SYNTHESIS AND ANTIALLERGIC ACTIVITY IN A SERIES OF CINNAMIC ACID

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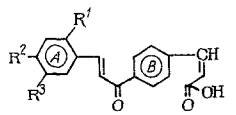
In recent years, intensive research has been conducted on cinnamic acid derivatives, with the goal of creating new polyfunctional drugs based on them [4, 9, 10]. The increased interest in this group of compounds is due to the varied aspects of their pharmacological activity, their ability to regulate the activity of a number of enzyme systems participating in cell activation processes. A whole series of drugs has been created on the basis of cinnamic acid which have pronounced antiallergic activity (Cinnarizine, Cinanserin, Tranilast, etc.), depressing the secretion of mediators from target cells for allergy (fat cells, basophiles), reducing the sensitivity of effector organs and tissues to the mediators (histamine, serotonin, slow-acting anaphylaxis agent) [5, 12, 17]. This class of compounds is even of interest because its representatives (caffeic, ferulic acids, etc.) are widely represented in natural specimens (plants, fruits, vegetables, etc.), and together with flavonoids participate in many biochemical processes, regulating biosynthetic and exchange reactions in plant and animal organisms [21]. Cinnamic acids are possible products of the metabolism of polyphenol compounds in the organism, and therefore biological activity of a number of flavonoids is connected specifically with them [13]. Caffeic and ferulic acids inhibit 5- and 12-lipoxygenases, reduce the level of leucotrienes in tissues, and potentially may be used to treat bronchial asthma [18, 19, 22].

This paper involves the prediction and subsequent goal-directed synthesis of new series of cinnamic acid derivatives. We have studied the structure vs. activity interrelationships with the goal of further search for and creation on their basis of effective new polyfunctional antiallergic drugs.

The physicochemical characteristics of the compounds obtained and their antiallergic activity are presented in Table 1.

In preliminary experiments on the passive skin anaphylaxis reaction model in rats, it was established that unsubstituted cinnamic acid (I) does not display antiallergic activity while ferulic acid (II) displays pronounced activity, which can be explained by the increase in the polarity of the molecule on the whole as a result of introduction of electron-donor substituents.

In our opinion, it was of interest to study the effect of lengthening the conjugation chain in the cinnamic acid molecule until an antiallergic effect appeared. With this goal, by condensation of the corresponding acetophenones with 4-formylcinnamic acid in the presence of base we synthesized derivatives of 4-benzoylvinylene cinnamic acid (III).



III a-h

R^1=H(IIIa-c), OH(IIId-f,h), OC_2H_5(IIIg); R^2=H(IIIa, d), Br(IIIb), OCH_3(IIIc), OH(IIIe,f,h), OC_2H_5(IIIg); R^3=H(IIIa-e,g), B (IIIf), $COCH_3$(IIIh)

The synthesized compounds, in contrast to the corresponding chalcones containing identical substituents on ring A but not having the carboxyvinylene group on ring B, are characterized by pronounced antiallergic activity. And while lengthening of the conjugation chain in itself does not lead to the appearance of activity (IIIa), introduction of electron-donor

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TABLE 1. Physicochemical Characteristics and Antiallergic Activity of the Compounds

