H, m, CH); 0.95 (4H, m, (CH$_2$)$_2$); 0.58 (6H, t, (CH$_3$)$_2$)
1o	2195	3147, 3210, 3485	12.62	3.81, d	6.74	7.36-7.69 (5H, m, Ph); 0.68-1.81 (11H, m, cyclohexyl)
1p	2190	3210, 3274, 3499	12.69	3.99, d	6.83	7.35-7.70 (5H, m, Ph); 5.48 (2H, m, CH=CH); 0.92-1.93 (7H, m, cyclohexenyl)
1q	2187	3256, 3364, 3410	12.63	4.35, t	6.66	7.04-8.11 (10H, m, Ph$_2$); 2.75, (2H, dd, CH$_2$)
1r	2190	3180, 3247, 3496	12.02	3.49, d	6.78	5.50 (2H, m, CH=CH); 1.08-2.07 (11H, m, (CH$_2$)$_2$ and cyclohexenyl); 0.88 (3H, t, CH$_3$)
1s	2186	3155, 3246, 3450	12.77	4.11, t	6.85	7.02-7.59 (10H, m, Ph$_2$); 2.11 (1H, m, CH$_2$); 2.41 (1H, m, CH$_2$); 1.75 (2H, m, CH$_2$)
1t	2193	3146, 3250, 3477	11.82	3.41, d	6.49	5.61 (2H, m, CH=CH); 2.20 (3H, s, CH$_3$); 1.24-2.09 (7H, m, cyclohexenyl)
1u	2177	3163, 3254, 3510	12.65	4.00, d	6.82	7.33-7.64 (5H, m, Ph); 1.50 (2H, m, CH$_2$); 1.29 (2H, m, CH$_2$); 1.12 (1H, m, CH); 0.78 (3H, t, CH$_3$); 0.50 (3H, d, CH$_3$)
1v	2180	3154, 3229, 3498	12.69	4.01, d	6.80	7.36-7.68 (5H, m, Ph); 1.50 (2H, m, CH$_2$); 1.14 (1H, m, CH); 0.82 (3H, t, CH$_3$); 0.49 (3H, d, CH$_3$)
1w	2194	3185, 3241, 3476	11.70	3.50, d	6.34	6.99-7.28 (5H, m, Ph); 2.87 (1H, m, CH); 1.89 (3H, s, CH$_3$); 1.32 (3H, d, CH$_3$)
1x	2185	3147, 3352, 3420	11.92	3.77, t	6.66	6.93-7.15 (5H, m, Ph); 1.86 (3H, s, CH$_3$); 2.90 (1H, d. d, CH$_2$); 2.75 (1H, d. d, CH$_2$)
8	2193	3152, 3345, 3448	—	3.70, d	7.00	7.75 (2H, d, Ph); 7.48 (2H, t, Ph); 7.30 (1H, t, Ph); 2.28 (3H, s, CH$_3$); 1.50 (1H, m, CH); 1.42 (2H, m, CH$_2$); 1.19 (2H, m, CH$_2$); 1.00 (3H, t, CH$_3$); 0.85 (3H, t, CH$_3$)

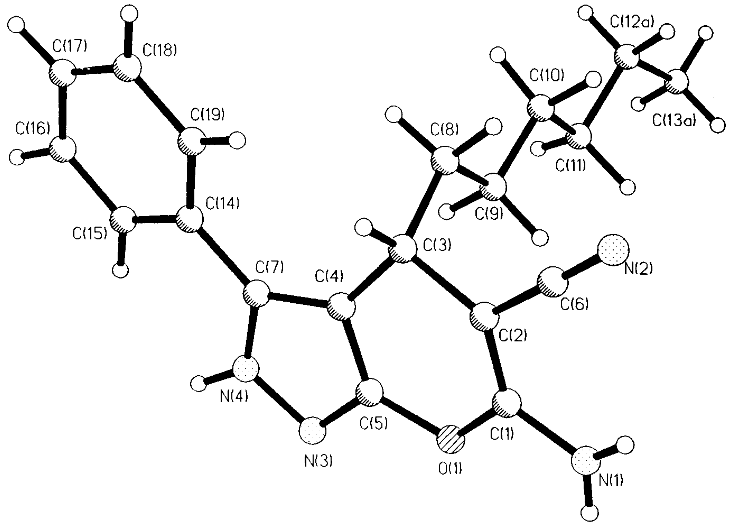


Fig. 1 General view of a molecule of compound **1a**.

