4-Methyl-3,4-(dipropoxymethylene)tetrahydropyran (IV). A 1-g sample of triethylbenzylammonium chloride was added to a heated (to 120°C) mixture of 5.6 g (100 mmole) of potassium hydroxide and 6 g (100 mmole) of propyl alcohol, after which 4.6 g (25 mmole) of IIIa was added dropwise in the course of 15 min. Heating was continued for another 10 h, after which the reaction product was extracted with ether. The extract was washed with water, dried with sodium sulfate, and vacuum distilled to give 2.7 g (48%) of dipropoxy derivative IV with bp 82-85°C (1 mm), n_D^{20} 1.4720, and d_4^{20} 0.9778. Found: C 64.5; H 11.8%. $C_{13}H_{14}O_3$. Calculated: C 64.8; H 11.8%.

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ONE-STEP SYNTHESIS OF 4-ETHOXY-6-BROMO-7-HYDROXYFLAVYLIUM SALTS AND THE CORRESPONDING FLAVONES

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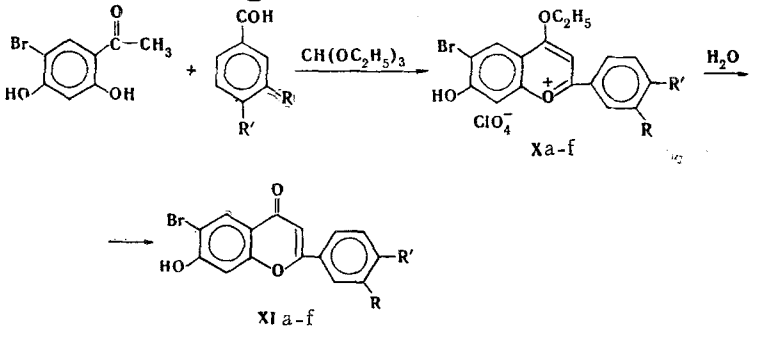
The boundaries of application of the one-step synthesis of flavylium salts on the basis of bromoresacetophenone were extended, and the conditions for heterocyclization of 2',4'-dihydroxy-5'-bromochalcones to 4-ethoxyflavylium salts were studied simultaneously. It was noted that similar reaction products were obtained in these two variants of the synthesis of the salts. The presence of electronegative substituents and a hydroxy group in the starting aldehydes hinders the formation of flavylium salts.

Benzoypyrlium salts are of interest for the preparation of some biologically active substances, viz., chromones, flavones, and isoflavones [1-3]. One of the most convenient methods for the preparation of 4-ethoxyflavylium salts is one-step acid condensation of o-hydroxyacetophenone and its derivatives with aromatic aldehydes and ethyl orthoformate in the presence of 70% perchloric acid [2, 3] or by cyclodehydration of o-hydroxychalcones with ethyl orthoformate and perchloric acid [4].



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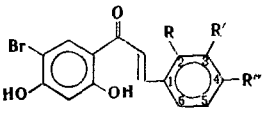
We used both of these methods in the 5-bromo-2-hydroxyacetophenone series in order to expand the boundaries of application of this method and to synthesize previously undescribed 6-bromoflavylium salts and 5-bromoflavones. The chalcones were obtained by alkaline condensation (Table 1).

A study of the biological action of these chalcones demonstrated their high antimicrobial activity. The corresponding 4-ethoxy-6-bromo-7-hydroxyflavylium salts were obtained in satisfactory yields (32-61%) and in quite high purity in the case of chalcones I-VI (Table 2). An attempt to convert chalcones VII-IX to flavylium salts did not give the desired result.

We also carried out the one-step condensation of 5-bromoresacetophenone with the corresponding aromatic aldehydes and ethyl orthoformate in the presence of 70% perchloric acid, which leads directly to 4-ethoxy-6-bromo-7-hydroxyflavylium salts.

