1,3,4,6-TETRACARBONYL COMPOUNDS. PART 2.[1] SYNTHESIS OF BIOLOGICALLY ACTIVE 2-HYDROXY-2,3-DIHYDRO-3-PYRROLONES AND SUBSTITUTED AMIDES OF AROYLPYRUVIC ACIDS

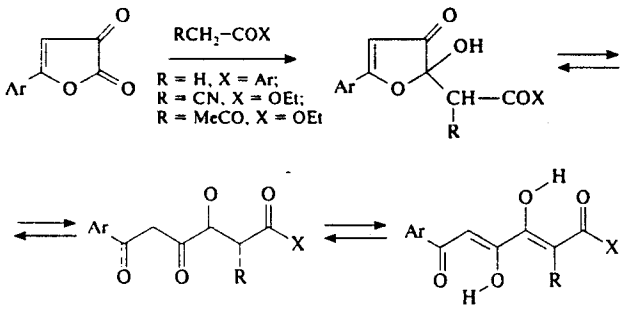
E. N. Koz'minykh,[2] N. M. Igidov,[2] E. S. Berezina,[2] G. A. Shavkunova,[2] I. B. Yakovlev,[2] S. A. Shelenkova,[2] V. É. Kolla,[2] É. V. Voronina,[2] and V. O. Koz'minykh[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 7, pp. 31 – 35, July, 1996.

Original article submitted January 16, 1996.

As is known, CH acids such as arylmethylketones, acetoacetic, and cyanoacetic esters readily interact with 5-aryl-2,3-dihydro-2,3-furandiones (I) in the presence of base catalysts with the formation of 2-acylmethyl-2-hydroxy2,3-dihydro-3-furanones — stable products of regioselective aldol condensation at the lactone carbonyl [1 – 7].

It was established that these cyclic semiacetals occur in solution in equilibrium with linear oxotautomeric forms, enolyzed at the carbonyl groups in positions 3 and 4, and with 1,3,4,6-tetracarbonyl compounds [1, 3, 5 – 7]. The structure of the latter compounds and the close cyclic heterofunctional derivatives, as well as their tautomeric equilibria in solutions, have been studied in sufficient detail [1, 3, 8 – 12].



It was expected that the reaction of 2,3-furandiones (I) with esters of substituted β-aminocrotonic and 2-arylamino-4-oxo-2-butenoic acids could proceed in two directions. There are two centers with excess electron density in these reagents: nitrogen atom of the enamine fragment and carbon atom of the methine fragment (in the above acids, C_2 and C_3, respectively). We believed that these centers may act upon 2,3-furandiones as either N-or C-nucleophiles. One of these reactions was previously briefly mentioned in [13, 14] and recently confirmed in [4, 7, 15, 16].

Interaction of 5-aryl-2,3-dihydro-2,3-furandiones (Ia – Ie) with ethyl ester of 3-benzylamino-2-butenoic acid (II) allowed us to synthesize 2-aroylmethyl-1-benzyl-2-hydroxy-5-methyl-4-ethoxycarbonyl-2,3-dihydro-3-pyrrole (IIIa – IIIe) and benzylamides of aroylpyruvic acids (IVa – IVe) [16]. However, we failed to obtain 2-hydroxy-2,3-dihydro-3-pyrrolones (analogous to compounds III) by condensation of substituted 2,3-pyrrolediones with arylmethylketones: only products of nucleophilic addition at the carbon atom in position 5 of the pyrrole cycle were isolated from the reaction mixture [4, 7].

Reaction of 2,3-furandiones (Ia, Ib) with methyl esters of 4-aryl-2-arylamino-4-oxo-2-butenoic acids (Va – Vc) (obtained via interaction of arylamines with methyl esters of aroylpyruvic acids [17]) led (as in the case of reaction between 2,3-furandiones with arylamines [18]) to the formation of only arylamines of aroylpyruvic acids (IVa – IVh). In this case, we did not observe the formation of the corresponding 2,3-dihydro-3-pyrrolones (III).

