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Five-Membered 2,3-Dioxo Heterocycles: LXXVI.* Reaction of Methyl 1-Aryl-3-benzoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates with 6-Amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione

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Abstract—Methyl 1-aryl-3-benzoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates reacted with 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione to give methyl 11-aryl-12-benzoyl-9-hydroxy-4,6-dimethyl-3,5,10-trioxo-4,6,8,11-tetraazatricyclo[7.2.1.$0^{2,7}$]dodec-2(7)-ene-1-carboxylates which underwent thermal recyclization to 1-aryl-3-benzoyl-4-hydroxy-1′,3′-dimethylspiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraones.

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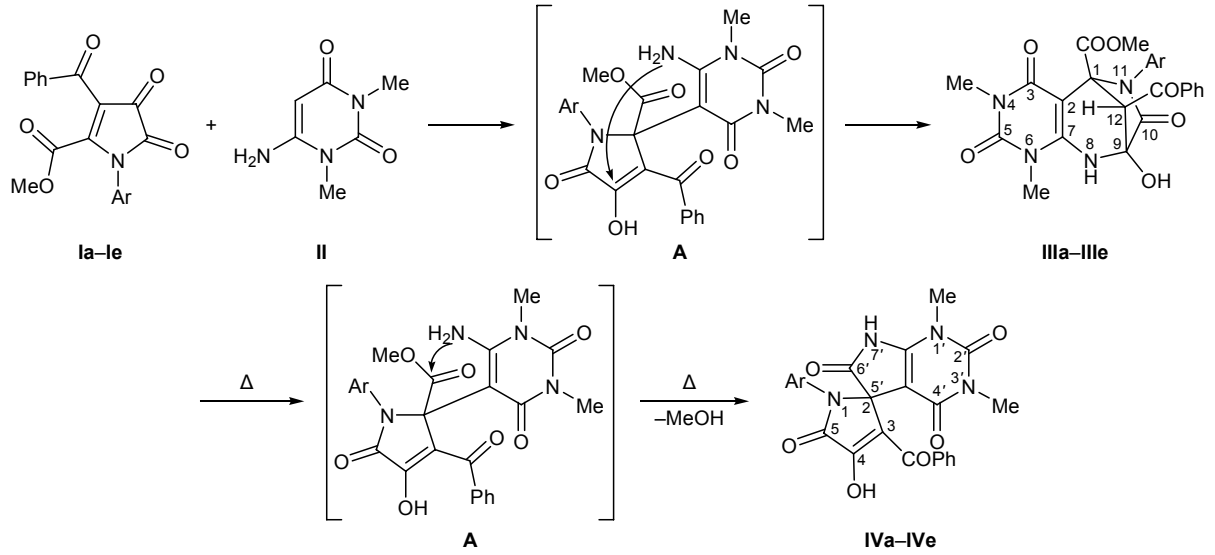
Monocyclic 1*H*-pyrrole-2,3-diones are known to react with difunctional nucleophiles to produce various five-, six-, and seven-membered nitrogen-containing heterocycles, as well as fused and spirocyclic systems [2, 3]. We previously showed that methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates react with 3-amino-5,5-dimethylcyclohex-2-en-1-one (as 1,3-C,N-binucleophile) via successive addition of the β-CH group and amino group in the enamino fragment of the binucleophile at the carbon atoms in positions *2* and *4* of dioxopyrrole with formation of diazatricyclo[7.2.1.$0^{2,7}$]dodec-2(7)-ene derivatives. The latter undergo recyclization on heating to give spiro[indole-3,2′-pyrroles] together with spiro[furan-2,3′-indoles] as by-products [4, 5]. Reactions of methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates with heterocyclic enamines were not studied.

