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Reactions of Acylpyruvic Acids and 2,3-Dihydrofuran-2,3-diones with 2,3-Diaminopyridine

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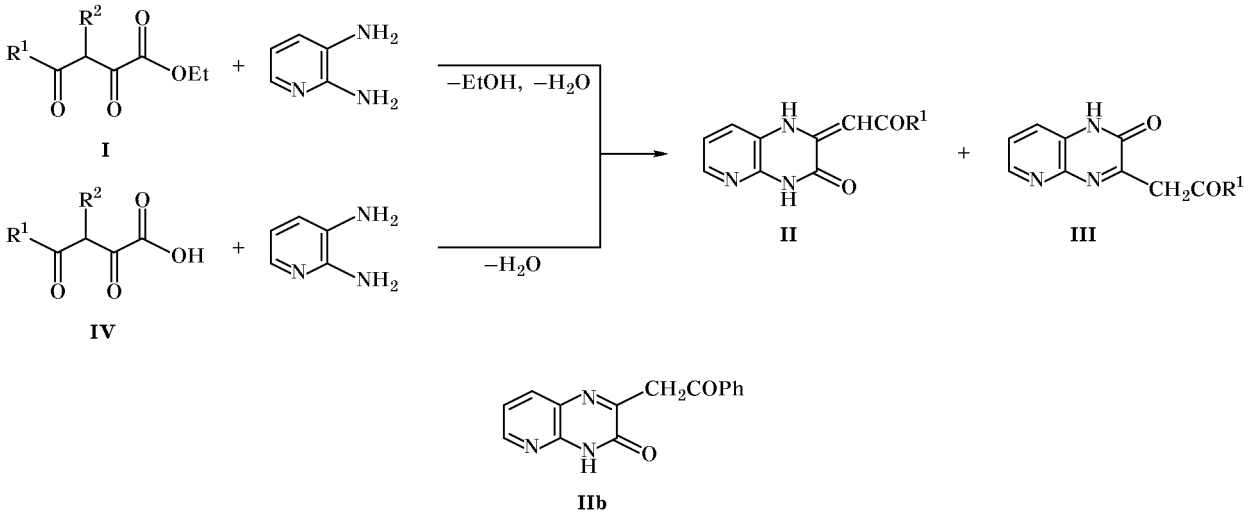
Abstract—Acylpyruvic acids readily react with 2,3-diaminopyridine to form (*Z*)-3-acylmethylene-1*H*-3,4-dihydropyrido[2,3-*b*]pyrazin-2-ones. 5-Aryl-2,3-dihydrofuran-2,3-diones which can be regarded as lactones derived from γ-enolized aroylpyruvic acids react with 2,3-diaminopyridine under mild conditions, yielding regioisomeric (*Z*)-2-aroylmethylene-4*H*-1,2-dihydropyrido[2,3-*b*]pyrazin-3-ones. The structure of the products and reaction chemoselectivity are discussed.

Some acylpyruvic acid esters **I** are known to react with 2,3-diaminopyridines, yielding 3-acylmethylenepyrido[2,3-*b*]pyrazin-2-ones **II** and isomeric pyrido-[2,3-*b*]pyrazin-3-ones **III** [1–3] (Scheme 1). According to published data [1–3], compounds **III** are formed in the presence of sulfuric acid; however, factors responsible for the different reaction pathways were not discussed. Bodforss [4] briefly reported that the reaction of benzoylpyruvic acid (**IVb**) with 2,3-diaminopyridine in ethanol initially gives an intermediate salt (its structure was not given) which undergoes cyclization to 3-phenacyl derivative of pyrido[2,3-*b*]pyrazin-2-one **IIb** on heating in boiling acetic acid (Scheme 1). Mashevskaya *et al.* [5, 6] recently reported on the synthesis of (*Z*)-3-acylmethylene-1*H*-3,4-dihydropyrido[2,3-*b*]pyrazin-2-ones **II** (R^1 = Ht), which were mistakenly named pyrido-[2,3-*b*]pyrazin-3-ones, by reaction of 4-(2-furyl)- and 4-(5-thiazolyl)-2,4-dioxobutanoic acids **IV** with 2,3-diaminopyridine on heating in boiling acetic acid for a short time (Scheme 1). The regioisomeric structure of compounds **II** (R^1 = Ht) (with respect to

Scheme 1.



I, **II**, **III**, **IV**, **IIb**

R^1 = Me, Ar; R^2 = H, Me; **II**, **III**, R^1 = Ph, 2-furyl, 5-thiazolyl.

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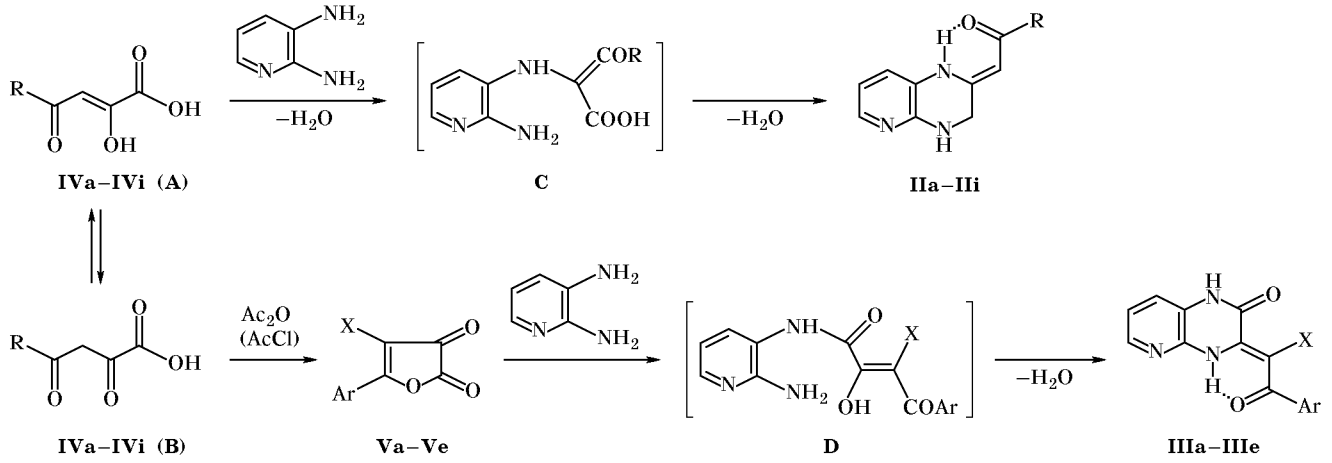
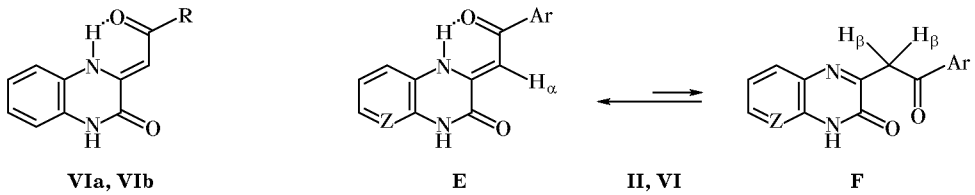
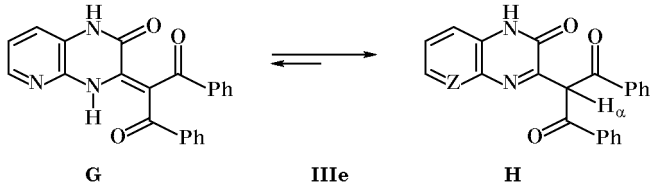
Scheme 2.



