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Chemistry of 2-Ylidenefuran-3(2*H*)-ones: XIX.* Reaction of 5-Aryl-2-(oxoylidene)furan-3(2*H*)-ones with Carboxylic Acid Hydrazides

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Abstract—2-[2-(4-Chlorophenyl)-2-oxoethylidene]-5-phenylfuran-3(2*H*)-one and methyl (5-aryl-3-oxo-2,3-dihydrofuran-2-ylidene)acetates react with carboxylic acid hydrazides to give the corresponding 3-substituted 2-acyl-6-aryl-3-hydroxy-2,3-dihydropyridazin-4(1*H*)-ones. Specificities of the product structure are discussed.

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It was found previously that reactions of 2-ylidenefuran-3(2*H*)-ones with hydrazine and aryl- or hetarylhydrazines are quite versatile: they lead to the formation of hydrazino derivatives of 3-oxofuran [2] and cyclic azoles or azines, e.g., 3-acylpyrazoles [3–6], 3-(3-oxopyrazol-5-yl)pyrazoles [6, 7], or substituted pyridazin-4(1*H*)-ones [3, 6, 8, 9]. Published data on reactions of acylhydrazines with five-membered 2-ylidene-2,3-dihydro-3-oxo heterocycles are limited to our short communications [10–12]. In the present work we examined reactions of 2-oxoylidenefuran-3(2*H*)-ones with carboxylic acid hydrazides and their derivatives in comparison with simpler hydrazines.

The direction of the reaction of 5-aryl-2-(oxoylidene)furan-3(2*H*)-ones **Ia**–**Ic** with carboxylic acid hydrazides depended on neither substrate nor reagent structure. Methyl (5-aryl-3-oxo-2,3-dihydrofuran-2-ylidene)acetates **Ia** and **Ib** [13, 14] and 2-[2-(4-chlorophenyl)-2-oxoethylidene]-5-phenylfuran-3(2*H*)-one (**Ic**) [15] reacted with acetic, benzoic, *p*-methoxybenzoic, *p*-nitrobenzoic, and salicylic acid hydrazides in ethanol on heating for a short time (10–30 min) under reflux to give 44–86% of 3-substituted 2-acyl-6-aryl-3-hydroxy-2,3-dihydropyridazin-4(1*H*)-ones **IIa**–**IIh** (Scheme 1); the products were identified on the basis of spectral data in comparison with known 4-oxopyridazines [6, 9]. Compounds **II** exist in solution as two tautomers **A** and **B**. From the reaction mixtures we also isolated small amounts of 1,2-diacylhydrazines **III** which were identified by comparison with authentic samples.

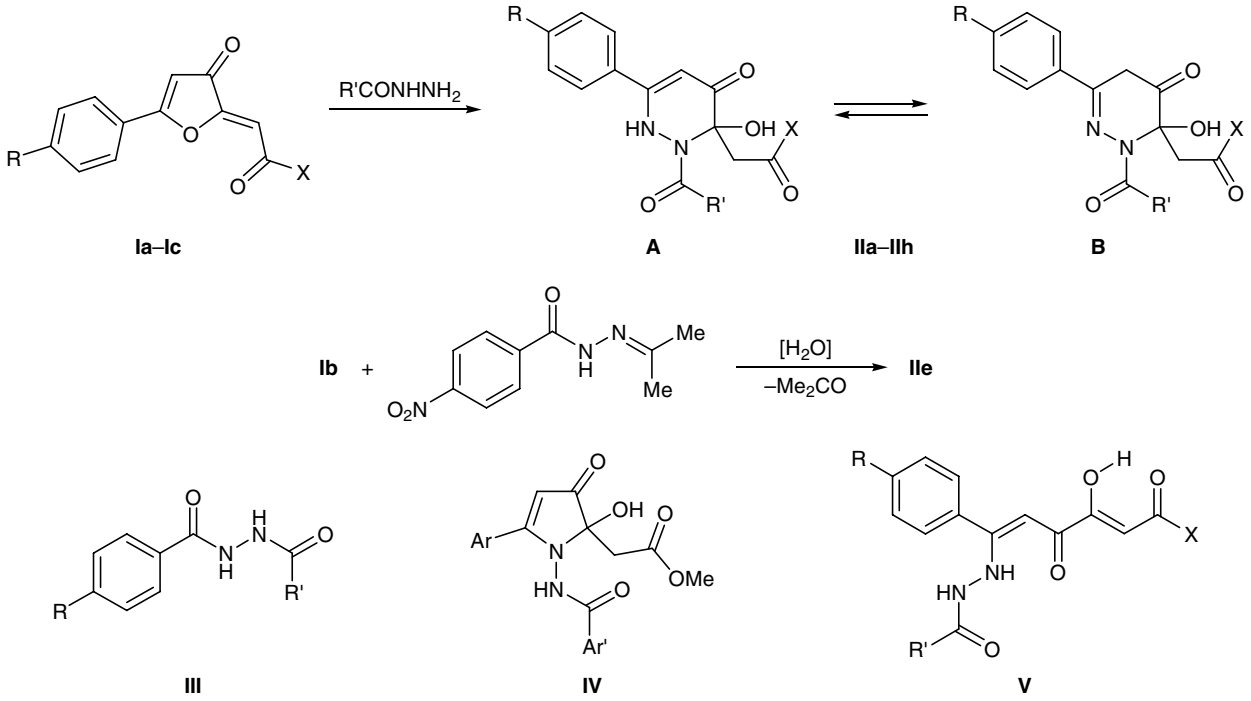
Pyridazinone **IIe** was also synthesized by reaction of *N*′-isopropylidene-4-nitrobenzohydrazide with methyl (3-oxo-5-phenyl-2,3-dihydrofuran-2-ylidene)-acetate (**Ib**) under analogous conditions. It should be noted that other *N*′-ylidene-substituted hydrazides, e.g., *N*′-benzylidene-4-nitrobenzohydrazide, failed to react with furanylidene acetate **Ib**.