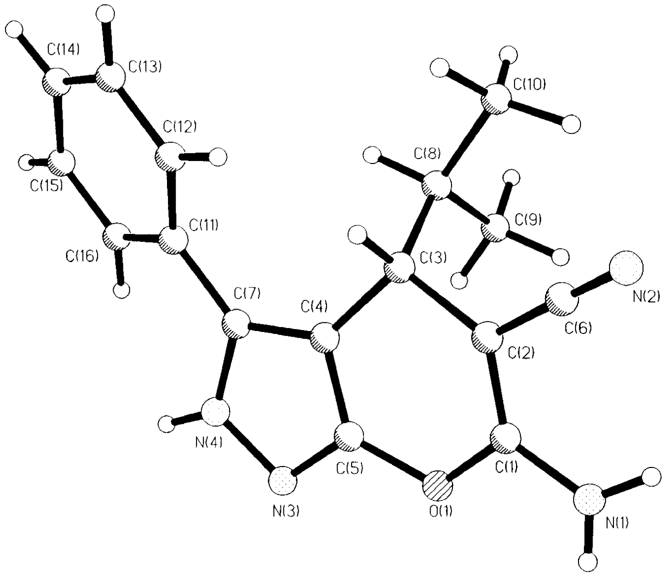


Fig. 2 General view of a molecule of compound **1k**.

of the N and C atoms is 3.20 Å [6]) leads to substantial nonequivalence of the exocyclic angles at the $C_{(1)}$ atom; in both compounds, the bond angle $N_{(1)}$–$C_{(1)}$–$C_{(2)}$ is significantly increased compared with the $N_{(1)}$–$C_{(1)}$–$O_{(1)}$ angle: for **1a** it is 128.0(3) and 109.9(3)°, while for **1k** it is 127.2(3) and 110.3(3)° respectively. Similarly, the repulsion between the rather bulky Ph and Alk substituents causes an increase in the bond angle $C_{(4)}$–$C_{(7)}$–$C_{(14)}$–$C_{(11)}$ up to 133.6(3)-133.1(3)°, compared with the angle $N_{(4)}$–$C_{(7)}$–$C_{(4)}$ of 105.6(3)°.

The atoms $N_{(1)}$ and $N_{(4)}$ in compound **1a** have a trigonal planar configuration of the bonds. In this case, the orientation of the NH_2 group is quite favorable for conjugation between the unshared electron pair of the $N_{(2)}$ atom and the π system of the $C_{(1)}$–$C_{(2)}$ double bond: the angle between them is no greater than 4°. In fact, the