In continuation of studies in this line, in the present work we examined reactions of methyl 1-aryl-3-benzoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **Ia**–**Ie** with 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**II**) which may be regarded as potential 1,3-C,N-binucleophile (heterocyclic enamine). The reactions were carried out by heating equimolar amounts of pyrroledione **Ia**–**Ie** and enamine **II** in boiling anhydrous 1,2-dichloroethane over a period of 4–6 h (until bright red color intrinsic to initial compounds **I** disappeared). As a result, we isolated the corresponding methyl 11-aryl-12-benzoyl-9-hydroxy-4,6-dimethyl-3,5,10-trioxo-4,6,8,11-tetraazatricyclo-[7.2.1.$0^{2,7}$]dodec-2(7)-ene-1-carboxylates **IIIa**–**IIIe** (Scheme 1) [6]. Compounds **IIIa**–**IIIe** are colorless or light yellow high-melting crystalline substances which are readily soluble in dimethyl sulfoxide and dimethylformamide, poorly soluble in other common organic solvents, and insoluble in water and saturated hydrocarbons. They showed negative color test for enolic hydroxy group with an alcoholic solution of iron(III) chloride.

The IR spectra of **IIIa**–**IIIe** contained absorption bands due to stretching vibrations of the NH group (3316–3340 cm^{-1}), OH group (a broad band at 3145–3165 cm^{-1}), lactam carbonyl groups in the pyrimidine fragment (C^3=O, C^5=O, 1738–1770 cm^{-1}), ester carbonyl group (1721–1735 cm^{-1}), lactam carbonyl group in the diazepine fragment (C^{10}=O, 1702–1710 cm^{-1}), and benzoyl carbonyl group (1620–1643 cm^{-1}). Compounds **IIIa**–**IIIe** displayed in the ^{1}H NMR spectra

* For communication LXXV, see [1].

Scheme 1.



Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-BrC_6H_4 (**e**).

signals from protons in the aromatic rings and substituents attached thereto, two singlets from methyl protons (δ 3.07–3.16 ppm), a singlet from the ester methoxy group (δ 3.36–3.38 ppm), a singlet from 12-H (δ 4.80–4.85 ppm), a singlet from the hydroxy proton (δ 7.80–7.96 ppm), and a singlet from the NH proton (δ 8.48–8.56 ppm). The ^{13}C NMR spectrum of **IIIa** contained the following signals, δ_C, ppm: 27.73 and 30.14 (Me), 51.37 (C^{12}), 54.70 (C^1), 65.50 (MeO), 85.64 (C^9); 125.43, 127.97, 128.87, 133.86, 137.33 (C_{arom}); 150.80 (C^5), 157.85 (C^2), 166.08 (C=O, ester), 167.05 (C^{10}), 196.15 (Ph**C**O). The spectral parameters of **IIIa**–**IIIe** are fairly similar to those of model 13-allyl-20-(4-bromobenzoyl)-12-hydroxy-16,16-dimethyl-3-phenyl-3,10,13-triazapentacyclo-[10.7.1.$0^{1,10}$.$0^{4,9}$.$0^{14,19}$]eicosa-4,6,8,14(19)-tetraene-2,11,18-trione whose structure was proved by X-ray analysis [7].

The formation of bridged tricyclic structure **III** may be rationalized as follows. Initial addition of the C^5 atom in the pyrimidine ring of **II** at the carbon atom in position *2* of pyrroledione **I** gives intermediate **A** which undergoes intramolecular nucleophilic attack by the primary amino group in the pyrimidine ring on C^4 in the pyrrole ring (Scheme 1). Analogous nucleophilic [3+3]-addition was observed previously in the reaction of pyrrolediones **I** with N-unsubstituted dimedone imine, which occurred under milder conditions (on heating in boiling anhydrous benzene over a period of 1–2 min) [4]. Presumably, the reaction described in the present work requires more severe conditions due to lower nucleophilicity of aminouracil **II** as compared to dimedone imine.

