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Five-Membered 2,3-Dioxoheterocycles: XC.* Reaction of 4,5-Bis(methoxycarbonyl)-1*H*-pyrrole-2,3-diones with Enaminoesters. Crystal and Molecular Structure of 4-Methyl 9-Ethyl 7-Benzyl-3-hydroxy-8-methyl-1-(4-methoxyphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylate

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Abstract—1-Aryl-4,5-bis(methoxycarbonyl)-1*H*-pyrrole-2,3-diones react with ethyl 3-(benzylamino)but-2-enoate and ethyl 3-(benzylamino)-3-phenylacrylate giving 4-methyl 9-ethyl 1-aryl-7-benzyl-3-hydroxy-8-methyl- and 4-methyl 9-ethyl 1-aryl-7-benzyl-3-hydroxy-8-phenyl-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylates.

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Substituted 1*H*-pyrrole-2,3-diones (5-phenyl-4-ethoxycarbonyl-, 4-isopropoxallyl-5-phenyl-, and 4-aroyl-5-methoxycarbonyl-1*H*-pyrrole-2,3-diones) react with carbocyclic enamines affording spiro[acridine-9,3'-pyrroles] [2, 3], spiro[furan-2,3'-indoles] [4], spiro[indole-3,2'-pyrroles], or spiro[furan-2,3'-indoles] [5] depending on the structure of the substituents in the positions *4* and *5* of the pyrrolediones.

The recyclizations of 4,5-bis(methoxycarbonyl)-1*H*-pyrrole-2,3-diones at the treatment with enamines are poorly studied. A reaction is described of 1-aryl-4,5-bis(methoxycarbonyl)-1*H*-pyrrole-2,3-diones with carbocyclic enamines proceeding as an addition of the β-CH group of enamines to the atom C^5 of the pyrrolediones followed by the intramolecular cyclization involving the amino group of the enamines and the methoxycarbonyl substituent in the position *5* of the pyrrolediones [6, 7]. The reactions of these pyrrolediones with acyclic enamines were not described. The latter enamines unlike the carbocyclic enamines exist in the form of *Z*-isomers with an intramolecular hydrogen bond of an H-chelate type preventing their reactions in the role of binucleophiles, therefore it is expectable that they may react in another way.

The reaction of 1-aryl-4,5-bis(methoxycarbonyl)-1*H*-pyrrole-2,3-diones **Ia–Id** with ethyl 3-(benzyl-amino) but-2-enoate (**IIa**) and ethyl 3-(benzylamino)-3-phenylacrylate (**IIb**) in a ratio 1 : 1 carried out by boiling in anhydrous toluene within 3–4 h furnished in good yields 4-methyl 9-ethyl 1-aryl-7-benzyl-3-hydroxy-8-methyl-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylates **IIIa–IIId** and 4-methyl 9-ethyl 1-aryl-7-benzyl-3-hydroxy-8-phenyl-2,6-dioxo-1,7-diazaspiro[4.4]-nona-3,8-diene-4,9-dicarboxylates **IIIe, IIIf** whose structure was proved by XRD analysis by the example of compound **IIIc**.

Compounds **IIIa–IIIf** are colorless crystalline substances of high melting points, readily soluble in DMF and DMSO, sparingly soluble in methanol, ethanol,

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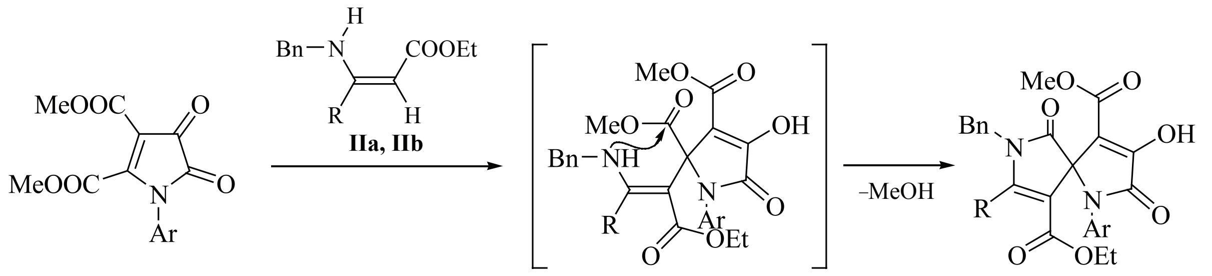
* For Communication LXXXIX, see [1].



