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Five-Membered 2,3-Dioxo Heterocycles: LXXXII.* Recyclization of Dimethyl 4,5-Dioxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates in Reaction with Monosubstituted Hydrazines. Crystalline and Molecular Structure of Dimethyl 1-Benzyl-5-(4-methylphenylcarbamoyl)-1*H*-pyrazole-3,4-dicarboxylate

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Abstract—Dimethyl 1-aryl(benzyl)-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates reacted with phenylhydrazine and benzylhydrazine to give dimethyl 1-aryl(benzyl)-5-[(aryl or benzyl)carbamoyl]-1*H*-pyrazole-3,4-dicarboxylates.

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Methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates and 4,5-diaroyl-1-aryl-2,3-dihydro-1*H*-pyrrole-2,3-diones were reported to react with substituted hydrazines to give substituted methyl 1,5-diaryl-4-(*N*-aryloxamoyl)-1*H*-pyrazole-3-carboxylates [2, 3] and 3-aroyl-5-aryl-4-(*N*-aryloxamoyl)-1*H*-pyrazoles [4, 5], respectively. In both cases, the process involves successive nucleophilic attacks by the primary and secondary amino groups of substituted hydrazine at the carbon atom in position *2* (*5*) and carbonyl carbon atom in the aroyl substituent on C^3 (C^4), followed by opening of the pyrrole ring at the N^1–C^2(C^5) bond. Reactions of 4,5-bis(alkoxycarbonyl)-substituted 1*H*-pyrrole-2,3-diones with hydrazine derivatives were not studied.

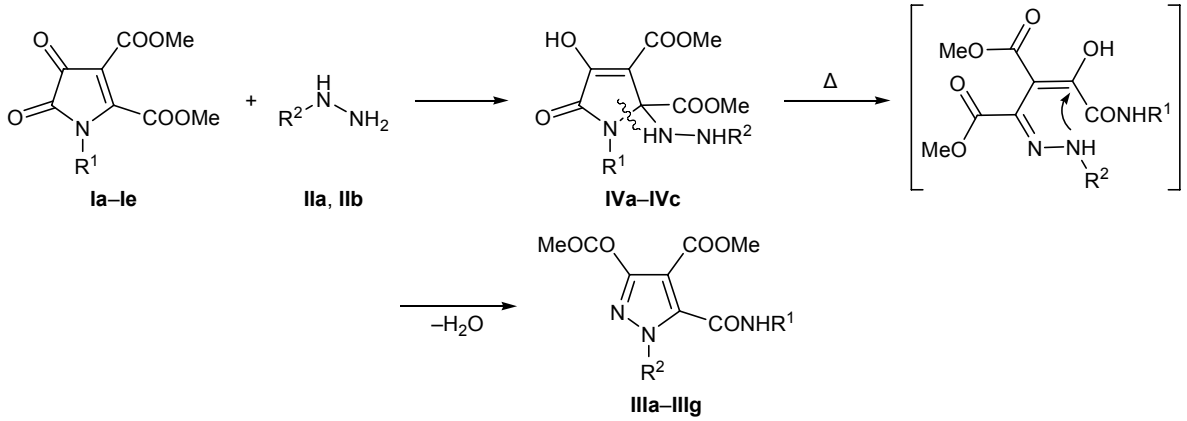
We found that dimethyl 1-aryl- and 1-benzyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **Ia**–**Ie** react with an equimolar amount of phenylhydrazine (**IIa**) or benzylhydrazine (**IIb**) on heating in a boiling 2:1 mixture of anhydrous benzene and 1,4-dioxane (reaction time 20–30 min; TLC monitoring) to give dimethyl 5-[(aryl or benzyl)carbamoyl]-1-phenyl(benzyl)-1*H*-pyrazole-3,4-dicarboxylates **IIIa**–**IIIg** in good yield (Scheme 1). The product structure was confirmed by X-ray analysis of a single crystal of compound **IIIf**.

Compounds **IIIa**–**IIIg** were isolated as colorless or light yellow crystalline substances which are poorly soluble in common organic solvents and insoluble in water and saturated hydrocarbons. The solubility of *N*-phenyl derivatives **IIIa**–**IIIe** is appreciably lower than that of their *N*-benzyl analogs **IIIf** and **IIIg**.

