antihistaminic activity of compounds Ii and Ij is equal to and near to that of theophylline. With compounds with a piperidine or morpholine rings, but with one or two methylene groups in the alkyl chain (Ia, Ib, Ie, and If) the antihistaminic activity was absent in the dose range studied.

The antianaphylactic (antiexudative) activity of the 7-substituted theophylline derivatives was expressed weakly: only compounds Ib, Ic, and If showed activity equivalent to theophylline, but none of them exceeded it. The antianaphylactic activity was shown by those compounds which weakly expressed antihistaminic properties.

The majority of the studied compounds was more toxic than theophylline by single injection. The compounds with cyanoethyl (IIb) and cyanopropyl (IIc) substituents were less toxic than theophylline, and also showed antihistaminic (broncholytic) activity: compounds IIa and Ig surpass theophylline in the width of their therapeutic range (ratio of ED_{50} for antihistaminic activity to LD_{50}).

Thus, these 7-substituted theophylline derivatives show relatively high antihistaminic (broncholytic) activity and a significantly weaker influence on the anaphylactic (exudative) reaction. Earlier we studied 7,8-substituted theophylline derivatives, which contrastingly possessed more significant activity on the anaphylactic component of the reaction [1].

This study of these derivatives concludes that modification of the theophylline molecule in the 7- or 7,8-positions may bring about the creation of compounds selectively influencing different stages of the allergic reaction.

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RELATIONSHIP BETWEEN STRUCTURE AND ACTIVITY OF FLAVONE DERIVATIVES POSSESSING ANTIALLERGIC ACTIVITY*

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About 2000 natural flavonoid compounds have now been described, and more than 40 types of biological activity have been detected for them [33]. The structural variety of this class of compounds has made it possible to create a number of highly effective and relatively nontoxic drug preparations on the basis of them, exhibiting capillary-strengthening, anti-inflammatory, antiallergic, cholagogic, venotoning, hepatoprotective, and other types of action [7]. It has been computed that a person consumes an average of up to 1 g of various flavonoids per day with plant products [29, 36].

The broad spectrum of biological activity of flavonoids is due to their varied influence on numerous enzyme systems: transport ATPases [25], cyclic nucleotide phosphodiesterases [21, 37], phospholipase A_2 [32], phospholipase C [27], 5- and 12-lipoxygenases [22, 28, 40], cyclooxygenase [23, 30], protein kinase C, etc. [27, 38]. Flavonoids, capable of changing

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the functional activity of various cell systems, including secretion (mast cells, basophils, neutrophils), mitogenesis (human lymphocytes), contracture of smooth-muscle organs, platelet aggregation, the reaction of hepatocytes to hepatotoxic substances, etc. [34, 36]. As a result of the influence of flavonoids on enzyme systems and secretory cell processes, the content of prostaglandins [22], leukotrienes [28], cAMP and cGMP [37], Ca^{2+} [38], histamine [35], and other biologically active substances is changed.

All these data suggest that the chromone (benzene-γ-pyrone) ring system is universal in its biological properties. And, consequently, by introducing various substituents, it is possible to regulate the concrete type of activity, which depends largely on the correct selection of the corresponding structural characteristics. The logical structural approach (LSP) in conjunction with the dialog method [1, 15, 16] is the most expedient for this purpose.

The present communication is devoted to the substantiation of promising chromone derivatives, possessing antiallergic activity, and to their synthesis.

An analysis of this group of compounds and their comparison with the antiallergic preparations used in medicine has revealed a number of structural characteristics:

1) the presence of a benzo-γ-pyrone fragment (chromolyn-sodium, baicalein, quercetin) is obligatory; it probably determines the high affinity of the entire molecule for the phospholipid components of the cell membranes [26];

2) the introduction of a carboxyl group into the chromone ring system enhances the acid function of the molecules, which is a necessary condition for increasing the antiallergic activity [10-13, 18, 20];

3) an analogous effect can be achieved by introducing residues of nitrogen- and oxygen-containing heterocyclic substituents, which enhance the polar coupling with the carbonyl center, into the 2-position of chromone [8, 9, 14, 19, 24];

4) alkyl substituents enhance the lipophilicity and decrease the absorption from the gastrointestinal tract [6];

5) aliphatic alkylaminoalkyl fragments (in dimedrol, suprastin, diprazine, etc.) promote a decrease in the sensitivity of the H_1-receptors to histamine [5]. The nitrogen atom can also participate in the formation of a heterocyclic fragment (diazoline, fencarol, tavegil);

6) high antihistamine activity is characteristic of systems containing a heteroatom of pyridine-type nitrogen (the fragment $-C=N-$) [6];

7) flavonoid glycosides are less active than the corresponding aglycones [35].