II, **IV**, **VI**, R = *t*-Bu (**a**), Ph (**b**), 4-MeC_6H_4 (**c**), 2,4,6-$Me_3C_6H_2$ (**d**), 3-$MeOC_6H_4$ (**e**), 3,4-$(MeO)_2C_6H_3$ (**f**), 4-BrC_6H_4 (**g**), 4-ClC_6H_4 (**h**), 4-FC_6H_4 (**i**); **III**, **V**, X = H, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-ClC_6H_4 (**d**); X = PhCO, Ar = Ph (**e**).



II, Z = N; **VI**, Z = CH.



position of the nitrogen atom in the pyridine moiety) was assigned with no proof, on the basis of indirect data. The mechanism of this reaction and its chemoselectivity were not discussed. It should be noted that the article [6] appeared by more than 6 months after the present paper was submitted for publication.

Apart from our preliminary communications [7–10], there is no information on reactions of 2,3-diaminopyridine with other acylpyruvic acids, their derivatives, and alternative systems having a 1,2,4-trioxo or 1,3,4,6-tetraoxo fragments.

In the present work we studied in detail reactions of acylpyruvic acids **IVa**–**IVi** [11–13] and their derivatives, 5-aryl-2,3-dihydrofuran-2,3-diones **Va**–**Ve** [14–16] with 2,3-diaminopyridine. It should be emphasized that only two examples of reactions of five-membered monocyclic and fused α-dioxoheterocycles with 2,3-diaminopyridines are known. One of these is the reaction of 4,5-dihydropyrazole-4,5-diones with 2,3-diaminopyridine and its 5-bromo derivative, leading to 4-azaflavazoles [17–19], and the second is the reaction of 2,3-diaminopyridine with 2,3-dihydropyrrole-2,3-diones fused through the *a* bond to a number of oxa and aza heterocycles; as a result, pyrrolo[2,3-*b*][1,5]pyridodiazepine-6,7,15-trione derivatives were isolated [20, 21].

Acylpyruvic acids **IVa**–**IVi** can exist in solution as at least two tautomers, keto–enol **A** and β-diketone **B** [13, 22–24]. They reacted with 2,3-diaminopyridine on heating in ethanol for a short time to afford (*Z*)-3-acylmethylene-1*H*-3,4-dihydropyrido[2,3-*b*]pyrazin-2-ones **IIa**–**IIi** [9] (Scheme 2). 5-Aryl-2,3-dihydrofuran-

Table 1. Yields, melting points, and elemental analyses of pyrido[2,3-*b*]pyrazines **IIa**–**IIi** and **IIIa**–**IIIe**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N (Hlg)		C	H	N (Hlg)
IIa	63	246–247	63.87	6.34	16.90	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13
IIb	74	267–268[a]	68.32	4.41	15.56	$C_{15}H_{11}N_3O_2$	67.92	4.18	15.84
IIc	73	297–298	68.42	4.84	15.31	$C_{16}H_{13}N_3O_2$	68.81	4.69	15.05
IId	57	265–266	70.13	5.69	13.46	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67
IIe	52	283–284	64.83	4.72	14.49	$C_{16}H_{13}N_3O_3$	65.08	4.44	14.23
IIf	53	297–298	62.45	4.34	13.17	$C_{17}H_{15}N_3O_4$	62.76	4.65	12.92
IIg	49	302–303	52.58	2.76	12.50 (23.49)	$C_{15}H_{10}BrN_3O_2$	52.35	2.93	12.21 (23.22)
IIh	54	313–314	59.92	3.21	13.75 (11.60)	$C_{15}H_{10}ClN_3O_2$	60.11	3.36	14.02 (11.83)
IIi	75	303–304	63.77	3.80	14.56	$C_{15}H_{10}FN_3O_2$	63.60	3.56	14.83 (6.71)
IIIa	72	257–258	67.64	3.89	15.97	$C_{15}H_{11}N_3O_2$	67.92	4.18	15.84
IIIb	59	303–304	69.04	4.82	15.22	$C_{16}H_{13}N_3O_2$	68.81	4.69	15.05
IIIc	68	264–265	52.57	2.88	12.40 (23.49)	$C_{15}H_{10}BrN_3O_2$	52.35	2.93	12.21 (23.22)
IIId	68	275–276	60.28	3.47	13.78 (12.14)	$C_{15}H_{10}ClN_3O_2$	60.11	3.36	14.02 (11.83)
IIIe	43	317–318	71.86	3.77	11.65	$C_{22}H_{15}N_3O_3$	71.54	4.09	11.38

[a] Published data [4]: mp 283°C.

2,3-diones **Va**–**Ve** can be regarded as lactones derived from the γ-enol of aroylpyruvic acids; their reactions with 2,3-diaminopyridine occurred under mild conditions with formation of (*Z*)-2-aroylmethylene-4*H*-1,2-dihydropyrido[2,3-*b*]pyrazin-3-ones **IIIa**–**IIIe** [8, 9] which are regioisomeric to heterocyclization products **II** (Scheme 2). The yields, melting points, and elemental analyses of compounds **IIa**–**IIi** and **IIIa**–**IIIe** are collected in Table 1, and Tables 2 and 3 contain their spectral parameters. Pyrido[2,3-*b*]pyrazine derivatives **IIb**, **IIc**, **IIe**, **IIg**, **IIIa**, and **IIIc** were described previously [1, 2, 4].

The spectral parameters of azines **II** and **III** are consistent with their structure and those found for the known analogs, (*Z*)-3-acylmethylene-1*H*-3,4-dihydro-2-quinoxalinones **VI** [25–30], which were selected as model compounds (Scheme 2). The IR spectra of pyrido[2,3-*b*]pyrazinones **II** and **III** contain absorption bands from the two NH groups (3060–3085 and 3130–3160 cm^{-1}) and amide carbonyl group (1690–1695 cm^{-1}) and a broadened low-frequency band due to stretching vibrations of the carbonyl group and the double in the 3-acylmethylene moiety (1585–1635 cm^{-1}) which indicates formation in the *Z* isomers of **II** and **III** of NH-chelate ring through N−H···O=C intramolecular hydrogen bond [13, 29]. No appreciable difference in the IR spectra of regioisomers **II** and **III** was observed, except for slightly greater NH frequency of the amide carbonyl group in compounds **III**.