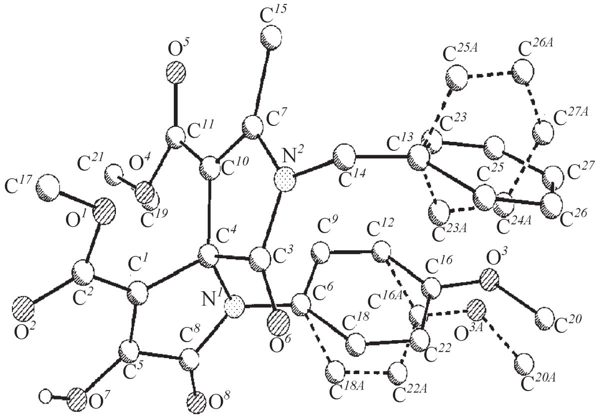
Ia–Id **IIIa–IIIf**

I, Ar = Ph (**a**), C_6H_4Me-4 (**b**), C_6H_4OMe-4 (**c**), C_6H_4Cl-4 (**d**); **II**, R = Me (**a**), Ph (**b**); **III**, R = Me, Ar = Ph (**a**), C_6H_4Me-4 (**b**), C_6H_4OMe-4 (**c**), C_6H_4Cl-4 (**d**); R = Ph, Ar = Ph (**e**), C_6H_4Me-4 (**f**).

acetone and other solvents, insoluble in alkanes and water, exhibiting a positive reaction (cherry color) for the presence of the enol hydroxy group with the alcoholic solution of iron(III) chloride.

IR spectra of compounds **IIIa–IIIf** contain the characteristic bands of the stretching vibrations of the enol hydroxy group (3167–3335 cm^{-1}), of lactam carbonyl groups C^6=O (1732–1740 cm^{-1}), and of C^2=O (1705–1723 cm^{-1}), of the carbonyl groups of the ethoxycarbonyl (1676–1698 cm^{-1}) and methoxycarbonyl substituents; the latter is involved in the formation of the intramolecular hydrogen bond and has an absorption band in the region 1628–1653 cm^{-1}.

In the ^{1}H NMR spectra of compounds **IIIa–IIIf** alongside the proton signals of the aromatic substituents and the groups attached to them the singlet appears of the protons of the methoxycarbonyl group (3.65–3.71 ppm); a triplet of a methyl and a quartet of a methylene group of the ethoxycarbonyl substituent (0.83–1.12 and 3.82–4.07 ppm respectively), two doublets of the methylene group of the benzyl substituent with a characteristic coupling constant ($^2J_{HH}$ 16.0–16.4 Hz) (4.28–4.87 ppm), a singlet of the methyl protons in the position *8* (2.25–2.30 ppm in the spectra of compounds **IIIa–IIId**), and a broadened singlet of the proton of the enol hydroxy group (12.32–12.57 ppm) were observed.



General view of the molecule of 4-methyl 9-ethyl 7-benzyl-3-hydroxy-8-methyl-1-(4-methoxyphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylate (**IIIc**) according to XRD data shown as a ball-rod model (hydrogen atoms are omitted to facilitate the image perception).

In the ^{13}C NMR spectra of compound **IIIf** along with the carbon signals of the aromatic and aliphatic substituents and the ethylene fragments of the heterocyclic system the signals of the carbon atoms are present from two lactam and two ester carbonyl groups in the region 158.69–165.17 ppm, and also a signal of the spiro carbon atom at 70.10 ppm.

To prove the structure of obtained compounds **IIIa–IIIf** and to establish the special features of their spatial structure we carried out the XRD analysis of a single crystal of compound **IIIc** whose general appearance is shown in the figure.