By heating tricyclic compounds **IIIa**–**IIIe** in boiling *m*-xylene over a period of 14–16 h (TLC) we obtained 1-aryl-3-benzoyl-4-hydroxy-1′,3′-dimethylspiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraones **IVa**–**IVe** (Scheme 1). Compounds **IVa**–**IVe** were isolated as yellow high-melting crystalline substances which were readily soluble in dimethyl sulfoxide and dimethylformamide, poorly soluble in other common organic solvents, and insoluble in water and saturated hydrocarbons. They showed positive color test for enolic hydroxy group with an alcoholic solution of iron(III) chloride. The IR spectra of **IVa**–**IVe** contained absorption bands belonging to stretching vibrations of the NH group (3349–3360 cm^{-1}), OH group (a broad band at 3165–3195 cm^{-1}), lactam carbonyl groups $C^{2'}$=O and $C^{4'}$=O in the pyrimidine fragment (1720–1742 cm^{-1}), lactam carbonyl groups C^5=O and $C^{6'}$=O in the pyrrole fragments (1665–1676 cm^{-1}), and benzoyl carbonyl group (1618–1631 cm^{-1}). Compounds **IVa**–**IVe** displayed in the ^1H NMR spectra signals from protons in the aromatic rings and substituents therein, two singlets from methyl protons (δ 3.54–3.81 ppm), a singlet from the NH proton (δ 10.56–10.79 ppm), and a singlet from the hydroxy proton (δ 12.02–12.21 ppm). The following signals were observed in the ^{13}C NMR spectrum of **IVd**, δ_C, ppm: 27.12 and 31.26 (Me), 55.19 (OMe), 70.67 (C^2), 114.53 (C^3); 114.54, 127.92, 128.49, 128.68, 128.76, 132.17, 134.01, 137.87 (C_{arom}); 150.68

($C^{2'}$), 156.67 (C^5), 158.85 ($C^{4'}$), 166.39 ($C^{6'}$), 175.79 (C^4), 188.20 (Ph**C**O). The spectral parameters of compounds **IVa**–**IVe** were quite similar to those of model 3′-benzoyl-1-cyclohexyl-4′-hydroxy-6,6-dimethyl-1′-phenyl-1,1′,2,2′,3,4,5,5′,6,7-octahydrospiro[indole-3,2′-pyrrole]-2,4,5′-trione [8] and 3′-benzoyl-4′-hydroxy-11,11-dimethyl-1′-phenyl-1,2,2′,5′,10,11-hexahydro-1′*H*-spiro[benzo[*h*]pyrrolo[2,1-*a*]isoquinoline-2,2′-pyrrole]-1,5′-dione [9], whose structures were proved by X-ray analysis.

Presumably, heating of compounds **IIIa**–**IIIe** in boiling xylene promotes cleavage of the hemiaminal NH–C(OH) bond, followed by closure of new pyrrole ring via intramolecular attack by the primary amino group in the pyrimidine fragment on the ester carbonyl carbon atom with elimination of methanol (Scheme 1). Analogous heterocyclization of pyrrolediones **I** by the action of acyclic and cyclic enamines was observed by us previously most frequently [4, 5, 8, 9].

EXPERIMENTAL

The IR spectra were recorded on FSM-1201 and Bruker IFS-66 spectrometers from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz for ^{1}H) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The purity of the isolated compounds was checked by TLC on Silufol plates using ethyl acetate and ethyl acetate–benzene (1:5) as eluent; spots were visualized by treatment with iodine vapor.

Methyl 12-benzoyl-9-hydroxy-4,6-dimethyl-3,5,10-trioxo-11-phenyl-4,6,8,11-tetraazatricyclo-[7.2.1.0^{2,7}]dodec-2(7)-ene-1-carboxylate (IIIa). A solution of 1 mmol of compound **Ia** and 1 mmol of aminouracil **II** in 10 ml of anhydrous 1,2-dichloroethane was heated for 4 h under reflux. The mixture was cooled, and the precipitate was filtered off. Yield 74%, mp 210–211°C (decomp., from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3330 (NH), 3160 br (OH), 1759 (C^5=O), 1738 (C^3=O), 1721 (C=O, ester), 1704 (C^{10}=O), 1643 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.09 s and 3.16 s (3H each, Me), 3.37 s (3H, OMe), 4.83 s (1H, 12-H), 7.18–7.99 m (10H, H_{arom}), 7.84 s (1H, OH), 8.52 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 27.73 and 30.14 (Me), 51.37 (C^{12}), 54.70 (C^1), 65.50 (MeO), 85.64 (C^9), 125.43, 127.97, 128.87, 133.86, 137.33, 150.80 (C^5), 157.85 (C^2), 166.08 (C=O, ester), 167.05 (C^{10}), 196.15 (Ph**C**O). Found, %: 61.24; H 4.50; N 11.41. $C_{25}H_{22}N_4O_7$. Calculated, %: C 61.22; H 4.52; N 11.42.