According to published data [1, 3, 25], absorption bands from the conjugated carbonyl group in the phenacylidene fragments coincide for compounds **II** and analog **VIb** containing no pyridine nitrogen atom (1622–1650 cm^{-1}). It should be noted for comparison that the amide carbonyl band in the IR spectra of quinoxalinones **VI** has a slightly lower frequency than that found for compounds **II** and **III**; the broad band belonging to vibrations of the 3-acylmethylene moiety is located at 1600–1623 cm^{-1} [3, 27, 29].

In the ^1H NMR spectra (DMSO-d_6) *of* **IIb**–**IIi** and **IIIa**–**IIId** having an aroylmethylene substituent, the H_α signal appears at δ 6.75–6.90 ppm, i.e., almost at the same position as the corresponding signal of (*Z*)-3-aroylmethylene-1*H*-3,4-dihydro-2-quinoxalinones **VI** (δ 6.72–7.00 ppm) [3, 27, 29, 30]. The H_α signal in the spectra of heteryl-substituted pyrido[2,3-*b*]pyrazinones **II** (R^1 = Ht, Scheme 1) is observed in a considerably stronger field, at δ 6.17 (!) and 6.61 ppm [5]. The chemical shifts of H_α in (*Z*)-3-pivaloylmethylene-

Table 2. ^{1}H NMR spectra of pyrido[2,3-*b*]pyrazinones **IIa**–**IId**, **IIh**, **IIi**, **IIIa**, **IIIb**, and **IIIe** in DMSO-d_6

Comp. no.	Chemical shifts δ, ppm
IIa	1.17 s (9H, $3CH_3$), 6.31 s (1H, CH), 7.12 t (1H, 6-H), 7.88 d (1H, 5-H), 8.04 d (1H, 7-H), 12.21 s (1H, 1-H), 12.90 s (1H, 4-H)
IIa[a]	1.17 s (9H, $3CH_3$), 6.34 s (1H, CH), 7.02–8.07 m (3H, 5-H, 6-H, 7-H), 12.98 br.s (1H, NH)
IIb[b]	6.90 s (1H, CH), 7.28–8.15 m (8H, H_{arom}, 5-H, 6-H, 7-H), 13.50 s (1H, NH)
IIc[c]	2.40 s (3H, CH_3), 4.53 s (2H, H_β, tautomer **F**, 6%), 6.84 s (1H, H_α, tautomer **E**, 94%), 7.15–8.10 m (7H, H_{arom}, 5-H, 6-H, 7-H), 12.30 br.s (1H, 1-H), 13.37 s (1H, 4-H)
IId[d]	2.48 br.s (9H, $3CH_3$), 6.75 s (1H, CH), 7.10–7.85 m (5H, H_{arom}, 5-H, 6-H, 7-H), 13.25 s (1H, NH)
IIh[e]	6.88 s (1H, CH), 6.95–7.80 m (7H, H_{arom}, 5-H, 6-H, 7-H)
IIi	6.85 s (1H, CH), 7.17–8.11 m (7H, H_{arom}, 5-H, 6-H, 7-H), 12.38 br.s (1H, 1-H), 13.35 s (1H, 4-H)
IIIa	6.81 s (1H, CH), 7.22–8.02 m (8H, H_{arom}, 5-H, 6-H, 7-H), 11.08 br.s (1H, 4-H), 12.10 s (1H, 1-H)
IIIb	2.42 s (3H, CH_3), 6.86 s (1H, CH), 7.10–8.08 m (7H, H_{arom}, 5-H, 6-H, 7-H), 12.02 br.s (1H, 4-H), 13.30 s (1H, 1-H)
IIIe	6.58 s (1H, CH, tautomer **H**, 71%), 6.92–8.15 m (13H, H_{arom}, 5-H, 6-H, 7-H, tautomers **G** and **H**), 11.92 s (1H, 4-H, tautomer **H**), 12.24 s (1H, 4-H, tautomer **G**, 29%), 14.33 br.s (1H, 1-H, tautomer **G**)

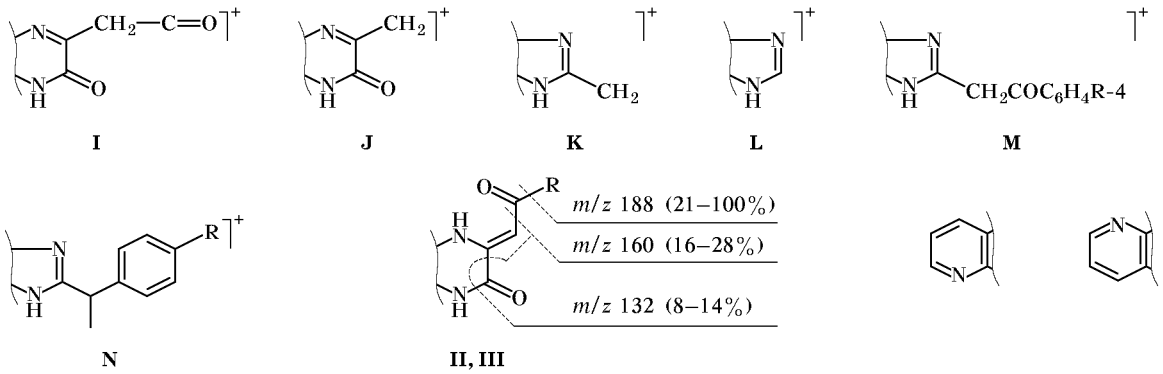
[a] In DMSO-d_6–CF_3COOH, 10 : 1.
[b] According to published data [3], at 50°C in DMSO-d_6 0.8% of tautomer **F** was present (99.2% of **E**; Scheme 2).
[c] Two tautomeric forms **E** and **F** were detected (Scheme 2).
[d] Poorly soluble in DMSO.
[e] In CF_3COOH.

