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# POLYFUNCTIONAL PYRAZOLES. 8*. SYNTHESIS OF 6-ALKYL-2-ARYL-2*H*-PYRAZOLO[4,3-*d*]PYRIMIDINE-5,7(4*H*,6*H*)-DIONES BASED ON ETHYL 1-ARYL-4-ISOCYANATOPYRAZOLE-3-CARBOXYLATES

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*A method for the preparation of 6-alkyl-2-aryl-2H-pyrazolo[4,3-d]pyrimidine-5,7(4H,6H)-diones in reaction of ethyl 1-aryl-4-isocyanatopyrazole-3-carboxylates with aliphatic amines followed by cyclization of the obtained 4-ureidopyrazole-3-carboxylic acid esters in the presence of bases is proposed.*

**Keywords:** 6-alkyl-2-arylpyrazolo[4,3-*d*]pyrimidine-5,7-diones, 1-aryl-3-ethoxycarbonylpyrazole-4-carboxylic acids, 1-aryl-4-ureidopyrazole-3-carboxylic acids, ethyl 1-aryl-4-formylpyrazole-3-carboxylates, ethyl 1-aryl-4-isocyanatopyrazole-3-carboxylates, intramolecular cyclization.

Pyrazolo[4,3-*d*]pyrimidine-5,7-diones are pharmacologically promising heterocyclic systems. An important reason for their systematic investigation is the discovery among them of the C-nucleoside antibiotic oxoformycin B [2], stimulants of insulin secretion [3], corticotropin-releasing factor receptor antagonists [4], and selective calcitonin inducers [5]. Representatives of pyrazolo[4,3-*d*]pyrimidine-5,7-diones are also important synthons for the design of adenosine receptor antagonists [6, 7] and fluorescent probes in receptor-binding enzymatic systems [8].

Two methods are usually employed for the preparation of pyrazolo[4,3-*d*]pyrimidine-5,7-diones. The first method is based on pyrazole annelation of polyfunctional uracils [5, 9-11]. The second is based on the principle of the formation of a pyrimidine ring as a result of intramolecular condensation of amides [12-15] or esters [16] of 4-aminopyrazole-3-carboxylic acids. It should be mentioned that in the last case toxic and challenging alkyl isocyanates are used as electrophilic component for the closure of the pyrimidine ring. Moreover, the synthetic value of the method is low due to the complexity of isolation of the initial 4-aminopyrazole-5-carboxylates, which are formed in a mixture with the isomeric 4-aminopyrazole-5-carboxylates.

We have proposed a more effective and scalable method for the synthesis of 6-alkyl-2-arylpyrazolo-[4,3-*d*]pyrimidine-5,7-diones that requires the use of ethyl 4-isocyanatopyrazole-3-carboxylates **3a**,**b** as key

*For Communication 7, see [1].

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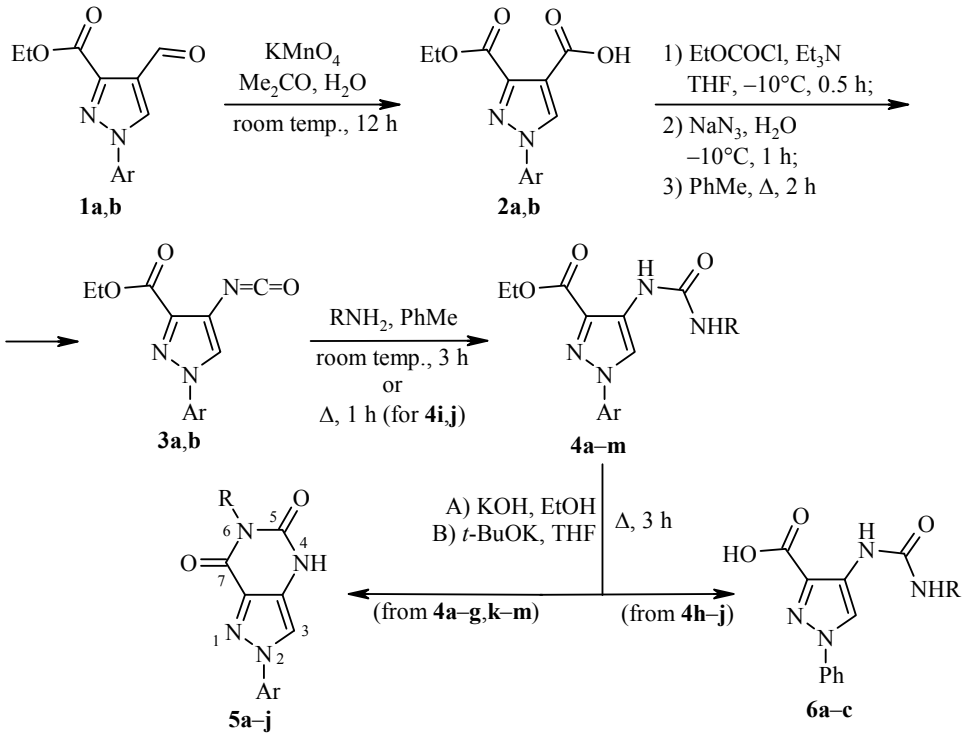
synthetic intermediates. These compounds are formed smoothly by a modified Curtius reaction [17] from 3-ethoxycarbonylpyrazole-4-carboxylic acids **2a**,**b**, which obtained through oxidation of the accessible [18] 4-formylpyrazole-3-carboxylates **1a**,**b**. It was shown that the use of 4-isocyanatopyrazoles **3a**,**b** has an advantage over the use of 4-aminopyrazoles [16] since it is possible to obtain a wide range of pyrazolylureas **4a-m** in reaction with primary amines, including those containing *N*-alkyl-functionalized substituents in the ureide fragment. The presence of these substituents is essential for the subsequent modifications of the pyrazolo[4,3-*d*]pyrimidinedione system.