Initially [16, 17], we erroneously assigned some pyridazin-4(1*H*)-ones **II** the structure of (1-aroylamino-5-aryl-2-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrol-2-yl)acetates **IV** (Ar = 4-RC_6H_4, Ar′ = R′, X = OMe). The ^{1}H NMR spectra of compounds **II** in chloroform-*d* contain a downfield signal at δ 7.95–8.15 ppm which belongs to the N^{1}H proton in tautomer **A**; this signal disappears completely upon addition of trifluoroacetic acid due to fast proton exchange.

Presumably, the reaction of carboxylic acid hydrazides with furanones **Ia**–**Ic** involves nucleophilic attack by the hydrazide NH_2 group [or NH group of the enamino tautomer of *N*′-isopropylidene-4-nitrobenzohydrazide, NHC(Me)=CH_2] at the electrophilic C^5 atom of the furan ring in **I**. Intermediate enehydrazino-

* For communication XVIII, see [1].

Scheme 1.



I, X = OMe, R = Me (**a**), H (**b**); X = 4-ClC_6H_4, R = H (**c**); **II**, X = OMe, R = R′ = Me (**a**); R = Me, R′ = Ph (**b**); R = H, R′ = Ph (**c**), 2-HOC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**); X = 4-ClC_6H_4, R = H, R′ = Ph (**f**), 4-$MeOC_6H_4$ (**g**), 2-HOC_6H_4 (**h**).

carbonyl structure **V** (Scheme 1) undergoes intramolecular heterocyclization at the NH group of the acylhydrazine moiety to give pyridazin-4(1*H*)-ones **II**. The hydroxy group in salicylic acid hydrazide does not participate in the reaction with furanones **I**, and the corresponding products (pyridazinones **IId** and **IIh**) have unchanged hydroxy group in the aromatic ring. Regioselective nucleophilic attack by hydrazides at the electron-deficient C^5 atom in compound **I**, despite the presence of other electrophilic centers (C^2, $C^{2'}$, C^3), indicates that the reaction is likely to be orbital-controlled [18].

Pyridazinones **II** showed a pronounced bacteriostatic activity against *Staphylococcus aureus* P-209 and *Escherichia coli* M_{17} [10].

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from samples dispersed in mineral oil. The ^1H NMR spectra were measured on RYa-2310 (60 MHz), Bruker AC-300 (300 MHz), and Bruker DRX-500 (500 MHz) instruments using $CDCl_3$, DMSO-d_6, or DMSO-d_6–CF_3COOH (10:1) as solvent and HMDS or TMS as internal reference. The ^{13}C NMR spectrum of compound **IIg** was obtained on a JEOL EX90A FT-NMR spectrometer (22 MHz) in $CDCl_3$ using TMS as internal reference. The mass spectra (electron impact, 70 eV) were recorded on a Kratos MS-30 mass spectrometer (United Kingdom) with direct sample admission into the ion source (emission current 1000 mA, vaporizer temperature 100–120°C). The progress of the reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene–diethyl ether–acetone (10:9:1) as eluent; spots were visualized by treatment with iodine vapor.

Initial 5-aryl-2-(oxoylidene)furan-3(2*H*)-ones **Ia–Ic** were prepared by the procedures described in [13–15].

