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INTERACTION OF 5-ARYL-2,3-DIHYDRO-FURAN-2,3-DIONES WITH FUNCTIONALLY SUBSTITUTED HYDRAZIDES AND DIAMINOGLYOXAL DIPHENYLHYDRAZONE

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The reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with cyanoacetylhydrazide, o-(hydrazinocarbonyl)phenylthiourea, and the diphenylhydrazone of diaminoglyoxal leads to the synthesis of the corresponding N-cyanoacetylhydrazides of aroylpyruvic acids, 2-(N-aroylpyruvoylhydrazinocarbonyl)-phenylthioureas, and 5,6-bis(phenylhydrazono)-3-aroylmethylenepiperazin-2-ones. The results of the primary investigation of the biological activity of N-cyanoacetylhydrazides of aroylpyruvic acids are given.

Keywords: 5-aryl-2,3-dihydrofuran-2,3-diones, aroylpyruvoylhydrazides, 5,6-bis(phenylhydrazono)-3-aroylmethylenepiperazin-2-ones, biological activity, decyclization, recyclization.

Study of the interaction of 4-substituted and unsubstituted 5-aryl-2,3-dihydrofuran-2,3-diones with hydrazines and their derivatives [1-9] has shown that the direction of the reaction is determined by the presence of methyl, phenyl, and benzoyl substituents in position 4 of the furandione ring and by the structure of the reagent. In addition the ratio of the components and the synthetic conditions influence the course of the process. To investigate the reaction of 4-unsubstituted furandiones with functional derivatives of hydrazine we used cyanoacetylhydrazine, *o*-(hydrazinocarbonyl)phenylthiourea, and diaminoglyoxal phenylhydrazone. Interest in this reaction is also linked with the biological activity of the products formed [10-14].

As has been established, the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones **1** with cyanoacetic acid hydrazide proceeds in anhydrous dioxane at room temperature. The N-cyanoacetylhydrazides of aroylpyruvic acids **2a-f** were formed in high yield in this way, and are the products of fission of the furan ring at the O–C(2) bond by the primary amino group of the reactant.

A broad intense band is observed in the IR spectra of compounds **2a-f** corresponding to the stretching vibrations of the NH bond at 3190-3320 cm^{-1}. Absorption bands caused by the stretching vibrations of the –CH= group at 3070-3090, and also by the C≡N group at 2267-2270 cm^{-1} were also observed. There were two absorption bands in the 1667-1710 cm^{-1} region for the amide carbonyls, and at 1580-1620 cm^{-1} an intense band caused by the absorption of the aromatic ring and of the C=O group involved in an intramolecular hydrogen bond.