Investigation toward intramolecular cyclization of compounds **4a-m** showed that the substituent R in the ureide fragment plays a significant role in a process. Thus, upon treatment with potassium hydroxide (method A) or potassium *tert*-butoxide (method B) the ureido esters **4a-g**,**k-m** containing sterically unhindered alkyl substituents undergo intramolecular cyclization with the formation of pyrazolo[4,3-*d*]pyrimidinediones **5a-j** with yields of 57-78% (Table 1). On the other hand, under analogous conditions *N*-cyclohexyl- or *N*-arylureido esters (compounds **4h** or **4i**,**j**, respectively) are not susceptible to closure of the pyrimidine ring but undergo hydrolysis of the ethoxycarbonyl group with the formation of the ureido acids **6a-c**. This fact confirms the predominant effect of the steric and electronic factors of the substituents at the N-3 atom of the ureide group on the pyrimidine annelation of compound **4**.




**1–3 a**, **4a–j**, **5a–g**, **6a–c** Ar = Ph, **1–3 b**, **4k–m**, **5h–j** Ar = 4-$BrC_6H_4$;
**4**, **5 a** R = *n*-$C_4H_9$; **b** R = $(CH_2)_2OH$; **c** R = $(CH_2)_2NMe_2$; **e** R = 4-$ClC_6H_4CH_2$; **f** R = 4-$MeC_6H_4CH_2$;
**4d**,**k**, **5d**,**h** R = $PhCH_2$; **4g**,**m**, **5g**,**j** R = 4-$MeOC_6H_4(CH_2)_2$; **4l**, **5i** R = 4-$MeOC_6H_4CH_2$;
**4h**, **6a** R = *cyclo*-$C_6H_{11}$; **4i**, **6b** R = Ph; **4j**, **6c** R = 4-$MeC_6H_4$

The starting isocyanates **3a**,**b** are light-yellow crystals that are sensitive to atmospheric moisture and require the use of dry solvents. Their structure is consistent with the results of $^1$H NMR spectroscopy and also with the data from the IR spectra, in which strong absorption bands for the C=O (1730 $cm^{-1}$) and N=C=O (2250 $cm^{-1}$) groups are observed. The structure and composition of the intermediate ureido carboxylates **4a-m** and also of the final products **5a-j**, **6a-c** were confirmed by complex physicochemical investigation using elemental analysis, chromato-mass spectrometry, and IR and NMR spectroscopy (Tables 1-4).