2-Acyl-6-aryl-3-hydroxy-2,3-dihydropyridazin-4(1*H*)-ones IIa–IIh (*general procedure*)**.** *a.* A mixture of equimolar amounts (5.0 mmol) of compound **Ia–Ic** and the corresponding carboxylic acid hydrazide in 100–150 ml of ethanol was stirred on heating until it became homogeneous and was then heated under reflux for 10–30 min (TLC). The solvent was distilled off, and the residue was recrystallized from ethanol, acetonitrile, or chloroform–hexane (1:1) to obtain compounds **IIa–IIh** as colorless crystals. Recrystallization of the residue from toluene gave a small amount of 1,2-diacylhydrazine **III**.

b. Compound **IIe** was also synthesized by reaction of **Ib** with *N*′-isopropylidene-4-nitrobenzohydrazide, following an analogous procedure.

Methyl [2-acetyl-3-hydroxy-6-(4-methylphenyl)-4-oxo-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IIa). Yield 0.70 g (44%), mp 149–150°C (decomp., from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.12 s (3H, 4-C**H**$_3$C$_6$H$_4$), 2.45 s (3H, COCH$_3$), 3.42 d.d (2H, 3-CH$_2$, J = 15.8 Hz), 3.72 s (3H, COOCH$_3$), 4.05 s (2H, 5-H, tautomer **B**), 7.30–7.95 m (4H, C$_6$H$_4$). Found, %: C 60.54; H 5.89; N 8.61. $C_{16}H_{18}N_2O_5$. Calculated, %: C 60.37; H 5.70; N 8.80.

Methyl [2-benzoyl-3-hydroxy-6-(4-methylphenyl)-4-oxo-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IIb). Yield 1.50 g (79%), mp 139–140°C (decomp., from acetonitrile). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 2.31 s (3H, 4-C**H**$_3$C$_6$H$_4$), 3.65 d.d (2H, 3-CH$_2$, J = 9.2 Hz), 3.71 s (3H, COOCH$_3$), 5.82 s (1H, 5-H, tautomer **A**), 7.05–7.89 m (9H, C$_6$H$_4$, C$_6$H$_5$), 7.95 s (1H, 1-H). Found, %: C 66.20; H 5.48; N 7.22. $C_{21}H_{20}N_2O_5$. Calculated, %: C 66.31; H 5.30; N 7.36.

Methyl (2-benzoyl-3-hydroxy-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridazin-3-yl)acetate (IIc). Yield 1.43 g (78%), mp 118–119°C (decomp., from ethanol). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 3.63 d.d (2H, 3-CH$_2$, J = 8.5 Hz), 3.73 s (3H, COOCH$_3$), 5.37 s (1H, 5-H, tautomer **A**), 7.33–8.05 m (10H, C$_6$H$_5$), 8.10 s (1H, 1-H). Found, %: C 65.32; H 5.18; N 7.49. $C_{20}H_{18}N_2O_5$. Calculated, %: C 65.57; H 4.95; N 7.65.

Methyl [3-hydroxy-2-(2-hydroxybenzoyl)-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IId). Yield 1.41 g (74%), mp 120–121°C (decomp., from chloroform–hexane, 1:1). IR spectrum, ν, cm^{-1}: 3422 (N–H); 1730 (C=O, ester); 1711 (C^4=O); 1665, 1647, 1620 (C=O, amide; C=C, C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: in DMSO-d_6: 3.65 m (5H, 3-CH$_2$-COOCH$_3$), 5.84 s (1H, 5-H, tautomer **A**), 7.06–8.10 m (10H, C$_6$H$_5$, C$_6$H$_4$, 1-H), 10.35 br.s (1H, C$_6$H$_4$OH); in DMSO-d_6–CF$_3$COOH (10:1): 3.70 d.d and 4.06 d.d (1H each, 3-CH$_2$, J = 9.6 Hz), 3.78 s (3H, COOCH$_3$), 5.90 s (1H, 5-H, tautomer **A**), 7.12–8.17 m (9H, C$_6$H$_5$, C$_6$H$_4$), 10.65 br.s (1H, HOC$_6$H$_4$). Mass spectrum, m/z (I_{rel}, %): 382 (3) [M]$^+$, 351 (0.5) [M – CH$_3$O]$^+$, 281 (56) [M – CH$_3$O – CH$_2$CO]$^+$, 263 (3) [M – CH$_3$O – CH$_2$CO – H$_2$O – H]$^+$, 161 (88) [C$_6$H$_5$C(=NH)CH$_2$CONH]$^+$, 160 (5) [C$_6$H$_5$C$_3$H$_3$N$_2$O]$^+$, 121 (100) [HOC$_6$H$_4$C≡O]$^+$, 103 (6) [C$_6$H$_5$C≡N]$^+$, 93 (18) [HOC$_6$H$_4$]$^+$, 77 (14) [C$_6$H$_5$]$^+$. Found, %: C 62.74; H 4.85; N 7.46. $C_{20}H_{18}N_2O_6$. Calculated, %: C 62.82; H 4.74; N 7.33. M 382.