TABLE 3 Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **1a**

Bond	*d*, Å	Angle	ω, deg.
$O_{(1)}-C_{(1)}$	1.368(3)	$C_{(1)}-O_{(1)}-C_{(5)}$	115.6(3)
$O_{(1)}-C_{(5)}$	1.369(4)	$N_{(4)}-N_{(3)}-C_{(5)}$	101.9(2)
$N_{(1)}-C_{(1)}$	1.331(5)	$N_{(3)}-N_{(4)}-C_{(7)}$	113.9(3)
$N_{(1)}-H_{(1NA)}$	0.89(4)	$N_{(1)}-C_{(1)}-O_{(1)}$	109.9(3)
$N_{(1)}-H_{(1NB)}$	0.78(4)	$N_{(1)}-C_{(1)}-C_{(2)}$	128.0(3)
$N_{(2)}-C_{(6)}$	1.158(4)	$O_{(1)}-C_{(1)}-C_{(2)}$	122.1(3)
$N_{(3)}-N_{(4)}$	1.355(4)	$C_{(1)}-C_{(2)}-C_{(6)}$	116.6(3)
$N_{(3)}-C_{(5)}$	1.326(4)	$C_{(1)}-C_{(2)}-C_{(3)}$	125.5(3)
$N_{(4)}-C_{(7)}$	1.361(4)	$C_{(3)}-C_{(2)}-C_{(6)}$	117.5(3)
$N_{(4)}-H_{(4N)}$	0.92(4)	$C_{(2)}-C_{(3)}-C_{(4)}$	106.6(3)
$C_{(1)}-C_{(2)}$	1.369(5)	$C_{(5)}-C_{(4)}-C_{(7)}$	103.5(3)
$C_{(2)}-C_{(6)}$	1.409(4)	$C_{(3)}-C_{(4)}-C_{(5)}$	121.2(3)
$C_{(2)}-C_{(3)}$	1.532(5)	$C_{(3)}-C_{(4)}-C_{(7)}$	135.3(3)
$C_{(3)}-C_{(4)}$	1.506(4)	$N_{(3)}-C_{(5)}-O_{(1)}$	118.1(3)
$C_{(4)}-C_{(5)}$	1.384(5)	$N_{(3)}-C_{(5)}-C_{(4)}$	115.1(3)
$C_{(4)}-C_{(7)}$	1.392(4)	$O_{(1)}-C_{(5)}-C_{(4)}$	126.8(3)
		$N_{(2)}-C_{(6)}-C_{(2)}$	179.0(3)
		$N_{(4)}-C_{(7)}-C_{(4)}$	105.6(3)
		$N_{(4)}-C_{(7)}-C_{(14)}$	120.8(3)
		$C_{(4)}-C_{(7)}-C_{(14)}$	133.6(3)

TABLE 4 Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **1k**

Bond	*d*, Å	Angle	ω, deg.
$O_{(1)}-C_{(1)}$	1.364(4)	$C_{(1)}-O_{(1)}-C_{(5)}$	115.4(3)
$O_{(1)}-C_{(5)}$	1.366(4)	$C_{(5)}-N_{(3)}-N_{(4)}$	102.4(3)
$N_{(1)}-C_{(1)}$	1.321(5)	$N_{(3)}-N_{(4)}-C_{(7)}$	113.4(3)
$N_{(1)}-H_{(1N)}$	0.84(6)	$N_{(1)}-C_{(1)}-O_{(1)}$	110.3(3)
$N_{(1)}-H_{(2N)}$	0.87(4)	$N_{(1)}-C_{(1)}-C_{(2)}$	127.2(3)
$N_{(2)}-C_{(6)}$	1.139(4)	$O_{(1)}-C_{(1)}-C_{(2)}$	122.5(3)
$N_{(3)}-N_{(4)}$	1.352(4)	$C_{(1)}-C_{(2)}-C_{(6)}$	114.7(3)
$N_{(3)}-C_{(5)}$	1.315(4)	$C_{(1)}-C_{(2)}-C_{(3)}$	125.0(3)
$N_{(4)}-C_{(7)}$	1.355(4)	$C_{(6)}-C_{(2)}-C_{(3)}$	120.3(3)
$N_{(4)}-H_{(4N)}$	0.92(4)	$C_{(2)}-C_{(3)}-C_{(4)}$	106.8(3)
$C_{(1)}-C_{(2)}$	1.373(5)	$C_{(7)}-C_{(4)}-C_{(5)}$	103.7(3)
$C_{(2)}-C_{(6)}$	1.409(5)	$C_{(5)}-C_{(4)}-C_{(3)}$	121.2(3)
$C_{(2)}-C_{(3)}$	1.512(5)	$C_{(7)}-C_{(4)}-C_{(3)}$	134.9(3)
$C_{(3)}-C_{(4)}$	1.509(5)	$N_{(3)}-C_{(5)}-O_{(1)}$	119.0(3)
$C_{(4)}-C_{(5)}$	1.385(5)	$N_{(3)}-C_{(5)}-C_{(4)}$	114.6(3)
$C_{(4)}-C_{(7)}$	1.381(4)	$O_{(1)}-C_{(5)}-C_{(4)}$	126.4(3)
		$N_{(2)}-C_{(6)}-C_{(2)}$	178.2(4)
		$N_{(4)}-C_{(7)}-C_{(4)}$	105.8(3)
		$N_{(4)}-C_{(7)}-C_{(11)}$	121.0(3)
		$C_{(4)}-C_{(7)}-C_{(11)}$	133.1(3)

bond $N_{(1)}-C_{(1)}$ of 1.331(5) Å is considerably shortened compared with the standard range of 1.43-14.5 Å for an $N_{(sp2)}-C_{(sp2)}$ single bond [7,8], while the bond $C_{(1)}-C_{(2)}$ of 1.369(5) Å is appreciably elongated compared with the value of 1.33 Å typical of a $C_{(sp2)}-C_{(sp2)}$ double bond [8].