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **4a-m**, **5a-j**

| Compound | Empirical formula | Found, % / Calculated, % | | | Mp, °C | Yield, % (method) |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **4a** | $C_{17}H_{22}N_4O_3$ | 61.78 / 61.80 | 6.79 / 6.71 | 16.88 / 16.96 | 90-91 | 84 |
| **4b** | $C_{15}H_{18}N_4O_4$ | 56.72 / 56.60 | 5.61 / 5.70 | 17.35 / 17.60 | 155-157 | 73 |
| **4c** | $C_{17}H_{23}N_5O_3$ | 59.31 / 59.12 | 6.91 / 6.71 | 20.38 / 20.28 | 103-104 | 70 |
| **4d** | $C_{20}H_{20}N_4O_3$ | 65.66 / 65.92 | 5.41 / 5.53 | 15.29 / 15.37 | 160-162 | 88 |
| **4e** | $C_{20}H_{19}ClN_4O_3$ | 59.96 / 60.23 | 4.61 / 4.80 | 13.85 / 14.05 | 178-179 | 92 |
| **4f** | $C_{21}H_{22}N_4O_3$ | 66.87 / 66.65 | 5.98 / 5.86 | 14.61 / 14.80 | 182-183 | 86 |
| **4g** | $C_{22}H_{24}N_4O_4$ | 64.93 / 64.69 | 5.86 / 5.92 | 13.87 / 13.72 | 105-106 | 77 |
| **4h** | $C_{19}H_{24}N_4O_3$ | 64.15 / 64.03 | 6.80 / 6.79 | 15.68 / 15.72 | 100-101 | 87 |
| **4i** | $C_{19}H_{18}N_4O_3$ | 65.08 / 65.13 | 5.18 / 5.18 | 16.01 / 15.99 | 134-135 | 90 |
| **4j** | $C_{20}H_{20}N_4O_3$ | 65.85 / 65.92 | 5.60 / 5.53 | 15.29 / 15.37 | 148-149 | 87 |
| **4k** | $C_{20}H_{19}BrN_4O_3$ | 54.41 / 54.19 | 4.19 / 4.32 | 12.48 / 12.64 | 160-161 | 81 |
| **4l** | $C_{21}H_{21}BrN_4O_4$ | 53.53 / 53.29 | 4.31 / 4.47 | 11.77 / 11.84 | 185-187 | 84 |
| **4m** | $C_{22}H_{23}BrN_4O_4$ | 54.03 / 54.22 | 4.91 / 4.76 | 11.36 / 11.50 | 150-151 | 73 |
| **5a** | $C_{15}H_{16}N_4O_2$ | 63.61 / 63.37 | 5.53 / 5.67 | 19.49 / 19.71 | 190-191 | 63 (A)<br>68 (B) |
| **5b** | $C_{13}H_{12}N_4O_3$ | 57.61 / 57.35 | 4.59 / 4.44 | 20.36 / 20.58 | 225-226 | 70 (A) |
| **5c** | $C_{15}H_{17}N_5O_2$ | 60.47 / 60.19 | 5.49 / 5.72 | 23.66 / 23.40 | 295-298 | 64 (B) |
| **5d** | $C_{18}H_{14}N_4O_2$ | 67.68 / 67.92 | 4.31 / 4.43 | 17.45 / 17.60 | 282-284 | 78 (B) |
| **5e** | $C_{18}H_{13}ClN_4O_2$ | 61.47 / 61.28 | 3.80 / 3.71 | 15.51 / 15.88 | >300 | 74 (A) |
| **5f** | $C_{19}H_{16}N_4O_2$ | 68.71 / 68.66 | 5.03 / 4.85 | 16.88 / 16.86 | 210-212 | 77 (A)<br>75 (B) |
| **5g** | $C_{20}H_{18}N_4O_3$ | 66.07 / 66.29 | 5.10 / 5.01 | 15.30 / 15.46 | 259-262 | 66 (B) |
| **5h** | $C_{18}H_{13}BrN_4O_2$ | 54.70 / 54.43 | 3.16 / 3.30 | 14.31 / 14.10 | 279-283 | 67 (A) |
| **5i** | $C_{19}H_{15}BrN_4O_3$ | 53.17 / 53.41 | 3.62 / 3.54 | 12.81 / 13.11 | 268-271 | 61 (B) |
| **5j** | $C_{20}H_{17}BrN_4O_3$ | 54.19 / 54.44 | 3.70 / 3.88 | 12.85 / 12.70 | 259-261 | 57 (B) |

Thus, it was established that ethyl 1-aryl-4-isocyanatopyrazole-3-carboxylates are convenient new starting compounds for the preparative synthesis of 6-alkyl-2-aryl-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones.

## EXPERIMENTAL

The IR spectra were recorded in $CH_2Cl_2$ (compounds **3a**,**b**) and in pellets with KBr (the other compounds) on a UR-20 spectrometer. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 and 125 MHz, respectively) in $CDCl_3$ (compounds **3a**,**b**) and DMSO-$d_6$ (the other