According to the data of XRD analysis the pyrroline rings of the spiro-system are flat (in one of them the deviation of the atoms from the mean-square plane does not exceed 0.01 Å, in another, 0.02 Å), and they are turned with respect to each other by an angle of 89.4°. The distribution of the bond lengths in the rings may be regarded as common for the conjugated diene systems. The bond lengths C–COOR equal ~1.45 Å indicating that the electrons of their carbonyl groups are involved in the system of the conjugated bonds of the heterocyclic rings. The hydroxy group takes part in the formation of an intramolecular hydrogen bond with the carbonyl group of the methoxycarbonyl substituent (O^7–H···O^2). The molecules are packed in the crystals by layers parallel to the [001] plane with the alteration of the zones of heterocyclic and aromatic fragments. The phenyl ring of the benzyl substituent and the methoxyphenyl substituent are disordered by two positions with the population factors 0.5 (the second disordered components are designated in the figure by an additional index "*A*"). It is difficult to make a conclusion on the nature of the disordering, but for the molecule (and within the monomolecular layer) the coordinated positions of the disorder should be retained to avoid the appearance of inadmissibly short interatomic contacts C_{Ar}–H···C_{Ar} (up to ~1.9 Å) and C_{Ar}···C_{Ar} (up to ~2.5 Å). The appearance of such unfavorable contacts can be avoided if in the limits of a monomolecular layer the alternation occurs of the molecules with different disorder components probably capable to the synchronized variations provided by the thermal oscillations.

The formation of compounds **IIIa–IIIf** proceeds evidently as a result of the initial addition of the activated β-CH group of the enamine fragment of compounds **IIa, IIb** to the carbon atom in the position *5* of pyrrolediones **Ia–Id** followed by the subsequent intramolecular closure of the pyrrolone ring due to the nucleophilic attack of the amino group of the enamine fragment on the carbonyl group of the ester substituent in the position *5* of pyrrolediones accompanied by the methanol elimination according to the scheme earlier described in [5–7]. Therewith the existence of the reagent in the unfavorable form of the *Z*-isomer affects the reaction rate by increasing the time required for the completion of the reaction. This reaction is one more example of the direct spiro-bis-heterocyclization of monocyclic pyrrolediones under the action of enamines with the building up a difficultly available heterocylic system of 1,7-diazaspiro[4.4]nona-3,8-diene and with the possibility to vary substituents in several positions.

EXPERIMENTAL

IR spectra of compounds synthesized were recorded on a spectrophotometer FSM-1201 from mulls in mineral oil. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-400 [operating frequencies 400 (^{1}H) and 100 MHz (^{13}C)] from solutions in DMSO-d_6, internal reference TMS. The homogeneity of compounds synthesized was checked and the reaction progress was monitored by TLC on Silufol plates, eluents benzene–ethyl acetate, 5:1, and ethylacetate, development in iodine vapor and at heating.

4-Methyl 9-ethyl 7-benzyl-3-hydroxy-8-methyl-1-phenyl-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylate (IIIa). A solution of 1.0 mmol of pyrroledione **Ia** and 1.0 mmol of enaminoester **IIa** in 20 ml of anhydrous toluene was boiled for 4 h (TLC monitoring), the mixture was cooled, the separated precipitate was filtered off and recrystallized from toluene. Yield 73%, mp 161–162°C. IR spectrum, *ν*, cm^{-1}: 3310 (OH), 1736 (C^{6}=O), 1723 (C^{2}=O), 1690 (COOEt), 1649 (COOMe). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $C\underline{H}_3CH_2$, *J* 7.0 Hz), 2.26 s (3H, Me), 3.65 s (3H, COOMe), 4.06 q (2H, OCH_2, *J* 7.0 Hz), 4.74 d (1H, CH_2Ph, *J* 16.4 Hz), 4.87 d (1H, CH_2Ph, *J* 16.4 Hz), 6.90–7.41 group of signals (10H, 2Ph), 12.40 (1H, OH). Found, %: C 65.48; H 5.06; N 5.89. $C_{26}H_{24}N_2O_7$. Calculated, %: C 65.54; H 5.08; N 5.88.

