SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF BENZOFURYLOXYACETIC ACID DERIVATIVES

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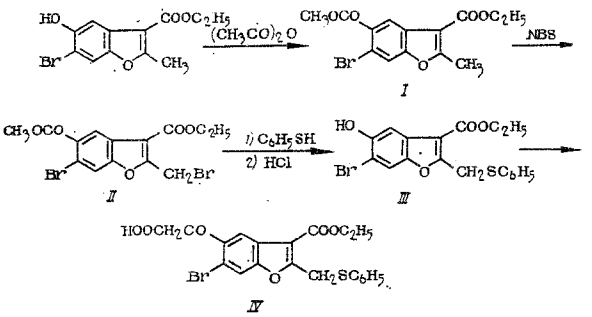
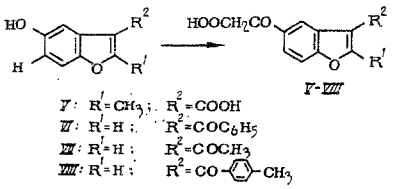
Among the benzofuran derivatives, medicinal compounds have been found with coronary-dilating [1-3], anesthetic [4], and spasmolytic activity [3]. It has also been reported in the literature that among the derivatives of benzofurylacetic acid, compounds have been discovered that have antiinflammatory properties [5].

On the basis of these data, and also taking into account the urgency of the search for new nonsteroid antiinflammatory preparations, we continued systematic studies on the synthesis of new derivatives of benzofuryloxyacetic acid to study their antiinflammatory activity.

5-(2-Phenylthiomethyl-3-carbethoxy-6-bromobenzofuryl)oxyacetic acid (IV) was prepared from the known 2-methyl-3-carbethoxy-5-hydroxy-6-bromobenzofuran [6]. Acylation of the last compound with acetic anhydride in the presence of triethylamine gave the O-acetyl derivative (I). Bromination of I by N-bromosuccinimide (NBS) with illumination in the presence of benzoyl peroxide led to 2-bromoethyl-3-carbethoxy-5-acetoxy-6-bromobenzofuran (II). When the last compound was reacted with thiophenol in an acid medium, substitution of the bromine atom for the phenylthio residue and hydrolysis of the acetoxy group were observed; 2-phenylthiomethyl-3-carbethoxy-5-hydroxy-6-bromobenzofuran (III) was thus formed. Compound III was converted into a sodium derivative, which was successively treated by bromoacetic ester and aqueous alkali to form IV.



Similarly, other derivatives of 5-benzofuryloxyacetic acid (V-VIII) were obtained from known 2-methyl-3-carbethoxy-5-hydroxy- [7] and 3-acyl-5-hydroxybenzofurans [8]:



4-(2-Carbethoxy)-3-methylbenzofuryl)oxyacetic acid (IX) was obtained by treating 2-carbethoxy-3-methyl-4-hydroxybenzofuran with sodium alcoholate and monochloroacetic acid [9].

EXPERIMENTAL CHEMICAL PART

2-Methyl-2-carbethoxy-5-acetoxy-6-bromobenzofuran (I). A solution of 38.6 g (0.129 mole) of 2-methyl-3-carbethoxy-5-hydroxy-6-bromofuran in 160 ml of acetic anhydride and 3 ml of triethylamine was boiled for 3 h. Most of the acetic anhydride was distilled in vacuo, water

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was added to the residue, and the precipitate was separated. The yield of I was 43 g (97.7%), mp 120-121°C (from methanol). Found, %: C 29.50; H 4.00; Br 22.93. $C_{14}H_{13}BrO_5$. Calculated, %: C 49.28; H 3.84; Br 23.42.

2-Bromoethyl-3-carbethoxy-5-acetoxy-6-bromobenzofuran (II). A solution of 10.23 g (0.03 mole) of I in 100 ml of carbon tetrachloride was boiled for 5 h with 5.35 g (0.03 mole) of N-bromosuccinimide with illumination and in the presence of benzoyl peroxide. The succinimide precipitate was filtered, and carbon tetrachloride distilled in vacuo. The yield of II was 11.28 g (89.4%), mp 130°C (from alcohol). Found, %: C 39.94; H 3.08; Br 38.19. $C_{13}H_{12}Br_2O_5$. Calculated, %: C 40.3; H 2.88; Br 38.04.