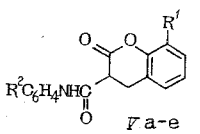
Compound	Empirical formula	T.mp, °C	UV spectra λmax, nm	Inhibition of skin reaction, in %
I	$C_6H_{18}O_2$	133	273, 224, 205	0
II	$C_{10}H_{10}O_4$	171	319, 287, 216	9,7
IIIa	$C_{18}H_{14}O_3$	239	342, 203	0
IIIb	$C_{18}H_{13}BrO_3$	216	293, 207	15,7
IIIc	$C_{19}H_{16}O_4$	199	347, 240, 210	16,4
IIId	$C_{18}H_{14}O_4$	258	347, 285, 204	16,3
IIIe	$C_{18}H_{14}O_5$	190	282, 208	20,3
IIIf	$C_{18}H_{13}BrO_5$	216	332, 297, 207	36,0
IIIg	$C_{22}H_{22}O_5$	184	342, 206	38,2
IIIh	$C_{20}H_{16}O_6$	220	273, 257, 206	42,7
IV	$C_{10}H_6O_4$	192	290	0
Va	$C_{16}H_{11}NO_3$	182	335, 305	13,4
Vb	$C_{17}H_{11}NO_5$	300	314, 265	20,8
Vc	$C_{19}H_{15}NO_5$	289	335, 325, 209	32,8
Vd	$C_{23}H_{25}ClN_2O_5$	239	302, 224, 203	58,1
Ve	$C_{23}H_{27}ClN_2O_6$	255	330, 261, 206	60,9
VIa	$C_{15}H_{13}NO$	149	296, 222	18,5
VIb	$C_{16}H_{13}NO_3$	260	310	29,3
VIc	$C_{18}H_{17}NO_3$	173	330, 220	41,9
VId	$C_{38}H_{48}Cl_2N_4O_8$	123	300, 225, 203	43,5
VIe	$C_{23}H_{27}ClN_2O_5$	210	320, 296, 219	52,3
VIf	$C_{22}H_{26}ClN_3O_5$	240	310, 215, 203	54,1
VIg	$C_{23}H_{29}ClN_2O_4$	193	332, 226	60,8
VIh	$C_{24}H_{31}ClN_2O_5$	197	340, 252	63,7
VIi	$C_{26}H_{31}ClN_2O_7$	172	315, 221, 203	65,5
VIj	$C_{24}H_{29}ClN_2O_5$	170	312, 222	69,1
VIk	$C_{25}H_{31}ClN_2O_6$	163	320, 240	79,1

Note. Elemental analysis data satisfy the calculated values.

substituents into the benzoyl fragment of the molecule leads to substantial increase in activity. Introduction of electron-acceptor and electron-donor substituents in the 4 position (IIIb, c) only insignificantly increases the activity. Electron-donor substituents at the 2 and 4 positions, characterized by identical electronic contributions (IIIc, d, e, g), lead to an increase in the polarity of the molecule, which promotes the appearance of a more pronounced effect. Compounds containing electron-acceptor substituents at the 5 position, for simultaneous presence of electron-donor substituents at the 2 and 4 positions, also display pronounced antiallergic properties (IIIf, h).

Thus, the most active compounds are those containing electron-donor substituents in the benzoyl moiety in the o- and p-positions; the presence of electron-acceptor substituents is preferred in the m-position. On this basis, we may suggest that the cinnamic acid moiety is the determining factor in the appearance of activity for this series of compounds, and that substituents on the benzoyl moiety only enhance the antiallergic effect. These results are confirmed not only by the absence of activity in the corresponding chalcones but also by the effect of dimethylaminochalcones, stimulating the intensity of the passive skin anaphylaxis reaction [7]. Furthermore, as we showed earlier, in the series of 4-iminoflavenes the most pronounced retardation effect on the passive skin anaphylaxis reaction is displayed in compounds containing the cinnamic acid moiety [6].

Antiallergic activity is also characteristic for derivatives of coumarin [2, 3, 14, 15], which is the lactone of 2-hydroxycinnamic acid. On this basis, there is interest in investigating the antiallergic activity of new coumarin derivatives. With this goal, by condensation of the acid chloride of coumarin-3-carboxylic acid with aromatic amines, we synthesized the corresponding arylamides.



I a-e

R^1=H (Va-d), CH_3 (Ve); R^2=H (Va), COOH (Vb), $COOC_2H_5$ (Vc), $COO(CH_2)_2N(C_2H_5)_2$ (Vd,e)

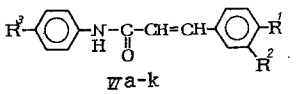
While the original coumarin-3-carboxylic acid does not display antiallergic action, amidization at the carboxy group leads to the appearance of pronounced activity (Va). Intro-

duction of a carboxyl group into the amide moiety promotes increase in activity, which is connected with enhancement of the acid function of the molecule (Vb). Upon esterification of the carboxy group, we observe a significant increase in the inhibiting effect (Vc). Esterification of the carboxyl group by diethylaminoethanol leads to an even more pronounced antiallergic effect (Vd, e). The effect obtained is explained by the presence in the molecule of a tertiary nitrogen, which enters into the structure of antihistamine drugs as an alkylaminoalkyl moiety (dimedrol, diprazin, suprastin), or as a nitrogen-containing heterocyclic moiety (diazoline, phencarol, tavegyl) [5].

