ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 8, pp. 1165–1168. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © M.V. Dmitriev, P.S. Silaichev, Z.G. Aliev, A.N. Maslivets, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 8, pp. 1147–1150.

Five-Membered 2,3-Dioxoheterocycles: LXXIX.* Three-Component Condensation of 1*H*-Pyrrol-2,3-diones with Acetonitriles and Dimedone. Crystal and Molecular Structure of Substituted Spiro[chromene-4,3'-pyrrole]

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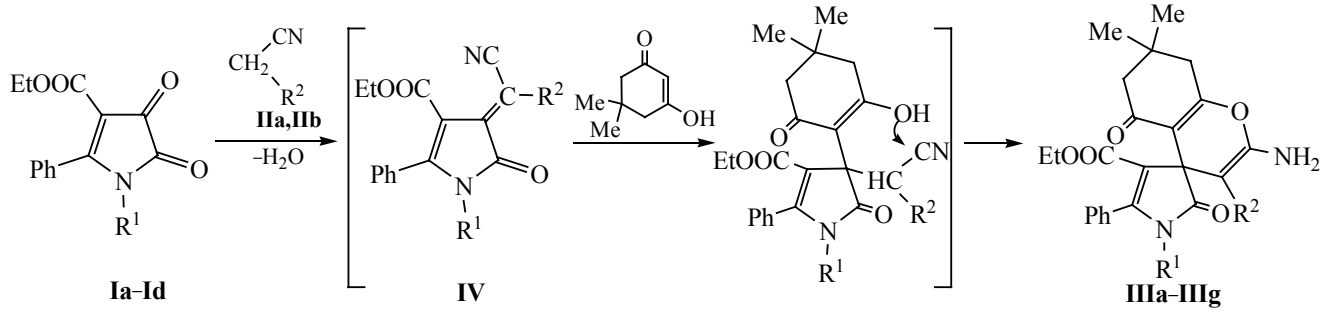
Received October 26, 2010

Abstract—5-Phenyl-4-ethoxycarbonyl-1*H*-pyrrole-2,3-diones react with acetonitriles and dimedone to form ethyl 2-amino-7,7-dimethyl-2',5-dioxo-5'-phenyl-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-4'-carboxylates. The crystal and molecular structure of ethyl 2-amino-1'-benzyl-7,7-dimethyl-2',5-dioxo-5'-phenyl-3-cyano-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-4'-carboxylate was proved by XRD analysis.

DOI: 10.1134/S1070428011080082

The three-component condensation of isartin with acetonitriles and β-diketones resulting in 2'-aminospiro[indole-3,4'-pyran]-2(1*H*)-ones was reported [2, 3].

We carried out the reaction of 5-phenyl-4-ethoxycarbonyl-1*H*-pyrrole-2,3-diones **Ia–Id** [4] with substituted acetonitriles [malononitrile (**IIa**) and methyl cyanoacetate (**IIb**)] and dimedone in the ratio 1 : 1 : 1 by boiling the solution of the reagents in anhydrous benzene in the presence of triethylamine for 1.5–3 h (TLC monitoring) to obtain in good yields ethyl 2-amino-7,7-dimethyl-2',5-dioxo-5'-phenyl-3-cyano-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-4'-carboxylates **IIIa–IIId** and 3-methyl 4'-ethyl 2-amino-7,7-dimethyl-2',5-dioxo-5'-phenyl-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-3,4'-dicarboxylates **IIIe**–**IIIg** whose structure was proved by XRD analysis by an example of compound **IIIa**.**



I, R^1 = CH_2Ph (**a**), Ph (**b**), cyclo-C_6H_{11} (**c**), H (**d**); **II**, R^2 = CN (**a**), COOMe (**b**); **III**, R^2 = CN, R^1 = CH_2Ph (**a**), Ph (**b**), cyclo-C_6H_{11} (**c**), H (**d**); R^2 = COOMe, R^1 = CH_2Ph (**e**), Ph (**f**), cyclo-C_6H_{11} (**g**).

* For Communication LXXVIII, see [1].

