SUMMARY

The new glycoside haploside C has been isolated from the epigeal part of the plant *Haplophyllum perforatum*, and its structure has been established as 3,4',5,7-tetrahydroxy-3',8-dimethoxyflavone 7-O [O-α-L-rhamnopyranosyl-(1 → 2)-(6"-O-acetyl-β-D-glucopyranoside)].

When this compound is introduced into the animal organism, a fall in the level of urea and residual nitrogen in the blood serum is observed, as on the use of lespenephryl.

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REACTIVITY OF CARBONYL-CONTAINING DERIVATIVES OF 1-MONO- AND 1,3-DIPHENYLPROPANES.

I. KINETICS OF THE OXIMATION REACTION OF FURANOCHROMONE, DIHYDROFLAVONONE, AND CHALCONE DERIVATIVES

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The rate constants of the oximation reaction of more than twenty compounds belonging to the 1-mono and 1,3-diphenylpropane derivatives, and their activation energies have been determined. The oximation reaction depends on the structure and position of the substituents in the γ-pyrone nucleus where such is present, and on the degree of oxidation (reduction) of the pyrone fragment of 2-phenylbenzo-γ-pyrone, and also on the temperature.

Carbonyl compounds belonging to derivatives of 1-phenylpropane — benzopyrones (furanochromones) — and of 1,3-diphenylpropane — chalcones (chalcone, isoliquiritigenin and its glycosides — licuroside), flavones (luteolin), flavanones (liquiritigenin, naringenin) and others — are widely distributed in the vegetable kingdom [1]. Some of them are used in medical practice as vessel-strengthening, cholagogic, antiinflammatory, antiulcer, spasmolytic, antimicrobial, and other agents [2-5]. Analysis of these compounds is carried out mainly by spectral methods [6]. However, the most selective method for the quantitative estimation of these substances is analysis from functional groups (aldehyde, ketone, etc., groups). The hydroxylamine method is frequently used to determine aliphatic and aromatic aldehydes and ketones, sugars, and steroid hormones [7, 8]. This method is also used for the analysis of such a spasmolytic drug as khellin [7]. However, the influence of the position, structure, and number of substituents in the molecules of furanochromone, flavone, flavanone, and 1,3-diphenylpropane derivatives on their reactions with hydroxylamine has not been investigated.

The present paper gives the results of a study of the kinetics of the oximation reaction at the carbonyl group of the γ-pyrone ring for benzopyrone derivatives and for 1,3-diphenylpropane derivatives containing such a ring and of a determination of the dependence of the rate

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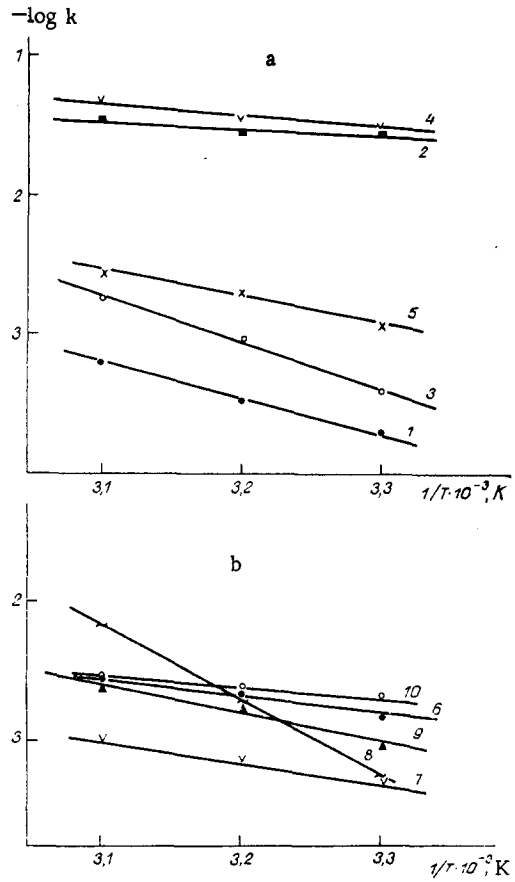


Fig. 1. Graphs of the dependence of the logarithms of the rate constants of the oximation reactions on the reciprocal temperature: 1) 5-hydroxykhellin; 2) khellin; 3) 5-diethylaminoethylkhellin; 4) 5-acetoxykhellin; 5) 5-nicotinoyloxykhellin; 6) liquiritigenin; 7) naringenin; 8) chalcone; 9) isoliquiritigenin; 10) licuroside.

constants of the oximation reaction on the structure and position of substituents in the γ-pyrone nucleus and on the degree of oxidation (reduction) of the pyrone fragment of 2-phenylbenzo-γ-pyrone.

The kinetic investigations were performed at a concentration of the reagents of 0.25 M and of the compounds under investigation of 0.002 M. The kinetics of the reaction were determined for the substance under investigation by the fixed-time method. The concentration of the oxime obtained was determined by titration with a 0.05 N solution of perchloric acid in methanol in the presence of the indicator Thymol Blue. The reaction in the mixture was stopped by cooling in an ice bath. The rate constants and activation energies were calculated by known formulas [9] with statistical treatment of the results obtained [10].

