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CONVERSIONS OF 7-ARYL-7*H*-PYRAZOLO[3,4-*d*]-[1,2,3]TRIAZIN-4-OLS BY THE ACTION OF PHOSPHORUS PENTOXIDE, PENTASULFIDE, AND OXYCHLORIDE

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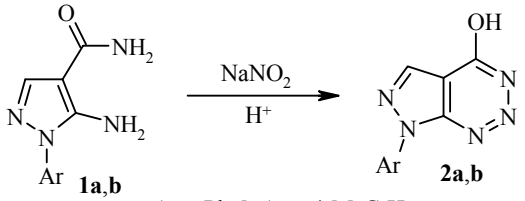
The interaction of 7-aryl-7H-pyrazolo[3,4-d][1,2,3]triazin-4-ols with phosphorus pentoxide or pentasulfide leads to the formation of 6-(5-amino-1-aryl-1H-pyrazol-4-yl)-1-aryl-1H,4H-pyrazolo[3,4-d][1,3]oxazin-4-ones and 6-(5-amino-1-aryl-1H-pyrazol-4-yl)-1-aryl-1H,4H-pyrazolo[3,4-d][1,3]thiazine-4-thiones, respectively. Reaction with phosphorus oxychloride leads to 1-aryl-5-chloro-1H-pyrazole-4-carbonyl chlorides, from which the corresponding amides, hydrazides, and substituted 1,3,4-oxadiazoles were synthesized.

Keywords: phosphorus pentoxide, phosphorus pentasulfide, phosphorus oxychloride, pyrazolooxazines, pyrazolothiazines, pyrazolotriazines.

Multifunctional heterocycles containing a 1,2,3-triazine fragment possess a broad spectrum of biological activity [1-4], which in its turn stimulates development of methods for the synthesis of new types of heterocyclic systems based on them. The present work is devoted to the investigation of the synthetic possibilities of the poorly studied 7*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4-ols **2a**,**b**, in particular products formed in reactions of these compounds with phosphorus-containing electrophiles: phosphorus pentoxide, phosphorus pentasulfide, and phosphorus oxychloride. Compounds **2a**,**b** were obtained by the diazotation of 5-amino-1-aryl-1*H*-pyrazole-4-carboxamides **1a**,**b** with an aqueous solution of sodium nitrite in a mixture of acetic and hydrochloric acids [5], or in a dilute hydrochloric acid [6, 7].



a Ar = Ph, **b** Ar = 4-MeC_6H_4

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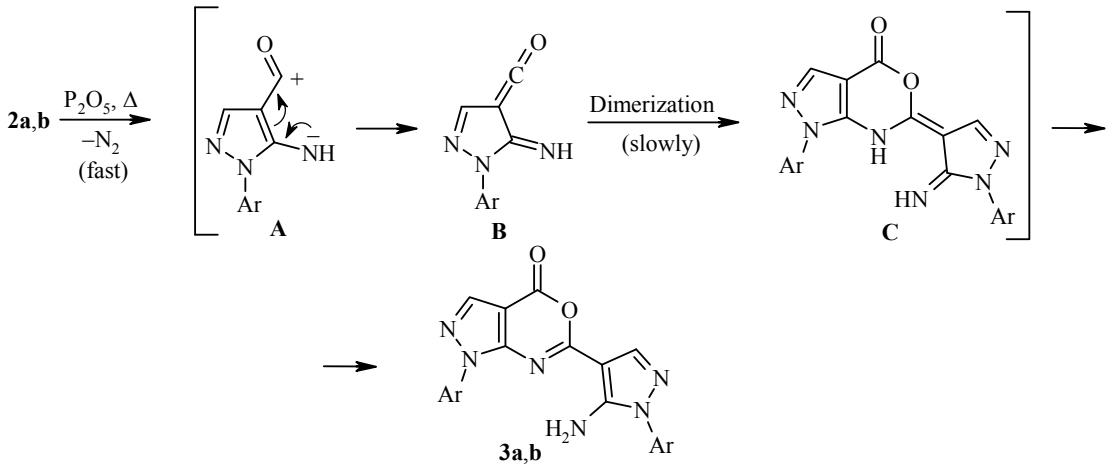
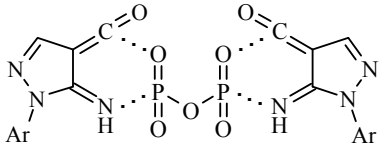
Heating pyrazolotriazinols **2a**,**b** with phosphorus pentoxide in refluxing dioxane leads to the formation of substituted pyrazolo[3,4-*d*][1,3]oxazin-4-ones **3a**,**b** in 35-38% yield (Table 1). A similar reaction is known for 3,4-dihydro-1,2,3-benzotriazinones [8, 9].

The formation of oxazines **3a**,**b** may be represented as the result of a series of sequential processes: elimination of a nitrogen molecule, formation of ketenes **B**, dimerization into intermediates **C** as a result of [4+2] cycloaddition, and then prototropic isomerization.



a Ar = Ph, **b** Ar = 4-MeC_6H_4

Phosphorus pentoxide is apparently needed in this process for the stabilization of ketenes **B** as a result of the formation of type **D** intermediates, which slowly convert to the final products **3a**,**b**.



D

The structure of compounds **3a**,**b** was demonstrated by X-ray structural analysis and NMR spectroscopy. In the ^{1}H NMR spectra (Table 2) of 6-(5-amino-1-aryl-1*H*-pyrazol-4-yl)-1-arylpyrazolo[3,4-*d*]-[1,3]oxazin-4(1*H*)-ones **3a**,**b** signals were present for the aromatic protons, a broadened signal of the NH_2 group protons at 6.78-6.93 ppm, and the signals of the pyrazole fragment protons (singlets at 7.94-8.02 and 8.32-8.41 ppm). In the ^{13}C NMR spectra of oxazine **3b** there were signals of the pyrazole ring carbon nuclei, the exocyclic C=O group (160.3 ppm), and also signals of the aliphatic and aromatic carbon nuclei.

Complex NMR analysis (NOESY, COSY, HSQC, HMBC) (Fig. 1, Table 3) was also used for compound **3b**. The signals of 2D spectroscopy NOESY 7.45 (H-2",6") ↔ 6.78 (NH_2), 7.75 (H-2"',6"') ↔ 6.78 (NH_2) and HMBC 7.94 (H-3') → 95.0 (C-4'), 7.94 (H-3') → 154.7 (C-5'), 8.32 (H-3) → 99.0 (C-3a), 8.32 (H-3) → 149.5 ppm (C-7a) were in agreement with the proposed structure.