The IR spectra of **IIIa**–**IIIg** contained absorption bands due to stretching vibrations of NH (3248–3380 cm^{-1}), "free" ester carbonyl group (1736–1752 cm^{-1}) and that involved in intramolecular hydrogen bond (1698–1712 cm^{-1}), and amide carbonyl group (1661–1680 cm^{-1}); amide II band was observed at 1557–1568 cm^{-1}. Compounds **IIIa**–**IIIg** displayed in the ^1H NMR spectra signals from protons in the aromatic rings and substituents therein, two singlets from ester methoxy groups (δ 3.70–3.91 ppm), and NH singlet at δ 10.73–11.03 ppm. Methylene protons in the benzyl substituent of compounds **IIIf** and **IIIg** resonated as a singlet at δ 5.48–5.49 ppm. In the ^{13}C NMR spectrum of **IIIc**, signals from the ester carbonyl carbon atoms appeared at δ_C 156.30 and 161.79 ppm,

* For communication LXXXI, see [1].

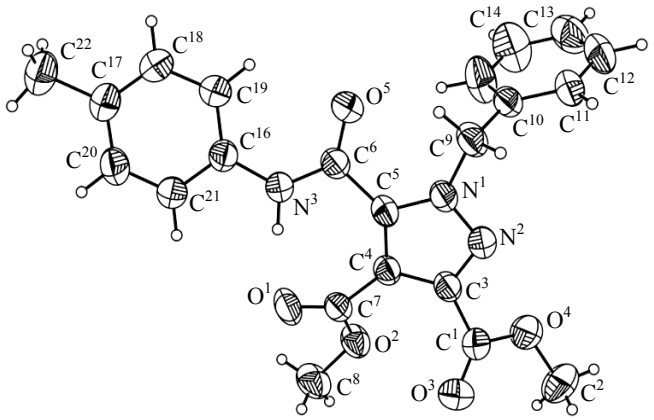
Scheme 1.



I, R^1 = Ph (**a**), $PhCH_2$ (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-ClC_6H_4 (**e**); **II**, R^2 = Ph (**a**), $PhCH_2$ (**b**); **III**, R^2 = Ph, R^1 = Ph (**a**), $PhCH_2$ (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-ClC_6H_4 (**e**); R^2 = $PhCH_2$, R^1 = 4-MeC_6H_4 (**f**), 4-$MeOC_6H_4$ (**g**); **IV**, R^2 = Ph, R^1 = $PhCH_2$ (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**).

and the amide carbonyl carbon atom gave a signal at δ_C 160.92 ppm.

The structure of compound **IIIf** was unambiguously determined by X-ray analysis (see figure). Compound crystallized in triclinic crystal system (centrosymmetric space group). The bond lengths in molecule **IIIf** conform to the corresponding standard values. The molecular conformation is determined by intramolecular hydrogen bond $N^3H\cdots O^1$ with a distance of 2.731(2) Å. Polar methoxycarbonyl and amide groups are turned with respect to the pyrazole ring plane; the corresponding dihedral angles are as follows: $C^4C^5C^6N^3$ 25.3(2), $O^1C^7C^4C^5$ –30.4(2), $C^4C^3C^1O^3$ –35.9(2)°. Packing of molecules **IIIf** in crystal is governed by van der Waals interactions without appreciable contribution of specific contacts (π–π interactions, intermolecular hydrogen bonds, etc.).



Structure of the molecule of dimethyl 1-benzyl-5-(4-methylphenylcarbamoyl)-1*H*-pyrazole-3,4-dicarboxylate (**IIIf**) according to the X-ray diffraction data; non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

Presumably, compounds **IIIa**–**IIIg** are formed via initial addition of the primary amino group in monosubstituted hydrazine at the C^2 atom of dioxopyrrole **Ia**–**Ie** with formation of intermediate **IV** which undergoes cleavage of the pyrrole ring at the N^1–C^2 bond. The subsequent intramolecular nucleophilic attack by the secondary amino group in the hydrazine fragment on the carbonyl carbon atom neighboring to the carbamoyl fragment and elimination of water molecule yields final pyrazole structure **III** (Scheme 1).