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

Methyl 12-benzoyl-9-hydroxy-4,6-dimethyl-11-(4-methylphenyl)-3,5,10-trioxo-4,6,8,11-tetraazatricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene-1-carboxylate (IIIb). Yield 72%, mp 219–220°C (decomp., from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3316 (NH), 3145 br (OH), 1760 (C^5=O, C^3=O), 1727 (C=O, ester), 1702 (C^{10}=O), 1620 (COPh). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, C_6H_4**Me**), 3.08 s and 3.14 s (3H each, Me), 3.37 s (3H, OMe), 4.81 s (1H, 12-H), 7.08–7.98 m (9H, H_{arom}), 7.80 s (1H, OH), 8.49 s (1H, NH). Found, %: C 61.85; H 4.84; N 11.13. $C_{26}H_{24}N_4O_7$. Calculated, %: C 61.90; H 4.80; N 11.11.

Methyl 12-benzoyl-11-(4-chlorophenyl)-9-hydroxy-4,6-dimethyl-3,5,10-trioxo-4,6,8,11-tetraazatricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene-1-carboxylate (IIIc). Yield 76%, mp 217–218°C (decomp., from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3323 (NH), 3150 br (OH), 1760 (C^5=O, C^3=O), 1732 (C=O, ester), 1705 (C^{10}=O), 1620 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.10 s and 3.15 s (3H each, Me), 3.36 s (3H, OMe), 4.85 s (1H, 12-H), 7.30–7.99 m (9H, H_{arom}), 7.91 s (1H, OH), 8.56 s (1H, NH). Found, %: C 57.23; H 4.06; Cl 6.71; N 10.63. $C_{25}H_{21}ClN_4O_7$. Calculated, %: C 57.20; H 4.03; Cl 6.75; N 10.67.

Methyl 12-benzoyl-9-hydroxy-11-(4-methoxyphenyl)-4,6-dimethyl-3,5,10-trioxo-4,6,8,11-tetraazatricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene-1-carboxylate (IIId). Yield 69%, mp 219–220°C (decomp., from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3340 (NH), 3158 br (OH), 1770 (C^5=O, C^3=O), 1730 (C=O, ester), 1710 (C^{10}=O), 1625 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.07 s and 3.13 s (3H each, Me), 3.38 s (3H, COOMe), 3.74 s (3H, OMe), 4.80 s (1H, 12-H), 6.85–7.98 m (9H, H_{arom}), 7.96 s (1H, OH), 8.48 s (1H, NH). Found, %: C 60.03; H 4.69; N 10.79. $C_{26}H_{24}N_4O_8$. Calculated, %: C 60.00; H 4.65; N 10.76.

Methyl 12-benzoyl-11-(4-bromophenyl)-9-hydroxy-4,6-dimethyl-3,5,10-trioxo-4,6,8,11-tetraazatricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene-1-carboxylate (IIIe). Yield 71%, mp 226–227°C (decomp., from 1,2-dichloroethane). IR spectrum, ν, cm^{-1}: 3332 (NH), 3165 br (OH), 1760 (C^5=O, C^3=O), 1735 (C=O, ester), 1709 (C^{10}=O), 1622 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.10 s and 3.15 s (3H each, Me), 3.36 s (3H, OMe), 4.85 s (1H, 12-H), 7.25–7.99 m (9H, H_{arom}), 7.91 s (1H, OH), 8.56 s (1H, NH). Found, %: C 52.71;

H 3.79; Br 14.06; N 9.87. $C_{25}H_{21}BrN_4O_7$. Calculated, %: C 52.74; H 3.72; Br 14.03; N 9.84.

3-Benzoyl-4-hydroxy-1′,3′-dimethyl-1-phenylspiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraone (IVa). A solution of 0.5 mmol of compound **IIIa** in *m*-xylene was heated for 16 h under reflux. After cooling, the precipitate was filtered off. Yield 68%, mp 238–240°C (decomp., from ethyl acetate). IR spectrum, ν, cm^{-1}: 3355 (NH); 3185 br (OH); 1740, 1720, 1665 ($C^{4'}$=O, $C^{6'}$=O, $C^{2'}$=O, C^5=O); 1630 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.60 s and 3.81 s (3H each, Me), 7.08–7.71 m (10H, H_{arom}), 10.67 s (1H, NH), 12.17 br.s (1H, OH). Found, %: C 62.90; H 3.94; N 12.21. $C_{24}H_{18}N_4O_6$. Calculated, %: C 62.88; H 3.96; N 12.22.