The corresponding parameters for compound **1k** are close. The $N_{(1)}$ and $N_{(4)}$ atoms in compound **1k** have a trigonal planar configuration of the bonds, where the sums of the bond angles at these atoms are respectively 360.0(1.0)° and 360.0(2.4)°, the orientation of the $N_{(1)}H_2$ group is quite favorable for conjugation between the unshared electron pair of the $N_{(1)}$ atom and the π-system of the $C_{(1)}$–$C_{(2)}$ double bond: the dihedral angle between the planes $O_{(1)}N_{(1)}C_{(1)}C_{(2)}C_{(3)}C_{(6)}$ and $N_{(1)}H_{(1N)}H_{(2N)}$ is 17.1°. As a result of this conjugation, the $N_{(1)}$–$C_{(1)}$ bond of 1.321(5) Å, as in the **1a** case, is considerably shortened, while the $C_{(1)}$–$C_{(2)}$ bond of 1.373(5) Å is appreciably elongated. In both compounds, in the five-membered heterocycle $N_{(3)}N_{(4)}C_{(4)}C_{(5)}C_{(7)}$, all the endocyclic interatomic distances correspond to a bond multiplicity of approximately 1.5, which indicates significant delocalization of the electron density in this system.

In the crystal, the molecules of compound **1a**, as a result of the hydrogen bonds $N_{(1)}$–$H_{(11)}\cdots N_{(3)}$ ($N_{(1)}\cdots N_{(3)}$ 3.025(4) Å, $N_{(1)}$–$H_{(11)}$ 0.89(4) Å, $N_{(3)}\cdots H_{(11)}$ 2.141(4) Å, $N_{(1)}$–$H_{(11)}\cdots N_{(3)}$ 176(2)°), are organized into centrosymmetric dimers. In turn, these dimers, *via* the hydrogen bonds $N_{(4)}$–$H_{(4)}\cdots N_{(2)}$ ($N_{(4)}\cdots N_{(2)}$ 3.024(4) Å, $N_{(4)}$–$H_{(4)}$ 0.92(4) Å, $N_{(2)}\cdots H_{(4)}$ 2.189(4) Å, $N_{(4)}$–$H_{(4)}\cdots N_{(2)}$ 150(2)°) form an infinite network (Fig. 3).

In the crystal of compound **1k**, as a result of the hydrogen bonds $N_{(1)}$–$H_{(1N)}\cdots N_{(3)}$ ($N_{(1)}\cdots N_{(3)}$ 2.999(4) Å, $N_{(1)}$–$H_{(1N)}$ 0.84(6) Å, $N_{(3)}$–$H_{(1N)}$ 2.17(6) Å, $N_{(1)}$–$H_{(1N)}\cdots N_{(3)}$ 172(3)°), the molecules are also organized into centrosymmetric dimers which in turn, via the the hydrogen bonds $N_{(4)}$–$H_{(4N)}\cdots N_{(2)}$ ($N_{(4)}\cdots N_{(2)}$ 2.913(4) Å, $N_{(4)}$–$H_{(4N)}$ 0.92(4) Å, $N_{(2)}\cdots H_{(4N)}$ 2.01(4) Å, $N_{(4)}$–$H_{(4N)}\cdots N_{(2)}$ 167(2)°) form an infinite chain along the *a* crystallographic axis (Fig. 4). For H bonds of the type N–H···N, the statistical mean of the interatomic distance N···N is 2.98 Å for $\sigma = 0.16$ Å^2 [9].

Thus, the N(1)-unsubstituted pyrano[2,3-*c*]pyrazoles **1** exist in the crystalline state as the 2H,4H-isomers **1A** rather than the 1H,4H-isomers **1B**, as maintained in earlier papers [13-16].