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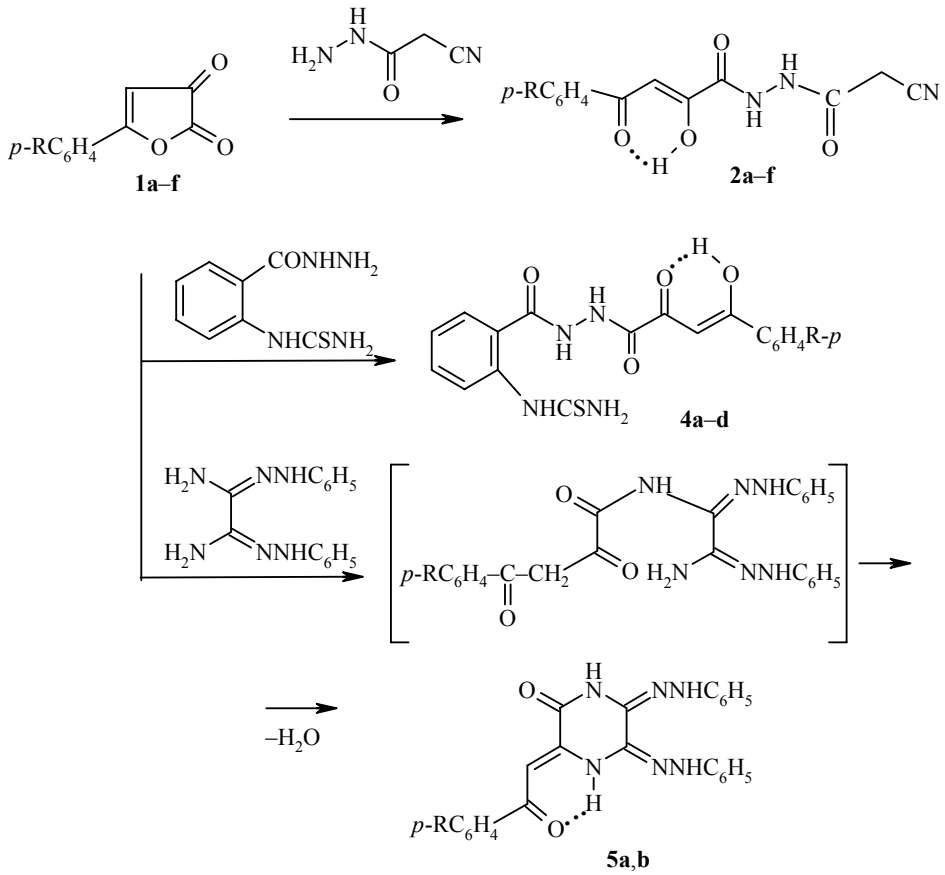
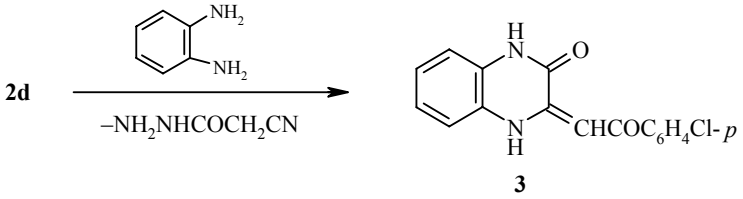


1, **2**, **4 a** R = H, **b** R = Me, **c** R = Et, **d** R = Cl, **e** R = Br, **f** R = F; **5 a** R = Me, **b** R = Cl

In the ^{1}H NMR spectra a singlet was present for the protons of the methylene group at 3.77-3.82, a singlet for the methine proton at 6.76-7.10, a multiplet for the aromatic protons with center at 7.53-7.83 ppm, and also a broadened signal for the NH group at 10.48-10.69 ppm. No signal was observed for the proton of the enolic hydroxyl, probably due to broadening by rapid exchange. The spectral characteristics of compounds **2a-f** agree well with the literature data for similar compounds [11-14]. The interaction of compound **2d** with *o*-phenylenediamine was carried out to confirm by chemical methods the structure of the compounds formed.

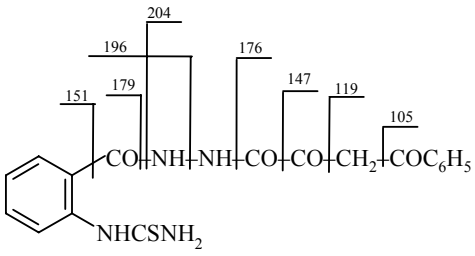


Heating the reactants in absolute ethanol for 30 min leads to the formation of a bright-yellow product, soluble with difficulty in alcohol, but well soluble in dioxane. Study of the IR and ^{1}H NMR spectra, and also the absence of a depression of melting point when mixed with an authentic specimen of the product, confirmed the formation of 3-*p*-chlorophenacylidene-3,4-dihydro-2-quinoxalone [15]. It is evident that in the course of the reaction fission of cyanoacetylhydrazine occurs with the formation of quinoxaline **3**.

On interacting furandiones **1** with 2-(hydrazinocarbonyl)phenylthiourea reaction in several directions is possible: at the thiourea fragment with the formation of a 3-substituted 5-phenacylidene-4-oxoimidazolidine-2-thione ring [16] and at the hydrazinocarbonyl fragment with the fission of the furandiones **1** ring [14]. However

investigations showed that on reacting compounds **1** with the indicated reactant (dioxane, 100°C, 30 min), the sole products were the 1-(N-aroylpyruvoylhydrazino-carbonyl)phenylthioureas **4a-d**. The constants, yields, and data of elemental analysis of these compounds are given in Table 1.