Data on the yields and constants of compounds II, IIIa – IIIe, and IVa – IVe are given in Table 1, and the spectral characteristics of some of the obtained compounds are presented in Table 2. The results of elemental analyses (C, H, N, halogen) of the synthesized compounds agree with the calculated values.

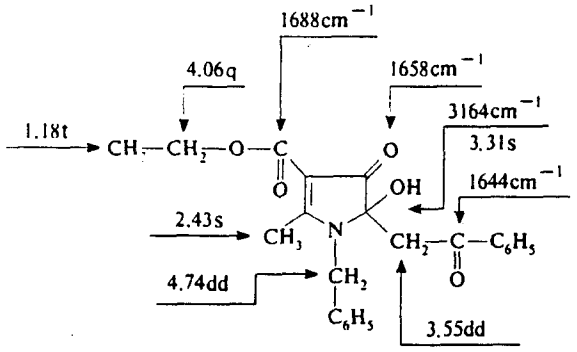
The structure of 3-pyrrolones (III) was established on the basis of spectroscopic data and by comparison with structurally similar 2-hydroxy-2,3-dihydro-3-pyrrolones obtained by other methods [11, 19 – 21].

Substituted amides of aroylpyruvic acids (IV) were identified by comparison with the published data [18, 22, 23].

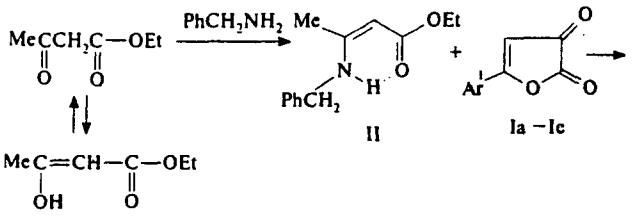
The ^{1}H NMR spectra of compounds III measured in DMSO-d_6 solutions contain no signals due to protons of the NH group (in the spectrum of enaminoester II, a broadened signal of the proton of amino group is observed at 8.95 ppm), but show a signal due to hydroxyl proton of the cyclic semiaminal at 3.31 – 3.45 ppm (Table 2) vanishing on adding

[2] Perm' Pharmaceutical Academy, Perm', Russia.

