SYNTHESIS AND BIOLOGICAL ACTIVITY OF HETERYLAMIDES OF AROYLPYRUVIC ACIDS AND 5-ARYLPYRAZOLE-3-CARBOXYLIC ACIDS*

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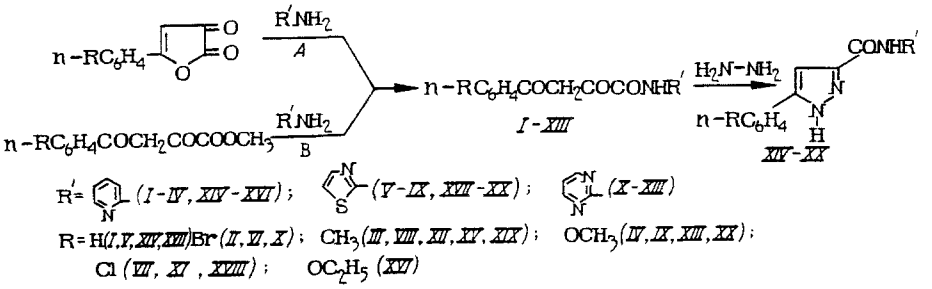
It has previously been established that the amides of aroylpyruvic acids possess analgetic and antispasmodic activity [5-7]. At the same time, these compounds display an extraordinarily low toxicity. Among the amides of aroylpyruvic acid, only arylamides and to a lesser extent alkyl amides were previously described in the literature [2, 4]. Consequently, it was of interest to synthesize hetarylamides of aroylpyruvic acids and to study their biological activity. In the present work we describe the synthesis and the results of pharmacological evaluation of 2-pyridyl-, 2-pyrimidyl-, and 2-thiazolylamides of aroylpyruvic acids. One of the factors determining the selection of the above heterocyclic substituents is the possibility of increasing the solubility of the amides in water by the formation of salts with mineral acids.

It is known that the method most often used for the preparation of amides, consisting in the reaction of esters with amines, is not appropriate for the preparation of aroylpyruvic acid amides [3]. This is because in the reaction of aroylpyruvic acid esters with nucleophilic reagents, the α-ketonic carbonyl is more reactive than the ester carbonyl. As a result, the reaction products are generally esters of 4-aryl-2-amino-4-oxo-2-butenoic acids [10, 12]. Therefore for the preparation of heteryl amides of aroylpyruvic acids (I-XIII), we used the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with heterylamines. The reaction proceeds on boiling toluene solutions of equimolar amounts of the reagents. On cooling the solutions, compounds I-XIII separate out in a high yield (see Table 1) (method A).

α-Pyridylamides II-IV were also obtained by the reaction between methyl esters of aroylpyruvic acids and α-pyridylamine



on heating (method B). The anomalous course of the reaction in the case of aminopyridine, is possibly due to the higher basicity of the nitrogen atom in the heterocyclic ring. Therefore, the association of the reagent at the α-ketonic carbonyl becomes possible, and as a result the primary amino group acquires an orientation favorable for attack on the ester carbonyl.

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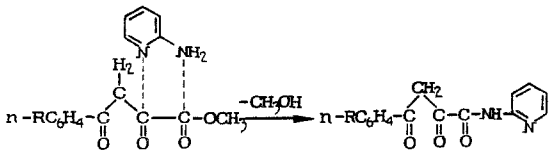

The synthesized compounds I-IV and X-XIII are white or yellowish crystalline substances. Thiazolylamides V-IX have a lemon-yellow color. As with other derivatives of aroylpyruvic acids, the heterylamides acquire a pink color with an alcoholic solution of $FeCl_3$, due to the enolization of their α-carbonyl [9]. Compounds I-IV form hydrochlorides on saturation of their benzene solutions with hydrogen chloride.

In the PMR spectra of compounds I-XIII taken in DMSO, there is a multiplet of aromatic and heterocyclic protons with a center at 7.28-7.72 ppm, a singlet of the methine proton at 6.78-6.95 ppm, and a broadened singlet of the amide proton and the enolic hydroxyl at 9.44-10.52 ppm. Thus, the PMR spectral data indicate the complete enolization of one of the carbonyl groups. Considering the previously revealed tendency in an asymmetric α,γ-dicarbonyl system of enolization of a carbonyl group bound to a strong electron acceptor substituent [9, 12], the α-carbonyl is the group which most probably undergoes enolization in compounds I-XIII. This does not contradict the above mentioned association scheme of α-aminopyridine with the aroylpyruvic acid ester, since the noncatalytic reaction of aroylpyruvic acid derivatives with nitrogeneous bases, despite the complete enolization of the former according to the IR and PMR spectra data, proceeds via their dicarbonyl form [1].