The X-ray structural investigation of compound **3b** (Fig. 2) showed that the 1,3-oxazin-6-one fragment on the whole has geometric characteristics similar to those of previously investigated compounds containing this ring [10, 11].

The N(3)=C(4) bond length was 1.288(5) Å, which is characteristic for a standard C=N double bond. At the same time, the N(3)–C(3) bond length was 1.360(5) Å, which is typical of conjugated aromatic systems. Overall the values of the bond lengths and valence angles in the pyrazole rings correspond to the standard values.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %					Mp*, °C	Yield, %
		C	H	Cl	N	S		
2a	$C_{10}H_7N_5O$	56.61 / 56.34	3.38 / 3.31	—	32.56 / 32.85	—	140-142 (decomp.) (136 (decomp.) [6])	88
2b	$C_{11}H_9N_5O$	58.23 / 58.15	3.92 / 3.99	—	30.93 / 30.82	—	144-145	84
3a	$C_{20}H_{14}N_6O_2$	64.65 / 64.86	3.93 / 3.81	—	22.43 / 22.69	—	221-223	38
3b	$C_{22}H_{18}N_6O_2$	66.55 / 66.32	4.71 / 4.55	—	21.13 / 21.09	—	236-237	35
4a	$C_{20}H_{14}N_6S_2$	59.45 / 59.68	3.60 / 3.51	—	20.67 / 20.88	16.20 / 15.93	254-256	34
4b	$C_{22}H_{18}N_6S_2$	61.18 / 61.37	4.08 / 4.21	—	19.83 / 19.52	15.16 / 14.89	283-284	36
5a	$C_{10}H_6Cl_2N_2O$	50.15 / 49.82	2.31 / 2.51	29.43 / 29.41	11.73 / 11.62	—	133-134 (134 [14])	65
5b	$C_{11}H_8Cl_2N_2O$	51.98 / 51.79	3.28 / 3.16	27.77 / 27.79	10.71 / 10.98	—	93–94	63
6a	$C_{17}H_{13}ClN_4O_2$	60.21 / 59.92	4.01 / 3.85	10.67 / 10.40	16.78 / 16.44	—	206–208	70
6b	$C_{18}H_{15}ClN_4O_2$	61.12 / 60.94	4.24 / 4.26	10.21 / 9.99	15.65 / 15.79	—	216–217	67
6c	$C_{15}H_{11}ClN_4O_2S$	52.11 / 51.95	3.24 / 3.20	10.01 / 10.22	15.87 / 16.16	8.98 / 9.23	236-238	62
7a	$C_{17}H_{11}ClN_4O$	63.48 / 63.26	3.43 / 3.44	10.89 / 10.98	17.42 / 17.36	—	109-110	74
7b	$C_{18}H_{13}ClN_4O$	63.90 / 64.20	3.90 / 3.89	10.71 / 10.53	16.70 / 16.64	—	112-113	77
7c	$C_{15}H_9ClN_4OS$	55.03 / 54.80	3.01 / 2.76	10.56 / 10.78	16.83 / 17.04	10.04 / 9.75	149-150	51
8	$C_{10}H_9ClN_4O$	50.48 / 50.75	3.63 / 3.83	15.13 / 14.98	23.43 / 23.67	—	177-179	78
9	$C_{11}H_7ClN_4OS$	47.08 / 47.40	2.48 / 2.53	13.01 / 12.72	19.89 / 20.10	11.32 / 11.50	210-212	88
10a	$C_{13}H_{11}ClN_4OS$	51.04 / 50.90	3.48 / 3.61	11.88 / 11.56	18.54 / 18.26	10.66 / 10.45	Oil	88
10b	$C_{19}H_{15}ClN_4OS$	59.85 / 59.60	4.06 / 3.95	9.56 / 9.26	14.97 / 14.63	8.49 / 8.37	73-75	62
11a	$C_{13}H_{14}ClN_3O$	59.39 / 59.21	5.46 / 5.35	13.72 / 13.44	15.66 / 15.93	—	113-114	73
11b	$C_{12}H_{12}ClN_3O$	57.53 / 57.72	4.68 / 4.84	14.03 / 14.20	16.98 / 16.83	—	83-84	58
11c	$C_{17}H_{14}ClN_3O$	65.18 / 65.49	4.28 / 4.53	11.18 / 11.37	13.18 / 13.48	—	96-99	66
11d	$C_{14}H_{16}ClN_3O$	60.71 / 60.54	5.86 / 5.81	12.98 / 12.76	15.07 / 15.13	—	104-105	89
11e	$C_{13}H_{14}ClN_3O$	59.48 / 59.21	5.58 / 5.35	13.61 / 13.44	15.68 / 15.93	—	98-99	68
11f	$C_{18}H_{16}ClN_3O$	66.59 / 66.36	5.07 / 4.95	10.80 / 10.88	12.78 / 12.90	—	181-182	79

*Solvents for crystallization: MeCN (compounds **3a**,**b**, **4a**,**b** **7a-c**), hexane (compounds **5a**,**b**, **11a**,**b**,**d**), EtOH (compound **8**), petroleum ether (fraction 60-95°C, compounds **10b**, **11e**), C_6H_6 (compounds **11c**,**f**).