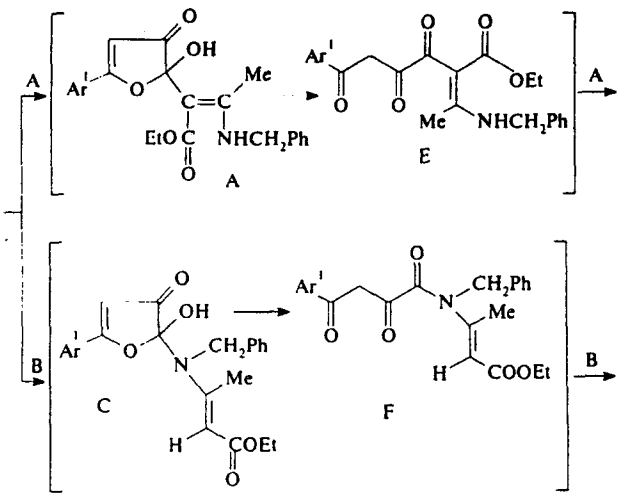
0091-150X/96/3007-0458$15.00



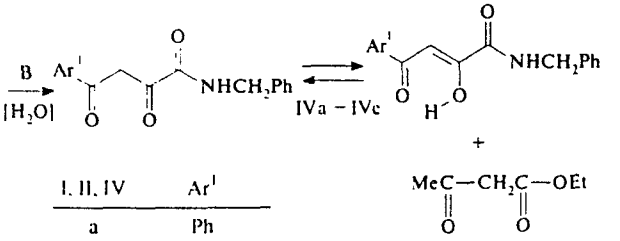
IIIa



II Ia – Ic

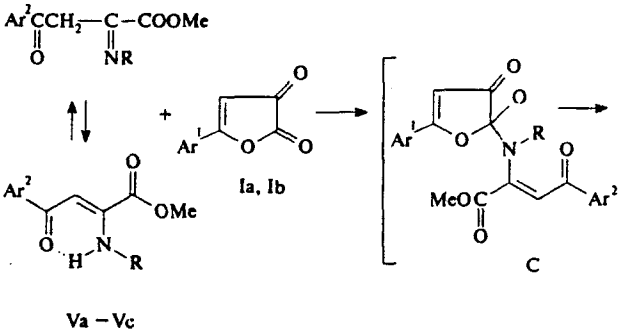


IIIa – IIIc

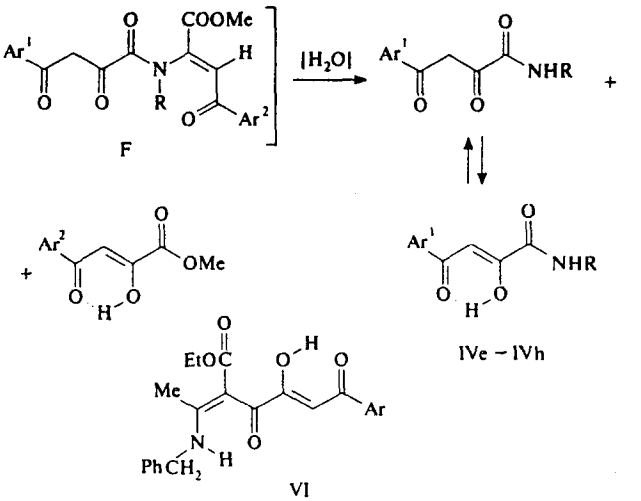


I, II, IV	Ar^1
a	Ph
b	4-MeC_6H_4
c	4-MeC_6H_4
d	4-BrC_6H_4

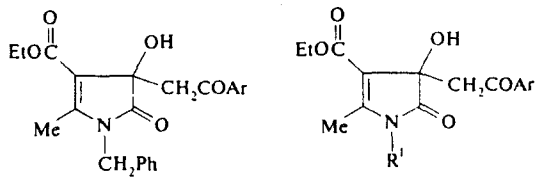
a drop of trifluoroacetic acid. (Note that the singlet signal at 3.58 ppm was misinterpreted in [14] as due to the methyl group.) The presence of the signal due to the hydroxyl proton indicates that the solutions contain no possible chain tautomeric form of enaminoketoester (VI). However, the fact that 2-hydroxy-2,3-dihydro-3-pyrrolones (III) represent a stable cyclic form of enaminoketoesters (VI) allows us to include them in the group of nitrous derivatives of 1,3,4,6-tetracarbonyl compounds.



Va – Vc Ia, Ib C



F IVe – IVh VI



VII VIII

R^1 = H, CH_2Ph, Ph;
R^2 = OH, OAlk
[25, 26]

IV	Ar^1	R	V	Ar^2	R
f	Ph	Ph	a	Ph	Ph
g	Ph	4-MeC_6H_4	b	Ph	4-MeC_6H_4
h	4-MeC_6H_4	4-MeC_6H_4	c	4-MeC_6H_4	4-MeC_6H_4

Vibrational frequencies of the absorption bands of carbonyl groups in the IR spectra of most pyrrolones IIIm do not exceed 1690 cm^{-1}, in complete agreement with the literature data [11, 19 – 21]. This fact allows us to reject an alternative structure of regioisomeric 3-hydroxy-2,3-dihydro-2-pyrrolones (VII), for which the absorption band of lactam carbonyl must occur in the region above 1720 cm^{-1} (as can be judged from data published for the structurally close 3-substituted 2,3-dihydro-3-pyrrolones (VIII) [24, 25]).

Recently, Aliev et al. [14] published the x-ray diffraction data for compound IIIa, which confirmed the structure of 2-hydroxy-2,3-dihydro-3-pyrrolones (III) established in our earlier works [4, 7, 15, 16].