In the IR spectra of compounds I-XIII there are bands of the stretching vibrations of the NH amide group (3330-3200 cm^{-1}), of the amide carbonyl (1705-1698 cm^{-1}), and the ketonic carbonyl conjugated with a double bond (1640-1610 cm^{-1}).

It is known that α,γ-dicarbonyl compounds react with hydrazine with the formation of 3,5-disubstituted pyrazoles [13]. To obtain heterylamides of pyrazolecarboxylic acids, we reacted hydrazine hydrate with heterylamides I, III, VII, IX. The reaction proceeds by adding hydrazine hydrate to a hot dioxane solution of the heterylamide of aroylpyruvic acid. The reaction products, heteryl amides of 5-aryl-3-pyrazolecarboxylic acids (XIV-XX) (Table 1) are white crystalline substances which are sparingly soluble in most organic solvents.

In the IR spectra of compounds XIV-XX there are bands of the stretching vibrations of the pyrazole ring NH group (3370-3340 cm^{-1}), of the NH-amide group (3250-3220 cm^{-1}), and the amide carbonyl (1670-1660 cm^{-1}). In the PMR spectra of these compounds there are multiplets of aromatic and heterocyclic protons with a center at 7.25-7.52 ppm, of the NH group protons of the pyrazole ring and of the NHCO groups at 13.62-13.65 and 9.48-9.65 ppm.

EXPERIMENTAL (CHEMICAL)

The IR spectra of the compounds obtained were run in mineral oil on a UR-20 spectrophotometer (GDR). The PMR spectra were recorded on a RYa-23 spectrometer with a working frequency of 60 MHz in deuteroacetone or DMSO solution. The chemical shifts were measured relative to HMDS.

2-Pyridylamides of Aroylpyruvic Acids (I-IV). Method A. A solution of 5 mmoles of 2-aminopyridine in 20 ml of benzene was added to a solution of 5 mmoles of the corresponding 5-aryl-2,3,-dihydrofuran-2,3-dione in 40 ml of the same solvent, and the mixture was boiled for 15 min. After cooling, the precipitate was filtered off, and recrystallized from ethanol or toluene. The yields and melting points are given in Table 1.

Method B. A mixture of 10 mmoles of 2-aminopyridine and 10 mmoles of methyl ester of aroylpyruvic acid was dissolved in 30 ml of benzene and the solution was boiled for 30-50 min. After cooling the precipitate was filtered off and recrystallized from ethanol or toluene. The yield of compounds II and IV was 82 and 85%, respectively.

2-Thiazolylamides (V-IX) and 2-pyrimidylamides of aroylpyruvic acids (X-XIII) were prepared in a similar way as compounds I-IV (method A). The compounds were purified by recrystallization from a mixture of ethanol and DMFA.

TABLE 1. Heterylamides of Aroylpyruvic I-XIII and 5-Arylpyrazole-3-carboxylic acids XIV-XX

Compound	Yield, %	mp, °C	Empirical formula
I	92	167—168	$C_{15}H_{12}N_2O_3$
II	93	189—190	$C_{15}H_{11}BrN_2O_3$
III	90	186—187	$C_{16}H_{14}N_2O_3$
IV	86	160—162	$C_{16}H_{14}N_2O_4$
V	87	212—213	$C_{13}H_{10}N_2O_3S$
VI	82	208—210	$C_{13}H_9BrN_2O_3S$
VII	87	221—222	$C_{13}H_9ClN_2O_3S$
VIII	85	211—212	$C_{14}H_{12}N_2O_3S$
IX	90	216—217	$C_{14}H_{12}N_2O_4S$
X	90	159—160	$C_{14}H_{10}BrN_3O_3$
XI	83	163—164	$C_{14}H_{10}ClN_3O_3$
XII	85	139—141	$C_{15}H_{13}N_3O_3$
XIII	93	145—146	$C_{15}H_{13}N_3O_4$
XIV	94	214—215	$C_{15}H_{12}N_4O$
XV	87	263—265	$C_{16}H_{14}N_4O$
XVI	90	246—247	$C_{17}H_{16}N_4O_2$
XVII	81	295—296	$C_{13}H_{10}N_4OS$
XVIII	80	334—235	$C_{13}H_9ClN_4OS$
XIX	83	285—287	$C_{14}H_{12}N_4OS$
XX	82	314—316	$C_{14}H_{12}N_4O_2S$

Note. The results of the elemental analyses correspond to the calculated values.