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)
2b	2.40 (3H, s, CH_3); 7.41 (2H, d, *J* = 6.0, H Ar); 7.90 (2H, d, *J* = 6.0, H Ar); 8.57 (1H, s, H-5); 15.31 (1H, br. s, OH)
3a	6.93 (2H, s, NH_2); 7.48 (2H, t, *J* = 7.5, H Ar); 7.55-7.68 (6H, m, H Ar); 7.89 (2H, d, *J* = 7.5, H Ar); 8.02 (1H, s, H-3'); 8.41 (1H, s, H-3)
3b	2.38 (3H, s, CH_3); 2.39 (3H, s, CH_3); 6.78 (2H, s, NH_2); 7.36 (2H, d, *J* = 7.5, H Ar); 7.37 (2H, d, *J* = 7.0, H Ar); 7.45 (2H, d, *J* = 7.0, H Ar); 7.75 (2H, d, *J* = 7.5, H Ar); 7.94 (1H, s, H-3'); 8.32 (1H, s, H-3)
4a	7.19 (2H, s, NH_2); 7.49 (1H, t, *J* = 7.0, H Ar); 7.50 (1H, t, *J* = 7.6, H Ar); 7.54 (2H, d, *J* = 7.6, H Ar); 7.56 (2H, t, *J* = 7.6, H Ar); 7.58 (2H, t, *J* = 7.0, H Ar); 7.79 (2H, d, *J* = 7.0, H Ar); 8.06 (1H, s, H-3'); 8.42 (1H, s, H-3)
4b	2.42 (6H, s, $2CH_3$); 7.15 (2H, s, NH_2); 7.34-7.50 (6H, m, H Ar); 7.72 (2H, d, *J* = 7.0, H Ar); 8.10 (1H, s, H-3'); 8.49 (1H, s, H-3)
5b	2.43 (3H, s, CH_3); 7.31 (2H, d, *J* = 8.0, H Ar); 7.49 (2H, d, *J* = 8.0, H Ar); 8.20 (1H, s, H-3)
6a	7.47-7.72 (8H, m, H Ar); 7.94 (2H, d, *J* = 6.5, H Ar); 8.38 (1H, s, H-3); 10.35 (1H, s, NH); 10.53 (1H, s, NH)
6b	2.39 (3H, s, CH_3); 7.41 (2H, d, *J* = 4.2, H Ar); 7.51-7.66 (5H, m, H Ar); 7.68-7.80 (2H, m, H Ar); 8.37 (1H, s, H-3); 10.33 (1H, s, NH); 10.46 (1H, s, NH)
6c	7.21 (1H, t, *J* = 4.0, H thiophene); 7.48-7.70 (5H, m, H Ar); 7.85 (1H, d, *J* = 4.0, H thiophene); 7.89 (1H, d, *J* = 4.0, H thiophene); 8.34 (1H, s, H-3); 10.28 (1H, s, NH); 10.48 (1H, s, NH)
7a	7.55-7.75 (8H, m, H Ar); 8.15 (2H, d, *J* = 7.6, H Ar); 8.39 (1H, s, H-3)
7b	2.44 (3H, s, CH_3); 7.48 (1H, d, *J* = 7.5, H Ar); 7.53 (1H, t, *J* = 7.5, H Ar); 7.60 (1H, t, *J* = 7.0, H Ar); 7.65 (2H, t, *J* = 7.0, H Ar); 7.69 (2H, d, *J* = 7.0, H Ar); 7.90 (1H, d, *J* = 7.5, H Ar); 7.93 (1H, br. d, *J* = 7.5, H Ar); 8.55 (1H, s, H-3)
7c	7.34 (1H, t, *J* = 4.0, H thiophene); 7.60 (1H, t, *J* = 7.0, H Ar); 7.64 (2H, t, *J* = 7.0, H Ar); 7.69 (2H, d, *J* = 7.0, H Ar); 7.91 (1H, d, *J* = 4.0, H thiophene); 7.99 (1H, d, *J* = 4.0, H thiophene); 8.51 (1H, s, H-3)
8	4.46 (2H, br. s, NH_2); 7.49-7.62 (5H, m, H Ar); 8.19 (1H, s, H-3); 9.53 (1H, s, NH)
9	7.52-7.72 (5H, m, H Ar); 8.39 (1H, s, H-3); 14.70 (1H, br. s, SH)
10a	1.52 (3H, t, *J* = 8.0, $CH_2C\underline{H}_3$); 3.33 (2H, q, *J* = 8.0, $C\underline{H}_2CH_3$); 7.50-7.76 (5H, m, H Ar); 8.19 (1H, s, H-3)
10b	2.24 (3H, s, CH_3); 4.53 (2H, s, CH_2); 7.15 (2H, d, *J* = 7.8, H Ar); 7.35 (2H, d, *J* = 7.8, H Ar); 7.50-7.76 (5H, m, H Ar); 8.40 (1H, s, H-3)
11a	0.92 (3H, t, *J* = 7.2, $CH_2CH_2C\underline{H}_3$); 1.52-1.55 (2H, m, $CH_2C\underline{H}_2CH_3$); 3.19 (2H, q, *J* = 7.2, NCH_2); 7.42-7.68 (5H, m, H Ar); 8.13 (1H, t, *J* = 7.2, NH); 8.18 (1H, s, H-3)
11b	2.99 (3H, s, NCH_3); 3.08 (3H, s, NCH_3); 7.48-7.65 (5H, m, H Ar); 7.97 (1H, s, H-3)
11c	2.28 (3H, s, CH_3); 7.16 (2H, d, *J* = 7.8, H Ar); 7.48-7.75 (7H, m, H Ar); 8.42 (1H, s, H-3); 10.00 (1H, s, NH)
11d	0.90 (3H, t, *J* = 7.2, $CH_2CH_2C\underline{H}_3$); 1.51-1.55 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.40 (3H, s, $ArC\underline{H}_3$); 3.19 (2H, q, *J* = 7.2, NCH_2); 7.38 (2H, d, *J* = 7.6, H Ar); 7.43 (2H, d, *J* = 7.6, H Ar); 8.18 (1H, t, *J* = 7.2, NH); 8.21 (1H, s, H-3)
11e	2.40 (3H, s, $ArC\underline{H}_3$); 2.99 (3H, s, NCH_3); 3.07 (3H, s, NCH_3); 7.38 (2H, d, *J* = 7.6, H Ar); 7.47 (2H, d, *J* = 7.6, H Ar); 7.99 (1H, s, H-3)
11f	2.29 (3H, s, CH_3); 2.42 (3H, s, CH_3); 7.16 (2H, d, *J* = 7.8, H Ar); 7.41 (2H, d, *J* = 7.6, H Ar); 7.47 (2H, d, *J* = 7.6, H Ar); 7.60 (2H, d, *J* = 7.8, H Ar); 8.41 (1H, s, H-3); 9.98 (1H, s, NH)

The bicyclic N(1,2)O(1)C(1-5) fragment is planar within the limits of 0.0156(26) Å, the pyrazole ring N(4,5)C(6-8) is practically coplanar and is twisted by merely 2.21(19)°, while the phenyl ring C(9-14) is twisted by 28.35(12)°. The 4-methylphenyl substituent C(16)–C(22) is twisted relative to the pyrazole ring by 48.55(11)°. In the crystal both intra- (N(6)–H(1)···N(3)) and intermolecular (N(6)–H(2)···O(2)_ $1) hydrogen bonds are formed with the following parameters: N(6)–H(1) 0.97(6), N(6)···N(3) 2.910(5), N(6)–H(1)–N(3) 125(4)°; N(6)–H(2) 1.08(7), N(6)···O(2)_$1 2.950(5), N(6)–H(2)–O(2)_$1 1.44(6)° (the symbol $1 denotes an atom linked with the main atoms by the symmetry operation *x*+0.5, 1-*y*, *z*).