Compounds **IIIb–IIIf** were analogously synthesized.

4-Methyl 9-ethyl 7-benzyl-3-hydroxy-8-methyl-1-(4-methylphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]-nona-3,8-diene-4,9-dicarboxylate (IIIb). Yield 78%, mp 158–160°C (toluene). IR spectrum, *ν*, cm^{-1}: 3170 (OH), 1740 (C^{6}=O), 1705 (C^{2}=O), 1690 (COOEt), 1630 (COOMe). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $C\underline{H}_3CH_2$, *J* 7.0 Hz), 2.25 s (3H, Me), 2.34 s (3H, Me), 3.65 s (3H, COOMe), 4.05 q (2H, OCH_2, *J* 7.0 Hz), 4.73 d (1H, CH_2Ph, *J* 16.4 Hz), 4.86 d (1H, CH_2Ph, *J* 16.4 Hz), 6.84–7.27 group of signals (9H, Ph + C_6H_4), 12.35 br.s (1H, OH). Found, %: C 66.05; H 5.35; N 5.69. $C_{27}H_{26}N_2O_7$. Calculated, %: C 66.11; H 5.34; N 5.71.

4-Methyl 9-ethyl 7-benzyl-3-hydroxy-8-methyl-1-(4-methoxyphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]-nona-3,8-diene-4,9-dicarboxylate (IIIc). Yield 77%, mp 174–175°C (toluene). IR spectrum, *ν*, cm^{-1}: 3174 (OH), 1738 (C^{6}=O), 1721 (C^{2}=O), 1698 (COOEt), 1640 (COOMe). ^{1}H NMR spectrum, δ, ppm: 1.13 t (3H, $C\underline{H}_3CH_2$, *J* 7.0 Hz), 2.26 s (3H, Me), 3.65 s (3H, COOMe), 3.78 s (3H, OMe), 4.07 q (2H, OCH_2, *J* 7.0 Hz), 4.70 d (1H, CH_2Ph, *J* 16.4 Hz), 4.87 d (1H, CH_2Ph, *J* 16.4 Hz), 6.85–7.27 group of signals (9H, Ph + C_6H_4), 12.32 br.s (1H). Found, %: C 63.98; H 5.14; N 5.50. $C_{27}H_{26}N_2O_8$. Calculated, %: C 64.03; H 5.17; N 5.53.

XRD structural analysis of compound IIIc. The unit cell parameters and the array of the experimental reflections of compound with empirical formula $C_{27}H_{26}N_2O_8$ were measured on an automatic four-circle diffractometer equipped with a CCD-detector Xcalibur 3 (Oxford Diffraction) by the method of $\omega/2\theta$-scanning using the monochromatic MOK_α-radiation in the range of angles $2.79 < \theta < 26.37$. Crystals triclinic: *a* 8.8556(13), *b* 11.4626(12),

c 13.0462(11) Å, α 94.294(8), β 93.286(8), γ 109.262(7)°, V 1241.9(2) Å^3, M 506.50, d_{calc} 1.354 g/cm^3, Z 2, space group P-1. The total number of 7707 rflections was measured, among them 5033 independent (R_{int} 0.0235), 2195 with $I > 2\sigma(I)$. The completeness of the experiment at the angle θ 26.37$^{\text{O}}$ was 99.3%. No correction for extinction was introduced (μ 0.101 mm^{-1}). The structure was solved by the direct statistical method and was refined by full-matrix root-mean-square method with respect to F^2 in the anisotropic approximation for all nonhydrogen atoms. Hydrogen atoms of OH group were solved directly and refined independently, the other hydrogen atoms were placed in the geometrically calculated positions. All calculations were carried out using SHELX 97 software [8]. The final results of refining are as follows: R_1 0.0396, wR_2 0.0866 for reflections with $I > 2\sigma(I)$, R_1 0.1018, wR_2 0.0925 (for all reflections), S 1.001. Maximal and minimal peaks of the residual electron density are 0.157 and –0.157 $\bar{e}$Å^{-3}.