** For preliminary communication, see [5].

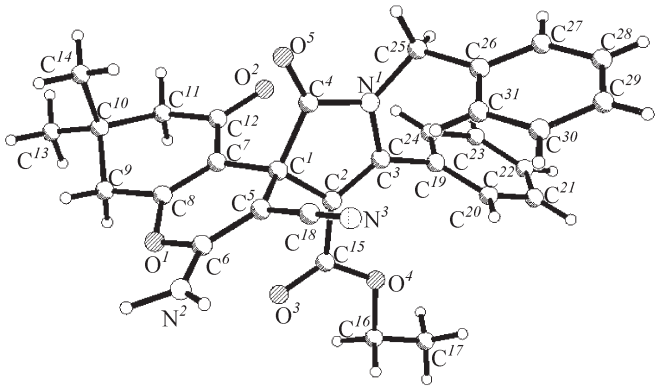


Fig. 1. General appearance of molecule of ethyl 2-amino-1'-benzyl-7,7-dimethyl-2',5-dioxo-5'-phenyl-3-cyano-1',2',5,6,7,8-hexahydro-spiro[chromene-4,3'-pyrrole]-4'-carboxylate (**IIIa**).

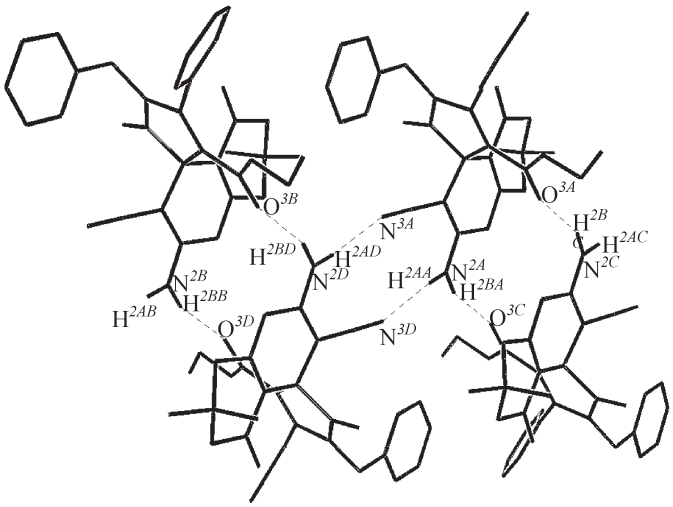


Fig. 2. Schematic view of the hydrogen bond formation in the crystal of compound **IIIa**.

Compounds **IIIa–IIIg** are colorless high-melting crystalline substances, readily soluble in DMSO and DMF, sparingly soluble in ordinary organic solvents, insoluble in alkanes and water, giving a negative test for enol hydroxy group with the ethanol solution of iron(III) chloride.

The IR spectra of compounds **IIIa–IIIg** contain the absorption bands of the stretching vibrations of the NH_2 group, (3154–3453 cm^{-1}), cyano group (2189–2199 cm^{-1}) (in compounds **IIIa–IIId),** of lactam carbonyl group (1694–1734 cm^{-1}), ester and keto carbonyl groups (1657–1694 cm^{-1}).

In the ^1H NMR spectra of compounds **IIIa–IIIg** alongside the proton signals of the aromatic rings and the groups attached thereto two singlets appeared of the methyl protons (0.95–1.09 ppm), doublets of doublets of nonequivalent methylene protons C^8H_2 and C^6H_2 (2.11–2.70 ppm) with characteristic coupling constants (J 15.6–17.7 Hz), a broadened singlet of NH_2 protons (7.20–7.97 ppm), a triplet and a multiplet of protons of the ethoxycarbonyl substituent (0.82–1.00 and 3.66–3.87 ppm respectively).

In the ^{13}C NMR spectra of compounds **IIIa** and **IIIf** characteristic signals were present of the carbon atoms of the keto carbonyl group (195.23–195.30 ppm), of lactam carbonyl group (164.11–164.77 ppm), and of the spiro carbon (43.91–47.45 ppm).

According to XRD data all bond distances and bond angles in molecule **IIIa** (Fig. 1) are of the magnitude common for such bonds. The molecules in the crystal are bound by two hydrogen bonds. The hydrogen bond N^2–H^{2a}···N^3 between the amino group and the nitrogen of the cyano group (bonds N^2···N^3 3.099, H^{2a}···N^3 2.27 Å, the angle at the hydrogen atom 173°) leads to the formation of the centrosymmetrical dimeric associates with the coordinates of the symmetry center 0.5 0 0. These dimeric associates are grouped around another symmetry center with the coordinates 0.5 0.5 0 and are bound by the hydrogen bond N^2–H^{2c}···O^3 (bonds N^2···O^3 2.898, H^{2c}···O^3 1.89 Å, the angle at the hydrogen atom 151°). Thus in the crystal the molecules are bound by the hydrogen bonds in endless bands in the direction c of the unit cell. A fragment of this band is shown in Fig. 2.