TABLE 1. Nitrogen Derivatives of Benzopyrones and Their Antiallergic Activity

Compound	Yield, %	mp, °C	UV spectrum in octanol, λ_{max}, nm	IR spectrum (liquid petrolatum), ν, cm^{-1}	% inhibition of PSA reaction
IV a	76	197—9	380, 272	1710, 1600, 1520, 1310, 1260, 1180, 1080	6,2
IV b	72	229—30	330,262	1720, 1600, 1310, 1260, 1190, 1100, 1030, 1010	21,7*
IV c	64	195—7	317, 253	1710, 1667, 1615, 1283	28,5*
IV d	58	218—20	372, 272	1720, 1680, 1600, 1530, 1275, 1190, 1100	32,6*
IV e	62	230—1	291, 240, 223	1610, 1530, 1270, 1210, 3270, 2700	17,2*
IV f	61	348—50	309, 266	1690, 1630, 1610, 1560, 1515, 1250, 1176, 1130	24,5*
IV g	59,5	186—8	307, 257	1710, 1600, 1570, 1530, 1320, 3270, 1260, 1180, 1110	31,0*
IV h	93,1	110—12	309, 270	1710, 1620, 1600, 1570, 1265, 1180, 1100	25,0*
IV and 4-methoxyflavone†	55	149—50	326, 300	3300, 1750, 1620, 1250, 1195, 1110	16,3* 5,5

*Significant differences

†The compound was described earlier [17].

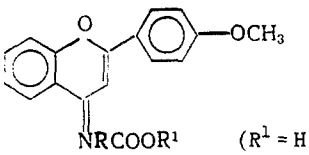
All the aforementioned permitted us to compile a prognosis of the structures, on which the following characteristics are based:

1) a nontoxic p-methoxyphenyl substituent should be introduced into the 2-position of the chromone ring. The electron-donor methoxy group enhances the polar conjugation with the carbon atom in position 4 of the chromone fragment;

2) position 4 of the chromone ring system is the most rational for the formation of the fragment $-C=N-$, since this promotes a lengthening of the main chain of coupling and an intensification of the polarity of the molecule as a whole;

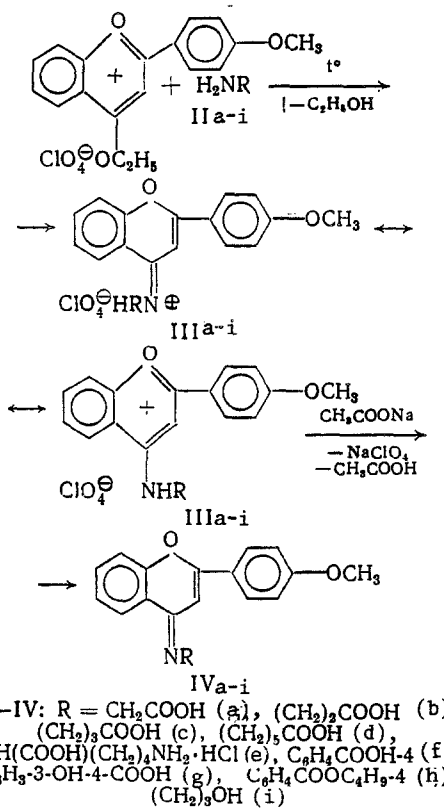
3) the substituent at the nitrogen atom should have an aliphatic or aromatic acid residue, since the carboxy group in this case enhances the acid properties of the molecule.