TABLE 1. Yields and Analytical Characteristics of Compounds II, III, and IV

Compound	Yield, %	M.p., °C	Empirical formula
II	96	61 – 62	$C_{13}H_{17}NO_2$
IIIa	48	168 – 169[1]	$C_{25}H_{23}NO_5$
IIIb	52	161 – 162	$C_{26}H_{25}NO_5$
IIIc	43	136 – 137	$C_{26}H_{25}NO_6$
IIId	31	175 – 176	$C_{25}H_{22}BrNO_5$
IIIe	27	147 – 148	$C_{25}H_{22}ClNO_5$
IVa	37	89 – 90[2]	$C_{17}H_{15}NO_3$
IVb	29	94 – 95	$C_{18}H_{17}NO_3$
IVc	33	91 – 92	$C_{18}H_{17}NO_4$
IVd	40	121 – 122	$C_{17}H_{14}BrNO_3$
IVe	46	97 – 98	$C_{17}H_{14}ClNO_3$
IVf	72	124 – 125[3]	–
IVg	60	138 – 139[4]	–
IVh	54	146 – 147[5]	–

Notes. Reported m.p. (°C): [1] 161 – 162 [14]; [2] 92 – 93 [14]; [3] 113 – 114 [19]; [4] 128 – 129 [19]; [5] 161 – 162 [19].

Interaction of 5-aryl-2,3-dihydro-2,3-furandiones (I) with esters of β-aminocrotonic and 2-arylamino-4-oxo-2-butenoic acids apparently proceeds by two competing pathways. Depending on the structure, the enaminoester either attaches at a lactone carbonyl of compound I, acting like both a C-nucleophile (with participation of the electron-donor carbon atom in the α-position with respect to the ester group — pathway A) and a N-nucleophile (at the secondary amino group — pathway B), or proceeds by the latter pathway alone in the case of compounds V, where the maximum electron density is accumulated on the nitrogen atom of amino group. Intermediate products, represented by semiacetals A – C, exhibit subsequent decyclization with scission of the $C_2 - O$ bond and the formation of ketoesters D or aroylpyruvoyl amides E, F. The subsequent cyclization of intermediate D yields 2-hydroxy-2,3-dihydro-3-pyrrolones (III), while amides E, F are hydrolyzed in the presence of trace water to the corresponding amides of aroylpyruvic acids (IV).

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds II – IV were recorded on an UR-20 spectrophotometer using samples prepared as nujol mulls. The ^1H NMR spectra of II – IV were obtained on an RYa-2310 spectrometer operated at 60 MHz, using DMSO-d_6 as the solvent and HMDS as the internal standard. The course of the reactions was followed and the purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates eluted in the benzene – hexane 3 : 1 system and developed by iodine vapor. The initial 5-aryl-2,3-dihydro-2,3-furandiones (Ia – Ie) were obtained by a modified method described in [26], and methyl esters of 4-aryl-2-arylamino-4-oxo-2-butenoic acids (Va – Vc) were obtained according to [17].