The formation of compounds **IIIa–IIIg** proceeds apparently via the primary condensation of the keto carbonyl group of pyrroledione **Ia–Id** with substituted acetonitriles **IIa, IIb** to form pyrrolones **IV** followed by the nucleophilic addition of the β-CH group and the hydroxy group of the enol fragment of dimedone to the carbon atom in the position *3* and to the cyano group of pyrrolones **IV** respectively.

The reaction described is a rare example of the spiro-bis-heterocyclization of monocyclic 1*H*-pyrrole-2,3-diones in the three-component condensation with nucleophilic reagents, and also an example of the synthesis of difficultly accessible heterocyclic system of spiro[chromene-4,3'-pyrrole].

EXPERIMENTAL

IR spectra of compounds obtained were recorded on a spectrophotometer FSM -1201 from mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on a spec-

trometer Bruker AM-400 [400 (^{1}H) and 100 (^{13}C) MHz] in DMSO-d_6, internal reference TMS. The homogeneity of compounds obtained was proved by TLC on Silufol plates, eluents benzene–ethyl acetate, 5 : 1, ethyl acetate, development in iodine vapor.

XRD investigation of compound IIIa. Colorless crystals $C_{31}H_{29}N_3O_5$, well formed tetragonal prisms belonging to monoclinic crystal system: *a* 13.753(3), *b* 9.398(2), *c* 21.610(4) Å, β 98.77(3), *V* 2760.5(10) Å^3, *M* 523.57, d_{calc} 1.260 g/cm^3, *Z* 4, space group P2(1)/*C*. The set of experimental reflections was obtained on an automatic four-circle diffractometer QM-4 (KUMA DIFFRACTION) with χ-geometry by ω/2Θ scanning with the use of monochromatized MOK_α-radiation (2Θ ≤ 52°). Overall number of measured reflections 5589, among them 5433 independent reflections (R_{int} 0.0229). No correction for extinction was done (μ 0.086 mm^{-1}). The structure was solved by the direct method applying the program SIR92 [6] followed by a series of calculations of the electron density maps. Hydrogen atoms were placed geometrically. The full-matrix least-squares anisotropic refinement of nonhydrogen atoms along the program SHELXL-97 [7] was finished at R_1 0.0570 and wR_2 0.11524 for 2278 reflections with $I \geq 2\sigma(I)$. Refined parameters 361, $\Delta\rho_{max}$ 0.249, *GOOF* 0.890.

Ethyl 2-amino-1'-benzyl-7,7-dimethyl-2',5-dioxo-5'-phenyl-3-cyano-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-4'-carboxylate (IIIa). To a solution of 1 mmol of pyrroledione **Ia** in 20 ml of anhydrous benzene was added 1 mmol of malononitrile, 1 mmol of dimedone, and 1 mmol of triethylamine, the mixture was boiled for 2 h, cooled, the formed precipitate was filtered off and recrystallized from toluene. Yield 89%, mp 243–244°C. IR spectrum, ν, cm^{-1}: 3399, 3328, 3214 (NH_2), 2191 (CN), 1734 (C$^{2'}$=O), 1674 (COO, C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.84 t (3H, $CH_2C\underline{H}_3$, *J* 7.4 Hz), 1.01 s (3H, Me), 1.08 s (3H, Me), 2.22 d, 2.35 d (2H, C$^8H_2$, *J* 15.6 Hz), 2.40 d, 2.69 d (2H, C$^6H_2$, *J* 17.7 Hz), 3.77 m (2H, $OC\underline{H}_2CH_3$), 4.47 s (2H, $C\underline{H}_2Ph$), 7.06–7.41 group of signals (12H, 2Ph + NH_2). ^{13}C NMR spectrum, δ, ppm: 13.41 ($\underline{C}H_3CH_2$), 26.19 (Me), 28.15 (Me), 31.91 (C^7), 39.89 (C^8), 43.91 (C^4), 47.71 ($\underline{C}H_2Ph$), 49.80 (C^6), 55.05 (C^3), 58.75 ($CH_3\underline{C}H_2$), 110.19 (C$^{4'}$), 111.32 (C^{4a}), 117.52 (CN), 126.47–136.51 (C_{arom}), 154.70 (C$^{5'}$), 159.77 (C^{8a}), 161.48 (C^2), 164.77 (C$^{2'}$), 178.63 (COO), 195.30 (C^5). Found, %: C 71.02; H 5.47; N 8.08. $C_{31}H_{29}N_3O_5$. Calculated, %: C 71.11; H 5.58; N 8.03.