From literature data on the isomerism of 4H-pyrans condensed with six-membered carbon rings, we know that the *boat* conformation is typical in the crystalline form [17, 18]. In the structures of **1a,k** studied in this work, the 4H-pyran ring, like the pyrazole ring, is practically flat. This fact is probably also responsible for the stability of the 2H,4H-isomers 1A.

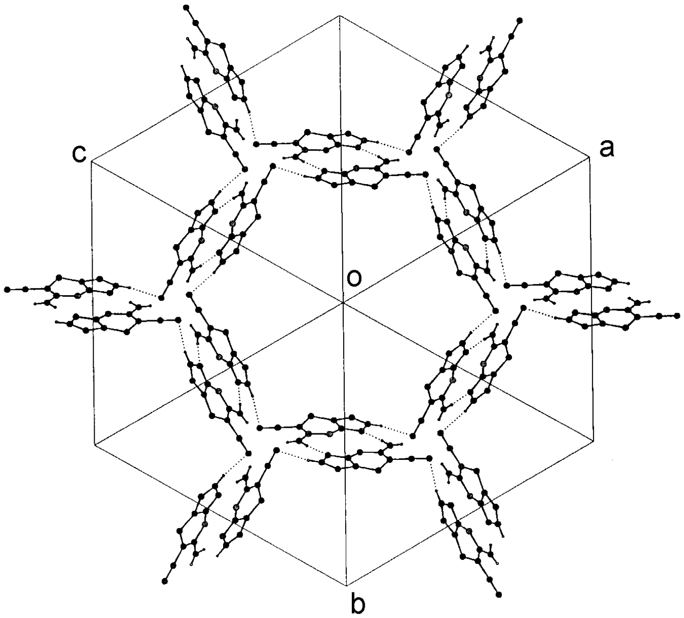


Fig. 3. Crystal packing for compound **1a** (*bc* projection). The dotted lines indicate hydrogen bonds.

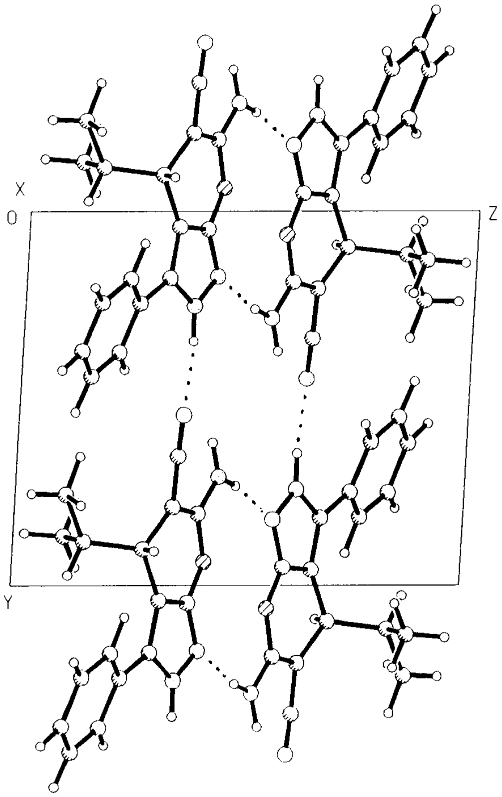


Fig. 4. Crystal packing for compound **1k** (the Ph and $-(CH_2)_5CH_3$ substituents are not shown).