Methyl [3-hydroxy-2-(4-nitrobenzoyl)-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridazin-3-yl]acetate (IIe). Yield 1.77 g (86%) (*a*), 1.38 g (67%) (*b*), mp 153–154°C (decomp., from ethanol). IR spectrum, ν, cm^{-1}: 3385 (N–H); 3280 (O–H); 1734 (C=O, ester); 1716 (C^4=O); 1678, 1656, 1635 (C=O, amide; C=C, C=C$_{arom}$). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 3.77 s (3H, COOCH$_3$), 3.82 d.d (2H, 3-CH$_2$, J = 9.8 Hz), 5.62 s (1H, 5-H, tautomer **A**), 6.11 s (1H, 3-OH), 7.25–8.08 m (9H, C$_6$H$_5$, C$_6$H$_4$), 8.17 s (1H, 1-H). Found, %: C 58.70; H 4.32; N 9.88. $C_{20}H_{17}N_3O_7$. Calculated, %: C 58.39; H 4.17; N 10.21.

2-Benzoyl-3-[2-(4-chlorophenyl)-2-oxoethyl]-3-hydroxy-6-phenyl-2,3-dihydropyridazin-4(1*H*)-one (IIf). Yield 1.59 g (71%), mp 162–163°C (decomp., from acetonitrile). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.55 d.d (2H, 3-CH$_2$, J = 16.4 Hz), 4.95 s (2H, 5-H, tautomer **B**, 72%), 7.05 s (1H, 5-H, tautomer **A**, 28%), 7.55–8.10 m (15H, C$_6$H$_5$, C$_6$H$_4$, 1-H). Found, %: C 67.06; H 4.45; Cl 7.81; N 6.10. $C_{25}H_{19}ClN_2O_4$. Calculated, %: C 67.19; H 4.29; Cl 7.93; N 6.27.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-3-hydroxy-2-(4-methoxybenzoyl)-6-phenyl-2,3-dihydropyridazin-4(1*H*)-one (IIg). Yield 2.00 g (85%), mp 180–181°C (decomp., from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.66 d.d (2H, 3-CH$_2$, J = 16.0 Hz), 3.84 s (3H, MeO, tautomer **B**), 3.85 s (3H, MeO, tautomer **A**), 4.72 s (2H, 5-H, tautomer **B**, 64%), 7.06 s (1H, 5-H, tautomer **A**, 36%), 7.50–8.10 m (14H, C$_6$H$_5$, C$_6$H$_4$, 1-H). ^{13}C NMR spectrum (CDCl$_3$), δ$_C$, ppm: 45.9 (C^5, tautomer **B**), 49.1 (3-CH$_2$), 55.2 (CH$_3$O), 91.8 (C^3), 93.3 (5-H, tautomer **A**), 113.6–176.7 (C$_{arom}$, C^6, 1-C=O), 194.3 and 197.2 (C^4, tautomers **A** and **B**), 203.2 (4-ClC$_6$H$_4$**C**O). Found, %: C 65.79; H 4.15; Cl 7.52; N 6.03. $C_{26}H_{21}ClN_2O_5$. Calculated, %: C 65.48; H 4.44; Cl 7.43; N 5.87.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-3-hydroxy-2-(2-hydroxybenzoyl)-6-phenyl-2,3-dihydropyridazin-4(1*H*)-one (IIh). Yield 1.46 g (63%), mp 172–173°C (decomp., from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.54 d.d (2H, 3-CH$_2$, J = 17.2 Hz), 4.91 s (2H, 5-H, tautomer **B**, 78%), 6.95 s (1H, 5-H, tautomer **A**, 22%), 7.25–8.08 m (14H, C$_6$H$_5$, C$_6$H$_4$, 1-H), 10.30 s (1H, 2-**H**OC$_6$H$_4$). Found, %: C 64.70; H 4.28; Cl 7.48; N 5.91. $C_{25}H_{19}ClN_2O_5$. Calculated, %: C 64.87; H 4.14; Cl 7.66; N 6.05.

1,2-Dibenzoylhydrazine (IIIa). Yield 0.18 g (15%), mp 241–242°C (decomp., from toluene). Mass spectrum, m/z (I_{rel}, %): 240 (23) [M]$^+$, 136 (1) [C$_6$H$_5$CONHNH$_2$]$^+$, 121 (2) [C$_6$H$_5$CONH$_2$]$^+$, 105 (100)

$[C_6H_5C{\equiv}O]^+$, 77 (44) $[C_6H_5]^+$, 51 (15). Found, %: C 70.12; H 4.94; N 11.73. $C_{14}H_{12}N_2O_2$. Calculated, %: C 69.99; H 5.03; N 11.66. *M* 240.

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