We made an attempt to isolate intermediate products in the above reaction with a view to confirm the proposed mechanism. By reacting compounds **Ib**–**Id** with phenylhydrazine (**IIa**) in benzene at room temperature (reaction time 1–2 min) we succeeded in isolating the primary addition products, dimethyl 1-aryl(benzyl)-4-hydroxy-5-oxo-2-(2-phenylhydrazino)-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **IVa**–**IVc**.

Compounds **IVa**–**IVc** are colorless crystalline substances which melt with decomposition. They are readily soluble in DMSO and DMF, poorly soluble in other common organic solvents, and insoluble in alkanes and water. Compounds **IVa**–**IVc** showed positive color test (cherry color) for enol hydroxy group upon treatment with an alcoholic solution of iron(III) chloride.

The IR spectra of **IVa**–**IVc** contained absorption bands typical of stretching vibrations of NH and enol OH groups (broadened band at 3243–3324 cm^{-1}), ester carbonyl groups (1712–1752 cm^{-1}), and lactam car-

bonyl group (1680–1703 cm^{-1}). In the ^1H NMR spectra of **IVa**–**IVc** we observed signals from protons in the aromatic rings and substituents therein, two singlets at δ 3.00–3.78 ppm from the ester methoxy groups, two singlets at δ 5.93–6.48 ppm from the NH protons, and a broadened singlet in the region δ 9.03–11.94 ppm due to enol hydroxy proton.

Heating of compounds **IVa**–**IVc** in a boiling 2:1 mixture of anhydrous benzene and 1,4-dioxane over a period of 20–30 min (i.e., under the conditions corresponding to the synthesis of compounds **III**), resulted in their recyclization with formation of compounds **IIIa**, **IIIc**, and **IIId** in good yield. The products were identical to those obtained directly from pyrrolediones **I** and monosubstituted hydrazines.

The described reaction is an example of recyclization of pyrrolediones by the action of hydrazines, which follows previously unknown scheme.

EXPERIMENTAL

The IR spectra were recorded on an FSM-1201 spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent, and tetramethylsilane as internal reference. The purity of the isolated compounds was checked by TLC on Silufol plates using benzene–ethyl acetate (5:1) as eluent.

Dimethyl 1-phenyl-5-phenylcarbamoyl-1*H*-pyrazole-3,4-dicarboxylate (IIIa). A solution of 1 mmol of phenylhydrazine in 10 ml of anhydrous 1,4-dioxane was added to a solution of 1 mmol of compound **Ia** in 20 ml of anhydrous benzene. The mixture was heated for 25 min under reflux and evaporated, and the residue was recrystallized from ethanol. Yield 82%, mp 181–183°C (from ethanol). IR spectrum, ν, cm^{-1}: 3298 (NH), 1746 (3-C=O), 1703 (4-C=O), 1661 (C=O, amide), 1563 (δNH). ^1H NMR spectrum, δ, ppm: 3.75 s and 3.91 s (3H each, OMe), 7.13–7.62 m (10H, C_6H_5), 11.03 s (1H, NH). Found, %: C 63.37; H 4.42; N 10.99. $C_{20}H_{17}N_3O_5$. Calculated, %: C 63.32; H 4.52; N 11.08.

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

Dimethyl 5-benzylcarbamoyl-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (IIIb). Yield 79%, mp 147–149°C (from ethanol). IR spectrum, ν, cm^{-1}: 3314 (NH), 1736 (3-C=O), 1712 (4-C=O), 1676 (C=O, amide), 1563 (δNH). ^1H NMR spectrum, δ, ppm: 3.58 s and 3.69 s (3H each, OMe), 6.24 s (2H, CH_2), 7.12–7.41 m (10H, C_6H_5), 10.91 t (1H, NH). Found, %: C 64.16; H 4.86; N 10.61. $C_{21}H_{19}N_3O_5$. Calculated, %: C 64.12; H 4.87; N 10.68.