TABLE 2. Parameters of IR and ^1H NMR Spectra of Compounds III and IV

Compound	IR spectrum, ν_{max}, cm^{-1}, (crystals)	NMR spectrum, δ, ppm
IIIa	3164(OH), 1688(COOEt), 1658(C^3 = O), 1644(COPh)	1.18 (t, 3H, $COOCH_2Me$), 2.43 (s, 3H, Me), 3.31 (s, 1H, OH), 3.55 (dd, 2H, CH_2COPh), 4.06 (q, 2H, $COOCH_2Me$), 4.74 (dd, 2H, CH_2Ph), 7.40 – 7.80 (m, 10H, 2Ph)
IIIb	3260(OH), 1688(COOEt), 1656(C^3 = O, COC_6H_4Ph-4)	1.18 (t, 3H, $COOCH_2Me$), 2.31 (s, 3H, 4-MeC_6H_4), 2.38 (s, 3H, Me), 3.37 (s, 1H, OH), 3.53 (dd, 2H, CH_2COPh), 4.05 (q, 2H, $COOCH_2Me$), 4.71 (dd, 2H, CH_2Ph), 7.35 – 7.60 (m, 9H, Ph, C_6H_4)
IIIc	3275(OH), 1678(COOEt), 1660(C^3 = O), 1637(COC_6H_4OMe-4)	—
IIId	3300(OH), 1664(COOEt), 1632(C^3 = O, COC_6H_4OBr-4)	—
IIIe	3416(OH), 1716(COOEt), 1688(C^3 = O), 1646(COC_6H_4Cl-4)	1.20 (t, 3H, $COOCH_2Me$), 2.46 (s, 3H, Me), 3.42 (s, 1H, OH), 3.55 (dd, 2H, CH_2COPh), 4.01 (q, 2H, $COOCH_2Me$), 4.76 (dd, 2H, CH_2Ph), 6.95 – 7.80 (m, 9H, Ph, C_6H_4)
IVa	3296(NH), 1644(CONH), 1565 – 1580(CO_{chel}, C = C)	4.45 (d, 2H, CH_2Ph), 5.91 (s, 1H, CH), 6.95 – 7.85 (m, 10H, 2Ph), 10.90 (bs, 1H, NH)
IVb	3284(NH), 1656(CONH), 1565 – 1620(CO_{chel}, C = C)	2.33 (s, 3H, Me), 4.60 (d, 2H, CH_2Ph), 5.68 (s, 1H, CH), 7.10 – 7.60 (m, 9H, Ph, C_6H_4), 11.21 (bs, 1H, NH)
IVc	3265(NH), 1594(CONH), 1540 – 1570(CO_{chel}, C = C)	3.78 (s, 3H, MeO), 4.56 (d, 2H, CH_2Ph), 5.65 (s, 1H, CH), 6.80 – 7.80 (m, 9H, Ph, C_6H_4), 11.15 (bs, 1H, NH)
IVd	3288(NH), 1652(CONH), 1540 – 1565(CO_{chel}, C = C)	4.41 (d, 2H, CH_2Ph), 5.93 (s, 1H, CH), 6.95 – 7.75 (m, 9H, Ph, C_6H_4), 9.30 (bs, 1H, NH)
IVe	3284(NH), 1720(CONH), 1575 – 1592(CO_{chel}, C = C)	4.41 (d, 2H, CH_2Ph), 5.66 (s, 1H, CH), 6.95 – 7.80 (m, 9H, Ph, C_6H_4), 9.38 (bs, 1H, NH)
IVg	3204(NHCO), 1688(NHCO), 1580 – 1605(CO_{chel}, C = C)	6.74 (s, 3H, MeO), 7.02 (s, 1H, CH), 7.20 – 8.00 (m, 9H, Ph, C_6H_4), 12.05 (bs, 1H, NH)

Ethyl ester of 3-benzylamino-2-butenoic acid (II). To a solution of 6.5 g (0.05 mole) of acetoacetic ester in 30 ml of diethyl ester was added with stirring 5.35 g (0.05 mole) of benzylamine. The precipitate was filtered and recrystallized from diethyl ester. Yield of compound II: 10.6 g (96%); m.p., 61 – 62°C; IR spectrum (ν, cm^{-1}): 3360 (NH), 1666 (COOEt); ^1H NMR spectrum (δ, ppm): 1.19 (t, 3H, $COOCH_2\underline{Me}$), 1.80 (s, 3H, Me), 4.00 (q, 2H, $COO\underline{CH_2}Me$), 4.37 (d, 2H, $\underline{CH_2}Ph$), 6.95 – 7.40 (m, 6H, CH, Ph), 8.95 (bs, 1H, NH).