At the same time, coumarin under the action of strong base can be isomerized to trans-2-hydroxycinnamic acid [16].

We can hypothesize that such isomerization also occurs in animal organisms under the action of enzymes, and consequently cinnamic acids may be considered as possible metabolites of coumarins.

Based on the data obtained on the pronounced antiallergic activity of amides of coumarin-3-carboxylic acid, we may expect that the corresponding arylamides of cinnamic acid would also display high antiallergic activity. On this basis, by condensation of the acid chlorides of cinnamic acid and cinnamic acids substituted in the phenyl radical with aromatic amines, we synthesized the corresponding arylamides of cinnamic acids.



VIa-k

R^1=H(VIa-c), $OCOCH_3$(VId,i-k), NO_2(VIf), OCH_3(G, H);
R^2=H(VIa-c, e-g, j),
$CONHC_6H_4COO(CH_2)_2N(C_2H_5)_2$-4(VId),
OCH_3(VIh-k), $OCOCH_3$VIi); R^3=H(VIa,j,k),
COOH(VIb), $COOC_2H_5$(VIc), $COO(CH_2)_2N(C_2H_5)_2$(VId-j);
R^1+R^2=—OCH_2O— (VIe).

The investigation results showed that the synthesized arylamides of cinnamic acid VIa-k display a pronounced antiallergic effect, and in activity surpass the corresponding arylamides of coumarin-3-carboxylic acid (Va-VIa, Vb-VIb, Vc-VIc, Vd-VIj, Ve-VIk). In this case, the effect of substituents on the appearance of activity, in both the cinnamoyl and amide moieties of the molecules, follow the regularities described above.

The results obtained may serve only as indirect confirmation for decyclization of the alpha-pyrone moiety of the coumarin molecules in animal organisms to the corresponding derivatives of 2-hydroxycinnamic acid.

The several derivatives of cinnamic acid and coumarin described above with the most pronounced antiallergic activity were studied in different models for hypersensitivity of the non-slow type in different animal species, at the levels of organism, systems, organs, tissues, and cells in vivo and in vitro [11]. The experimental data revealed some specific mechanisms for antiallergic action of the compounds and showed the polyfunctionality of the studied structures. For a number of substances, it has been established that they can inhibit secretion of histamine from fat cells and simultaneously reduce the sensitivity of effector tissues and mediators of the allergy.

Thus, a further goal-directed search for compounds displaying pronounced antiallergic activity in the series of derivatives of cinnamic acid is a promising direction for creation of effective new polyfunctional drugs.

EXPERIMENTAL (CHEMICAL)

Compounds I, II, and IV were obtained from the corresponding benzaldehydes and malonic acid according to the familiar techniques in [8].

4-Benzoylvinylene Cinnamic Acids (IIIa-h). Method A (IIIa, d, g). First 0.4 g (0.01 moles) sodium hydroxide and then 0.0048 moles of the corresponding acetophenone and 0.88 g (0.005 moles) 4-formylcinnamic acid were dissolved in a mixture consisting of 3.4 ml water and 1.8 ml ethanol. The reaction mixture was stirred for 1 h and allowed to stand for 24 h.

Then it was decanted into a mixture of water with ice (acidified with hydrochloride acid). The precipitate was separated, washed with water until neutral reaction, and dried. The yields were 87-95%, crystallized from ethanol.

Method B (IIIe, f, h). 0.0048 moles of the corresponding acetophenone and 0.88 g (0.005 moles) 4-formylcinnamic acid were dissolved in 6 ml of a 50% aqueous solution of potassium hydroxide. The reaction mixture was heated at 115°C for 20 min. After cooling, the reaction mixture was decanted into ice-water acidified by hydrochloric acid. The precipitate was separated, washed with water, and dried. The yields were 80-90%; crystallized from acetic acid or a mixture of DMF with water.

Amides of Coumarin-3-carboxylic Acid and Cinnamic Acids. A solution of the corresponding aromatic amine in 20-30 ml pyridine was added to 0.01 moles of the acid chloride of the corresponding acid in 50 ml toluene. The reaction mixture was allowed to stand for 12 h. The precipitate was separated, washed with toluene and diethyl ether and dried. Quantitative yields were crystallized from ethanol or 2-propanol.