Table 3. Mass spectra of pyrido[2,3-*b*]pyrazinones **IIa**, **IIb**, **IIi**, **IIIa**, and **IIIb**

Comp. no.	*m*/*z* (I_{rel}, %)[a]
IIa	245 (18) $M^{+\cdot}$, 189 (10), 188 (100) $[M-(CH_3)_3C]^+$ (**I**), 161 (10), 160 (18) $[M-(CH_3)_3C-CO]^+$ (**J**), 132 (12) $[M-(CH_3)_3C-2CO]^+$ (**K**), 120 (5), 119 (6) (M), 105 (5), 91 (7), 78 (8), 57 (19) $[(CH_3)_2CHCH_2]^+$, 53 (5), 41 (27), 39 (22)
IIb	266 (15), 265 (100) $M^{+\cdot}$, 264 (34), 237 (9), 236 (45) $[M-CO-H]^+$ (**M**), 208 (5) $[M-2CO-H]^+$ (**N**), 188 (30) $[M-C_6H_5]^+$ (**I**), 160 (28) $[M-C_6H_5-CO]^+$ (**J**), 134 (5), 132 (10) $[M-C_6H_5-2CO]^+$ (**K**), 120 (5), 105 (32) $[C_6H_5C{\equiv}O]^+$, 91 (5), 78 (5), 77 (19) $[C_6H_5]^+$
IIi	284 (16), 283 (100) $M^{+\cdot}$, 282 (15), 255 (8), 254 (40) $[M-CO-H]^+$ (**M**), 226 (5) $[M-2CO-H]^+$ (**N**), 188 (21) $[M-4\text{-}FC_6H_4]^+$ (**I**), 160 (24) $[M-4\text{-}FC_6H_4-CO]^+$ (**J**), 159 (13), 149 (5), 134 (9), 132 (14) $[M-4\text{-}FC_6H_4-2CO]^+$ (**K**), 123 (59) $[4\text{-}FC_6H_4C{\equiv}O]^+$, 120 (20), 105 (5), 104 (7), 96 (5), 95 (42), 92 (6), 91 (5), 78 (7), 75 (11), 64 (5), 53 (5), 40 (9), 39 (8)
IIIa	266 (12), 265 (100) $M^{+\cdot}$, 264 (52), 237 (10), 236 (41) $[M-CO-H]^+$ (**M**), 220 (6), 208 (6) $[M-2CO-H]^+$ (**N**), 188 (21) $[M-C_6H_5]^+$ (**I**), 160 (16) $[M-C_6H_5-CO]^+$ (**J**), 132 (8) $[M-C_6H_5-2CO]^+$ (**K**), 120 (5), 119 (10) (**L**), 105 (27) $[C_6H_5C{\equiv}O]^+$, 91 (5), 78 (6), 77 (20) $[C_6H_5]^+$, 76 (5), 51 (6)
IIIb	280 (11), 279 (100) $M^{+\cdot}$, 265 (7), 264 (40) $[M-CH_3]^+$, 251 (14), 250 (42) $[M-CO-H]^+$ (**M**), 222 (11) $[M-2CO-H]^+$ (**N**), 188 (42) $[M-4\text{-}CH_3C_6H_4]^+$ (**I**), 163 (56), 161 (13), 148 (9), 135 (44), 131 (37) $[M-4\text{-}CH_3C_6H_4-2CO-H]^+$, 120 (9), 119 (54) $[4\text{-}CH_3C_6H_4C{\equiv}O]^+$, 116 (6), 108 (12), 107 (13), 105 (33), 101 (6), 97 (11), 94 (7), 92 (7), 91 (51) $[4\text{-}CH_3C_6H_4]^+$, 85 (6), 83 (5), 81 (17), 80 (12), 78 (24), 77 (23), 76 (5), 71 (6), 69 (33), 67 (8)

[a] Given are ion peaks with $I_{rel} > 5\%$; bold characters in parentheses denote common fragment ions (see Scheme 3).

Scheme 3.



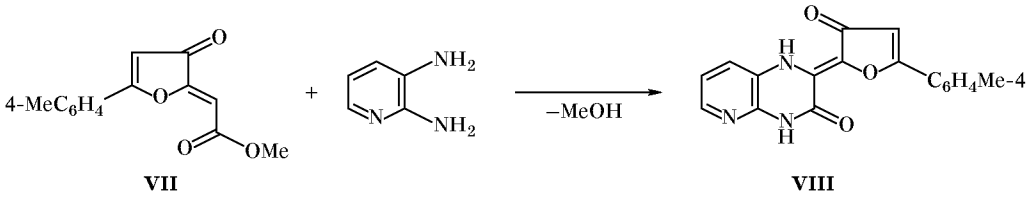
1*H*-3,4-dihydropyrido[2,3-*b*]pyrazin-2-one (**IIa**) and (*Z*)-3-pivaloylmethylene-1*H*-3,4-dihydroquinoxalin-2-one (**VIa**) almost coincide (δ 6.31 and 6.27 ppm, respectively. Strangely enough, this indicates the absence of appreciable effect of the pyridine nitrogen atom on the signal position of the methine proton in the activated alkene chain. The NH protons in the pyrazine ring of compounds **II** give more downfield signals (on the average by 0.6 ppm), as compared with isomers **III**; obviously, the deshielding effect on these protons of the nitrogen atom in the pyridine ring is weak. There are no other appreciable difference in the ^{1}H NMR spectra of regioisomers **II** and **III**. This is consistent with published data on isomeric pyrido[2,3-*b*]pyrazinones [1–3].

In the ^{1}H NMR spectrum of pyrido[2,3-*b*]pyrazin-2-one (**IIc**), apart from the H_α signal at δ 6.84 ppm, we observed a two-proton singlet at δ 4.53 ppm, belonging to the CH_2^β group. This pattern suggests the existence of equilibrium in solution between enamine tautomer **E** (major isomer) and imino form **F** (minor isomer); the fraction of the latter is 6% (according to the corresponding signal intensity; Table 2, Scheme 2). In keeping with the data of [3], a solution of **IIb** in DMSO-d_6 contains only traces (0.8%) of tautomer **F**. As shown in [29], 2-quinoxalinones **VI** in trifluoroacetic acid give rise to a clearly defined CH_2^β signal at δ 4.39–4.79 ppm together with that of H_α. The presence of an H_α signal at δ 6.58 ppm in the ^{1}H NMR spectrum of pyrido[2,3-*b*]pyrazin-3-one (**IIIe**) unambiguously indicates that its imino form **H** predominates (71%; Table 2, Scheme 2).

No considerable difference was found in the mass spectra of compounds **II** and **III**. A little difference was observed only in the intensity of some common fragment ions (Table 3, Scheme 3). Peaks with *m*/*z* values of 188, 160, and 132 are stronger for compounds **II**; e.g., the intensity of the first of these (*m*/*z* 188) is greater by a factor of ~1.5. Relatively easy elimination of the R fragment (Scheme 3) is likely to result from the *meta*-orienting effect of the nitrogen atom in the pyridine ring of **II**.

According to the quantum-chemical calculation data, nucleophilic attack on aroylpyruvic acids **IV** should be directed at the C^2 atom of the α-carbonyl moiety [13, 31]. Presumably, in reactions of **IV** with 2,3-diaminopyridine nucleophilic attack by the electron-rich 3-NH_2 group of the latter occurs just at the C^2 center, affording intermediate α-enamino acid **C**. In the reaction with 2,3-furandiones **V**, an alternative intermediate, aroylpyruvic acid amide **D**, is formed via attack by the 3-amino group of 2,3-diaminopyridine on the lactone carbonyl group of **V**. This pathway does not contradict the known concepts on the mechanism of reactions of 2,3-furandiones **V** with NH nucleophiles and is consistent with the results of quantum-chemical calculations [13, 15, 31, 32]. The subsequent dehydration of intermediates **C** and **D** leads to heterocyclization and formation of regioisomeric 3-acylmethylene-1*H*-3,4-dihydropyrido-

Scheme 4.