Interaction of 5-aryl-2,3-dihydro-2,3-furandiones (Ia – Ie) with ethyl ester of 3-benzylamino-2-butenoic acid (II). To a solution of 0.024 mole of the corresponding 5-aryl-2,3-dihydro-2,3-furandione (Ia – Ie) [26] in 150 – 200 ml of benzene was added with stirring a solution of 0.52 g (0.024 mole) of compound II in 30 ml of benzene and the mixture was heated to boiling. Then the solvent was distilled off, and the residue was separated by fractional crystallization from benzene – hexane (5:2), dichloroethane, and isopropanol to obtain 2-aroylmethyl-1-benzyl-2-hydroxy-5-methyl-4-ethoxycarbonyl-2,3-dihydro-3-pyrrolones (IIIa – IIIe) and benzylamides of aroylpyruvic acids (IVa – IVe).

Interaction of 5-aryl-2,3-dihydro-2,3-furandiones (Ia, Ib) with methyl esters of 4-aryl-2-arylamino-4-oxo-2-butenoic acids (Va – Vc). To a solution of 0,01 mole of the corresponding 5-aryl-2,3-dihydro-2,3-furandiones (Ia, Ib) was added with stirring a solution of 0.01 mole of compound Va, Vb, or Vc in 100 – 150 ml of benzene and the mixture was heated to boiling. Then the solvent was distilled off, and the residue was recrystallization from ethanol or toluene to obtain arylamides of aroylpyruvic acids (IVf – IVh).

EXPERIMENTAL BIOLOGICAL PART

We have studied the antimicrobial, anticonvulsive, and analgesic activity of the synthesized compounds, and evaluated their acute toxicity.

The acute toxicity (LD_{50}) was determined only for the active compounds (III, IV) by single intraperitoneal injection of a 2% starch suspension to white mice weighing 18 – 25 g. The LD_{50} value was determined by the conventional method [27].

The antimicrobial activity of the synthesized compound with respect to standard strains *Escherichia coli* M_{17} and *Staphylococcus aureus* P-209 was determined by a conventional method of sequential double serial dilutions in a beef-infusion broth for a bacterial load of 250×10^3 microbial cells per ml solution [28]. The active dose was determined as the minimum inhibiting concentration (MIC) of the compound, that is, the maximum dilution ensuring complete suppression of the growth of test microbes. the antimicrobial activity of the synthesized compounds was compared to that of flumequine and oxolinic and nalydixic acids, modern efficient antibacterial compounds belonging to the 4-quinoline-3-carboxylic acid group [29, 30].

The anticonvulsive activity was studied using the maximum electroshock test [31]. The compounds were intraperitoneally injected to white mice weighing 18 – 22 g in the form of a 2% starch suspension at a dose of up to 400 mg/kg. The effective dose (ED_{50}, mg/kg) was determined using the rapid method described in [32]. In the absence of visible effects, the compound was classified as inactive. Phenobarbital was used as the reference drug.

The analgesic activity was assessed by the thermal irritation (hot-plate) method, whereby the animal feet were thermally irritated (54°C × 0.2 sec) and the onset of the defensive licking reflex was monitored. The test was performed on preselected mice with a control defensive reflex time not exceeding 15 sec. The test was carried out 30, 60, 120, and 180 min after intraperitoneal injection of the synthesized compounds at a dose of 50 mg/kg. An increase in the defensive reflex time by not less than 50% against the initial control value was considered as an indication of the analgesic effect. The analgesic activity was compared to that of analgin.

The acute toxicity of compounds III and IV for a single administration exceeded 1000 mg/kg [16]. Therefore, the compounds can be considered virtually nontoxic, which is an advantage over the reference drugs used for the biological activity evaluation (Tables 3 and 4).