6-(5-Amino-1-aryl-1*H*-pyrazol-4-yl)-1-arylpyrazolo[3,4-*d*][1,3]thiazin-4(1*H*)-thiones **4a**,**b** were formed in 34-36% yield as a result of the reaction of compounds **2a**,**b** with phosphorus pentasulfide.

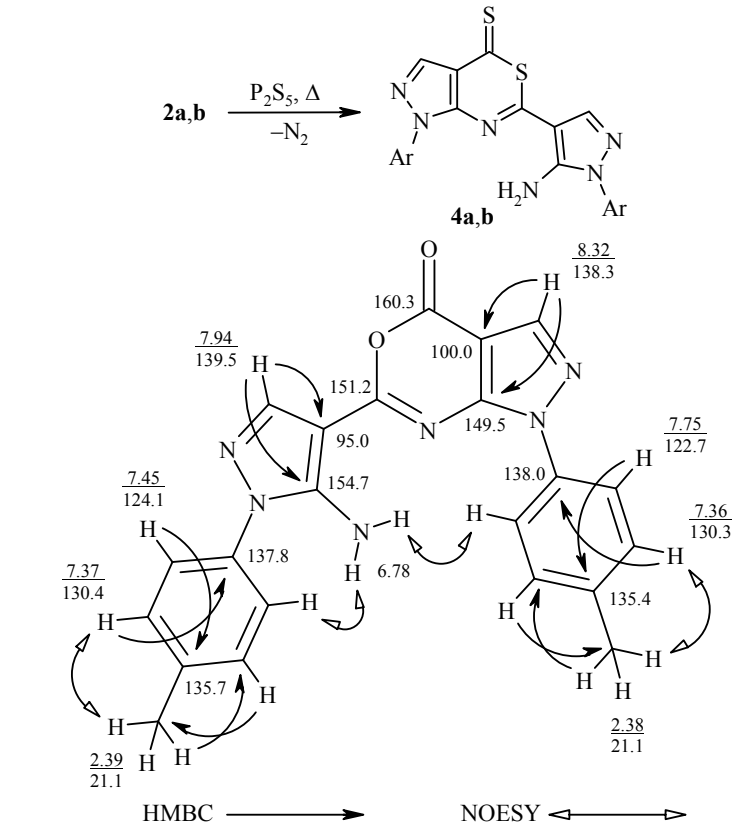


Fig. 1. Main correlations and assignment of signals (ppm) in the ^{1}H and ^{13}C NMR spectra of compound **3b**.

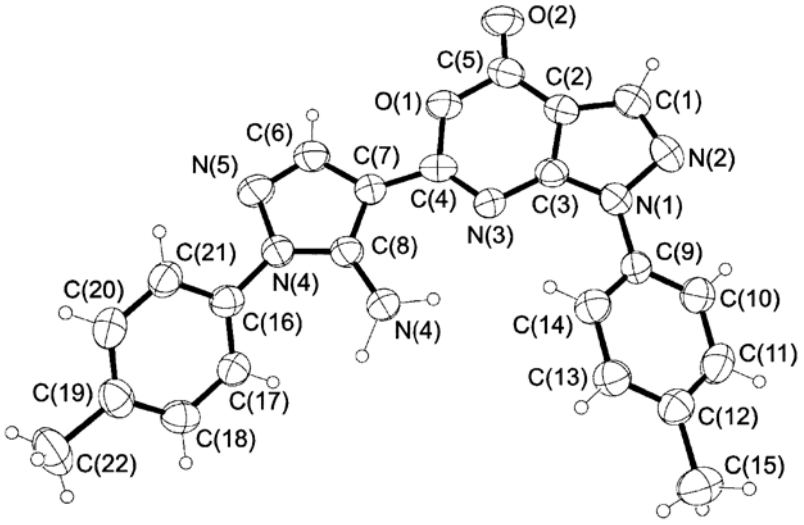


Fig. 2. General view of the compound **3b** molecule with atoms represented by thermal vibration ellipsoids of 50% probability.

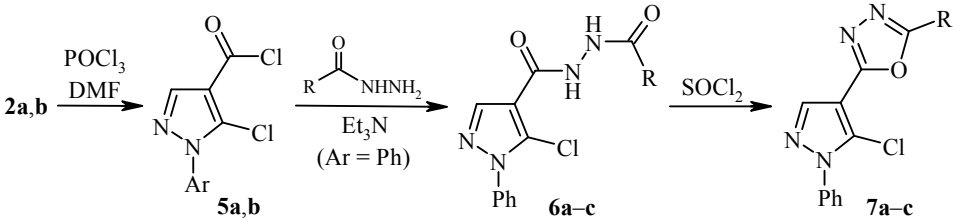
It may be proposed that compounds **3a**,**b** are formed initially and are then converted by the action of phosphorus pentasulfide into thiazines **4a**,**b**. Similar conversions of benzoxazines into benzothiazines have been described in the literature [12, 13]. Comparison of the ^{13}C NMR spectra of compounds **3a**,**b** and **4a**,**b**

TABLE 3. Correlations Found in the COSY, NOESY, HSQC, and HMBC Spectra of Compound **3b***

^{1}H, δ	^{1}H, δ		^{13}C, δ	
	COSY	NOESY	HSQC	HMBC
2.39	7.37	7.37	21.1	130.4
7.37	2.39; 7.45	2.39; 7.45	130.4	21.1; 130.4; 137.8
7.45	7.37	7.37; 6.78	124.1	124.1; 135.7
7.94	—	7.75	139.5	95.0; 151.2; 154.7
6.78	—	7.45; 7.75	—	—
8.32	—	—	138.3	100.0; 149.5
7.75	7.36	7.36; 7.94	122.7	122.7; 135.4
7.36	7.75	7.75; 2.38	130.3	21.1; 130.3; 138.0
2.38	7.36	7.36	21.1	130.3

*For assignment of signals, see Fig. 1.

indicate the presence of C=S groups in the latter (197.7 and 194.6 ppm for compounds **4a** and **4b**, respectively). In addition, NMR analysis (NOESY, COSY, HSQC, HMBC) was used for compound **4a** (Fig. 3, Table 4). The NOESY signals 7.79 (H-2",6") ↔ 7.19 (NH_2) and HMBC 8.06 (H-3') → 100.9 (C-4'), 8.42 (H-3) →117.2 (C-3a), 8.42 (H-3) → 146.6 ppm (C-7a) were similar to the signals of oxazine **3b**, which unequivocally proves the structure of compounds **4a**,**b**.