[2,3-*b*]pyrazin-2-ones **II** and 2-aroylmethylene-4*H*-1,2-dihydropyrido[2,3-*b*]pyrazin-3-ones **III**, respectively. Azines **II** and **III** exhibited bacteriostatic activity against *S. aureus* and *E. coli* [9, 10].

Taking into account specific features of the reaction of 2,3-diaminopyridine with compounds **IV** and **V**, it should be stressed out that the same reagent chemoselectively reacts with acylmethylene derivatives of 2,3-furandiones, e.g., with methyl 2-(5-aryl-2,3-dihydro-3-oxofuran-2-ylidene)acetate (**VII**), at the exocyclic double bond to afford 3-(5-aryl-2,3-dihydro-3-oxo-2-furyl)-1*H*-3,4-dihydropyrido[2,3-*b*]pyrazin-2-one (**VIII**) [13] (Scheme 4).

EXPERIMENTAL

The IR spectra of compounds **II**–**IV** were recorded on UR-20 and Specord M-80 spectrometers from samples dispersed in mineral oil. The ^{1}H NMR spectra of **II**–**IV**, **VI**, and **VIII** were obtained on RYa-2310 (60 MHz), Gemini-200 (200 MHz), Bruker AC-300 (300.13 MHz), and Bruker DRX-500 (500.13 MHz) instruments in DMSO-d_6, DMSO-d_6–CF_3COOH (10:1), or $CDCl_3$ using tetramethylsilane or hexamethyldisiloxane as internal reference. The ^{13}C NMR spectrum of quinoxalinone **VIb** was obtained on a Bruker WP-400 spectrometer (100.63 MHz) in DMSO-d_6. The mass spectra (electron impact, 70 eV) of **II**–**IV** and **VIa** were measured on a Kratos MS-30 instrument (United Kingdom) with direct sample admission into the ion source; emission current 1000 mA, vaporizer temperature 100–130°C. The purity of the products was checked by TLC on Silufol UV-254 plates using benzene–diethyl ether–acetone (10:9:1) as eluent; spots were visualized with iodine vapor. Initial acylpyruvic acids **IV** were synthesized by the Claisen condensation of the corresponding methyl ketones with diethyl oxalate in the presence of excess sodium methoxide or ethoxide [11–13].

5-Aryl-2,3-dihydrofuran-2,3-diones (Andreichikov's furandiones) **Va**–**Vd** were obtained by dehydration of aroylpyruvic acids by the action of acetic anhydride [13, 14]. Aroylpyruvic acids **IV** were heated with a minimal amount of acetic anhydride (it must be sufficient to dissolve acid **IV**). In the presence of excess acetic anhydride the yield of target products **V** was lower. Trifluoroacetic anhydride or acetyl chloride can be used instead of acetic anhydride. We were unable to convert the *E* isomers of **IVd** and **IVe** into the corresponding 2,3-furandiones **V** by the above procedure [13]. 4-Benzoyl-5-phenyl-2,3-dihydrofuran-2,3-dione (Ziegler's furandione) was synthesized by the known reaction of dibenzoylmethane with oxalyl chloride [16, 33].

Model 3-acylmethylene-1*H*-3,4-dihydroquinoxalin-2-ones **VIa** and **VIb** were prepared by heterocyclization of acylpyruvic acids with *o*-phenylenediamine [28, 29]. Commercial 2,3-diaminopyridine (from Maybridge Chemical Company, Tintagel, Cornwall, United Kingdom; mp 111–112°C) was used without additional purification. Physical constants of pyrido-[2,3-*b*]pyrazinones **IIb**, **IIc**, **IIe**, **IIg**, **IIIa**, and **IIIc** were reported in [1, 2, 4].

(*Z*)-3-Acylmethylene-1*H*-3,4-dihydropyrido-[2,3-*b*]pyrazin-2-ones IIa–IIi. A mixture of 0.005 mol of acylpyruvic acid **IVa**–**IVi** and 0.55 g (0.005 mol) of 2,3-diaminopyridine in 20–30 ml of ethanol was heated for a short time until it became homogeneous. After cooling, the precipitate was filtered off and recrystallized from ethanol, dioxane, or 2:1 ethanol–dioxane.

(*Z*)-3-Pivaloylmethylene-1*H*-3,4-dihydropyrido-[2,3-*b*]pyrazin-2-one (IIa). IR spectrum, ν, cm^{-1}: 3130 (N^1–H), 3070 (N^4–H), 1690 (CO, amide), 1610–1635, 1590 (C=O_{chelat}, C=C), 1465.

(*Z*)-3-Benzoylmethylene-1*H*-3,4-dihydropyrido-[2,3-*b*]pyrazin-2-one (IIb). IR spectrum, ν, cm^{-1}: 3150 (N^1–H), 3085 (N^4–H), 1692 (CO, amide), 1585–1615, 1545 (C=O_{chelat}, C=C), 1467. IR spectrum of model quinoxalinone **VIb** (which lacks pyridine nitrogen atom), ν, cm^{-1}: 3160 (N^1–H), 3050 (N^4–H), 1670 (CO, amide) [30].

(*Z*)-2-Aroylmethylene-4*H*-1,2-dihydropyrido-[2,3-*b*]pyrazin-3-ones IIIa–IIIe. A solution of 0.55 g (0.005 mol) of 2,3-diaminopyridine in 10 ml of benzene was added with stirring to a solution of 0.005 mol of appropriate 5-aryl-2,3-dihydrofuran-2,3-dione **Va**–**Ve** in 30–50 ml of benzene. After 24 h, the precipitate was filtered off, washed with diethyl ether, and recrystallized from ethanol.

(*Z*)-2-Benzoylmethylene-4*H*-1,2-dihydropyrido-[2,3-*b*]pyrazin-3-one (IIIa). IR spectrum, ν, cm^{-1}: 3140–3160 (N^4–H), 3060–3080 (N^1–H), 1695 (C=O, amide), 1630, 1590–1605, 1555 (C=O_{chelat}, C=C), 1468.