Realization of our prognosis can be achieved by synthesizing compounds with the general formula:



$NRCOOR^1$ (R^1 = H or alkyl),

produced by interaction of 4-ethoxy-4'-methoxyflavylium perchlorate (I) with the corresponding amino acids or their esters (IIa-i). The synthesized perchlorates of 4-N-substituted flavylium derivatives (IIIa-i) are converted to the corresponding bases (IVa-i) by treatment with an alcohol solution of sodium acetate:



IIIa-i

IIIa-i

IVa-i

I—IV: R = CH_2COOH (a), $(CH_2)_2COOH$ (b), $(CH_2)_3COOH$ (c), $(CH_2)_5COOH$ (d), $CH(COOH)(CH_2)_4NH_2 \cdot HCl$ (e), C_6H_4COOH-4 (f), C_6H_3-3-OH-4-COOH (g), $C_6H_4COOC_4H_9$-4 (h), $(CH_2)_3OH$ (i)

The initial 4-ethoxyflavylium perchlorate was produced according to the well-known procedure [3, 4, 17].

The characteristics of the compounds synthesized are presented in Table 1.

The antiallergic activity of the compounds obtained was studied on a model of the passive skin anaphylaxis reaction (PSA reaction) in white rats, mediated by IgE antibodies. Table 1 presents data on the inhibition of the PSA reaction. The introduction of an amino acid residue into the 4-methoxyflavone molecule, on the whole, enhances the ability to inhibit the PSA reaction. As the length of the aliphatic chain of the amino acid increases,

the activity increases, and the maximum percent inhibition of the PSA reaction is observed in the case of ε-aminocaproic acid. The necessity of the presence of a carboxy group is confirmed by replacement of the γ-aminobutyric acid residue (compound IVd) by an aminopropanol residue (compound IVi) which leads to a 1.5-fold decrease in the activity. Substantial enhancement of the activity is achieved by the introduction of aromatic amino acid residues. This peculiarity can probably be explained by the influence of p—π conjugation of the amino acid fragment on the heterocyclic ring system. Esterification of the carboxyl group in the aromatic amino acid fragment (compound IVh) has no substantial influence on the ability to inhibit the PSA reaction. The introduction of an o-hydroxy group into this fragment, however, enhanced the activity.

EXPERIMENTAL

4-Ethoxy-4'-methoxyflavylium Perchlorate (I). To a mixture of 0.01 mole of o-hydroxyacetophenone, 0.03 mole of p-methoxybenzaldehyde and 0.1 mole of freshly redistilled orthoformic ester, 0.01 mole of 70% perchloric acid was added dropwise. Yield of I, 92%. mp 183-184°C (from glacial acetic acid).

4-Iminoflavenes (IV). A 0.01-mole portion of the corresponding perchlorate was dissolved in 25 ml of glacial acetic acid, and 0.01 mole of the corresponding amino derivatives were added. The mixture was heated at 115-120°C for 60 min. It was cooled, diluted with a fivefold amount of diethyl ether, the precipitate formed was filtered off, washed with ether, dissolved in ethanol, and an equimolar amount of sodium acetate was added to the solution obtained; the mixture was brought to a boil, cooled, diluted with water, and the precipitate formed was filtered off and washed with water. After recrystallization from ethanol, yellow crystalline substances were obtained (see Table 1).

EXPERIMENTAL (BIOLOGICAL)

The antiallergic action of the compounds was studied on the model of the PSA reaction, mediated by IgE antibodies [2].

Serum containing specific homocytotropic antibodies was obtained at the third week after sensitization of CBA mice with ovalbumin (0.5 μg) with ammonium hydroxide (2.5 mg/mouse) [39]. The serum obtained, in a dilution of 1:100, was injected subcutaneously in an amount of 30 μl into six shaved regions of the skin of the back on male white rats of the Wistar strain (190-220 g). After 24 h, the rats were injected intravenously with a resolving dose of ovalbumin (1 mg/kg) in 1 ml of 0.5% solution of Evans blue dye in physiological saline solution. After 30 min the rats were decapitated under ether anesthesia, the skin was turned inside-out, and the stained portions were cut out and the dye extracted with formamide at 37°C for 4 days. The amount of the dye in the extravasate was determined spectrophotometrically at 600 nm according to a calibration graph [31].

All the investigated compounds were injected intraperitoneally in a dose of 50 mg/kg 90 min before the resolving dose of the antigen. The control rats were injected intraperitoneally with physiological saline solution.

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