5 a Ar = Ph, **b** Ar = 4-MeC_6H_4; **6**, **7 a** R = Ph, **b** R = 3-MeC_6H_4, **c** R = 2-thienyl

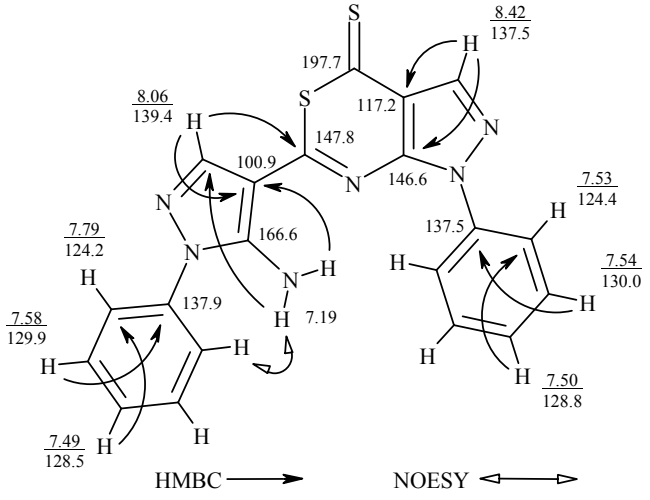


Fig. 3. Main correlations and assignments of signals (ppm) in the ^{1}H and ^{13}C NMR spectra of compound **4a**.

TABLE 4. Correlations Found in the COSY, NOESY, HSQC, and HMBC Spectra of Compound **4a***

^{1}H, δ	^{1}H, δ		^{13}C, δ	
	COSY	NOESY	HSQC	HMBC
7.49	7.58	7.58	128.5	124.2
7.58	7.49; 7.79	7.49; 7.79	128.9	129.9; 137.9
7.79	7.58	7.58; 7.19	124.2	124.2; 128.5
8.06	—	—	139.4	100.9; 147.8
7.19	—	7.79	—	100.9; 139.4
8.42	—	—	137.5	117.2; 146.6
7.53	7.54	7.54	124.4	124.4; 128.8
7.54	7.53; 7.50	7.53; 7.50	130.0	130.0; 137.5
7.50	7.54	7.54	128.8	124.4

*For assignments of signals, see Fig. 3.

On interacting 7-aryl-7*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4-ols **2a**,**b** with phosphorus oxychloride, the corresponding 4-chloro derivatives were not formed. 1-Aryl-5-chloro-1*H*-pyrazole-4-carbonyl chlorides **5a**,**b** were formed as a result of the reaction. Compound **5a** was converted into compounds **6a-c** and then into 1,3,4-oxadiazoles **7a-c**. The physicochemical and spectral characteristics of acyl chloride **5a** were identical to those of the same product described in [14].

The ^{1}H NMR spectra of the obtained products given in Table 2 confirmed the structures of compounds **5b**, **6a-c**, **7a-c**. The characteristic signals of the proton at the C-3 carbon atom of the pyrazole fragment were at 8.20-8.55 ppm.

An X-ray structural investigation of compound **7a** (Fig. 4) was carried out by us in order to consider the spatial structure of 2-(5-chloro-1-phenyl-1*H*-pyrazol-4-yl)-5-R-1,3,4-oxadiazoles **7a-c**. The 1,3,4-oxadiazole ring has geometric characteristics usual for heterocycles with two nitrogen atoms, lying in a plane (mean deviation of atoms from the plane was 0.0096 Å), but the distribution of bond lengths and valence angles in it was close to the related compound investigated previously [15]. The pyrazole ring also has the structure usual for the same type of compound [16], and is twisted relative to the oxadiazole ring by 14.9(1)°. The phenyl substituents C(6-11) and C(12-17) are twisted relative to the pyrazole and oxadiazole heterocycles by 42.7(1) and 6.0(2)°, respectively. In the crystal, slightly shortened intermolecular contacts were detected in the form of endless chains along the *y* crystallographic axis between the atoms of chlorine Cl(1) and nitrogen N(2) at a distance of 3.228(2) Å (this value is somewhat less than the sum of the van der Waals radii of these atoms, which is 3.38 Å [17]). No other shortened intermolecular contacts were found in the crystal.

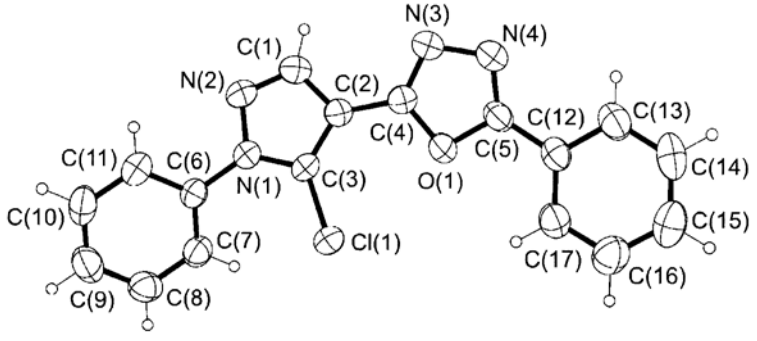
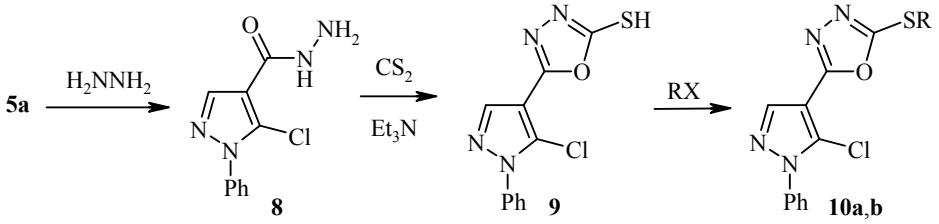


Fig. 4. General form of the molecule of compound **7a** with atoms represented by thermal vibration ellipsoids of 50% probability.

