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Five-Membered 2,3-Dioxo Heterocycles: LXXX.* Recyclization of 1*H*-Pyrrole-2,3-diones into Pyrazolo[1,5-*a*]pyrimidines by the Action of Pyrazolamine. Crystalline and Molecular Structure of Substituted Pyrazolo[1,5-*a*]pyrimidine

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Abstract—Methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates reacted with 3-methyl-4-phenyl-1*H*-pyrazol-5-amine to give methyl 7-arylcarbamoyl-6-aroyl-2-methyl-3-phenylpyrazolo[1,5-*a*]-pyrimidine-5-carboxylates. The molecular and crystalline structures of methyl 6-benzoyl-7-(4-chlorophenyl-carbamoyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate were studied by X-ray analysis.

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Monocyclic 1*H*-pyrrole-2,3-diones are known to react with difunctional nucleophiles to give various five-, six-, and seven-membered nitrogen-containing heterocycles, as well as fused, bridged, and spiroheterocyclic systems [2, 3]. Reactions of methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **I** with N,N-binucleophiles are quite sensitive to the reagent structure, and several reaction paths are possible. For example, their reactions with *o*-phenylenediamine [4] and arylhydrazines [5, 6] involve successive addition of amino groups in the nucleophile at the carbon atom in position *2* of the pyrrole ring and aroyl carbonyl carbon atom at C^3 and cleavage of the pyrrole ring at the N^1–C^2 bond. In the reactions with diphenylguanidine [7] and *N*-phenyl-*o*-phenylenediamine [8] nucleophilic attack by amino groups in the reagent is directed at the C^2 carbon atom and ester carbonyl group of the substrate; reactions of compounds **I** with *N*-phenyl-*o*-phenylenediamine also involve opening of the pyrrole ring at the N^1–C^2 bond. Reactions of methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **I** with 2-amino-1*H*-azoles were not studied previously.

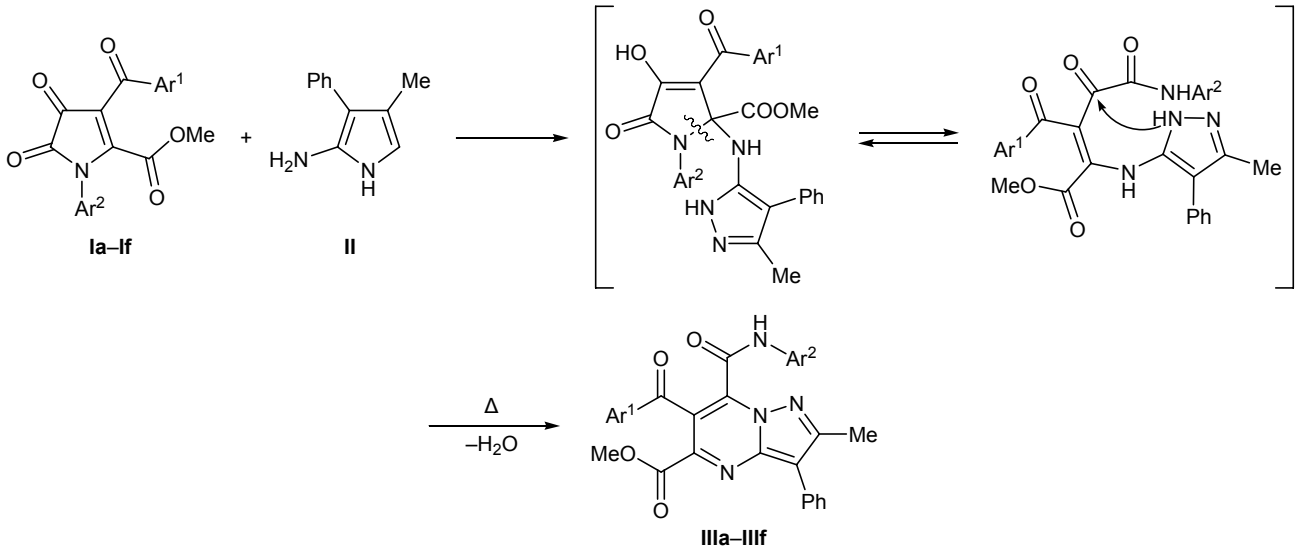
We found that 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **Ia**–**If** react with 3-methyl-4-phenyl-1*H*-pyrazol-5-amine (**II**) at a ratio of 1:1 on heating in boiling anhydrous 1,2-dichloroethane (reaction time 2–3 h; TLC monitoring) to produce the corresponding methyl 7-arylcarbamoyl-6-aroyl-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylates **IIIa**–**IIIf** [9] (Scheme 1) whose structure was confirmed by the X-diffraction data for **IIIa**.