TABLE 2. The IR and Mass Spectra of Compounds **4a-m**, **5a-j**

| Compound | IR spectrum, ν, $cm^{-1}$ | | Mass, spectrum *m/z* $[M+H]^+$ | Compound | IR spectrum, ν, $cm^{-1}$ | | Mass, spectrum *m/z* $[M+H]^+$ |
|---|---|---|---|---|---|---|---|
| | C=O | NH | | | C=O | NH | |
| **4a** | 1690, 1725 | 3255, 3340 | 331 | **4m** | 1700, 1725 | 3255, 3345 | 488 |
| **4b*** | 1690, 1725 | 3260, 3345 | 319 | **5a** | 1675, 1715 | 3345 | 285 |
| **4c** | 1695, 1720 | 3240, 3335 | 346 | **5b***[2] | 1675, 1720 | 3360 | 273 |
| **4d** | 1700, 1730 | 3255, 3365 | 365 | **5c** | 1670, 1715 | 3365 | 300 |
| **4e** | 1690, 1730 | 3250, 3360 | 399 | **5d** | 1670, 1715 | 3350 | 319 |
| **4f** | 1685, 1730 | 3270, 3355 | 379 | **5e** | 1675, 1720 | 3360 | 353 |
| **4g** | 1700, 1725 | 3270, 3350 | 409 | **5f** | 1675, 1720 | 3370 | 333 |
| **4h** | 1695, 1720 | 3245, 3345 | 357 | **5g** | 1680, 1720 | 3375 | 363 |
| **4i** | 1695, 1725 | 3250, 3360 | 351 | **5h** | 1675, 1715 | 3365 | 398 |
| **4j** | 1700, 1730 | 3245, 3355 | 365 | **5i** | 1670, 1715 | 3355 | 428 |
| **4k** | 1695, 1730 | 3245, 3365 | 444 | **5j** | 1675, 1720 | 3360 | 442 |
| **4l** | 1700, 1725 | 3250, 3360 | 474 | | | | |

* ν(OH) 3430.
*[2] ν(OH) 3405.

TABLE 3. The $^1$H NMR Spectra of Compounds **4a-m**, **5a-j**

| Compound | Chemical shifts, δ, ppm (*J*, Hz) |
|---|---|
| 1 | 2 |
| **4a** | 0.89 (3H, t, *J* = 6.8, $(CH_2)_3C\underline{H}_3$); 1.32-1.43 (7H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$, $OCH_2C\underline{H}_3$); 3.11 (2H, t, *J* = 6.6, $NHCH_2$); 4.38 (2H, q, *J* = 6.8, $OC\underline{H}_2CH_3$); 7.37-7.55 (4H, m, H Ph, NH); 7.83 (2H, d, *J* = 8.2, H Ph); 8.39 (1H, s, H-5); 8.68 (1H, s, NH) |
| **4b** | 1.35 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$); 3.19 (2H, t, *J* = 5.8, $NHC\underline{H}_2CH_2OH$); 3.57 (2H, t, *J* = 5.8, $NHCH_2C\underline{H}_2OH$); 4.38 (2H, q, *J* = 6.8, $OC\underline{H}_2CH_3$); 4.75 (1H, br. s, OH); 7.18-7.38 (4H, m, H Ph, NH); 7.83 (2H, d, *J* = 7.6, H Ph); 8.40 (1H, s, H-5); 8.82 (1H, s, NH) |
| **4c** | 1.37 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$); 2.17 (6H, s, $N(CH_3)_2$); 2.32 (2H, t, *J* = 6.0, $NHCH_2C\underline{H}_2NMe_2$); 3.21 (2H, t, *J* = 6.0, $NHC\underline{H}_2CH_2NMe_2$); 4.39 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 7.39-7.55 (4H, m, H Ph, NH); 7.84 (2H, d, *J* = 8.0, H Ph); 8.48 (1H, s, H-5); 8.69 (1H, s, NH) |
| **4d** | 1.36 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$); 4.39 (2H, d, *J* = 5.4, $C\underline{H}_2Ph$); 4.41 (2H, q, *J* = 6.8, $OC\underline{H}_2CH_3$); 7.26-7.90 (11H, m, H Ph, NH); 8.52 (1H, s, H-5); 8.70 (1H, s, NH) |
| **4e** | 1.36 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 4.32 (2H, d, *J* = 5.2, $C\underline{H}_2Ar$); 4.39 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 7.31 (2H, t, *J* = 7.6, H Ar); 7.33-7.44 (5H, m, H Ph); 7.84-7.92 (3H, m, H Ar, NH); 8.53 (1H, s, H-5); 8.69 (1H, s, NH) |
| **4f** | 1.36 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$); 2.29 (3H, s, $ArC\underline{H}_3$); 4.28 (2H, d, *J* = 5.4, $C\underline{H}_2Ar$); 4.39 (2H, q, *J* = 6.8, $OC\underline{H}_2CH_3$); 7.15 (2H, d, *J* = 7.6, H Ar); 7.20 (2H, d, *J* = 7.6, H Ar); 7.38 (1H, t, *J* = 7.6, H Ph); 7.53 (2H, t, *J* = 7.6, H Ph); 7.84-7.88 (3H, m, H Ph, NH); 8.49 (1H, s, H-5); 8.70 (1H, s, NH) |
| **4g** | 1.36 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 2.70 (2H, t, *J* = 6.8, $NHCH_2C\underline{H}_2Ar$); 3.31 (2H, t, *J* = 6.8, $NHC\underline{H}_2CH_2Ar$); 3.73 (3H, s, $OCH_3$); 4.38 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 6.87 (2H, d, *J* = 8.0, H Ar); 7.16 (2H, d, *J* = 8.0, H Ar); 7.37-7.56 (4H, m, H Ph, NH); 7.85 (2H, d, *J* = 8.0, H Ph); 8.42 (1H, s, H-5); 8.70 (1H, s, NH) |
| **4h** | 1.06-1.08 (13H, m, $5CH_2$, $OCH_2C\underline{H}_3$); 3.48-3.53 (1H, m, $NHC\underline{H}$); 4.39 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 7.28-7.55 (4H, m, H Ph, NH); 7.83 (2H, d, *J* = 7.2, H Ph); 8.38 (1H, s, H-5); 8.67 (1H, s, NH) |
| **4i** | 1.38 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$); 4.41 (2H, q, *J* = 6.8, $OC\underline{H}_2CH_3$); 6.99 (1H, t, *J* = 7.2, H Ph); 7.29-7.42 (7H, m, H Ph); 7.87 (2H, d, *J* = 7.6, H Ph); 8.76 (1H, s, H-5); 8.82 (1H, s, NH); 9.84 (1H, s, NH) |
| **4j** | 1.35 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 2.38 (3H, s, $ArC\underline{H}_3$); 4.42 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.09 (2H, d, *J* = 7.6, H Ar); 7.39-7.56 (5H, m, H Ph); 7.87 (2H, d, *J* = 7.6, H Ar); 8.76 (1H, s, H-5); 8.81 (1H, s, NH); 9.74 (1H, s, NH) |