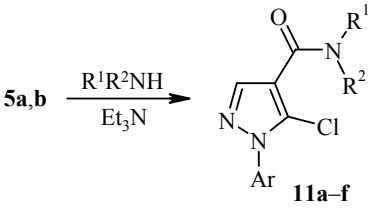
The acyl chloride **5a** interacts smoothly with hydrazine hydrate with the formation of hydrazide **8**. The latter was used by us to obtain 5-(5-chloro-1-phenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazole-2-thiol (**9**). The cyclization of hydrazide **8** by the action of carbon disulfide was evidenced by the disappearance from the IR spectra of the C=O group absorption band at 1655 cm^{-1}, of the $NHNH_2$ fragment at 3212-3286 cm^{-1}, and the appearance of a weak absorption band for the stretching vibrations of the SH group at 2782 cm^{-1}. In addition, in the ^1H NMR spectrum of oxadiazole **9** the signals of the $NHNH_2$ fragment protons at 4.46 and 9.53 ppm, characteristic for hydrazide **8**, were absent, and a signal appeared for the SH group proton as a broadened singlet at 14.70 ppm. Alkylation of the thio derivative **9** with ethyl iodide was carried out in DMF in the presence of K_2CO_3 at 20-25°C, and alkylation with 4-methylbenzyl chloride was carried out on refluxing in EtOH in the presence of Et_3N. Compounds **10a**,**b** were isolated in this way in 88 and 62% yield, respectively.



10 a R = Et, **b** R = 4-$MeC_6H_4CH_2$

It should be noted that similar compounds which contain a 1,3,4-oxadiazole heterocycle in the position 4 of the 5-chloro-1*H*-pyrazole fragment, were previously unknown. They may be of interest as biologically active substances (see by analogy [18-20]).

Pyrazolecarboxylic acid amides **11a-f** were formed on reacting 1-aryl-5-chloro-1*H*-pyrazole-4-carbonyl chlorides **5a**,**b** with amines.



11 a–c Ar = Ph, **d–f** Ar = 4-MeC_6H_4;
a, **d** R^1 = H, R^2 = *n*-Pr; **b**, **e** $R^1 = R^2$ = Me; **c**, **f** R^1 = H, R^2 = 4-MeC_6H_4

The composition and structure of products **8**, **9**, **10a**,**b**, **11a-f** were confirmed by the results of elemental analysis (Table 1) and by spectral data (Table 2). The signal of the proton at the C-3 atom of the pyrazole fragment at 7.97-8.42 ppm in the ^1H NMR spectra was a characteristic of them.

We have therefore investigated some conversions of 7-aryl-7*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4-ols under the action of phosphorus pentoxide, pentasulfide, and oxychloride, and it has been shown that the products formed in this way may be used to obtain various heterocyclic compounds.

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance DRX-500 instrument (500 and 125 MHz, respectively) in DMSO-d_6 solution (compounds **2b**, **3a**,**b**, **4a**,**b**, **6a-c**, **7a-c**, **8**, **9**, **10b**, **11a-f)** and $CDCl_3$ (compounds **5b**, **10a**), standard was TMS.

The COSY, NOESY, HSQC, and HMBC spectra were recorded using standard procedures with gradient separation of the signal. For the NOESY spectra τ_{mix} was 500 msec, for HMBC spectra τ_{mix} was 166 msec. Chromato-mass spectra were recorded using a liquid chromato-mass spectrometry system consisting of an Agilent 1100 series chromatograph with a fitted diode matrix with an Agilent LC\MSD SL mass selective detector. The parameters for chromato-mass spectrometry analysis were: column Zorbax SB-C18, 4.6×15 mm, 1.8 μm; solvents A) MeCN–H_2O, 95:5, 0.1% CF_3COOH, B) 0.1% aqueous CF_3COOH; eluent flow rate 3 ml/min; injection volume 1 μl; UV detectors 215, 254, 285 nm; chemical ionization at atmospheric pressure. Elemental analysis was carried out in the analytical laboratory of the Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine. Melting points were determined on a Fisher-Johns instrument. A check on the progress of reactions and the purity of the synthesized compounds was performed by TLC on Silufol UV-254 plates in a 10:1 $CHCl_3$–MeOH system.

The spectral characteristics of compound **2a** corresponded to literature values [5].

7-Aryl-7*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4-ols 2a,b (General Method). A solution of $NaNO_2$ (13.8 g, 20 mmol) in water (50 ml) was added dropwise over 40 min at -3°C to a solution of pyrazole **1a** [6] or **1b** [21] (10 mmol) in conc. HCl (600 ml). The reaction mixture was stirred at the same temperature for 2 h, then at 20°C for 10 h. The precipitated solid was filtered off, washed with H_2O, EtOH, and dried. Analytically pure compounds **2a**,**b** were obtained, which were used for subsequent conversions without further purification.

6-(5-Amino-1-aryl-1*H*-pyrazol-4-yl)-1-arylpyrazolo[3,4-*d*][1,3]oxazin-4(1*H*)-ones 3a,b (General Method). A mixture of compound **2a** or **2b** (10 mmol), P_2O_5 (2.98 g, 21 mmol) in abs. dioxane (50 ml) was refluxed for 3 h with vigorous stirring, during which a rapid evolution of gas and resinification were observed. The mixture was cooled to 20-25°C, the solution decanted, and the solvent removed at reduced pressure. 2-PrOH (2 ml) was added, the solid was filtered off, and purified by recrystallization.

Compound 3a. IR spectrum, ν, cm^{-1}: 3456, 3343 (NH_2); 1777 (C=O); 1627, 1585, 1541, 1506.

Compound 3b. ^{13}C NMR spectrum, δ, ppm: 21.1 ($2CH_3$); 95.0 (C-4 pyrazole); 99.0 (C-3a); 122.7, 124.1, 130.3, 130.4, 135.4, 135.7, 137.8, 138.0 (C 2Ar); 138.3 (C-3 pyrazolooxazine); 139.5 (C-3 pyrazole); 149.5 (C-7a); 151.2 (C-6 pyrazolooxazine); 154.7 (C-5 pyrazole); 160.3 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 397 $[M-H]^+$ (85).