Absorption bands were detected in the IR spectra of compounds **4a-d** for carbonyl groups at 1615-1710, for NH groups at 3150-3340, and for NH_2 at 3403-3485 cm^{-1}. The ^1H NMR spectra of the indicated compounds contain a singlet for the methine group proton at 7.2 ppm, signals for the aromatic protons at 6.70-7.80, singlets for the NH group protons at 8.46-8.56, 9.40-9.46, 10.66-10.80, and a singlet for the OH group proton at 12.23-12.40 ppm. The molecular ion was absent from the mass spectrum of compound **4a**, however the presence of the fragment ions indicated below agree with the proposed structure.



The scheme of forming compounds **4a-d** is analogous to the scheme of forming compounds **2a-f** and includes nucleophilic attack at the C(2) atom of furandiones **1** by the primary amino group of the hydrazinocarbonyl fragment of the molecule with ring opening of the latter, which leads to products **4a-d**. Attempts to cyclize compounds **4a-d** involving the residue of thiourea and the hydrazide fragment were unsuccessful.

TABLE 1. Characteristics of the Synthesized Compounds **2a-f**, **4a-d**, and **5a,b**

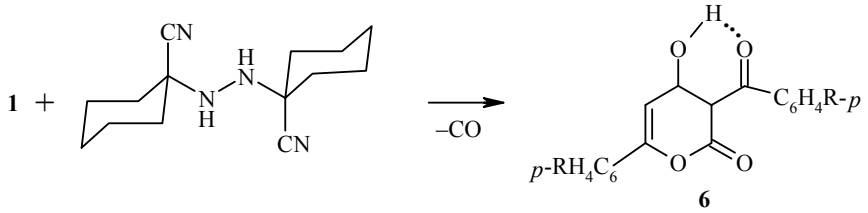
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N (Hal)		
2a	$C_{13}H_{11}N_3O_4$	57.0 / 57.0	3.9 / 4.0	15.3 / 15.4	190-192	96
2b	$C_{14}H_{13}N_3O_4$	57.9 / 58.5	4.5 / 4.5	14.3 / 14.6	203-204	94
2c	$C_{15}H_{15}N_3O_5$	56.7 / 56.8	4.6 / 4.7	13.1 / 13.3	205-206	97
2d	$C_{13}H_{10}ClN_3O_4$	50.8 / 50.7	3.3 / 3.3	13.7 (11.6) / 13.7 (11.5)	194-195	98
2e	$C_{13}H_{10}BrN_3O_4$	44.2 / 44.3	2.9 / 2.8	12.0 (22.5) / 11.9 (22.7)	208-209	98
2f	$C_{13}H_{10}FN_3O_4$	53.9 / 53.6	3.8 / 3.4	14.3 / 14.4	210-212	98
4a	$C_{18}H_{16}N_4O_4S$	56.3 / 56.2	4.3 / 4.2	14.7 / 14.6	224-225	85
4b	$C_{19}H_{18}N_4O_4S$	57.3 / 57.2	4.6 / 4.5	14.2 / 14.1	225-226	82
4c	$C_{20}H_{20}N_4O_5S$	56.2 / 56.0	4.8 / 4.7	13.0 / 13.1	228-230	80
4d	$C_{18}H_{15}ClN_4O_4S$	51.7 / 51.6	3.5 / 3.6	13.5 (8.5) / 13.4 (8.5)	220-222	85
5a	$C_{25}H_{22}N_6O_2$	68.5 / 68.4	5.2 / 5.1	19.3 / 19.2	166-168	81
5b	$C_{24}H_{19}ClN_6O_2$	62.9 / 62.8	4.4 / 4.2	18.4 (7.8) / 18.3 (7.7)	187-189	80