TABLE 3 (continued)

| 1 | 2 |
|---|---|
| **4k** | 1.35 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 4.34 (2H, d, *J* = 5.6, $C\underline{H}_2Ph$); 4.40 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 7.24-7.39 (5H, m, H Ph); 7.72 (2H, d, *J* = 7.8, H Ar); 7.86-7.91 (3H, m, H Ar, NH); 8.51 (1H, s, NH); 8.73 (1H, s, H-5) |
| **4l** | 1.35 (3H, t, *J* = 6.8, $OCH_2C\underline{H}_3$); 3.74 (3H, s, $OCH_3$); 4.25 (2H, d, *J* = 5.6, $C\underline{H}_2Ar$); 4.38 (2H, q, *J* = 6.8, $OC\underline{H}_2CH_3$); 6.86 (2H, d, *J* = 8.2, H Ar); 7.23 (2H, d, *J* = 8.2, H Ar); 7.70 (2H, d, *J* = 8.4, H Ar); 8.81-8.86 (3H, m, H Ar, NH); 8.47 (1H, s, NH); 8.74 (1H, s, H-5) |
| **4m** | 1.35 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 2.70 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2Ar$); 3.31-3.38 (2H, m, $NHC\underline{H}_2CH_2Ar$); 4.38 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 6.86 (2H, d, *J* = 8.4, H Ar); 7.16 (2H, d, *J* = 8.4, H Ar); 7.44 (1H, s, NH); 7.71 (2H, d, *J* = 8.4, H Ar); 7.84 (2H, d, *J* = 8.4, H Ar); 8.41 (1H, s, NH); 8.72 (1H, s, H-5) |
| **5a** | 0.93 (3H, t, *J* = 7.0, $NH(CH_2)_3C\underline{H}_3$); 1.40-1.47 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$); 3.62 (2H, *J* = 6.2, $NHC\underline{H}_2$); 7.38-7.54 (3H, m, H Ph); 7.88 (2H, d, *J* = 8.0, H Ph); 8.42 (1H, s, H-3); 11.22 (1H, s, NH) |
| **5b** | 3.55 (2H, t, *J* = 6.0, $NC\underline{H}_2CH_2OH$); 3.99 (2H, t, *J* = 6.0, $NCH_2C\underline{H}_2OH$); 4.80 (1H, br. s, OH); 7.42-7.51 (3H, m, H Ph); 7.95 (2H, d, *J* = 7.8, H Ph); 8.39 (1H, s, H-3); 11.32 (1H, s, NH) |
| **5c** | 2.20 (6H, s, $N(CH_3)_2$); 3.42 (2H, t, *J* = 6.0, $NCH_2C\underline{H}_2NMe_2$); 4.00 (2H, t, *J* = 6.0, $NC\underline{H}_2CH_2NMe_2$); 7.27-7.43 (3H, m, H Ph); 7.94 (2H, d, *J* = 7.6, H Ph); 8.37 (1H, s, H-3); 11.38 (1H, br. s, NH) |
| **5d** | 5.10 (2H, s, $C\underline{H}_2Ph$); 7.25-7.84 (10H, m, H Ph); 8.41 (1H, s, H-3); 11.46 (1H, s, NH) |
| **5e** | 5.07 (2H, s, $C\underline{H}_2Ar$); 7.36-7.57 (7H, m, H Ar); 7.95 (2H, d, *J* = 7.6, H Ar); 8.41 (1H, s, H-3); 11.49 (1H, s, NH) |
| **5f** | 5.05 (2H, s, $C\underline{H}_2Ar$); 7.10-7.56 (7H, m, H Ar); 7.96 (2H, d, *J* = 7.8, H Ar); 8.39 (1H, s, H-3); 11.46 (1H, s, NH) |
| **5g** | 2.81 (2H, t, *J* = 6.8, $NHCH_2C\underline{H}_2Ar$); 3.73 (3H, s, $OCH_3$); 4.07 (2H, t, *J* = 6.8, $NHC\underline{H}_2CH_2Ar$); 6.84 (2H, d, *J* = 8.4, H Ar); 7.15 (2H, d, *J* = 7.6, H Ph); 7.44 (1H, t, *J* = 7.8, H Ph); 7.57 (2H, d, *J* = 8.0, H Ph); 7.96 (2H, d, *J* = 8.4, H Ar); 8.38 (1H, s, H-3); 11.35 (1H, s, NH) |
| **5h** | 5.09 (2H, s, $C\underline{H}_2Ph$); 7.25-7.35 (5H, m, H Ph); 7.72 (2H, d, *J* = 8.0, H Ar); 7.94 (2H, d, *J* = 8.0, H Ar); 8.44 (1H, s, H-3); 11.49 (1H, s, NH) |
| **5i** | 3.73 (3H, s, $OCH_3$); 5.03 (2H, s, $C\underline{H}_2Ar$); 6.86 (2H, d, *J* = 7.8, H Ar); 7.29 (2H, d, *J* = 7.8, H Ar); 7.73 (2H, d, *J* = 8.0, H Ar); 7.91 (2H, d, *J* = 8.0, H Ar); 8.34 (1H, s, H-3); 11.29 (1H, s, NH) |
| **5j** | 2.79 (2H, t, *J* = 7.0, $NHCH_2C\underline{H}_2Ar$); 3.73 (3H, s, $OCH_3$); 4.05 (2H, t, *J* = 7.0, $NHC\underline{H}_2CH_2Ar$); 6.86 (2H, d, *J* = 8.0, H Ar); 7.15 (2H, d, *J* = 8.0, H Ar); 7.74 (2H, d, *J* = 8.4, H Ar); 7.93 (2H, d, *J* = 8.4, H Ar); 8.40 (1H, s, H-3); 11.37 (1H, s, NH) |