2-Phenylthiomethyl-3-carbethoxy-5-hydroxy-6-bromobenzofuran (III). To a solution of 1.12 g (0.02 mole) of potassium hydroxide in 50 ml of absolute alcohol, 2.04 ml (0.02 mole) of thiophenol were added with stirring, and then a solution of 8.4 g (0.02 mole) of II in 25 ml of absolute alcohol. After 3 h, 20 ml of concentrated hydrochloric acid were added, and the reaction mixture was boiled for 1 h. The alcohol was distilled in vacuo, the residue was distilled with water, and the precipitate was filtered. Yield, 7 g (86%), mp 158-160°C (from benzene). Found, %: S 7.71. $C_{18}H_{15}BrSO_4$. Calculated, %: S 7.87.

5-(2-Phenylthiomethyl-3-carbethoxy-6-bromobenzofuryl)oxyacetic Acid (IV). A 2.07 g portion (0.01 mole) of III and 1.5 ml (0.013 mole) of bromoacetic ester was added to an alcoholic solution of sodium alcoholate, obtained from 0.23 g (0.01 g-at) of sodium and 7 ml of absolute methanol. The reaction mixtures was boiled for 1 h, 7 ml of water containing 0.8 g (0.02 mole) of sodium hydroxide were added, and boiling was continued for 8-10 min. The solution was cooled, diluted with water, treated with carbon, filtered, and the filtrate was acidified by hydrochloric acid. The precipitate was purified on a column with KSK silica gel. Yield, 0.6 g (13%), mp 108-109°C (from a benzene–heptane mixture). Found, %: C 51.60; H 3.71. $C_{20}H_{17}BrSO_6$. Calculated, %: C 51.61; H 3.68.

The yields and physical constants of compounds V-VIII, obtained similarly, are listed in Table 1.

4-(2-Carbethoxy-3-methylbenzofuryl)oxyacetic acid (IX). A 6.6 g portion (0.03 mole) of 2-carbethoxy-3-methyl-4-hydroxybenzofuran and a solution of 8.5 g (0.09 mole) of chloroacetic acid in 25 ml of absolute alcohol were added to an alcoholic solution of sodium alcoholate, obtained from 4.14 g (0.18 mole) of sodium and 175 ml of absolute alcohol. The mixture was stirred and boiled for 1 h. The precipitate was filtered, the alcoholic mother liquid was evaporated, the residue was dissolved in water, and acidified with hydrochloric acid. The precipitate was recrystallized from acetone. The yield was 1.5 g (18%) of IX, decomposition temp. 256-8°C (from alcohol). Found, %: C 60.8; H 4.7. $C_{14}H_{14}O_6$. Calculated, %: C 60.5; H 5.0.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity of compounds IV-IX was studied on a model of a paw edema in male rats weighing 110-120 g each, estimated oncometrically. The acute inflammatory process was induced by administering 0.1 ml of a 1% solution of carrageenan [10] or formalin [11] under "lantern" aponeurosis of the right hind leg of the animal.

The analgesic action of the benzofuryloxyacetic acid derivatives was studied on a model of pain reactions (spasms), induced by an intraperitoneal administration of 0.25 ml of a 0.75% solution of acetic acid [12] to male mice weighing 18-22 g each. By using the "hot plate" method [13], we studied the influence of the compounds on the threshold of pain sensitivity in mice. In all the experiments, the preparations were administered orally in the form of a suspension in a 1% starch paste in doses of 10% of the LD_{50} value, calculated by the method described in [14] in the determination of the acute toxicity on male mice weighing 16-18 g each, using the same method of administration. The activity of the preparation was compared with the action of acetylsalicylic acid.

The experiments showed that several of the compounds studied have antiinflammatory activity (Table 2). Compounds V, VIII, and IX decreased the degree of expression of carrageenan-induced paw edema by 20-29%. Compound V is most active in its anti-exudative action. This compound also surpasses other preparations studied in its inhibiting action on the development of acute formalin-induced inflammation. However, in the intensity of their antiinflammatory action, all the compounds studied are inferior to acetylsalicylic acid.

TABLE 1. Properties of Compounds V-IX Obtained

Compound	mp, °C (from aqueous isopropanol)	Yield	Found, %		Empirical formula	Calculated, %	
			C	H		C	H
V	209—210	66	57,50	4,34	$C_{12}H_{10}O_6$	57,60	4,03
VI	135—136	81	69,10	4,25	$C_{17}H_{12}O_5$	68,91	4,08
VII	159—160	51	61,76	4,50	$C_{12}H_{10}O_5$	61,54	4,30
VIII	155—156	55	70,2	4,78	$C_{18}H_{14}O_5$	69,67	4,55

TABLE 2. Antiinflammatory Activity of Benzofuryloxyacetic Acids

Compound	Antiinflammatory activity*		Analgesic action†		Acute toxicity (LD_{50}), mg/kg (orally)
	carragenan-induced edema	formalin-induced edema	inhibition of spasms	increase in threshold of pain sensitivity	
IV	14‡	0	0	0	600
V	29	21	36	0	1500
VI	0	0	0	0	1000
VII	10‡	6‡	0	0	800
VIII	20	15	53	61	600
IX	25	18	36	20	850
Acetylsalicylic acid	55	45	60	30	1600

*Increase in degree of expression of paw edema in percent of control.
†In percent of control.
‡Difference with respect to control at P = 0.05.