(*Z*)-2-Hydroxy-5,5-dimethyl-4-oxo-2-hexenoic acid (IVa). Metallic sodium, 9.2 g (0.4 mol), was added to 100 ml of methanol preliminarily distilled over sodium, the solvent was removed, and 150 ml of diethyl ether was added to the dry residue. To the resulting suspension a mixture of 29.2 g (0.2 mol) of diethyl oxalate and 40 g (0.4 mol) of pinacolone was added dropwise, and the resulting mixture was left overnight. Hot water, 40 ml, was added with stirring

to the sodium enolate thus formed, and the mixture was acidified to pH 3–4 by adding in portions concentrated hydrochloric acid. The solvent was removed, and the dry residue was recrystallized from carbon tetrachloride or 1:1 toluene–hexane. Acid **IVa** was isolated as colorless needles. Yield 24.6 g (71%), mp 55–56°C; published data: mp 60°C [11]; 64°C [34]. IR spectrum, ν, cm^{-1}: 3455–3510 and 1675–1708 (COOH), 1615–1622 and 1580–1590 (C=O_{chelat}), 1458, 1372, 1293, 1257, 1138, 1115. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 s (9H, $3CH_3$), 6.62 s (1H, CH, 100% of tautomer **A**). Mass spectrum, *m*/*z* (I_{rel} > 5%): 172 (30) $M^{+\cdot}$, 144 (20) $[M-CO]^+$ or $[(CH_3)_3CCOCH_2COOH]^+$, 128 (8) $[M-CO_2]^{+\cdot}$, 127 (81) $[M-CO_2-H]^+$ or $[(CH_3)_3CCOCH_2C\equiv O]^+$, 116 (34) $[M-2CO]^+$, 115 (8), 111 (8), 88 (21), 83 (12), 69 (40) $[O=C-CH=C=O]^+$, 60 (5), 57 (100) $[(CH_3)_2CHCH_2]^+$, 55 (11), 45 (13), 44 (20), 43 (62), 42 (21), 41 (57), 40 (32), 39 (25). Found, %: C 56.24; H 6.73. $C_8H_{12}O_4$. Calculated, %: C 55.81; H 7.02.

4-Aryl-2-hydroxy-4-oxo-2-butenoic acids IVb–IVi. Metallic sodium, 4.6 g (0.2 mol), was added in portions to 50–70 ml of anhydrous ethanol or methanol (distilled over sodium). To the resulting solution we added with stirring a mixture of 14.6 g (0.1 mol) of diethyl oxalate and 0.1 mol of appropriate acetophenone. The mixture was left to stand overnight, and 100 ml of water was added with thorough stirring and grinding of lumps. The solution was filtered, and the filtrate was acidified with concentrated hydrochloric acid to pH 2–3. The precipitate was filtered off, washed with water and 50 ml of ether, and recrystallized from ethyl acetate, chloroform, 1:1 acetic acid–toluene, or ethanol. Acids **IVb–IVi** were isolated as colorless or yellow crystalline substances. The properties of the newly synthesized aroylpyruvic acids **IV** and ^{1}H NMR spectral data of some known compounds **IV** are given below.

(*Z*)-2-Hydroxy-4-oxo-4-phenyl-2-butenoic acid (IVb) [12]. mp 156–157°C (decomp.); published data [12]: mp 156°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.50 s (1H, CH_2, tautomer **B**, 4%), 7.03 s (1H, CH, tautomer **A**, 96%), 7.55–8.05 m (5H, H_{arom}), 13.65 br.s (1H, OH).

(*Z*)-2-Hydroxy-4-oxo-4-*p*-tolyl-2-butenoic acid (IVc) [12]. mp 141–142°C (decomp.); published data [12]: mp 139–140°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.42 s (3H, CH_3), 4.51 s (1H, CH_2, tautomer **B**, 4%), 7.02 s (1H, CH, tautomer **A**, 96%), 7.35 d and 7.98 d (4H, H_{arom}), 8.50 br.s (1H, COOH).

(*E*)-2-Hydroxy-4-oxo-4-(2,4,6-trimethylphenyl)-2-butenoic acid (IVd). Yield 23 g (98%). mp 224–225°C (decomp.). IR spectrum, ν, cm^{-1}: 1700 (COOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.22 s (9H, $3CH_3$), 5.62 s (1H, CN), 6.88 s (2H, H_{arom}); no CH_2 proton signal (typical of β-diketone form **B**) was detected in the spectrum. Mass spectrum, *m*/*z* (I_{rel} > 10%): 234 (22) $M^{+\cdot}$, 219 (13) $[M-CH_3]^+$, 189 (71) $[M-CO_2-H]^+$, 160 (67) $[M-CO_2-CO-2H]^+$, 147 (28) $[2,4,6\text{-}(CH_3)_3C_6H_2C\equiv O]^+$, 121 (79) $[2,4,6\text{-}(CH_3)_3C_6H_2]^+$, 115 (22), 105 (17), 91 (27), 77 (24), 69 (100) $[O=C=CHC\equiv O]^+$, 51 (16). Found, %: C 66.84; H 5.79. $C_{13}H_{14}O_4$. Calculated, %: C 66.66; H 6.02.

(*E*)-2-Hydroxy-4-(3-methoxyphenyl)-4-oxo-2-butenoic acid (IVe). Yield 20 g (90%). mp 136–138°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.82 s (3H, CH_3O), 6.75 s (1H, CH), 7.02–7.62 m (4H, H_{arom}); no signal assignable to the CH_2 group of β-diketone form **B** was detected. Found, %: C 59.21; H 4.67. $C_{11}H_{10}O_5$. Calculated, %: C 59.46; H 4.54.

(*Z*)-2-Hydroxy-4-(3,4-dimethoxyphenyl)-4-oxo-2-butenoic acid (IVf). Yield 20.4 g (81%). mp 179–180°C (decomp.). IR spectrum, ν, cm^{-1}: 1710 (COOH), 1620 (C=C, C_6H_3). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.75 s (6H, $2CH_3O$), 7.00–7.80 m (4H, CH, H_{arom}); no signal assignable to the CH_2 group of β-diketone form **B** was detected. Found, %: C 56.69; H 4.61. $C_{12}H_{12}O_6$. Calculated, %: C 57.15; H 4.80.

(*Z*)-4-*p*-Bromophenyl-2-hydroxy-4-oxo-2-butenoic acid (IVg) [12]. mp 164–165°C (decomp.); published data [12]: mp 170–172°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.04 s (1H, CH), 7.65 d, 7.92 d (4H, H_{arom}); no signal assignable to the CH_2 group of β-diketone form **B** was detected.

(*Z*)-4-*p*-Chlorophenyl-2-hydroxy-4-oxo-2-butenoic acid (IVh) [12]. mp 169–170°C (decomp.); published data [12]: mp 160–161°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.60 s (1H, CH_2, tautomer **B**, 7%), 7.12 s (1H, CH, tautomer **A**, 93%), 7.62 d and 8.10 d (4H, H_{arom}), 8.85 br.s (1H, COOH).