compounds) with TMS as internal standard. The mass spectra were recorded on an Agilent LC/MSD SL chromato-mass spectrometer; Zorbax SB-C18 column, 4.6×15 mm, 1.8 μm (PN 82(c)75-932). Solvents: A – MeCN–$H_2O$, 95:5, 0.1% trifluoroacetic acid; B – 0.1% aqueous trifluoroacetic acid; eluent flow rate 3 ml/min; injection volume 1 μl; UV detectors 215, 254, 285 nm; chemical ionization at atmospheric pressure, scan range *m*/*z* 80-1000. Elemental analysis was performed on a Perkin-Elmer CHN Analyzer in the analytical laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. The melting points were determined on a Kofler hot bench and were not corrected. Compounds **1a**,**b** were obtained by the described method [18].

**1-Aryl-3-(ethoxycarbonyl)-1*H*-pyrazole-4-carboxylic acids 2a,b (General Method)**. The ester **1a**,**b** (0.05 mol) in acetone (50 ml) was added with stirring to a suspension of $KMnO_4$ (7.90 g, 0.05 mol) in acetone (50 ml) and water (10 ml) at such a rate that the temperature of the reaction mixture did not exceed 20°C. The reaction mixture was stirred at room temperature for 12 h and poured into iced water (200 ml). The solid precipitate was filtered off and washed with of $H_2O$ (100 ml), and the filtrate was acidified with 20% HCl (10 ml). The solid precipitate was filtered off, washed with water (3×50 ml), dried, and recrystallized from EtOH.

**Compound 2a**. Yield 9.44 g (73%). White crystals, mp 139-140°C. IR spectrum, ν, $cm^{-1}$: 1730 (C=O), 2540-2850 (COOH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 4.34 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 7.39-7.42 (1H, m, H Ph); 7.50-7.55 (2H, m, H Ph); 7.92 (2H, d, *J* = 7.8, H Ph); 9.18 (1H, s, H-5); 11.98 (1H, s, COOH). Found, %: C 60.23; H 4.76; N 10.90. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60.00; H 4.65; N 10.76.