Analysis of the results (Tables 1 and 2) has shown that electron-accepting substituents introduced into the C_5 position of furanochromone, being present in the peri-position relative to the carbonyl group of the γ-pyrone moiety, cause a lowering of the rate constant of its oximation in the following sequence

$$-\overset{\overset{O}{\|}}{C}-C_6H_5 < -\overset{\overset{O}{\|}}{C}-C_5H_4N < -\overset{\overset{O}{\|}}{C}-CH_3$$

The introduction of electron-donating substituents into the furanochromane molecule, however, causes an increase in the rate of the reaction in the following sequence:

$$-CH_3 > -CH_2-C_6H_5 > -CH_2=CH_2-\mathbf{N}(C_2H_5)_2 > -H$$

TABLE 1. Dependence of the Rate Constant of the Oxim ation of Carbonyl-Containing Derivatives of 1-Mono- and 1,3-Diphenylpropanes on Their Structure and the Influence of the Temperature on the Yield of Oxime

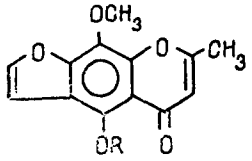
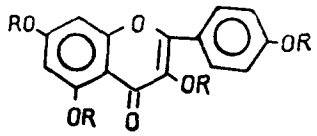
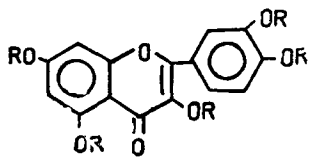
Compound	Substituent R	Yield of oxime after 2 h, %		Rate constant of the reaction at 64.5°C ($K \cdot 10^{-4}$, sec^{-1})
		20 °C	64.5 °C	
1 2	3	4	5	6
Furanochromone derivatives				
				
1. 5-Hydroxykhellin (5-hydroxy-9-methoxy-2-methylfurano-[3,2:6,7]chromone)	—H	0	12,5	11,1
2. Khellin (5,9-dimethoxy-2-methylfurano[3,2:6,7]chromone	$-CH_3$	10,2	99,6	347,2
3. 5-Benzyloxykhellin (5-benzyloxy-9-methoxy-2-methylfurano-[3,2:6,7]chromone)	$-CH_2C_6H_5$	0	95,2	229,9
4. 5-Diethylaminoethylkhellin	$-C_2H_4N(C_2H_5)_2$	0	32,2	30,8
5. 5-Diethylaminoethylkhellin hydrochloride	$-C_2H_4N(C_2H_5)_2 \cdot HCl$	0	27,7	27,1
6. 5-Acetoxykhellin	$-COCH_3$	96,4	99,8	484,0
7. 5-Nicotinoyloxykhellin	$-COC_5H_4N$	0	50,5	58,9
8. 5-Benzoylkhellin	$-COC_6H_5$	0	17,7	17,0
Flavone derivatives				
a) Kaempferol group				
				
9. Kaempferol (3,4',5,7-tetrahydroxyflavone)	—H	0	0	0
10. 3,4',5,7-Tetramethoxyflavone	$-CH_3$	0	36,7	38,1
11. 3,4',5,7-Tetraacetoxyflavone	$-COCH_3$	33,8	462,2 (92,4×5)	—
b) Quercetin group				
				
12. Quercetin (3,3',4',5,7-pentahydroxyflavone)	—H	0	0	0
13. 3,3',4',5,7-Pentamethoxyflavone	$-CH_3$	0	97,2	303,0
14. 3,3',4',5,7-Pentaacetoxyflavone	$-COCH_3$	37,6	615,0 (102,5×6)	—

TABLE 1 (Continued)

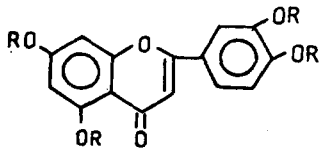
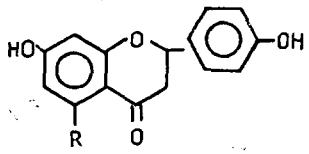
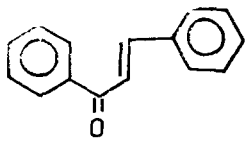
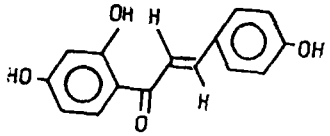
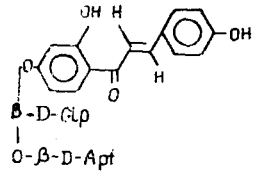
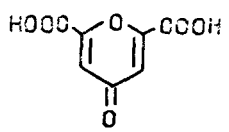
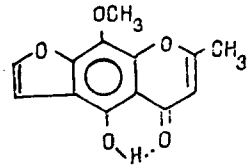
Compound	Substituent R	Yield of oxime after 2 h, %		Rate constant of the reaction at 64.5°C ($K \cdot 10^{-4}$, sec^{-1})
		20 °C	64.5 °C	
1 2	3	4	5	6
15. 3,3',4',5,7-Pentanicotinoyloxyflavone	COC_5H_4N	63,7	609,7 (101,6×6)	—
16. 3,3',4',5,7-Penta(acetylsalicyloxy)flavone	$-COC_6H_4COOCH_3$	7,5	1009,8 (91,8×11)	—
c) Luteolin group				
				