EXPERIMENTAL

An X-ray Diffraction Study of a Single Crystal of Compound 1a with linear dimensions 0.11 × 0.31 × 0.32 mm was carried out at -133°C on an Enraf-Nonius DIP2000 diffractometer (MoKα radiation, ω scanning, 90 frames every 2°, 600 sec/frame, crystal–detector distance 75 mm, $\theta_{max} = 26°$, spherical segment $-22 \leq h \leq 23$, $-21 \leq k \leq 23$, $-22 \leq l \leq 23$). The unit cell parameters were determined from 124 reflections and refined using the entire data file. We collected a total of 18366 reflections, of which 2350 were symmetry independent (R_{int} = 0.028). The crystals of compound **1a** were trigonal, a = 18.744(1) Å; α = 117.77(1)°; V = 2520.2(2) Å^3; M = 327.45; Z = 6; d_{calc} = 1.295 g/cm^3; μ = 0.82 cm^{-1}; space group R-3. The structure was deciphered by the direct method and refined by the least squares method in the full-matrix anisotropic approximation using the programs SHELXS and SHELXL93 [10, 11]. Refinement was carried out using 2341 reflections with $I > 2(I)$ (303 refined parameters, number of reflections times the parameter 7.73). Practically all the H atoms were determined from a difference electron density synthesis and isotropically refined. Only the hydrogen atoms for the disordered $C_{(12)}$ and $C_{(13)}$ atoms were placed geometrically and included in the calculation with fixed positions and thermal parameters. We used the weighting scheme $\omega = 1/[\sigma^2(Fo^2) + (0.0117P)_2 + 6.1294]$, where $P = (Fo^2 + 2Fc^2)/3$. Correction for absorption in the crystal was taken into account by scaling 90 frames using the SCALEPACK program [12]. The final values of the R factors were $R_1(F)$ = 0.0597 and $R_w(F^2)$ = 0.1271, GOF = 1.001. The residual electron density from a difference Fourier series was 0.27 and -0.42 e/Å^3.

X-ray Diffraction Study of a Single Crystal of Compound 1k with linear dimensions 0.16 × 0.25 × 0.34 mm was carried out at room temperature on an automatic four-circle Enraf-Nonius CAD-4 diffractometer (λMoKα radiation, graphite monochromator, ratio of $\omega/2\theta$ scanning rates = 1.2, $\theta_{max} = 23°$, spherical segment $0 \leq h \leq 7$, $-11 \leq k \leq 11$, $-13 \leq l \leq 13$). We collected a total of 2373 reflections, of which 2192 were independent (averaging R factor 0.040). The crystals of compound **1k** were triclinic, $a = 6.537(4)$, $b = 9.844(3)$, $c = 11.540(4)$ Å; $\alpha = 92.89(3)$, $\beta = 92.03(4)$, $\gamma = 103.88(4)°$; $V = 719.1(6)$ Å^3, $Z = 2$, $d_{calc} = 1.295$ g/cm^3, $\mu = 0.085$ mm^{-1}, $F(000) = 296$, space group P-1 (No. 2). The structure was deciphered by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation using the programs SHELXS and SHELXL93 [10, 11]. In the refinement, we used 1871 reflections with $I > 2\sigma(I)$ (254 refined parameters, number of reflections times the parameter 7.37, weighting scheme $\omega = 1/[\sigma^2(Fo^2) + (0.0731P)^2]$, where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximum/mean shift of the error in the last cycle was 0.033/0.005). A correction for anomalous scattering was included; no corrections for absorption were made. All the hydrogen atoms were determined objectively and isotropically refined. The final values of the R factors were $R_1(F) = 0.0612$ and $R_w(F^2) = 0.1322$, $GOF = 1.045$. The residual electron density from a difference Fourier series after the last refinement cycle was 0.22 and -0.23 e/Å^3.

The IR spectra of the synthesized compounds were recorded on an IKS-29 in vaseline oil. The ^{1}H NMR spectra were recorded on a Bruker WM-250 (250 MHz) (for compounds **1a-q, 8**), a Bruker AM-300 (300 MHz) (for compounds **1r-w**), and a Bruker WP-100 SY (100 MHz) (for compound **1x**) in DMSO-d$_6$, internal standard Me$_4$Si. The mass spectra were taken on a Kratos MS-890 (70 eV). The melting points were determined on a Kofler apparatus. The course of the reaction was monitored by TLC (Silufol UV-254; acetone–hexane, 3:5; visualizing agent, iodine vapors).

4-Alkyl-6-amino-5-cyano-3-methyl(propyl, phenyl)-2H,4H-pyrano[2,3-*c*]pyrazoles (1a-x). (General Method). A. Cyanothioacetamide **3** (1.0 g, 10 mmol) and morpholine (3 drops) were added to a mixture of the corresponding compound **2** (10 mmol) in ethanol (15 ml) at 20°C, after which they were stirred for 2 h and allowed to stand for 24 hours. The precipitate formed was filtered out and then washed with ethanol and hexane. We obtained compounds **1a-x**, which were recrystallized from ethanol (see Tables 1 and 2).