TABLE 1



Compound	R	R′	R″	mp,[a] °C	IR spectrum, cm^{-1}	Found, % C	Found, % H	Found, % Br	Empirical formula	Calc., % C	Calc., % H	Calc., % Br	Yield, %
I	H	H	H	162	3250, 1630, 1500, 1590	56,6	3,3	25,0	$C_{15}H_{11}BrO_3$	56,4	3,4	25,1	69
II	H	H	OCH_3	171	3210, 1640, 1600, 1500	55,1	3,8	23,1	$C_{16}H_{13}BrO_4$	55,0	3,7	22,9	89
III	H	OCH_3	OCH_3	145	3300, 1644, 1600, 1495	53,9	4,0	21,0	$C_{17}H_{15}BrO_5$	53,8	4,0	21,1	93
IV	H	OH	OCH_3	161	3250, 1660, 1595, 1505	52,5	3,5	22,1	$C_{16}H_{13}BrO_5$	52,6	3,6	21,9	75
V	H	OH	OH	168	3230, 1630, 1600, 1490	53,6	3,5	24,0	$C_{15}H_{11}BrO_4$	53,8	3,3	23,8	68
VI	H	COOH	OH	171	3240, 1720, 1660, 1590	50,9	2,9	21,0	$C_{16}H_{11}BrO_6$	50,9	2,9	21,1	75
VII	OH	H	H	175	3270, 1640, 1500, 1480	54,0	3,6	23,7	$C_{15}H_{11}BrO_4$	53,8	3,3	23,8	72
VIIIb	OH	Br	H	117	3300, 1630, 1600, 1505	36,3	2,0	49,0	$C_{15}H_9Br_3O_4$	36,5	1,8	48,6	75
IX	H	H	NO_2	190	3210, 1650, 1610, 1490	49,5	2,8	22,1	$C_{15}H_{10}BrNO_5$	49,4	2,7	22,0	55

[a]Recrystallization from acetic acid. [b]2-Hydroxy-3,5-dibromo derivative.

TABLE 2. 4-Ethoxyflavylium Salts (X)

Compound	R	R′	mp, °C	IR spectrum, cm^{-1}	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	Yield, %
Xa	H	H	118	3300, 1620, 1595, 1530, 1080	45,9	3,1	$C_{17}H_{14}BrClO_7$	45,8	3,2	A 38 B 42
Xb	H	OCH_3	125	3240, 1625, 1600, 1540, 1090	45,2	3,5	$C_{18}H_{16}BrClO_8$	45,4	3,4	A 32 B 69
Xc	OCH_3	OCH_3	178	3290, 1630, 1600, 1530, 1080	45,0	3,7	$C_{19}H_{18}BrClO_9$	45,1	3,6	A 61 B 77
Xd	OH	OCH_3	132	3180, 1640, 1590, 1530, 1100	44,1	3,2	$C_{18}H_{16}BrClO_9$	44,1	3,3	A 49 B 75
Xe	H	OH	120	3300, 1635, 1605, 1525, 1080	44,3	3,1	$C_{17}H_{14}BrClO_8$	44,2	3,0	A 42 B 80
Xf	COOH	OH	144	3230, 1700, 1630, 1540, 1100	43,0	2,6	$C_{18}H_{14}BrClO_{10}$	42,7	2,8	A 45 B 59

TABLE 3. 6-Bromo-7-hydroxyflavones (XI)

Compound	R	R′	mp, °C	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %		
					C	H	Br		C	H	Br
XIa	H	H	188	3330, 1640, 1600, 1505	56,9	3,0	25,4	$C_{15}H_9BrO_3$	56,8	2,8	25,2
XIb	H	OCH_3	174	3250, 1640, 1610, 1500	55,2	3,2	23,2	$C_{16}H_{11}BrO_4$	55,3	3,2	23,0
XIc	OCH_3	OCH_3	212	3240, 1650, 1615, 1495	54,1	3,6	21,0	$C_{17}H_{13}BrO_5$	54,1	3,4	21,2
XId	OH	OCH_3	202	3230, 1640, 1610, 1495	52,7	3,0	22,1	$C_{16}H_{11}BrO_5$	52,9	3,0	22,0
XIe	H	OH	193	3350, 1645, 1600, 1500	54,0	2,8	24,2	$C_{15}H_9BrO_4$	54,0	2,7	24,0
XIf	COOH	OH	228	3300, 1690, 1650, 1605, 1500	51,0	2,5	21,3	$C_{16}H_9BrO_6$	50,9	2,4	21,2

It is interesting to note that 4-ethoxyflavylium salts are obtained in higher yields (42-80%) in the case of the one-step acid condensation than from the corresponding chalcones, while the indicated method has considerable advantages since it does not require the prior synthesis of the chalcones which are generally obtained in 55-93% yields. This method was used to obtain flavylium salts Xa-f (Table 2), which we previously synthesized from 2',4'-dihydroxy-5'-bromochalcones I-VI; the condensation of 5-bromoresacetophenone with 5-formylsalicyclic acid leads to the production of previously unknown flavylium salts and flavones that contain a carboxy group. We were also unable to obtain flavylium salts from chalcones VII-IX, which have an o-hydroxy group in the second aromatic ring, by the one-step synthesis; this can evidently be explained by the presence of an intra- or intermolecular hydrogen bond which hinders cyclization. Absorption bands of a pyrylium cation (1620-1640 and 1530-1540 cm^{-1}), aromatic rings (1590-1610 cm^{-1}), and the ClO_4^- ion (1080-1100 cm^{-1}) are characteristic for the IR spectra of the salts obtained.