TABLE 4. The $^{13}C$ NMR Spectra of Compounds **4a-m**, **5a-j**

| Compound | Chemical shifts, δ, ppm | | | | | |
|---|---|---|---|---|---|---|
| | C-3 | C-3a | C-5 | C-7 | C-7a | R, Ar |
| **5a** | 112.8 | 132.1 | 150.2 | 157.3 | 138.7 | 17.8; 20.8; 31.4; 46.5; 119.3; 126.6; 127.4; 129.4 |
| **5b** | 112.7 | 132.2 | 150.1 | 157.4 | 138.9 | 44.4; 60.3; 119.9; 125.4; 127.0; 128.8 |
| **5c** | 112.6 | 132.0 | 150.5 | 157.3 | 139.1 | 37.8; 45.0; 56.4; 119.4; 127.0; 127.6; 129.2 |
| **5d** | 113.0 | 131.9 | 150.6 | 157.3 | 139.1 | 41.1; 119.4; 126.9; 127.1; 127.3; 127.8; 128.2; 129.5; 137.5 |
| **5e** | 113.1 | 131.9 | 150.5 | 157.4 | 139.1 | 42.5; 119.5; 127.1; 128.2; 129.3; 129.6; 129.9; 131.6; 136.5 |
| **5f** | 113.0 | 132.0 | 150.6 | 157.3 | 139.1 | 20.6; 45.8; 119.4; 127.1; 127.4; 127.8; 128.7; 129.6; 134.5; 136.0 |
| **5g** | 112.7 | 132.0 | 150.4 | 157.1 | 139.1 | 32.6; 41.7; 54.7; 113.7; 119.3; 127.0; 127.8; 129.4; 129.5; 130.4; 157.7 |
| **5h** | 113.1 | 132.4 | 150.5 | 157.3 | 138.3 | 43.1; 120.4; 126.7; 126.9; 127.1; 127.2; 127.3 |
| **5i** | 113.1 | 132.4 | 150.5 | 157.2 | 138.4 | 42.5; 55.0; 113.6; 120.4; 121.4; 127.1; 129.1; 129.5; 132.3; 158.3 |
| **5j** | 112.8 | 132.1 | 150.4 | 157.3 | 139.0 | 32.7; 42.0; 54.4; 113.8; 120.3; 121.5; 127.3; 129.1; 130.0; 132.4; 158.6 |

**Compound 2b**. Yield 10.30 g (61%). Light-yellow crystals, mp 168-170°C. IR spectrum, ν, $cm^{-1}$: 1730 (C=O), 2520-2860 (COOH). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 1.43 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.28 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.63 (2H, d, *J* = 8.2, H Ar); 7.97 (2H, d, *J* = 8.2, H Ar); 9.16 (1H, s, H-5); 12.11 (1H, s, COOH). Found, %: C 45.80; H 3.10; N 8.08. $C_{13}H_{11}BrN_2O_4$. Calculated, %: C 46.04; H 3.27; N 8.26.

**Ethyl 1-Aryl-4-isocyanato-1*H*-pyrazole-3-carboxylates 3a,b (General Method)**. Ethyl chloroformate (1.65 g, 0.015 mol) was added to a solution of the acid **2a**,**b** (0.010 mol) and $Et_3N$ (2.7 ml, 0.020 mol) in THF (30 ml) with stirring and cooling to -10°C. The mixture was stirred at this temperature for 0.5 h, and $NaN_3$ (1.62 g, 0.025 mol) in $H_2O$ (10 ml) was then added. The mixture was stirred at -10°C for a further 1 h. The reaction mixture was poured into iced water (100 ml), extracted with PhMe (3×25 ml), dried over anhydrous $MgSO_4$, filtered, and refluxed until the release of nitrogen had stopped (~2 h). The toluene was evaporated under vacuum, and the solid residue was recrystallized from a 3:1 mixture of benzene and hexane.

**Compound 3a**. Yield 2.10 g (82%). Light-yellow crystals, mp 93-95°C. IR spectrum, ν, $cm^{-1}$: 1730 (C=O), 2250 (N=C=O). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 1.44 (3H, t, *J* = 7.4, $OCH_2C\underline{H}_3$); 4.47 (2H, q, *J* = 7.4, $OC\underline{H}_2CH_3$); 7.34 (1H, t, *J* = 7.6, H Ph); 7.46 (2H, t, *J* = 7.8, H Ph); 7.66 (2H, d, *J* = 7.8, H Ph); 7.77 (1H, s, H-5). Found, %: C 60.30; H 4.35; N 16.16. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

**Compound 3b**. Yield 2.57 g (77%). Yellow crystals, mp 118-120°C. IR spectrum, ν, $cm^{-1}$: 1730 (C=O), 2250 (N=C=O). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 4.30 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 7.61 (2H, d, *J* = 8.4, H Ar); 7.80 (1H, s, H-5); 7.95 (2H, d, *J* = 8.4, H Ar). Found, %: C 46.22; H 2.90; N 12.35. $C_{13}H_{10}BrN_3O_3$. Calculated, %: C 46.45; H 3.00; N 12.50.