(*Z*)-4-*p*-Fluorophenyl-2-hydroxy-4-oxo-2-butenoic acid (IVi) [12]. mp 149–150°C (decomp.); published data [12]: mp 150–152°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.52 s (1H, CH_2, tautomer **B**, 3%), 7.08 s (1H, CH, tautomer **A**, 97%), 7.30–8.20 m (4H, H_{arom}), 8.55 br.s (1H, COOH).

(*Z*)-3-Pivaloylmethylene-1*H*-3,4-dihydroquinoxalin-2-one (VIa). To a solution of 0.86 g (0.005 mol) of pivaloylpyruvic acid **IVa** in 40 ml of ethanol we added with stirring 0.54 g (0.005 mol) of *o*-phenylenediamine. The solution was left to stand for 5–6 h at room temperature, and the precipitate was filtered off

and recrystallized from dimethylformamide. Yield 1.05 g (83%). mp 229–230°C; published data [26]: mp 226–227°C. ^{1}H NMR spectrum, δ, ppm: $CDCl_3$: 1.28 s (9H, $3CH_3$), 6.47 s (1H, CH), 7.12–7.30 m (4H, H_{arom}), 10.70 s (1H, NH); DMSO-d_6): 1.22 s (9H, $3CH_3$), 6.27 s (1H, CH), 7.05, 7.12, 7.28 m (4H, H_{arom}), 11.70 s (1H, 1-H), 13.22 s (1H, 4-H). Mass spectrum, *m*/*z* (I_{rel} > 5%): 244 (59) $M^{+\cdot}$, 187 (100) $[M-(CH_3)_3C]^+$ (**I**), 160 (8), 159 (6) $[M-(CH_3)_3C-CO]^+$ (**J**), 131 (15) $[M-(CH_3)_3C-2CO]^+$ (**K**), 90 (6), 77 (7), 65 (7). The fragmentation pattern of **VIa** is fully consistent with that observed for pyrido[2,3-*b*]-pyrazin-2-one **IIa** under electron impact.

(*Z*)-3-Benzoylmethylene-1*H*-3,4-dihydroquinoxalin-2-one (VIb) [25–30, 35]. mp 264–265°C; published data: mp 268–269°C [25], 266–267°C [26, 29, 30], 261–263°C [35]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.65 s (2H, CH_2^{β}, tautomer **F**, 3%; see Scheme 3), 6.72 s (1H, CH^{α}, tautomer **E**, 97%, see Scheme 3; published data: 6.76 s [30], 6.80 s [35]: 100% of tautomer **E**), 7.20–8.15 m (5H, H_{arom}), 10.45 s (1H, 1-H, tautomer **F**), 12.05 s (1H, 1-H, tautomer **E**; published data: 11.85 s [30], 10.65 s [35]), 13.68 s (1H, 4-H). According to published data [3], no imino form **F** of compound **VIb** is detected at 24°C in DMSO-d_6, but it appears at 70–150°C, and its fraction considerably increases as the temperature rises. ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 89.9 (**C**$HCOC_6H_5$); 116.3 (C^3); 117.4, 124.6, 124.9, 127.6, 127.8, 129.6, 132.8, 139.4, 146.5 (C_{arom}), 156.6 (**C**OC_6H_5), 189.3 (CONH).

3-(3-Oxo-5-*p*-tolyl-2,3-dihydro-2-furyl)-1*H*-3,4-dihydropyrido[2,3-*b*]pyrazin-2-one (VIII) [13]. To a solution of 0.73 g (0.003 mol) of methyl 2-(3-oxo-5-*p*-tolyl-2,3-dihydrofuran-2-ylidene)acetic acid (**VII**) [15, 36] in 25 ml of ethanol we added with stirring 0.33 g (0.003 mol) of 2,3-diaminopyridine. The mixture was heated for 10 min under reflux (TLC), the solvent was removed, and the residue was ground with 20 ml of ether and recrystallized from ethanol. Yield 0.5 g (52%), light brown crystals with mp 220–222°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.33 s (3H, CH_3), 3.42 br.s (3H, CHCH, 4-H), 6.55–7.90 m (8H, 4′-H, H_{arom}, 5-H, 6-H, 7-H); the signals were broadened and distorted because of the poor solubility of product **VIII** in DMSO. Found, %: C 67.42; H 5.11; N 12.87. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.28; H 4.71; N 13.08.

REFERENCES

1. Seki, T., Sakata, H., and Iwanami, Y., *J. Heterocycl. Chem.,* 1995, vol. 32, no. 1, pp. 337–338.
2. Seki, T., Sakata, H., and Iwanami, Y., *J. Heterocycl. Chem.,* 1995, vol. 32, no. 2, pp. 703–704.
3. Seki, T. and Iwanami, Y., *J. Heterocycl. Chem.,* 1997, vol. 34, no. 3, pp. 773–780.
4. Bodforss, S., *Justus Liebigs Ann. Chem.,* 1964, vol. 676, pp. 136–140.
5. Mashevskaya, I.V., Tolmacheva, I.A., and Maslivets, A.N., *Khim. Geterotsikl. Soedin.,* 2000, no. 9 (399), pp. 1277–1278.
6. Mashevskaya, I.V., Tolmacheva, I.A., Kol'tsova, S.V., and Maslivets, A.N., *Novye dostizheniya v khimii karbonil'nykh i geterotsiklicheskikh soedinenii. Sbornik nauchnykh trudov* (Advances in the Chemistry of Carbonyl and Heterocyclic Compounds. Collection of Scientific Papers), Saratov, 2000, p. 155.
7. Sof'ina, O.A., Igidov, N.M., Koz'minykh, E.N., Shironina, T.M., Makhova, S.E., and Koz'minykh, V.O., Abstracts of Papers, *Molodezhnaya nauchnaya shkola po organicheskoi khimii* (Young Scientists School on Organic Chemistry), Yekaterinburg, 1998, pp. 77–78.
8. Trapeznikova, N.N., Koz'minykh, E.N., Sof'ina, O.A., and Koz'minykh, V.O., *Materialy yubileinoi mezhvuzovskoi nauchno-prakticheskoi konferentsii "80 Let farmatsevticheskomu obrazovaniyu i nauke na Urale: itogi i perspektivy"* (Proc. Jubilee Interinstitution Scientific–Practical Conf. "80 Years of Pharmaceutical Education in the Urals: Results and Prospects"), Perm: Permsk. Gos. Tekh. Univ., 1998, pp. 61–62.
9. Sof'ina, O.A., Trapeznikova, N.N., Koz'minykh, E.N., Igidov, N.M., Berezina, E.S., and Koz'minykh, V.O., *Materialy regional'noi konferentsii "Sovremennye problemy ekologii, mikrobiologii i immunologii"* (Proc. Regional Conf. "Current Problems in Ecology, Microbiology, and Immunology"), Perm: Inst. Ekol. i Genet. Mikroorg. Ural. Otd. Ross. Akad. Nauk, 1999, pp. 105–106.
10. Sof'ina, O.A., Igidov, N.M., Koz'minykh, E.N., and Koz'minykh, V.O., Abstracts of Papers, *Nauchno-prakticheskaya konferentsiya "Farmatsevticheskaya nauka i praktika"* (Scientific–Practical Conf. "Pharmaceutical Science and Practice"), Kemerovo: Kemerovsk. Gos. Med. Akad., 1999, pp. 133–134.
11. Couturier, F., *C. R. Acad. Sci.,* 1910, vol. 150, no. 11, pp. 928–930; *Beilstein Handbuch der organischen Chemie,* EI, vol. 3, p. 264.
12. Andreichikov, Yu.S., *Metody sinteza biologicheski aktivnykh geterotsiklicheskikh soedinenii* (Methods of Synthesis of Biologically Active Heterocyclic Compounds), Perm: Perm. Gos. Univ., 1989.
13. Koz'minykh, E.N., *Doctoral (Chem.) Dissertation,* Perm, 1999.