Hydrochlorides (Vd, e, VId-k). 0.046 moles of the corresponding amide were dissolved in 20 ml 17% hydrochloric acid. 3.5 ml 2-propanol were added and the mixture was cooled at 0-2°C for 10-12 h. The precipitate was separated, washed with 2-propanol (twice, 2 ml each time). The yields were 55-70%.

EXPERIMENTAL (PHARMACOLOGICAL)

The antiallergic effect of the compounds was studied in the passive skin anaphylaxis reaction model, mediated by IgE antibodies [1].

Serum containing specific homocytotropic antibodies was obtained in the third week after sensitization of mice of the CBA line by ovalbumin (0.5 μg) with aluminum hydroxide (2.5 mg/mouse) [23]. 50 microliters of the serum obtained (1:120 dilution) were injected subcutaneously in six shaved sections of the skin on the back of male white rats of the Vistar line (160-180 g). After 24 h, the allowed dose of ovalbumin (1 mg/kg) in 1 ml 0.5% Evans blue solution in a physiological solution was administered intravenously to the rats. After 30 min, the rats were decapitated under ether narcosis, the skin was turned inside out, the dyed sections were cut out, and the dye was extracted with formamide at 37°C for 4 days. The amount of dye in the extravasate was determined spectrophotometrically at 600 nm using a calibration curve [20].

The studied compounds were administered intraperitoneally in a dose of 50 mg/kg in 90 min up to the allowed dose of antigen. The control rats were injected intraperitoneally with physiological solution.

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SYNTHESIS OF ALLENE DERIVATIVES OF 1,3,2-OXAZOPHOSPHOLANES AS POLYFUNCTIONAL INHIBITORS OF CHOLINESTERASES, MICROSOMAL MONOOXYGENASES, AND GLUTATHIONE TRANSFERASE

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Anticholinesterase (anti-ChE) substances that act by blocking the work of the parasympathetic nervous system, are finding use as drugs in ophthalmology, in toxicology, in the treatment of atropine poisoning, and in certain other cases [3]. The effectiveness and duration of the action of such drugs depends not only on their anticholinesterase activity but also on the rate of their elimination from the organism. Under these conditions hydrophobic compounds, which cannot be directly excreted by the kidneys, should be preliminarily subjected to metabolic conversions for this purpose. In these conversions the main role is played by the microsomal monooxygenase enzymes system, which catalyzes the oxidation of xenobiotics and thereby increases their polarity; the terminal component of this system is cytochrome P-450 (CT P-450, EC 1.14.14.1). An important role is also played by an assortment of transferases, the most active of which is glutathione-S-transferase (GT, EC 2.5.1.18) [5, 21, 24, 26]. The inhibition of CT P-450 and GT slows down these metabolic conversions and thereby prolongs the action of drugs, in particular, soporific drugs [5], and also makes it possible to overcome the drug resistance of organisms, which arises on account of induction of CT P-450 and GT synthesis. This decrease in resistance in certain parasitic protozoa, for example, in the malaria parasite to chloroquine and other quinoline antimalarial drugs [10, 28], is of special interest. Hence it is understandable that the search for drugs that act simultaneously both on the target enzyme ChE and on the major enzymes of their metabolism – CT P-450 and GT – is an extremely promising undertaking.

We began the search among 1,3,2-oxazophospholanes, synthesized on the basis of the alkaloid d-pseudoephedrine and possessing an allene fragment in the molecule. This selection was determined by the following considerations:

1) the largest number of highly effective inhibitors of acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BuChE, EC 3.1.1.8) has been found among organic compounds of pentavalent phosphorus [3, 12];

2) preparations that inhibit CT P-450 and consequently exhibit a synergestic effect with respect to certain pesticides are known among derivatives of a five-member heterocycle [14–16];

3) it is known that unsaturated bonds in a molecule can serve as a site of attack and, consequently, also as binding sites for GT [4, 17, 18].

It is also vital that the starting material for the synthesis of 1,3,2-oxazophospholanes is a side product in the industrial production of ℓ-ephedrine, used in medical practice [7].

The synthesis of optically active allenic 1,3,2-oxazophospholanes (IV-VI) was conducted by the reaction of the individual stereoisomer of 2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxa-

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