6-Bromo-7-hydroxyflavones (XIa-f, Table 3), which in contrast to the corresponding chalcones do not have biological activity, were obtained by refluxing the flavylium salts with water. Absorption at 1630-1650 cm^{-1} is characteristic for the IR spectra of the flavones.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer.

Chalcones. A 0.01-mole sample of the aromatic aldehyde and a solution of 2 g of sodium hydroxide in 3 ml of water were added to a solution of 2.32 g (0.01-mole) of bromoresacetophenone in 10-ml of alcohol, and the reaction mixture was stirred constantly at room temperature until a paste formed. The paste was then allowed to stand overnight, after which it was poured into cold water acidified with sulfuric acid. The chalcones were washed with water, dried, and crystallized from ethanol. Data on the yields and properties of the compounds obtained are presented in Table 1.

7-Hydroxy-6-bromo-4-ethoxyflavylium Salts. A) A 0.002-mole sample of the corresponding chalcone was heated for 15 min with 2 ml of ethyl orthoformate and 0.4 ml of 70% perchloric acid, after which the mixture was cooled and diluted with 10-15 ml of ethyl orthoformate. It was heated again for 2-3 min, and the precipitated crystals were removed by filtration, washed with dry ether, air dried, and crystallized from glacial acetic acid.

B) A 0.2-ml sample of 70% perchloric acid was added dropwise to a mixture of 0.002 mole of 5-bromoresacetophenone, 0.006 mole of the aromatic aldehyde, and 2.8 ml of ethyl orthoformate, and the mixture was maintained at room temperature for 3 h. The precipitated crystals were removed by filtration, washed with dry ether, air dried, and crystallized from acetic acid. Data on the yields and properties of the compounds obtained are presented in Table 2.

Flavones. The 7-hydroxy-6-bromo-4-ethoxyflavylium salts were refluxed with 50 ml of water for 5-10 min, after which the precipitates were removed by filtration and crystallized from aqueous ethanol. Data on the properties of the substances obtained are presented in Table 3.

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CHARACTER OF THE PRODUCTS OF BROMINATION OF 1,3-DIOXACYCLANES WITH N-BROMOSUCCINIMIDE

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The dependence of the character and composition of the products of the reaction of equimolar amounts of N-bromosuccinimide and 1,3-dioxacyclanes on the ring size and the character of the substituent in the 2 position of the 1,3-dioxacyclane ring was examined. Reasons for the primary formation of bromination products of different types for five-, six-, and seven-membered cyclic acetals are proposed.

It is known that acyclic acetals undergo virtually quantitative bromination by N-bromosuccinimide (NBS) to the corresponding α-bromoacetals [1], whereas this reaction pathway is not characteristic for 2-alkyl-1,3-dioxalanes and 1,3-dioxanes [2, 3], and they form primarily the corresponding bromoalkyl esters of carboxylic acids.

We have examined the dependence of the character and composition of the products of the reaction of 1,3-dioxacyclanes with an equimolar amount of NBS on the ring size and the nature of the substituents in the 2 position. The bromination was carried out in CCl_4 solution without traces of peroxide at 20-70°C. As expected, 4-bromobutyl esters of formic and benzoic acids, respectively, are formed in up to 75% yields in the case of 1,3-dioxepane and 2-phenyl-1,3-dioxepane at 70°C, while the bromination of 2,2-dimethyl-1,3-dioxane (40°C) leads exclusively to 2-methyl-2-bromomethyl-1,3-dioxane in 80% yield.

However, we were able to detect substantial differences in the primary reaction pathway as a function of the ring size in the case of dioxacyclanes with the general formula $CH_3\overline{CHOCH_2(CH_2)_nCH_2O}$. The compositions (in %) and the character of the reaction determined by gas–liquid chromatography (GLC) are presented in Table 1, in which I is $BrCH_2\overline{CHOCH_2(CH_2)_nCH_2O}$, II is $CH_3COOCH_2(CH_2)_nCH_2Br$, and III are unidentified products.

In the case of 2-butyl-1,3-dioxepane the I:II:III ratio at 70°C is 65:20:15. Irradiation of the reaction mixture at 20°C with a 60-W lamp in the case of 2-methyl-1,3-dioxepane

TABLE 1. Compositions of the Products of Bromination of 1,3-Dioxacyclanes

n	t, °C	I	II	III
0	70	0	85	15
1	40	20	80	—
1	70	14	86	—
2	40	80	10	10
2	70	53	25	22

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