TABLE 2. Spectral Characteristics of Compounds **2a-f**, **4a-d**, and **5a,b**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
2a	1590, 1667-1695, 2270, 3080, 3190-3320	3.77 (2H, s, CH_2); 6.76 (1H, s, CH); 7.53 (5H, m, C_6H_5); 10.48 (2H, br. s, 2NH)
2b	1600, 1668-1695, 2270, 3070, 3260-3312	2.04 (3H, s, CH_3); 3.78 (2H, s, CH_2); 7.02 (1H, s, CH); 7.60 (4H, m, C_6H_4); 10.62 (2H, br. s, 2NH)
2c	1605, 1680-1710, 2268, 3078, 3270-3310	1.30 (3H, t, $\underline{CH_3}CH_2O$); 3.78 (2H, s, CH_2); 4.17 (2H, q, $CH_3\underline{CH_2}O$); 7.05 (1H, s, CH); 7.60 (4H, m, C_6H_4); 10.55 (2H, br. s, 2NH)
2d	1590, 1675-1707, 2270, 3090, 3265-3308	3.82 (2H, s, CH_2); 6.97 (1H, s, CH); 7.66 (4H, m, C_6H_4); 10.59 (2H, br. s, 2NH)
2e	1590, 1683-1710, 2270, 3090, 3260-3308	3.80 (2H, s, CH_2); 7.10 (1H, s, CH); 7.83 (4H, m, C_6H_4); 10.69 (2H, br. s, 2NH)
2f	1600, 1670-1700, 2267, 3078, 3270-3305	3.78 (2H, s, CH_2); 7.07 (1H, s, CH); 7.65 (4H, m, C_6H_4); 10.54 (2H, br. s, 2NH)
4a	1615, 1665, 1705, 3200-3340, 3480	7.20 (1H, s, CH); 7.40-8.13 (11H, m, C_6H_4, C_6H_5, NH_2); 8.56 (1H, d, NH); 9.46 (1H, s, NH); 10.70 (1H, s, NH); 12.40 (1H, s, OH)
4b	1620, 1660, 1700, 3150-3340, 3460	2.33 (3H, s, CH_3); 7.20 (1H, s, CH); 7.26-8.16 (10H, m, $2C_6H_4$, NH_2); 8.56 (1H, m, NH); 9.46 (1H, s, NH); 10.70 (1H, s, NH); 12.40 (1H, s, OH)
4c	1610, 1670, 1700 (sh), 3200-3310, 3400	1.23 (3H, s, $\underline{CH_3}CH_2O$); 4.03 (2H, q, $CH_3\underline{CH_2}O$); 6.83-8.06 (11H, m, $2C_6H_4$, CH, NH_2); 8.46 (1H, m, NH); 9.4 (1H, s, NH); 10.8 (1H, s, NH); 12.23 (1H, s, OH)
4d	1625, 1660, 1700, 3200-3320, 3460	7.05-8.26 (11H, m, $2C_6H_4$, CH, NH_2); 8.46 (1H, m, NH); 9.46 (1H, s, NH); 10.66 (1H, s, NH); 12.33 (1H, s, OH)
5a	1585-1650, 1690, 3135-3280, 3350-3475	2.36 (3H, s, CH_3); 6.11 (1H, s, NH); 6.67-8.06 (15H, m, $2C_6H_5$, C_6H_4, CH); 8.36 (1H, s, NH); 8.73 (1H, s, NH)
5b	1580-1645, 1690, 3135-3275, 3350-3470	6.10 (1H, s, NH); 6.70-8.00 (15H, m, $2C_6H_5$, C_6H_4, CH); 8.40 (1H, s, NH); 8.70 (1H, s, NH)

5,6-Bis(phenylhydrazono)-3-aroylmethylenepiperazin-2-ones **5a,b** were formed on heating equimolar quantities of furandiones **1** and diaminoglyoxal diphenylhydrazone for 1 h in anhydrous toluene (Table 2). Absorption bands were present in the IR spectra of these compounds for the C=O group in position 2 of the piperazine ring at 1690-1693 cm^{-1}. The broad unresolved band at 1585-1650 cm^{-1} is caused by the overlap of absorptions of the C=C bonds of the phenyl rings and the C=O of the aroylmethylene substituent linked as a six-membered H-chelate ring. Bands for the stretching vibrations of the N–H bonds are in the ranges 3135-3280 and 3350-3475 cm^{-1}. The ^1H NMR spectrum of compound **5a** contains a singlet for the three protons of the methyl group of the tolylmethylene substituent at 2.36, and signals for the NH group protons at 6.11, 8.36, and 8.73 ppm. The signals for the protons of the aromatic rings and the CH group overlap one another and are found in the range 6.67-8.06 ppm. The signal for the NH group proton of the H-chelate ring was not detected, probably due to broadening as a result of rapid exchange. The ^1H NMR spectrum of compound **5b** has a similar picture. The data given are in good agreement with the spectral data of structurally close piperazinones [17].