6-(5-Amino-1-aryl-1*H*-pyrazol-4-yl)-1-arylpyrazolo[3,4-*d*][1,3]thiazine-4(1*H*)-thiones 4a,b (General Method). A mixture of compound **2a** or **2b** (2 mmol) and P_2S_5 (0.533 g, 2.4 mmol) in abs. dioxane (20 ml) was refluxed for 3 h with vigorous stirring, then cooled to 20-25°C. The solution was decanted, the solvent was removed under reduced pressure, 2-PrOH (2 ml) was added, the solid was filtered off, dried, and recrystallized.

Compound 4a. ^{13}C NMR spectrum, δ, ppm: 100.9 (C-4 pyrazole); 117.2 (C-3a); 124.2, 124.4, 128.5, 128.8, 129.9, 130.0, 137.5, 137.9 (C 2Ph); 137.5 (C-3 pyrazolothiazine); 139.4 (C-3 pyrazole); 146.6 (C-7a); 147.8 (C-6); 166.6 (C-5 pyrazole); 197.7 (C=S). Mass spectrum, *m/z* (I_{rel}, %): 402 $[M]^+$ (100).

Compound 4b. IR spectrum, ν, cm^{-1}; 3428, 3309 (NH_2); 1604, 1551, 1512, 1478. ^{13}C NMR spectrum, δ, ppm: 21.2 ($2CH_3$); 100.8 (C-4 pyrazole), 117.2 (C-3a); 124.0, 124.5, 130.3, 130.4, 135.1, 135.5, 138.2, 138.3 (C 2Ar); 138.3 (C-3 pyrazolothiazine); 139.1 (C-3 pyrazole); 146.5 (C-7a); 147.7 (C-6); 166.7 (C-5 pyrazole); 194.6 (C=S).

1-Aryl-5-chloro-1*H*-pyrazole-4-carbonyl Chlorides 5a,b (General Method). Abs. DMF (5 ml) was added dropwise to a mixture of compound **2a** or **2b** (20 mmol) and $POCl_3$ (50 ml) at a rate sufficient to boil the mixture. The solution was then refluxed for 2 h, and the excess of $POCl_3$ was removed at reduced pressure. The oily residue was extracted with hot abs. benzene (700 ml). The benzene was removed at reduced pressure and the residue was purified by recrystallization.

Compound **5b**. IR spectrum, ν, cm^{-1}: 1770 (C=O), 1511, 1409.

***N*'-Acyl-5-chloro-1-phenyl-1*H*-pyrazole-4-carbohydrazides 6a-c (General Method)**. A mixture of compound **5a** (0.482 g, 2 mmol), the hydrazide of the appropriate acid (2 mmol), and Et_3N (0.202 g, 2 mmol) in abs. EtOH (10 ml) was refluxed for 2 h. The precipitated solid was filtered off, dried, and analyzed without further purification.

Compound 6a. ^{13}C NMR spectrum, δ, ppm: 113.4 (C-4 pyrazole); 129.8 (C-5 pyrazole); 126.2, 128.0, 129.0, 129.8, 129.9, 132.4, 133.0, 137.6 (C 2Ph); 140.4 (C-3 pyrazole); 160.5 (C=O); 166.4 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 339 $[M-H]^+$ (98).

Compound 6b. IR spectrum, ν, cm^{-1}: 3212, 3008 ($NHNH_2$), 1674 (C=O), 1640 (C=O), 1561, 1499.

5-R-2-(5-Chloro-1-phenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazoles 7a-c (General Method). Compound **6a-c** (1 mmol) was refluxed for 2 h with $SOCl_2$ (5 ml). The excess of $SOCl_2$ was removed under reduced pressure. The residue was treated with water, the solid was filtered off, and purified by recrystallization.

Compound 7a. Mass spectrum, *m/z* (I_{rel}, %): 323 $[M+H]^+$ (97).

Compound 7b. IR spectrum, ν, cm^{-1}: 1623, 1595, 1551, 1501, 1424, 1397.

5-Chloro-1-phenyl-1*H*-pyrazole-4-carbohydrazide (8). A mixture of compound **5a** (0.964 g, 4 mmol) and $N_2H_4 \cdot H_2O$ (10 ml) was stirred at 20-25°C for 12 h. The solid was filtered off, washed with water, dried, and purified by recrystallization. IR spectrum, ν, cm^{-1}: 3286, 3212 ($NHNH_2$), 1655 (C=O), 1624, 1554, 1503, 1458. ^{13}C NMR spectrum, δ, ppm: 114.3 (C-4 pyrazole); 126.1 (C-2,6 Ph); 128.5 (C-5 pyrazole); 129.6 (C-1 Ph); 129.8 (C-3,5 Ph); 137.7 (C-4 Ph); 140.1 (C-3 pyrazole); 160.9 (C=O).

5-(5-Chloro-1-phenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazole-2-thiol (9). A mixture of compound **8** (0.592 g, 2.5 mmol), Et_3N (0.505 g, 5.0 mmol), and CS_2 (0.570 g, 7.5 mmol) in abs. MeCN (25 ml) was heated for 4 h at 50°C. The solvent was removed under reduced pressure, the residue was treated with H_2O (10 ml), the precipitated solid was filtered off, and compound **9** was obtained in an analytically pure state. IR spectrum, ν, cm^{-1}: 2782 (S–H); 1638, 1504, 1424, 1403. ^{13}C NMR spectrum, δ, ppm: 105.3 (C-4 pyrazole); 126.0 (C-2,6 Ph); 127.9 (C-5 pyrazole); 130.0 (C-3,5 Ph); 130.1 (C-1 Ph); 137.4 (C-4 Ph); 140.2 (C-3 pyrazole); 155.1 (C-5 pyrazole); 177.2 (C–S). Mass spectrum, *m/z* (I_{rel}, %): 277 $[M-H]^+$ (100).

2-(5-Chloro-1-phenyl-1*H*-pyrazol-4-yl)-5-ethylsulfanyl-1,3,4-oxadiazole (10a). A mixture of compound **9** (0.557 g, 2 mmol), K_2CO_3 (0.828 g, 6 mmol), and EtI (1.248 g, 8 mmol) in abs. DMF (5 ml) was stirred at 20-25°C for 16 h. The mixture was poured onto ice and extracted with CH_2Cl_2 (3×20 ml). The solvent was removed under reduced pressure, petroleum ether (bp 60-95°C) (50 ml) was added, the solvent was evaporated to dryness, and a yellow oil was obtained, which was analyzed without further purification.