TABLE 2. Anti-inflammatory and Analgetic Activity of Compounds I, V-IX, XIV, XV, XIX, XX

Compound	% of edema inhibition relative to control	Analgetic activity, time of reflex, sec
I	—8,6	17,3
V	12,9	18,5
VI	39,1	...
VII	—5,8	14,8
VIII	—4,5	19,4
IX	19,5	16,6
XIV	—65,7	...
XV	—6,7	...
XIX	—36,5	...
XX	—73,2	...
2% starch mucilage	...	11,9
Mephenamic acid	59,2	...
Amidopyrine	...	27,6

Heterylamides of 5-Aryl-3-pyrazolecarboxylic Acids (XIV-XX). A 3 mmole portion of hydrazine hydrate in 5 ml of dioxane was added with stirring to 3 mmoles of compounds I-IX in 30 ml of hot dioxane. After evaporation of the solvent the residue was recrystallized from i-PrOH or dioxane.

EXPERIMENTAL (PHARMACOLOGICAL)

The anti-inflammatory, analgetic, and antispasmodic activity of the synthesized compounds was tested.

The acute toxicity for white mice was evaluated by the Litchfield and Wilcoxon method [14]. The anti-inflammatory action was studied on white rats in accordance with the operating instructions for the experimental investigation of nonsteroid anti-inflammatory materials. The experiments were carried out on nonpedigree rats of both sexes each weighing 160-200 g, using acute inflammation edema as a model resulting from the subplantary administration of a 1% solution of Carraghenin into the rear paw of a rat. The anti-inflammatory action was estimated from the % increment in the volume of the paw relative to the initial value (control). Mephenamic acid was used as a standard preparation. All the preparations

and mephenamic acid were administered intraperitoneally in a dose of 50 mg/kg in a 2% starch mucilage.

The analgetic and antispasmodic activities were studied by intraperitoneal administration to white mice of both sexes, each weighing 18-24 g. The analgetic activity was examined using the "hot plate" method in a dose of 50 mg/kg. The antispasmodic activity was determined according to the maximal electrical shock method [11].

The acute toxicity of all the compounds tested did not exceed 600 mg/kg. Thus, the doses used for the investigation of the anti-inflammatory and analgetic activity exceed 1/12 LD_{50}. The results of the investigations are given in Table 2, which shows that among the heterylamides of the aroylpyruvic acids studied, compound VI has the most pronounced anti-inflammatory activity. At the same time the tests with pyrazolecarboxylic acid heterylamides XIV, XV, XIX, XX showed that these compounds promote the inflammatory action.

A weak analgetic activity is characteristic for 2-thiazolyl- and 2-pyridylamides of aroylpyruvic acids. In this respect they are inferior to amidopyrine, which is used as a standard [in double the dose (100 mg/kg)].

None of the compounds tested displayed antispasmodic activity in doses up to 300 mg/kg.

LITERATURE CITED

1. Yu. S. Andreichikov, A. P. Kozlov, Yu. A. Nalimova, and S. P. Tendryakova, Zh. Org. Khim., 13, 2559-2564 (1977).
2. Yu. S. Andreichikov, S. P. Tendryakova, Yu. A. Nalimova, and Ya. M. Vilenchik, Zh. Org. Khim., 14, No. 1, 160-163 (1978).
3. Inventor's Certificate 488,811 (USSR); Otkrytiya, No. 39 (1974).
4. Inventor's Certificate 630,253 (USSR); Otkrytiya, No. 40 (1978).
5. Inventor's Certificate 623,356 (USSR); Otkrytiya, No. 33 (1981).
6. Inventor's Certificate 769,992 (USSR); Otkrytiya, No. 33 (1981).
7. Inventor's Certificate 686,308 (USSR); Otkrytiya, No. 38 (1981).
8. E. V. Brigadnova, and Yu. S. Andreichikov, Zh. Org. Khim., 25, No. 6, 1169-1173 (1989).
9. L. N. Kurkovskaya, N. N. Shapet'ko, Yu. S. Andreichikov, and R. F. Saraeva, Zh. Strukt. Khim., 13, No. 6, 1026-1032 (1972).
10. GDR Patent 62,321 (1968); Ref. Zh. Khim., No. 23N290P (1969).
11. K. S. Raevskii, Farmakol. Toksikol., No. 4, 495-497 (1961).
12. P. Battesti, O. Battesti, and M. Selini, Bull. Chim. France, 26, No. 9, 2214-2220 (1974).
13. L. Knorr and E. Wenglein, Ann. Chim., 279, 253-255 (1894).
14. J. Litchfield and F. F. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99-114 (1949).
15. L. Woolfe and A. D. McDonald, J. Pharmacol. Exp. Ther., 80, 300-307 (1944).