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

Ethyl 2-amino-7,7-dimethyl-2',5-dioxo-1',5'-diphenyl-3-cyano-1',2',5,6,7,8-hexahydrospiro-[chromene-4,3'-pyrrole]-4'-carboxylate (IIIb). Yield 74%, mp 243–244°C (ethyl acetate–acetone, 1 : 1). IR spectrum, ν, cm^{-1}: 3453, 3279, 3167 (NH_2), 2199 (CN), 1721 (C$^{2'}$=O), 1690 (COO), 1663 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.91 t (3H, $CH_2C\underline{H}_3$, *J* 7.2 Hz), 1.02 C (3H, Me), 1.09 C (3H, Me), 2.23 d, 2.35 d (2H, C$^8H_2$, *J* 16.4 Hz), 2.41 d, 2.69 d (2H, C$^6H_2$, *J* 17.3 Hz), 3.83 m (2H, $OC\underline{H}_2CH_3$), 7.02–7.32 group of signals (10H, 2Ph), 7.40 br.s (2H, NH_2). Found, %: C 70.73; H 5.43; N 8.13. $C_{30}H_{27}N_3O_5$. Calculated, %: C 70.71; H 5.34; N 8.25.

Ethyl 2-amino-7,7-dimethyl-2',5-dioxo-5'-phenyl-3-cyano-1'-cyclohexyl-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-4'-carboxylate (IIIc). Yield 78%, mp 235–236°C (toluene). IR spectrum, ν, cm^{-1}: 3399, 3297, 3162 (NH_2), 2186 (CN), 1715 (C$^{2'}$=O), 1690 (COO), 1665 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.82 t (3H, $CH_2C\underline{H}_3$, *J* 7.0 Hz), 0.88–2.08 group of signals (10H, C_6H_{11}), 0.98 s (3H, Me), 1.07 s (3H, Me), 2.16 d, 2.30 d (2H, C$^8H_2$, *J* 16.0 Hz), 2.36 d, 2.63 d (2H, C$^6H_2$, *J* 17.6 Hz), 3.04 m (1H, NCH), 3.72 m (2H, $C\underline{H}_2CH_3$), 7.24–7.52 group of signals (7H, Ph + NH_2). Found, %: C 69.99; H 6.29; N 8.26. $C_{30}H_{33}N_3O_5$. Calculated, %: C 69.88; H 6.45; N 8.15.

Ethyl 2-amino-7,7-dimethyl-2',5-dioxo-5'-phenyl-3-cyano-1',2',5,6,7,8-hexahydrospiro-[chromene-4,3'-pyrrole]-4'-carboxylate (IIId). Yield 79%, mp 263–265°C (toluene–1,4-dioxane, 1:1). IR spectrum, ν, cm^{-1}: 3395, 3318, 3194 (NH_2), 2189 (CN), 1728 (C$^{2'}$=O), 1682 (COO), 1661 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.98 s (3H, Me), 1.00 t (3H, $CH_2C\underline{H}_3$, *J* 7.5 Hz), 1.06 s (3H, Me), 2.14 d, 2.29 d (2H, C$^8H_2$, *J* 16.1 Hz), 2.36 d, 2.63 d (2H, C$^6H_2$, *J* 17.6 Hz), 3.87 m (2H, $C\underline{H}_2CH_3$), 7.14–7.51 group of signals (7H, Ph + NH_2), 10.72 s (1H, NH). Found, %: C 66.64; H 5.28; N 9.81. $C_{24}H_{23}N_3O_5$. Calculated, %: C 66.50; H 5.35; N 9.69.