**Ethyl 4-({[Alkyl(aryl)amino]carbonyl}amino)-1-aryl-1*H*-pyrazole-3-carboxylates 4a-m (General Method)**. The corresponding amine (0.002 mol) was added to a solution of the isocyanate **3a**,**b** (0.002 mol) in PhMe (5 ml) and left at room temperature for 3 h (in the case of aliphatic amines) or refluxed for 1 h (in the case of aromatic amines). Hexane (5 ml) was added to the reaction mixture, and after 1 h the precipitate was filtered off, washed with hexane, dried, and recrystallized from EtOH.

**6-Alkyl-2-aryl-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones 5a-j and 1-Phenyl-4-ureido-1*H*-pyrazole-3-carboxylic Acids 6a-c (General Method)**. The ureido ester **4a-m** (0.001 mol) was added to a solution of KOH (0.12 g, 0.002 mol) in EtOH (10 ml) (method A) or *t*-BuOK (0.12 g, 0.001 mol) in THF (10 ml) (method B), and the mixture was refluxed for 3 h. The reaction mixture was acidified to pH 2 with 10% HCl, and the precipitate was filtered off, washed with water, dried, and recrystallized from AcOH.

**4-{[(Cyclohexylamino)carbonyl]amino}-1-phenyl-1*H*-pyrazole-3-carboxylic Acid (6a)**. Yield 0.21 g (63%, method A). White crystals, mp 235-237°C. IR spectrum, ν, $cm^{-1}$: 1665, 1710 (C=O), 2520-2830 (COOH),

3230-3300 (NH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.18-1.95 (10H, m, 5$CH_2$); 3.48-3.52 (1H, m, NHC<u>H</u>); 7.37-7.53 (4H, m, H Ph, NH); 7.83 (2H, d, *J* = 7.8, H Ph); 8.38 (1H, s, H-5); 8.65 (1H, s, NH); 13.11 (1H, s, COOH). Mass spectrum, *m*/*z* ($I_{rel}$, %): 329 $[M+H]^+$. Found, %: C 62.18; H 6.25; N 17.38. $C_{17}H_{20}N_4O_3$. Calculated, %: C 62.18; H 6.14; N 17.06.

**1-Phenyl-4-(3-phenylureido)-1*H*-pyrazole-3-carboxylic Acid (6b)**. Yield 0.24 g (75%, method B). White crystals, mp 231-233°C. IR spectrum, ν, $cm^{-1}$: 1670, 1705 (C=O), 2530-2870 (COOH), 3315-3345 (NH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.99-7.88 (10H, m, H Ph); 8.78 (1H, s, H-5); 8.86 (1H, s, NH); 9.88 (1H, s, NH); 13.27 (1H, br. s, COOH). $^{13}$C NMR spectrum, δ, ppm: 117.5 (C-5); 118.0, 118.9, 121.9, 127.0, 127.2, 128.8, 129.7, 135.2, 139.8 (C Ph); 132.2 (C-4); 139.3 (C-3); 151.7 (CONH); 164.5 (COOH). Mass spectrum, *m*/*z* ($I_{rel}$, %): 323 $[M+H]^+$. Found, %: C 63.57; H 4.50; N 17.16. $C_{17}H_{14}N_4O_3$. Calculated, %: C 63.35; H 4.38; N 17.38.

**4-[3-(4-Methylphenylureido)]-1-phenyl-1*H*-pyrazole-3-carboxylic Acid (6c)**. Yield 0.27 g (81%, method A). White crystals, mp 239-241°C. IR spectrum, ν, $cm^{-1}$: 1665, 1705 (C=O), 2560-2880 (COOH), 3310-3340 (NH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, $CH_3$); 7.09 (2H, d, *J* = 7.8, H Ar); 7.39-7.54 (5H, m, H Ph); 7.87 (2H, d, *J* = 7.8, H Ar); 8.75 (1H, s, H-5); 8.82 (1H, s, NH); 9.76 (1H, s, NH). $^{13}$C NMR spectrum, δ, ppm: 20.4 ($CH_3$); 117.4 (C-5); 118.1, 118.9, 127.1, 127.2, 129.2, 129.7, 130.7, 137.2 (C Ar); 132.3 (C-4); 139.3 (C-3); 151.8 (CONH); 164.5 (COOH). Mass spectrum, *m/z*: 337 $[M+H]^+$. Found, %: C 64.03; H 4.66; N 16.47. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.28; H 4.79; N 16.66.

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