2-(5-Chloro-1-phenyl-1*H*-pyrazol-4-yl)-5-{[(4-methylphenyl)methyl]sulfanyl}-1,3,4-oxadiazole (10b). A mixture of compound **9** (0.139 g, 0.50 mmol), Et_3N (0.076 g, 0.75 mmol), and 4-methylbenzyl chloride (0.085 g, 0.70 mmol) in abs. EtOH (7 ml) was refluxed for 3 h. The solvent was removed at reduced pressure, the residue was treated with H_2O, the resulting precipitate was filtered off, and purified by recrystallization.

***N*-R^{1}R^2-5-Chloro-1-phenyl-1*H*-pyrazole-4-carboxamides 11a-f (General Method)**. A mixture of compound **5a**,**b** (2 mmol), the corresponding amine (2 mmol), and Et_3N (0.202 g, 2 mmol) in abs. benzene (5 ml) was stirred at 20-25°C for 12 h, and the solvent was removed at reduced pressure. Water (30-50 ml) was added to the residue, the precipitated solid was filtered off, dried, and purified by recrystallization.

Compound 11a. ^{13}C NMR spectrum, δ, ppm: 11.9 (CH_3); 21.2 ($NCH_2\underline{C}H_2CH_3$); 40.9 ($N\underline{C}H_2CH_2CH_3$); 115.6 (C-4 pyrazole); 126.0 (C-2,6 Ph); 128.3 (C-5 pyrazole); 130.2 (C-3,5 Ph); 135.4 (C-1 Ph); 139.4 (C-4 Ph); 140.3 (C-3 pyrazole); 160.7 (C=O).

Compound 11d. IR spectrum, ν, cm^{-1}: 3277 (N–H), 1639 (C=O), 1567, 1517. Mass spectrum, *m/z* (I_{rel},%): 278 $[M]^+$ (100).

Compound 11e. IR spectrum, ν, cm^{-1}: 3109 (N–H), 1620 (C=O), 1543, 1515, 1403. Mass spectrum, *m/z* (I_{rel}, %): 264 $[M]^+$ (100).

Compound 11f. IR spectrum, ν, cm^{-1}: 3257 (N–H), 1645 (C=O), 1600, 1551, 1516, 1402. Mass spectrum, *m/z* (I_{rel}, %): 326 $[M]^+$ (100).

X-Ray Structural Investigation of Compound 3b. Monocrystal with linear dimensions 0.39×0.35×0.15 mm. Investigation was carried out at room temperature on a Bruker Smart Apex II diffractometer (λMoKα radiation, graphite monochromator, θ_{max} 27.5°, segment of sphere $-23 \le h \le 23$, $-5 \le k \le 5$, $-20 \le l \le 35$). Overall 10414 reflections were taken, of which 3035 were independent (average *R* factor

0.0834). A correction for absorption was introduced with the SADABS program by the multiscanning method (T_{min}/T_{max} 0.1527), and a correction was also introduced for isotropic extinction (0.0084(10)). Crystals of compound **3b** ($C_{22}H_{18}N_6O_2$, M 398.42) were rhombic, space group $Pca2_1$, a 17.815(4), b 3.8805(10), c 27.377(7) Å; V 1892.6(8) Å^3; Z 4; d_{calc} 1.398 g/cm^3, μ 0.094 mm^{-1}, F(000) 832. The structure was solved by the direct method and refined by least squares in a full-matrix anisotropic approximation using the Bruker SHELXTL set of programs [22]. Hydrogen atoms H(1) and H(2), which participate in the formation of hydrogen bonds, were found and refined isotropically, the positions of the remaining hydrogen atoms were determined geometrically. In the refinement 1660 reflections were used with $I > 2\sigma(I)$, 280 parameters were refined, number of reflections per parameter was 5.9. A weighting scheme was used $\omega = 1/(\sigma^2(Fo^2) + (0.0467P)^2)$, where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximum (mean) displacement to the error in the last cycle was 0.002 (0.000). The final values of the probability factors were $R1(F)$ 0.0476, $wR2(F^2)$ 0.094 for reflections with $I > 2\sigma(I)$, $R1(F)$ 0.1128, $wR2(F^2)$ 0.1204, $GOOF$ 0.967 at each independent reflection. The residual electron density from the Fourier difference series after the final refinement cycle was 0.16 and -0.17 e/Å^3.

X-Ray Structural Investigation of Compound 7a. Monocrystal with linear dimensions 0.43×0.27×0.10 mm. Investigation was carried out at room temperature on a Bruker Smart Apex II diffractometer (λMoKα radiation, graphite monochromator, θ_{max} 26.93°, segment of sphere $-9 \le h \le 9$, $-16 \le k \le 16$, $-18 \le l \le 19$). Overall 15082 reflections were gathered, of which 3225 were independent (mean R factor 0.0463). A correction was introduced for absorption with the SADABS program by the multiscanning method (T_{min}/T_{max} 0.774319). The crystals of compound **7a** ($C_{17}H_{11}ClN_4O$, M 322.75) were rhombic, space group $P2_12_12_1$; a 7.4094(3), b 12.9429(5), c 15.6245(6) Å; V 1498.38(10) Å^3; Z 4; d_{calc} 1.431 g/cm^3; μ 0.265 mm^{-1}, F(000) 664. The structure was solved by the direct method and refined by least squares in a full-matrix anisotropic approximation using the Bruker SHELXTL set of programs [22]. The positions of all hydrogen atoms were determined geometrically. In the refinement 2384 reflections were used with $I > 2\sigma(I)$, 208 parameters were refined , number of reflections per parameter 11.4, the weighting scheme used was $\omega = 1/(\sigma^2(Fo^2) + (0.0296P)^2 + 0.1849P)$, where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximum (mean) displacement to the error in the last cycle was 0.002(0.000). The final values of the probability factors were $R1(F)$ 0.0376, $wR2(F^2)$ 0.0709 on reflections with $I > 2\sigma(I)$, and $R1(F)$ 0.0681, $wR2(F^2)$ 0.0805, $GOOF$ 1.02 at each independent reflection. The Flack parameter was 0.04(7). The residual electron densities from a Fourier difference series after the last cycle of refinement were 0.14 and -0.16 e/Å^3,

The coordinates of atoms, the geometric parameters of the molecules, and the crystallographic data have been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 857126 for compound **3b** and CCDC 857127 for compound **7a**).

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