Substituted pyrazolo[1,5-*a*]pyrimidine-5-carboxylates **IIIa**–**IIIf** were isolated as bright red high-melting crystalline substances which are poorly soluble in common organic solvents, except for dimethylformamide and dimethyl sulfoxide and insoluble in saturated hydrocarbons and water. Compounds **IIIa**–**IIIf** showed a negative color test for enolic hydroxy group upon treatment with alcoholic solution of iron(III) chloride.

The IR spectra of **IIIa**–**IIIf** contained absorption bands due to stretching vibrations of the amide NH group as a narrow peak at 3320–3360 cm^{-1} and carbonyl groups in the ester (1724–1730 cm^{-1}), carbamoyl (1680–1690 cm^{-1}), and aroyl fragments (1665–1670 cm^{-1}). Compounds **IIIa**–**IIIf** displayed in the

* For communication LXXIX, see [1].

Scheme 1.



Ar^1 = Ph, Ar^2 = 4-ClC_6H_4 (**a**); Ar^1 = 4-$EtOC_6H_4$, Ar^2 = 4-MeC_6H_4 (**b**); Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$ (**c**); Ar^1 = 2,4-$Me_2C_6H_3$, Ar^2 = 4-MeC_6H_4 (**d**); Ar^1 = 4-MeC_6H_4, Ar^2 = Ph (**e**); Ar^1 = 2,4-$Me_2C_6H_3$, Ar^2 = Ph (**f**).

^{1}H NMR spectra (DMSO-d_6) signals from protons in the aromatic rings and substituents attached thereto, a singlet from the 2-methyl group at δ 2.64–2.70 ppm, a singlet from the ester methoxy group at δ 3.60–3.65 ppm, and a singlet from the NH proton in the carbamoyl group at δ 11.09–11.45 ppm. In the ^{13}C NMR spectrum of a solution of **IIIa** in DMSO-d_6 we observed the following signals, δ_C, ppm: 14.05 (Me), 52.96 (MeO), 163.64 (CONH), 164.42 (MeO**C**O), 190.60 (Ph**C**O), which are very consistent with the assumed structure.

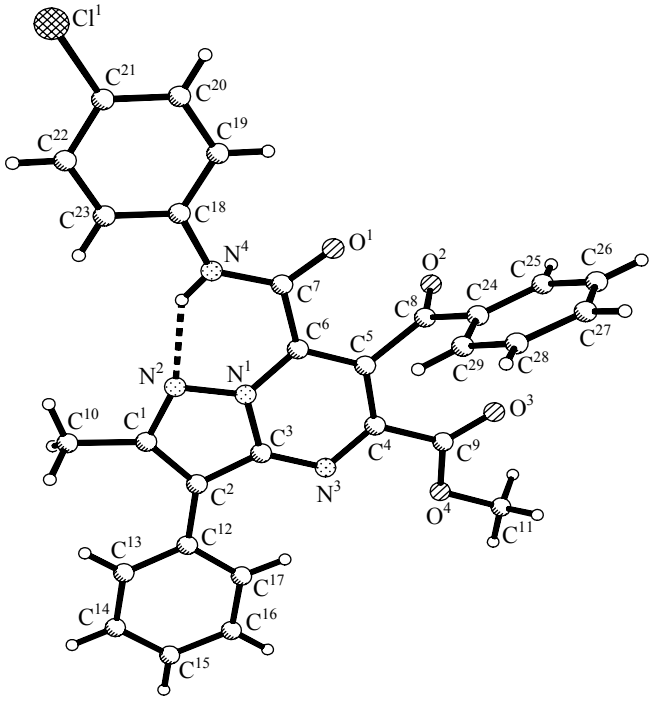


Fig. 1. Structure of the molecule of methyl 6-benzoyl-7-(4-chlorophenylcarbamoyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]-pyrimidine-5-carboxylate (**IIIa**) according to the X-ray diffraction data.

The molecular and crystalline structures of methyl 6-benzoyl-7-(4-chlorophenylcarbamoyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (**IIIa**) were studied by X-ray analysis (Fig. 1). The bicyclic pyrazolopyrimidine fragment is planar, and bond lengths therein indicate complete electron density delocalization; in particular, the C^1–C^2 and C^2–C^3 bonds, as well as N^3–C^3 and N^3–C^4 have almost equal lengths. The observed bond distribution is very consistent with structural data for other pyrazolo[1,5-*a*]pyrimidine derivatives [10]. All bond lengths in molecule **IIIa** conform to the corresponding standard values [11]. Orientation of the phenylcarbamoyl group with respect to the bicyclic fragment is characterized by the torsion angles $C^5C^6C^7N^4$ 174.8°, $C^6C^7N^4C^{18}$ 177°, and $C^7N^4C^{18}C^{23}$ 167.8°, i.e., the PhNHCO group lies almost in the plane of the bicyclic skeleton (the dihedral angle between their planes is 6°). This planar structure is stabilized by the intramolecular hydrogen bond N^4–$H^4\cdots N^2$ (2.653 Å). The phenyl ring on C^2 and methoxycarbonyl group also appear in the plane of the bicyclic fragment, whereas the phenyl ring in the benzoyl substituent is almost orthogonal to that plane (the corresponding dihedral angle is 86°). Thus, the