Besides antiinflammatory properties, compounds V, VIII, and IX also have analgesic activity, and in doses studied decrease by 36-53% the number of spasms induced by acetic acid. In intensity of action, compound VIII approaches salicylic acid. The analgesic properties of compounds VIII and IX were also shown in thermal pain irritation; their use increases the pain sensitivity threshold by 20-60%. In its intensity of action, compound IX approaches acetylsalicylic acid, and compound VIII is twice as strong.

Analysis of the data obtained shows that the presence of an acetic acid residue at positions 4 and 5 of the benzofuran ring favors the appearance of antiinflammatory properties of the compounds studied. The degree of expression of this type of biological activity is also influenced by the nature of the substituent at the 3-position of the benzofuran ring. Thus, in acyl derivatives of 5-benzofuryloxyacetic acids (compounds VI and VII), no antiinflammatory activity was observed, but the introduction of a methyl substituent into the para-position of the benzene ring (compound VIII) leads to the appearance of antiinflammatory properties and analgesic activity, more expressed than in the case of acetylsalicylic acid.

The toxicity of most of the compounds studied in a one-time administration to white mice (orally) is higher than the toxicity of acetylsalicylic acid.

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ANTIMICROBIAL ACTIVITY OF DERIVATIVES OF 2,4-SELENAZOLIDINEDIONE

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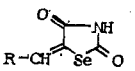
The pharmacological studies of the inorganic and organic derivatives of selenium carried out by us in this country and abroad have revealed that they have higher pharmocological activity than their thio- and oxo-isologs [1-3].

We decided to examine the antimicrobial activity of the 5-R-ylidene-2,4-selenazolidinediones [4]  which we have synthesized, since some of their thioanalogs have antimicrobial properties [4]. The antibacterial and antifungal activity of some 2,4-selenazolidinedione derivatives and, in particular, the 5-benzylidene and 5-salicylidene derivatives of 2,4-selenazolidinedione have been examined earlier. However, these compounds, among other 2,4-selenazolidinedione derivatives that were examined, revealed only weak antibacterial activity, which cast doubt on the potential value of further work on 2,4-selenazolinedione derivatives, since they did not have the expected activity [5]. We have examined more than 20 2,4-selenazolidinedione derivatives with various substituents in the benzylidene ring, together with the α-naphthylidene and furfurylidene derivatives.

EXPERIMENTAL

The compounds were prepared by the method that we developed [6] and were crystalline substances that were soluble with warming in the majority of organic solvents, insoluble in water and ether, and stable on storage and boiling. Their structures were verified by elemental analysis and UV and IR spectroscopy. The antimicrobial activity was assayed by the conventional method of twofold serial dilution in nutrient broth against a spectrum including Gram-positive and negative bacteria and fungi [7].

RESULTS AND DISCUSSION

The figures of Table 1 demonstrate that compounds IV, VII, X, XIV, XIX, and XXI have moderate antifungal activity toward the causative agent of microsporia (minimum mycostatic concentrations 12.5-50 μg/ml). These compounds, except for XXI, also have antibacterial activity toward Gram-negative bacteria, particularly *Staphylococcus* aureus 209-P (minimum bacteriostatic concentration 26-50 μg/ml). Compounds XIII and XV, conversely, have moderate antibacterial activity but no antifungal activity. The effects of halogens introduced into the benzylidene residue are different. Thus, while the compound with halogen in the para position, XI, is inactive toward the test microbes and fungi, that with o-halogen, X, reveals moderate activity toward both types of microorganisms. This is also the case when the dimethylaminobenzylidene residue is replaced in 2,4-selenazolidinedione by diethylaminobenzylidene (VI-VII). Replacement of chlorine in the benzylidene ring (XI) by fluorine (XIX), even in the p position, leads to the appearance of moderate antibacterial and antifungal activity. Introduction of a bromine atom into position 5 of the salicylidene derivative XVIII, which was examined earlier and which has no activity of any sort, also results in the appearance of both types of activity. Replacement of the oxygen atom in the five-membered ring (XX) by sulfur (XXI) enhances the antifungal activity. *Escherichia coli* was resistant to the test compounds at the maximum test concentration, 200 μg/ml. The toxicity of the compounds was

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