The maximum bacteriostatic activity among the compounds studied was observed for the benzoylpyruvic acid arylamides IVf and IVg, which suppressed the growth of *St. aureus* at MIC = 31.2 and 7.8 μg/ml, and the growth of *E. coli* at MIC = 62.5 and 15.6 μg/ml, respectively (Table 3). The antimicrobial activity of these compounds is virtually the same as that of the 4-quinolone derivatives. Both 2-hydroxy-2,3-dihydro-3-pyrrolones (III) and the methyl ester of 4-aryl-2-*n*-tolylamino-4-oxo-2-butenoic acids (Vb) exhibited com-

TABLE 3. Antimicrobial Activity of Compounds II, III, IV, and V

Compound	MIC, μg/ml	
	E. coli M_{17}	*St. aureus* P-209
II	1000	250
IIIa	1000	125
IIIb	Inactive	500
IIIc	1000	250
IIIe	1000	250
IVa	1000	125
IVb	1000	1000
IVc	1000	1000
IVf	62.5	31.2
IVg	15.6	7.8
Vb	1000	500
Oxolinic acid*	12.5 – > 256	0.5 – 16
Nalydixic acid*	12.5 – > 256	0.5 – 8
Flumequin*	12.5 – > 256	0.5 – 16

* MIC variation limits [30, 31].

TABLE 4. Anticonvulsive and Analgesic Activity of Compounds II, III, IV, and V

Compound	Anticonvulsive effect (ED_{50}, mg / kg)	Analgesic effect (defensive reflex, sec)
II	328 (259 – 397)	–
IIIa	328 (259 – 397)	29.6 (25 – 36)
IVa	Inactive	29.2 (26 – 33)
IVb	359 (284 – 435)	29.1 (26 – 32)
IVc	300 (273 – 363)	18.1 (16 – 20)
IVe	300 (273 – 363)	23.4 (18 – 29)
IVf	–	20.5 (16 – 25)
Vb	–	15.8 (13 – 18)
Phenobarbital	16 (13 – 19)	–
Analgin	–	21.5 (20 – 23)
Control	–	12.9 (12 – 14)

paratively weak bacteriostatic action with respect to both strains of bacterial cultures.

According to the maximum electroshock test data, the anticonvulsive effect of synthesized compounds was markedly lower than that of phenobarbital (Table 4).

The analgesic action of the compounds studied was comparable with that of analgin. The most active were 3-pyrrolone IIIa and aroylpyruvic acid benzylamides IVa and IVb, which produced a more than twofold increase in the defensive reflex time against the control (Table 4).