The scheme of forming compounds **5a,b**, as in the case of aromatic and heterocyclic 1,2-diamines [18-21], includes attack of the C(2) atom of furandiones **1** by a primary amino group of diaminoglyoxal diphenylhydrazone with opening of the furan ring and subsequent cyclization of the intermediate product in the second stage as a result of attack by the primary amino group of the C(2) atom on the acid residue. The possibility of diaminoglyoxal diphenylhydrazone participating in the reaction as a 1,3-diamine does not take place. Analogous processes were observed in the reaction of furandiones **1** with thiocarbohydrazide in [22]. On heating furandiones **1** with 1,2-bis(1-cyanocyclohexyl)hydrazine, 4-hydroxy-2H-pyran-2-ones **6** [23] and the initial hydrazine were isolated from the reaction mixture.



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The low reactivity of the hydrazine used is probably linked, on the one hand, with steric difficulties connected with the cyclohexyl rings, and on the other, with the electron-withdrawing influence of the cyano groups.

While continuing the study of the anti-inflammatory, analgesic, and antiviral activity of acylpyruvic acid hydrazides with various substituents in the acyl portion of the molecule and at the nitrogen atoms [11-14], we have investigated compounds **2a-f** on these forms of activity. Assessment of primary activity was carried out according to standard procedures of carrageenan inflammation [24], the hot plate test [25], and protection from viral infection [26]. It was established that hydrazides **2** possessed a marked anti-inflammatory action with inhibition of exudates in the range 42.0-62.1%. Compound **2c** displays an effect analogous to orthofen, and compound **2b** surpasses the standard in activity by almost 7%. The remaining compounds of this series were surpassed somewhat by orthofen in anti-inflammatory activity. The analgesic effect of compounds **2a**, **2b**, and **2f** were practically the same (22.2-24.2 sec), which indicates the lack of influence of the substituents in the aryl ring on the action displayed. Amidopyrine surpassed the investigated compounds **2** in the strength of effect displayed. Antiviral testing of hydrazide **2a** showed that this compound suppresses the reproduction of type A group influenza virus in developing chicken embryos, however in experiments on mice the compound is inactive in relation to this type of virus. The investigated hydrazide **2a** is exceeded in activity by the medicinal preparations rimantadine and adapromine, which makes the search for compounds with antiviral activity of little promise in this series.

EXPERIMENTAL

The IR spectra of compounds **2-5** were taken on a UR-20 instrument in nujol mulls. The ^{1}H NMR spectra were recorded on a PC-60 spectrometer (60 MHz) in DMSO-d_6 solution. HMDS was used as internal standard (δ 0.05 ppm). The mass spectra were obtained on a MX-1310 instrument, ionizing voltage was 50 V. The homogeneity of compounds was confirmed on Silufol-254 plates in the system benzene–ether, 1:1, visualizing with iodine. The characteristics of compounds **2-5** are given in Tables 1 and 2.

N-Cyanoacetylhydrazides of Aroylpyruvic Acids (2a-f). Cyanoacetylhydrazine (10 mmol) was added to a solution of the appropriate furandione **1** (10 mmol) in dioxane (20 ml), and the mixture stirred at room temperature for 30 min. The solid was filtered off and recrystallized from acetonitrile.

2-(N-Aroylpyruvoylhydrazinocarbonyl)phenylthioureas (4a-d). Furandione **1** (5 mmol) and the *o*-hydrazinocarbonylphenylthiourea (5 mmol) were dissolved in dioxane (15 ml), and the mixture was boiled for 30 min. The precipitated solid was filtered off, and recrystallized from DMF.

5,6-Bis(phenylhydrazono)-3-aroylmethylenepiperazin-2-ones (5a,b). A mixture of furandione **1** (5 mmol) and diaminoglyoxal diphenylhydrazone (5 mmol) in anhydrous toluene (20 ml) was heated for 1 h. The solution was cooled, the precipitated solid was filtered off, and recrystallized from toluene.

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