3-Benzoyl-4-hydroxy-1′,3′-dimethyl-1-(4-methylphenyl)spiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraone (IVb). Yield 63%, mp 269–270°C (decomp., from ethyl acetate). IR spectrum, ν, cm^{-1}: 3352 (NH); 3195 br (OH); 1735, 1724, 1668 ($C^{2'}$=O, $C^{4'}$=O, C^5=O, $C^{6'}$=O); 1631 (COPh). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, C_6H_4**Me**), 3.59 s and 3.80 s (3H each, Me), 6.94–7.65 m (9H, H_{arom}), 10.59 s (1H, NH), 12.10 br.s (1H, OH). Found, %: C 63.52; H 4.29; N 11.83. $C_{25}H_{20}N_4O_6$. Calculated, %: C 63.56; H 4.27; N 11.86.

3-Benzoyl-1-(4-chlorophenyl)-4-hydroxy-1′,3′-dimethylspiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraone (IVc). Yield 59%, mp 296–297°C (decomp., from ethyl acetate). IR spectrum, ν, cm^{-1}: 3349 (NH); 3180 br (OH); 1738, 1723, 1676 ($C^{4'}$=O, $C^{6'}$=O, $C^{2'}$=O, C^5=O); 1620 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.59 s and 3.80 s (3H, Me), 7.09–7.65 m (9H, H_{arom}), 10.79 s (1H, NH), 12.18 br.s (1H, OH). Found, %: C 58.51; H 3.51; Cl 7.15; N 11.40. $C_{24}H_{17}ClN_4O_6$. Calculated, %: C 58.49; H 3.48; Cl 7.19; N 11.37.

3-Benzoyl-4-hydroxy-1-(4-methoxyphenyl)-1′,3′-dimethylspiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraone (IVd). Yield 52%, mp 283–284°C (decomp., from ethyl acetate). IR spectrum, ν, cm^{-1}: 3356 (NH); 3175 br (OH); 1742, 1730, 1670 ($C^{2'}$=O, $C^{4'}$=O, C^5=O, $C^{6'}$=O); 1625 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.07 s and 3.59 s (3H each, Me), 3.75 s (3H, OMe), 6.77–7.71 m (9H, H_{arom}), 10.56 s (1H, NH), 12.02 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 27.12 and 31.26 (Me), 55.19 (OMe), 70.67 (C^2), 114.53 (C^3), 114.54, 127.92, 128.49, 128.68, 128.76, 132.17, 134.01, 137.87, 150.68 ($C^{2'}$), 156.67 (C^5), 158.85 ($C^{4'}$), 166.39 ($C^{6'}$), 175.79 (C^4), 188.20 (Ph**C**O). Found, %: C 61.49; H 4.14; N 11.49. $C_{25}H_{20}N_4O_7$. Calculated, %: C 61.47; H 4.13; N 11.47.

3-Benzoyl-1-(4-bromophenyl)-4-hydroxy-1′,3′-dimethylspiro[pyrrole-2,5′-pyrrolo[2,3-*d*]pyrimidine]-2′,4′,5,6′(1*H*,1′*H*,3′*H*,7′*H*)-tetraone (IVe). Yield 52%, mp 248–249°C (decomp., from ethyl acetate). IR spectrum, ν, cm^{-1}: 3360 (NH); 3165 br (OH); 1740, 1725, 1667 ($C^{2'}$=O, $C^{4'}$=O, C^5=O, $C^{6'}$=O); 1618 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.54 s and 3.60 s (3H each, Me), 7.04–7.99 m (9H, H_{arom}), 10.78 s (1H, NH), 12.21 br.s (1H, OH). Found, %: C 53.67; H 3.21; Br 14.88; N 10.44. $C_{24}H_{17}BrN_4O_6$. Calculated, %: C 53.65; H 3.19; Br 14.87; N 10.43.

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