entire molecule, except for the benzoyl fragment, is planar. Molecules **IIIa** in crystal are packed as centrosymmetric "head-to-tail" couples, as shown in Fig. 2, so that the pyrazolopyrimidine fragment is located in front of the benzene ring.

The distance between the molecular planes in a couple is 3.15 Å, which is considerably shorter than the sum of the van der Waals radii for carbon atoms; the shortest intermolecular contact (3.27 Å) is observed between the C^3 and C^{19} atom [12]. Presumably, additional π–π interaction exists within couples of molecules.

Compounds **IIIa**–**IIIf** are likely to be formed via initial nucleophilic attack by the exocyclic amino group in pyrazole **II** on the C^2 atom of pyrroledione **Ia**–**If**; next follows opening of the pyrrole ring at the N^1–C^2 bond and closure of pyrimidine ring as a result of intramolecular nucleophilic attack by the endocyclic nitrogen atom in the pyrazole fragment on the ketone carbonyl group in the oxamoyl fragment and elimination of water molecule. The described reaction of pyrroledione **I** with 3-methyl-4-phenyl-1*H*-pyrazol-5-amine (**II**) as difunctional nitrogen-centered nucleophile may be regarded as a new method of synthesis of functionalized pyrazolo[1,5-*a*]pyrimidine derivatives.

EXPERIMENTAL

The IR spectra were recorded on an FMS-1201 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker WP-400 spectrometer from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol plates using ethyl acetate as eluent; spots were visualized by treatment with iodine vapor.

Methyl 6-benzoyl-7-(4-chlorophenylcarbamoyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (IIIa). A solution of 1 mmol of compound **Ia** and 1 mmol of pyrazole **II** in 10 ml of anhydrous 1,2-dichloroethane was heated for 3 h under reflux. The mixture was cooled, and the precipitate was filtered off. Yield 69%, mp 257–258°C (from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3350 (NH), 1730 (C=O, ester), 1690 (C=O, amide), 1665 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, Me), 3.60 s (3H, OMe), 7.24–7.97 m (14H, H_{arom}), 11.45 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.05 (Me), 52.96 (MeO), 111.81–156.41 (C_{arom}, C^2, C^3, C^{3a}, C^5, C^6, C^7), 163.64 (CONH), 164.42 (MeO**C**O), 190.60 (Ph**C**O).

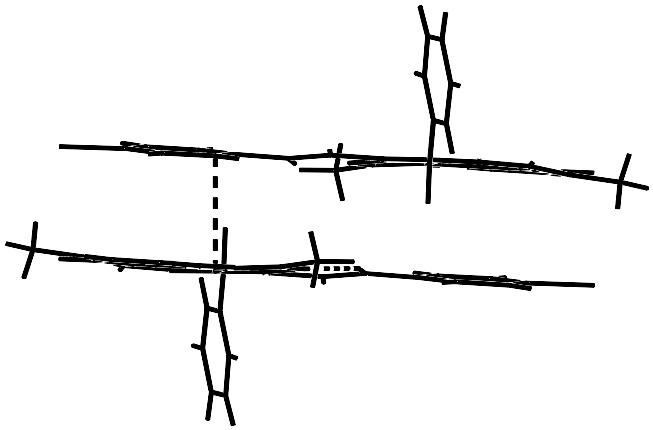


Fig. 2. Crystalline structure of methyl 6-benzoyl-7-(4-chlorophenylcarbamoyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]-pyrimidine-5-carboxylate (**IIIa**) according to the X-ray diffraction data.

Found, %: C 66.50; H 3.91; Cl 6.94; N 10.48. $C_{29}H_{21}ClN_4O_4$. Calculated, %: C 66.35; H 4.03; Cl 6.75; N 10.67.