14. Kozminykh, V.O., Igidov, N.M., Kozminykh, E.N., and Aliev, Z.G., *Pharmazie*, 1993, vol. 48, no. 2, pp. 99–106.
15. Andreichikov, Yu.S. and Shurov, S.N., *Khimiya pyatichlennykh 2,3-dioksogeterotsiklov* (Chemistry of Five-Membered 2,3-Dioxo Heterocycles), Perm: Perm. Gos. Univ., 1994, pp. 5–54; *Chem. Abstr.*, 1996, vol. 125, no. 195 292 b.
16. Kollenz, H., *Khimiya pyatichlennykh 2,3-dioksogeterotsiklov* (Chemistry of Five-Membered 2,3-Dioxo Heterocycles), Perm: Perm. Gos. Univ., 1994, pp. 55–73; *Chem. Abstr.*, 1996, vol. 125, no. 195 293 c.
17. Henseke, G. and Lehmann, D., *Angew. Chem.*, 1964, vol. 76, no. 23, pp. 954–955.
18. Pimenova, E.V. and Andreichikov, Yu.S., *Khimiya pyatichlennykh 2,3-dioksogeterotsiklov* (Chemistry of Five-Membered 2,3-Dioxo Heterocycles), Perm: Perm. Gos. Univ., 1994, pp. 188–204.
19. Kolehmainen, E., *Tetrahedron*, 1999, vol. 55, no. 28, pp. 8475–8480.
20. Mashevskaya, I.V., Kol'tsova, S.V., Duvalov, A.V., and Maslivets, A.N., *Khim. Geterotsikl. Soedin.*, 2000, no. 9 (399), pp. 1281–1282.
21. Mashevskaya, I.V., Tolmacheva, I.A., Kol'tsova, S.V., Golovnina, O.V., and Maslivets, A.N., *Materialy tret'ego Vserossiiskogo simpoziuma po organicheskoi khimii "Strategiya i taktika organicheskogo sinteza"* (Proc. 3rd All-Russian Symp. on Organic Chemistry "Strategy and Tactics of Organic Synthesis"), Yaroslavl: IPK ITAR TASS (Moscow), 2001, p. 77.
22. Koz'minykh, E.N., Igidov, N.M., and Koz'minykh, V.O., *Materialy yubileinoi mezhvuzovskoi nauchno-prakticheskoi konferentsii "80 Let farmatsevticheskomu obrazovaniyu i nauke na Urale: itogi i perspektivy"* (Proc. Jubilee Interinstitution Scientific–Practical Conf. "80 Years of Pharmaceutical Education in the Urals: Results and Prospects"), Perm: Permsk. Gos. Tekh. Univ., 1998, pp. 54–55.
23. Shironina, T.M., Sof'ina, O.A., Koz'minykh, E.N., Igidov, N.M., and Koz'minykh, V.O., *Permskii agrarnyi vestnik. Nauchno-proizvodstvennyi zhurnal. Vyp. III: Sovremennaya nauka – agrarnomu sektoru Prikam'ya* (Perm Agrarian Bulletin. Scientific–Industrial Journal. Issue III: Advances in Science for the Agrarian Department of the Near-Kama Region"), Perm: Perm. Gos. Sel'skokhoz. Akad., 1998, p. 25.
24. Koz'minykh, E.N., Igidov, N.M., Kolotova, N.V., Sof'ina, O.A., Shironina, T.M., and Koz'minykh, V.O., *Khimiya dlya meditsiny i veterinarii. Sbornik nauchnykh trudov* (Chemistry for Medicine and Veterinary. Collection of Scientific Papers), Saratov: Saratov. Gos. Univ., 1998, pp. 90–93.
25. Iwanami, Y., Seki, T., and Inagaki, T., *Bull. Chem. Soc. Jpn.*, 1971, vol. 44, no. 5, pp. 1316–1321.
26. Saraeva, R.F., *Cand. Sci. (Chem.) Dissertation*, Perm, 1973.
27. Iwanami, Y. and Inagaki, T., *J. Heterocycl. Chem.*, 1976, vol. 13, no. 4, pp. 681–684.
28. Andreichikov, Yu.S., Pitirimova, S.G., Saraeva, R.F., Gein, V.L., Plakhina, G.D., and Voronova, L.A., *Khim. Geterotsikl. Soedin.*, 1978, no. 3, pp. 407–410.
29. Pitirimova, S.G., *Cand. Sci. (Chem.) Dissertation*, Perm, 1979.
30. Maslivets, A.N., Smirnova, L.I., and Andreichikov, Yu.S., *Zh. Org. Khim.*, 1988, vol. 24, no. 10, pp. 2234–2235.
31. Kataev, S.S., *Cand. Sci. (Chem.) Dissertation*, Perm, 1999.
32. Kozlov, A.P. and Andreichikov, Yu.S., *Khimiya pyatichlennykh 2,3-dioksogeterotsiklov* (Chemistry of Five-Membered 2,3-Dioxo Heterocycles), Perm: Perm. Gos. Univ., 1994, pp. 122–147.
33. Ziegler, E., Eder, M., Belegratis, C., and Prewedourakis, E., *Monatsh. Chem.*, 1967, vol. 98, no. 6, pp. 2249–2251.
34. Meister, A. and Greenstein, J.P., *J. Biol. Chem.*, 1948, vol. 175, pp. 573–588; *Chem. Abstr.*, 1949, vol. 43, p. 705 g.
35. Milyutin, A.V., Amirova, L.R., Nazmetdinov, F.Ya., Makhmudov, R.R., Golovanenko, A.L., Andreichikov, Yu.S., and Kolla, V.E., *Khim.-Farm. Zh.*, 1996, vol. 30, no. 5, pp. 47–49.
36. Andreichikov, Yu.S., Koz'minykh, V.O., and Manelova, E.N., *Zh. Org. Khim.*, 1985, vol. 21, no. 2, pp. 402–406.