REFERENCES

1. V. O. Koz'minykh, L. O. Konshina, and N. M. Igidov, *J. Prakt. Chem.*, **335**(8), 714 – 716 (1993).
2. V. O. Koz'minykh, N. M. Igidov, and E. Yu. Sokolova, in: *Carbonyl Compounds in the Synthesis of Heterocycles*[in Russian], Part. 1. Saratov (1992), p. 42.
3. V. O. Koz'minykh, O. V. Bulkina, N. M. Igidov, et al., Russ. Patent No. 2002.729; *Byull. Otkryt. Izobret.*, No. 41 – 42 (1993); *Ref. Zh. Khim.*, No. 140, 11P (1994).
4. V. O. Koz'minykh, E. E. Kal'nitskaya, V. G. Armaginova, et al., *Problems of Pharmaceutics, Teaching and Employment of Pharmacists. Proc. Rep. Sci. Conf. on Pharmaceutics and Pharmacology* [in Russian], Pyatigorsk (1993), pp. 200 – 201.
5. V. O. Koz'minykh, in: *Pharmaceutics and Pharmacology: Abstracts of Papers. Int. Sci.-Pract. Conf.* [in Russian], Perm (1993), pp. 90 – 91.
6. N. M. Igidov, E. N. Koz'minykh, G. A. Shavkunova, et al., in: *Peterburg's Meetings-95: Symp. on Organic Chemistry* [in Russian], St Petersburg (1995), pp. 203 – 204.
7. G. A. Shavkunova, N. M. Igidov, E. S. Berezina, et al., in: *Current Problems of Pharmaceutics: Interinst. Collection of Sci. Papers* [in Russian], Perm' Pharmaceutical Institute, Perm' (1995), p. 20.
8. M. Poje and K. Balenovic, *J. Heterocycl. Chem.*, **16**(3), 417 – 420 (1979).
9. D. N. Shigorin, N. A. Rudenko, L. A. Chetkina, et al., *Zh. Fiz. Khim.*, **66**(8), 2128 – 2132 (1992).
10. L. A. Chetkina, *Kristallografiya*, **37**(1), 212 – 214 (1992).
11. V. O. Koz'minykh, N. M. Igidov, E. N. Koz'minykh, et al., *Pharmazie*, **47**(4), 261 – 263 (1992).
12. S. N. Shurov, E. Yu. Pavlova, L. I. Livantsova, et al., *Zh. Org. Khim.*, **29**(11), 2275 – 2289 (1993).
13. E. Yu. Pavlova, S. N. Shurov, Yu. S. Andreichikov, et al., in: *Abstracts of Papers. Enamines in Organic Synthesis. The 2nd Regional Conf.* [in Russian], Perm' (1991), p. 32.
14. Z. G. Aliev, S. N. Shurov, E. Yu. Pavlova, et al., *Izv. Ross. Akad. Nauk, Ser. Khim.*, No. 8, 1552 – 1555 (1995).
15. V. G. Armaginova, E. N. Koz'minykh, I. V. Polikutina, et al., *Abstracts of Papers. The 50th Sci.-Pract. Conf. of the Teaching Staff* [in Russian], Perm' Pharmaceutical Institute, Perm' (1994), pp. 8 – 9.
16. E. N. Koz'minykh, G. A. Shavkunova, N. M. Igidov, et al., *Manuscript Dep. VINITI* No. 20-B95 (10.01.95), Perm' (1995).
17. R. F. Saraeva, *Author's Abstract Cand. Sc. (Chem. Sci.) Thesis* [in Russian], Perm' (1973).
18. Yu. S. Andreichikov, Yu. A. Nalimova, S. P. Tendryakova, et al. *Zh. Org. Khim.*, **14**(1), 160 – 163 (1978).
19. S. Gelin, *Synthesis*, No. 4, 291 – 294 (1978).
20. B. Chantegrel and S. Gelin, *J. Heterocycl. Chem.*, **15**(7), 1215 – 1219 (1978).
21. Yu. S. Andreichikov and V. O. Koz'minykh, *Zh. Org. Khim.*, **25**(3), 618 – 622 (1989).
22. Yu. S. Andreichikov, S. P. Tendryakova, Yu. A. Nalimova, et al., *Zh. Org. Khim.*, **13**(3), 529 – 531 (1977).
23. Yu. S. Andreichikov, V. S. Zalesov, S. P. Tendryakova, et al., USSR Inventor's Certificate No. 769 992, *Byull. Otkryt. Izobret.*, No. 38 (1981); *Ref. Zh. Khim.*, No. 220, 58P (1982).
24. G. Shilagyi and H. Wamhoff, *Acta Chim. Acad. Sci. Hung.*, **82**(3), 375 – 377 (1974).
25. S. G. Agbalyan and L. A. Nersesyan, *Armyan. Khim. Zh.*, **22**(1), 40 – 45 (1969).
26. V. O. Koz'minykh, N. M. Igidov, E. N. Koz'minykh, et al., *Pharmazie*, **48**(2), 99 – 106 (1993).
27. V. B. Prozorovskii, M. P. Prozorovskaya, and V. M. Demchenko, *Farmakol. Toksikol.*, No. 4, 497 – 502 (1978).
28. G. N. Pershin (ed.), *Methods of Experimental Chemotherapy* [in Russian], Moscow (1971).
29. R. G. Glushkov, I. B. Levshin, N. B. Marchenko, et al., *Khim.-Farm. Zh.*, **18**(9), 1048 – 1064 (1984).
30. G. A. Mokrushina, V. N. Charushin, and O. N. Chupakhin, *Khim.-Farm. Zh.*, **29**(9), 5 – 19 (1995).
31. K. S. Raevskii, *Farmakol. Toksikol.*, No. 4, 495 – 497 (1961).
32. G. T. Frumin, *Khim.-Farm. Zh.*, **25**(6), 15 – 18 (1991).