The results of the structural research were deposited to the Cambridge Crystallographic Data Center, CCDC 901415. The data can be obtained free at the address http://www.ccdc.cam.ac.uk.

4-Methyl 9-ethyl 7-benzyl-3-hydroxy-8-methyl-1-(4-chlorophenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylate (IIId). Yield 69%, mp 174–176°C (toluene). IR spectrum, ν, cm^{-1}: 3180 (OH), 1732 (C^6=O), 1713 (C^2=O), 1676 (COOEt), 1653 (COOMe). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $C\underline{H}_3CH_2$, J 7.0 Hz), 2.30 s (3H, Me), 3.65 s (3H, COOMe), 4.06 q (2H, OCH$_2$, J 7.0 Hz), 4.76 d (1H, CH$_2$Ph, J 16.1 Hz), 4.86 d (1H, CH$_2$Ph, J 16.1 Hz), 6.92–7.47 group of signals (9H, Ph + C$_6$H$_4$), 12.48 br.s (1H, OH). Found, %: C 61.16; H 4.51; Cl 6.90; N 5.43. $C_{26}H_{23}ClN_2O_7$. Calculated, %: C 61.12; H 4.54; Cl 6.94; N 5.48.

4-Methyl 9-ethyl 7-benzyl-3-hydroxy-1,8-diphenyl-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylate (IIIe). Yield 71%, mp 198–199°C (toluene). IR spectrum, ν, cm^{-1}: 3167 (OH), 1732 (C^6=O), 1709 (C^2=O), 1682 (COOEt), 1628 (COOMe). ^{1}H NMR spectrum, δ, ppm: 0.83 t (3H, CH$_3$CH$_2$, J 7.2 Hz), 3.71 s (3H, COOMe), 3.82 m (2H, OCH$_2$), 4.31 d (1H, CH$_2$Ph, J 16.0 Hz), 4.62 d (1H, CH$_2$Ph, J 16.0 Hz), 6.48–7.83 group of signals (15H, 3Ph), 12.57 br.s (1H, OH). Found, %: C 69.10; H 4.90; N 5.17. $C_{31}H_{26}N_2O_7$. Calculated, %: C 69.14; H 4.87; N 5.20.

4-Methyl 9-ethyl 7-benzyl-3-hydroxy-1-(4-methylphenyl)-8-phenyl-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-4,9-dicarboxylate (IIIf). Yield 67%, mp 225–227°C (toluene). IR spectrum, ν, cm^{-1}: 3335 (OH), 1740 (C^6=O), 1713 (C^2=O), 1680 (COOEt), 1651 (COOMe). ^{1}H NMR spectrum, δ, ppm: 0.83 t (3H, CH$_3$CH$_2$, J 7.0 Hz), 2.39 s (3H, Me), 3.71 s (3H, COOMe), 3.83 m (2H, OCH$_2$), 4.28 d (1H, CH$_2$Ph, J 16.0 Hz), 4.63 d (1H, CH$_2$Ph, J 16.0 Hz), 6.45–7.42 group of signals (14H, 2Ph + C$_6$H$_4$), 12.52 br.s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 13.46 ($CH_2\underline{C}H_3$), 20.76 (Me), 43.97 ($\underline{C}H_2Ph$), 51.48 ($COO\underline{C}H_3$), 59.20 (OCH$_2$), 70.10 (C^5), 104.89 (C^9), 107.84 (C^4), 125.27–138.27, 155.73 (C^8), 158.69 (C^6), 160.86 ($\underline{C}OOEt$), 161.85 ($\underline{C}OOMe$), 165.17 (C^2), 173.66 (C^3). Found, %: C 69.63; H 5.06; N 5.05; $C_{32}H_{28}N_2O_7$. Calculated, %: C 69.56; H 5.11; N 5.07.

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