3-Methyl 4'-ethyl 2-amino-1'-benzyl-7,7-dimethyl-2',5-dioxo-5'-phenyl-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-3,4'-dicarboxylate (IIIe). Yield 74%, mp 235–236°C (toluene). IR spectrum, cm^{-1}: 3366, 3244, 3154 (NH_2), 1725, 1690 (C$^{2'}$=O, COO), 1663 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, $CH_2C\underline{H}_3$, *J* 7.0 Hz), 0.97 s (3H, Me), 1.08 s (3H, Me), 2.18 d, 2.35 d (2H, C$^8H_2$, *J* 16.1 Hz), 2.36 d, 2.69 d (2H, C$^6H_2$, *J* 17.7 Hz), 3.32 s (3H, COOMe), 3.71 m

(2H, C$\underline{H}_2$CH$_3$), 4.39 d, 4.45 d (2H, CH$_2$Ph, *J* 15.8 Hz), 7.09–7.45 group of signals (10H, 2Ph), 7.97 br.s (2H, NH$_2$). Found, %: C 69.07; H 5.91; N 4.92. $C_{32}H_{32}N_2O_7$. Calculated, %: C 69.05; H 5.79; N 5.03.

3-Methyl 4'-ethyl 2-amino-7,7-dimethyl-2',5-dioxo-1',5'-diphenyl-1',2',5,6,7,8-hexahydrospiro-[chromene-4,3'-pyrrole]-3,4'-dicarboxylate (IIIf). Yield 63%, mp 230–232°C (toluene). IR spectrum, ν, cm^{-1}: 3332, 3247, 3169 (NH$_2$), 1694 (C$^{2'}$=O, COO), 1657 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, CH$_2$C$\underline{H}_3$, *J* 7.1 Hz), 0.99 s (3H, Me), 1.08 s (3H, Me), 2.20 d, 2.35 d (2H, C^{8}H$_2$, *J* 15.8 Hz), 2.38 d, 2.70 d (2H, C^{6}H$_2$, *J* 17.5 Hz), 3.66 s (3H, COOMe), 3.77 m (2H, C$\underline{H}_2$CH$_3$), 7.08–7.30 group of signals (10H, 2Ph), 7.96 br.s (2H, NH$_2$). ^{13}C NMR spectrum, δ, ppm: 13.51 (C$\underline{H}_3$CH$_2$), 25.87 (Me), 28.39 (Me), 31.63 (C^7), 40.11 (C^8), 47.45 (C^4), 50.42 (C^6), 50.67 (COO$\underline{Me}$), 58.87 (CH$_3$C$\underline{H}_2$), 74.43 (C^3), 109.70 (C$^{4'}$), 112.30 (C^{4a}), 125.21–134.95 (C$_{arom}$), 154.43 (C$^{5'}$), 160.22 (C^{8a}), 162.12 (C^2), 164.11 (C$^{2'}$), 167.58 (C$\underline{O}$OMe), 179.46 (C$\underline{O}$OEt), 195.23 (C^5). Found, %: C 68.79; H 5.51; N 5.09. $C_{31}H_{30}N_2O_7$. Calculated, %: C 68.62; H 5.57; N 5.16.

3-Methyl 4'-ethyl 2-amino-7,7-dimethyl-2',5-dioxo-5'-phenyl-1'-cyclohexyl-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-pyrrole]-3,4'-dicarboxylate (IIIg). Yield 66%, mp 247–250°C (toluene). IR spectrum, ν, cm^{-1}: 3355, 3239, 3171 (NH$_2$), 1694 (C$^{2'}$=O, COO), 1659 (C^5=O). ^{1}H NMR spectrum, δ, ppm: 0.82 t (3H, CH$_2$C$\underline{H}_3$, *J* 7.0 Hz), 0.88–2.00 group of signals (10H, C$_6$H$_{11}$), 0.95 s (3H, Me), 1.06 s (3H, Me), 2.11 d, 2.30 d (2H, C^{8}H$_2$, *J* 16.0 Hz), 2.32 d, 2.64 d (2H, C^{6}H$_2$, *J* 16.8 Hz), 3.07 m (1H, NCH), 3.58 s (3H, COOMe), 3.66 m (2H, C$\underline{H}_2$CH$_3$), 7.16–7.50 group of signals (5H, Ph), 7.90 br.s (2H, NH$_2$). Found, %: C 67.80; H 6.77; N 5.02. $C_{31}H_{36}N_2O_7$. Calculated, %: C 67.87; H 6.61; N 5.11.

ACKNOWLEDGMENTS

The study was performed under the financial support of the Ministry of Education and Science of the Russian Federation (project no. 2.19.10) and the Russian Foundation for Basic Research (grant no. 08-03-01032).

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