B. Morpholine (3 drops) was added to a mixture of substituted pyrazolone **2** (10 mmol) and malononitrile **4** (0.66 g, 10 mmol) in ethanol (15 ml) at 20°C; this was stirred for 20 min and then was allowed to stand for 24 hours. The precipitate formed was filtered out and washed with ethanol and then hexane, and recrystallized from ethanol. We obtained compounds **1a-x** with chromatography data, melting points, and IR spectra identical to those obtained by method A. The characteristics of pyrazolopyrans **1a-x** are given in Tables 1 and 2.

The mass spectral data for compounds **1k,q**, *m/z* (I_{rel}, %): **1k** – 297 [M]$^+$ (8), 238(25), 237(100), 214(14), 77(47); **1q** – 328 [M]$^+$ (5), 262(43), 238(35), 237(100), 220(41), 219(88), 91(45), 77(40), 58(61).

6-Amino-3-methyl-4-(3'-pentyl)-1-phenyl-1H,4H-pyrano[2,3-*c*]pyrazole (8) was obtained similarly to compounds **1** by method A, starting from pyrazolone **7** (see Tables 1 and 2). Mass spectrum, *m/z* (I_{rel}, %): 322 [M]$^+$ (4), 252(40), 251(100), 118(28), 79(25), 77(83), 58(49).

REFERENCES

1. B. Y. Riad, A. O. Abdelhamid, F. A. Khalifa, and Y. E. Saleh, *Arch. Pharmacol. Res.*, **12**, 201 (1989).
2. Yu. A. Sharanin, L. G. Sharanina, and V. V. Puzanova, *Zh. Org. Khim.*, **19**, 2609 (1983).
3. H. F. Zohdi, A. H. H. Elghandour, N. M. Rateb, and M. M. M. Sallam, *J. Chem. Res. (S),* No. 12, 396 (1992).
4. F. F. Abdel-Latif and R. M. Shaker, *Indian J. Chem. (B)*, **29**, 322 (1990).
5. G. V. Klokol, S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1363 (1999).

6. L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, New York (1960).
7. R. W. Alder, N. C. Goode, T. J. King, J. M. Mellor, and B. W. Miller, *J. Chem. Soc. Chem. Commun.*, No. 5, 173 (1976).
8. M. Burke-Laing and M. Laing, *Acta Crystallogr.*, **B32**, 3216 (1976).
9. L. N. Kuleshova and P. M. Zorkii, *Acta Crystallogr.*, **B37**, 1363 (1981).
10. G. M. Sheldrick, *SHELXS-86. Program for the Solution of Crystal Structures*, University of Gottingen, Gottingen, Germany (1986).
11. G. M. Sheldrick, *SHELXS-93. Program for the Refinement of Crystal Structures*, University of Gottingen, Gottingen, Germany (1993).
12. Z. Otwinowski and W. Ninor, *Methods Enzymol.*, **276**, 307 (1997).
13. L. G. Sharanina, V. P. Marshtupa, and Yu. A. Sharanin, *Khim. Geterotsikl. Soedin*., 1420 (1980).
14. F. F. Latif and A. K. M. H. Gohar, *Bull. Soc. Chim. Belg.*, **95**, 21 (1986).
15. H. Junec and H. Aigner, *Chem. Ber.*, **106**, 914 (1973).
16. G. Tacconi, G. Gafti, and G. Desimoni, *J. Prakt. Chem.*, **322**, 831 (1980).
17. G. V. Klokol, L. G. Sharanina, V. N. Nesterov, V. E. Shklover, Yu. A. Sharanin, and Yu. T. Struchkov, *Zh. Org. Khim.*, **23**, 412 (1987).
18. M. Suarez, E. Salfran, Y. Verdecia, E. Ochoa, L. Alba, N. Martin, R. Martinez, M. Quinteiro, C. Seoane, H. Novoa, N. Blaton, O. M. Peeters, and C. De Ranter, *Tetrahedron*, **58**, 953 (2002).