Dimethyl 5-(4-methylphenylcarbamoyl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (IIIc). Yield 84%, mp 219–220°C (from ethanol). IR spectrum, ν, cm^{-1}: 3314 (NH), 1736 (3-C=O), 1712 (4-C=O), 1676 (C=O, amide), 1557 (δNH). ^1H NMR spectrum, δ, ppm: 2.26 s (3H, Me), 3.75 s and 3.91 s (3H each, OMe), 7.15 d (2H, J = 8.2 Hz), 7.41 d (2H, J = 8.3 Hz), 7.50–7.61 m (5H, Ph), 10.94 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 52.15 (OMe), 52.64 (OMe), 119.71–141.17 (C_{arom}, C^4, C^5), 143.41 (C^3), 156.30 (C=O), 160.92 (CONH), 161.79 (C=O). Found, %: C 64.17; H 4.86; N 10.59. $C_{21}H_{19}N_3O_5$. Calculated, %: C 64.12; H 4.87; N 10.68.

Dimethyl 5-(4-methoxyphenylcarbamoyl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (IIId). Yield 81%, mp 158–159°C (from ethanol). IR spectrum, ν, cm^{-1}: 3281 (NH), 1752 (3-C=O), 1698 (4-C=O), 1668 (C=O, amide), 1568 (δNH). ^1H NMR spectrum, δ, ppm: 3.73 s (3H, C_6H_4O**Me**), 3.76 s and 3.91 s (3H each, OMe), 6.91 d (2H, J = 8.6 Hz), 7.43 d (2H, J = 8.6 Hz), 7.50–7.62 m (5H, Ph), 10.87 s (1H, NH). Found, %: C 61.68; H 4.75; N 10.24. $C_{21}H_{19}N_3O_6$. Calculated, %: C 61.61; H 4.68; N 10.26.

Dimethyl 5-(4-chlorophenylcarbamoyl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (IIIe). Yield 78%, mp 208–210°C (from ethanol). IR spectrum, ν, cm^{-1}: 3300 (NH), 1746 (3-C=O), 1703 (4-C=O), 1661 (C=O, amide), 1563 (δNH). ^1H NMR spectrum, δ, ppm: 3.75 s and 3.91 s (3H each, OMe), 7.42 d (2H, J = 9.1 Hz), 7.45–7.61 m (5H, Ph), 7.56 d (2H, J = 9.1 Hz), 11.19 s (1H, NH). Found, %: C 59.01; H 4.22; Cl 8.26; N 9.84. $C_{21}H_{18}ClN_3O_5$. Calculated, %: C 58.95; H 4.24; Cl 8.29; N 9.82.

Dimethyl 1-benzyl-5-(4-methylphenylcarbamoyl)-1*H*-pyrazole-3,4-dicarboxylate (IIIf). Yield 73%, mp 208–210°C (from ethanol). IR spectrum, ν, cm^{-1}: 3344 (NH), 1751 (3-C=O), 1700 (4-C=O), 1662 (C=O, amide), 1562 (δNH). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, Me), 3.70 s and 3.85 s (3H each, OMe), 5.49 s (2H, CH_2), 7.18 d (2H, J = 8.8 Hz), 7.27–7.36 m (5H, Ph), 7.51 d (2H, J = 8.8 Hz), 10.80 s (1H, NH). Found, %: C 64.82; H 5.26; N 10.26. $C_{22}H_{21}N_3O_5$. Calculated, %: C 64.86; H 5.20; N 10.31.

X-Ray diffraction data for compound IIIf. X-Ray analysis was performed on an Xcalibur-3 diffractometer with a CCD detector [λ(MoK_α) 0.71073 Å,

graphite monochromator, ω-scanning through a step of 1°, temperature 295(2) K]. The structure was solved by the direct method and was refined with the aid of SHELXTL-97 software package [6]. No correction for absorption was introduced. The positions and temperature parameters of non-hydrogen atoms were refined first in isotropic and then in anisotropic approximation by the full-matrix least-squares procedure. Hydrogen atoms were localized by the electron density maxima, and their positions were refined according to the riding model. Triclinic crystal system, space group *P*-1; unit cell parameters: a = 7.9450(7), b = 11.2170(13), c = 11.7450(10) Å; α = 85.548(8), β = 84.326(7), γ = 76.264(9)°; V = 1010.20(17) Å^3; Z = 2; $C_{22}H_{21}N_3O_5$; μ = 0.096 mm^{-1}. Total of 5950 reflections were measured in the range 2.63 < θ < 28.28°, 4848 reflections were independent (R_{int} 0.0168), and 2291 reflections were characterized by $I > 2\sigma(I)$; completeness 98.4% for θ = 26.00°. The final divergence factors were R_1 = 0.0384, wR_2 = 0.0850 [reflections with $I > 2\sigma(I)$] and R_1 = 0.0922, wR_2 = 0.0905 (all reflections); goodness of fit S = 1.006; maximal and minimal residual electron density peaks 0.211 and –0.163 $\bar{e}$/Å^3. The complete set of crystallographic data for compound **IIIf** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 855435) and is available at *www.ccdc.cam.ac.uk/data_request/cif* upon request.