X-Ray diffraction data for compound (IIIa). Compound **IIIa** crystallized as 2:1 solvate with 1,2-dichloroethane. Dark red well defined tetragonal prisms, $C_{29}H_{21}ClN_4O_4 \cdot 0.5\,C_2H_4Cl_2$, monoclinic crystal system, space group $P2_1/n$; unit cell parameters: a = 9.521(2), b = 21.688(4), c = 13.257(3) Å; β = 101.82(3)°; V = 2679.4(9) Å^3; M 574.42; d_{calc} = 1.4242 g/cm^3; Z = 4. The X-ray diffraction data were acquired on a KM-4 (KUMA Diffraction) automatic four-circle diffractometer with χ-geometry (monochromatized MoK_α irradiation, ω/2Θ scanning, 2Θ ≤ 50.8°). Total of 4973 reflections were measured, 3746 of which were independent (R_{int} = 0.0595). No correction for absorption was introduced (μ = 0.287 mm^{-1}). The structure was solved by the direct method using SIR92 program [13], followed by a series of calculations of electron density maps. The H^4 atom in molecule **IIIa** was localized objectively by difference synthesis of electron density, while positions of the other hydrogen atoms were set on the basis of geometry considerations and refined according to the riding model. Atoms in the solvate dichloroethane molecule were characterized by large thermal vibration parameters, and hydrogen atoms therein were not localized. The structure was refined by the least-squares procedure in full-matrix anisotropic approximation (for non-hydrogen atoms) using SHELXL-97 software package [14]; the final divergence factors were R_1 = 0.0677 [for 2214 reflections with $I \geq 2\sigma(I)$] and R_1 = 0.1251 for all 3746 reflections; 364 refined parameters, goodness of fit 1.045.

Compounds **IIIb**–**IIIf** were synthesized in a similar way.

Methyl 6-(4-ethoxybenzoyl)-2-methyl-7-(4-methylphenylcarbamoyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (IIIb). Yield 74%, mp 245–246°C (from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3320 (NH), 1724 (C=O, ester), 1680 (C=O, amide), 1665 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 2.27 s (3H, Me), 2.64 s (3H, Me), 3.64 s (3H, OMe), 4.09 q (2H, CH_2O, J = 7.0 Hz), 6.95–7.79 m (13H, H_{arom}), 11.12 s (1H, NH). Found, %: C 70.06; H 5.14; N 10.21. $C_{32}H_{28}N_4O_5$. Calculated, %: C 70.05; H 5.11; N 10.17.

Methyl 6-benzoyl-7-(4-methoxyphenylcarbamoyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (IIIc). Yield 75%, mp 265–266°C (from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3340 (NH), 1725 (C=O, ester), 1685 (C=O, amide), 1665 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 2.70 s (3H, Me), 3.65 s (3H, COOMe), 3.78 s (3H, OMe), 6.94–7.88 m (14H, H_{arom}), 11.21 s (1H, NH). Found, %: C 69.39; H 4.53; N 10.91. $C_{30}H_{24}N_4O_5$. Calculated, %: C 69.23; H 4.65; N 10.76.

Methyl 6-(2,4-dimethylbenzoyl)-2-methyl-7-(4-methylphenylcarbamoyl)-3-phenylpyrazolo[1,5-*a*]-pyrimidine-5-carboxylate (IIId). Yield 69%, mp 238–239°C (from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3320 (NH), 1725 (C=O, ester), 1690 (C=O, amide), 1670 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 2.28 s and 2.31 s (3H each, Me), 2.44 s (3H, Me), 2.66 s (3H, Me), 3.65 s (3H, OMe), 7.03–7.91 m (12H, H_{arom}), 11.09 s (1H, NH). Found, %: C 72.16; H 5.30; N 10.52. $C_{32}H_{28}N_4O_4$. Calculated, %: C 72.15; H 5.31; N 10.57.

Methyl 2-methyl-6-(4-methylbenzoyl)-3-phenyl-7-phenylcarbamoylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (IIIe). Yield 63%, mp 219–220°C (from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3320 (NH), 1730 (C=O, ester), 1680 (C=O, amide), 1670 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, Me), 2.65 s (3H, Me), 3.61 s (3H, OMe), 7.13–7.78 m (14H, H_{arom}), 11.26 s (1H, NH). Found, %: C 71.42; H 4.79; N 11.10. $C_{30}H_{24}N_4O_4$. Calculated, %: C 71.45; H 4.71; N 11.14.

Methyl 6-(2,4-dimethylbenzoyl)-2-methyl-3-phenyl-7-phenylcarbamoylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (IIIf). Yield 59%, mp 223–224°C (from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3360 (NH), 1730 (C=O, ester), 1680 (C=O, amide), 1665 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 2.21 s (6H, Me), 2.65 s (3H, Me), 3.64 s (3H, OMe), 7.02–7.58 m (13H, H_{arom}), 11.15 s (1H, NH). Found, %: C 71.80; H 5.05; N 10.80. $C_{31}H_{26}N_4O_4$. Calculated, %: C 70.85; H 5.01; N 10.83.

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