Dimethyl 1-benzyl-5-(4-methoxyphenylcarbamoyl)-1*H*-pyrazole-3,4-dicarboxylate (IIIg). Yield 71%, mp 140–141°C (from ethanol). IR spectrum, ν, cm^{-1}: 3346 (NH), 1749 (3-C=O), 1709 (4-C=O), 1676 (C=O, amide), 1568 (δNH). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, C_6H_4O**Me**), 3.75 s and 3.84 s (3H each, OMe), 5.48 s (2H, CH_2), 6.95 d (2H, J = 9.2 Hz), 7.26–7.36 m (5H, Ph), 7.52 d (2H, J = 9.2 Hz), 10.73 s (1H, NH). Found, %: C 62.37; H 5.54; N 9.87. $C_{22}H_{21}N_3O_6$. Calculated, %: C 62.41; H 5.60; N 9.92.

Dimethyl 1-benzyl-4-hydroxy-5-oxo-2-(2-phenylhydrazino)-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (IVa). A solution of 1 mmol of phenylhydrazine in 10 ml of anhydrous benzene was added dropwise to a solution of 1 mmol of compound **Ib** in 20 ml of anhydrous benzene. The mixture was kept for 1 min at room temperature, the solvent was removed, and the product was purified by reprecipitation from benzene with hexane. Yield 72%, mp 127–128°C (from benzene–hexane). IR spectrum, ν, cm^{-1}: 3324, 3301, 3245 (OH, NH); 1752 (2-C=O); 1717 (3-C=O); 1703 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 3.00 s and 3.60 s (3H each, OMe), 4.29 d and 4.88 d (1H each, CH_2, J = 15.9 Hz), 5.93 s (1H, NH), 6.48 s (1H, NH), 6.57–7.33 m (10H, Ph), 11.94 br.s (1H, OH). Found, %: C 61.34; H 5.12; N 10.23. $C_{21}H_{21}N_3O_6$. Calculated, %: C 61.31; H 5.14; N 10.21.

Compounds **IVb** and **IVc** were synthesized in a similar way.

Dimethyl 4-hydroxy-1-(4-methylphenyl)-5-oxo-2-(2-phenylhydrazino)-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (IVb). Yield 74%, mp 114–116°C (from benzene–hexane). IR spectrum, ν, cm^{-1}: 3319, 3291, 3243 (OH, NH); 1752, 1707 (C=O, ester); 1680 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, Me), 3.63 s and 3.66 s (3H each, OMe), 5.39 s (1H, NH), 5.97 s (1H, NH), 6.57–7.33 m (9H, H_{arom}), 11.99 br.s (1H, OH). Found, %: C 61.34; H 5.12; N 10.23. $C_{21}H_{21}N_3O_6$. Calculated, %: C 61.31; H 5.14; N 10.21.

Dimethyl 4-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-(2-phenylhydrazino)-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (IVc). Yield 76%, mp 83–84°C (from benzene–hexane). IR spectrum, ν, cm^{-1}: 3301, 3298, 3246 (OH, NH); 1749 (2-C=O); 1713 (3-C=O); 1701 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 3.61 s (3H, C_6H_4O**Me**), 3.66 s and 3.78 s (3H each, OMe), 5.33 s (1H, NH), 6.57–7.17 m (10H, H_{arom}, NH), 9.03 br.s (1H, OH). Found, %: C 58.96; H 4.91; N 9.84. $C_{21}H_{21}N_3O_7$. Calculated, %: C 59.01; H 4.95; N 9.83.

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