17. Luteolin (3',4',5,7-tetrahydroxyflavone)	—H	0	10,3	9,2
18. 3',4',5,7-Tetraacetoxyflavone	$-COCH_3$	24,7	443,2 (88,6×5)	—
Flavanone (dihydroflavone) derivatives				
				
19. Liquiritigenin (4',7-dihydroxyflavonone)	—H	0	96,5	26,5
20. Naringenin (4',5,7-trihydroxyflavanone	—OH	0	81,8	14,2
Chalcone derivatives				
21. Chalcone (trans-chalcone)		10,2	72,0	106,0
22. Isoliquiritigenin (2,4,4'-trihydroxy-trans-chalcone)		0	84,4	47,2
23. Licuroside (2,4,4',-trihydroxy-trans-chalcone 4-O-(2-O-β-D-apiofuranosyl-β-D-glucoside)		0	98,6	33,7
24. Chelidonic acid (γ-pyrone-α,α'-dicarboxylic acid)		0	95,1	25,9

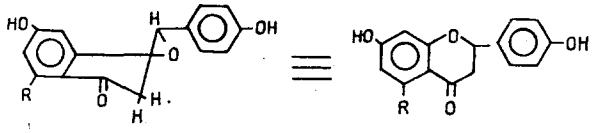
TABLE 2. Dependence of the Rate Constant of the Oximation Reaction on the Temperature, and the Activation Energies of the Reaction, for the Compounds Investigated

Compound	$k \cdot 10^{-1}$ (sec^{-1})			E_a, kJ/mole
	303 K	313 K	323 K	
Furanochromone derivatives				
1. 5-Hydroxykhellin	1,8±0,1	3,0±0,2	6,0±0,2	49,7
2. Khellin	244,2±0,4	254,5±0,3	333,2±0,4	13,4
3. 5-Diethylaminoethylkhellin	3,5±0,2	8,5±0,2	18,5±0,3	68,7
4. 5-Acetoxykhellin	286,2±0,3	334,7±0,2	463,7±0,3	20,0
5. 5-Nicotinoylkhellin	9,4±0,3	17,1±0,4	27,2±0,3	44,9
Flavanone derivatives				
6. Liquiritigenin	14,8±0,2	23,1±0,3	24,4±0,2	21,0
7. Naringenin	5,0±0,4	7,2±0,3	9,8±0,2	28,6
Chalcone derivatives				
8. Chalcone	5,5±0,3	27,5±0,3	67,4±0,3	104,1
9. Isoliquiritigenin	13,7±0,2	19,3±0,3	24,7±0,2	24,8
10. Licuroside	22,2±0,4	22,8±0,2	27,4±0,3	8,6

As can be seen, the lowest reactivity in the series of electron-donating substituents is possessed by 5-hydroxykhellin with a OH group in the C_5 position, which can be explained by the formation of a hydrogen bond with the carbonyl group of the furanochromane (I) [11].



It has also been established that a hydrogen bond formed by the OH group in the C_5 position has a smaller influence on the carbonyl group of the flavanones (Table 1, substances 19 and 20) than in the case of the furanochromone 5-hydroxykhellin by virtue of the fact that the furanochromone has a planar structure, while liquiritigenin (II) and naringenin (III) have the half-chair conformation because of the absence of a double bond in the dihydro-γ-pyrone moiety [12].



II. R=-H
III R=-OH

The difference in the rates of oximation of chalcone and its derivatives is also connected with their stereochemistries, since it is known [13] that isoliquiritigenin and licuroside have the trans conformation of the chalcone nucleus (Tables 1 and 2).

Flavone derivatives (kaempferol, quercetin) (Table 1, substances 9 and 12), having OH groups in the C_3 and C_5 positions, do not take part in the oximation reaction either at room temperature or at elevated temperatures, which can probably be explained by the formation of strong hydrogen bonds with the carbonyl group, as also for 5-hydroxykhellin (Tables 1 and 2). The introduction of an electron-donating substituent ($-CH_3$) causes some increase in the rate constant of the oximation reaction, while with electron-accepting substituents the reaction takes place with the formation of hydroxamates at the carbonyl group of the acid residue (Table 1, substances 11 and 14-16).

With a rise in the temperature, the rate constants of the oximation reaction increased (Table 2), and this the more sharply the higher the activation energy of the given reaction.

The results of the investigations of carbonyl-containing furanochromone, flavone, flavanone, and chalcone derivatives that have been performed have shown that the reactivity of the carbonyl groups depends on the nature of the substituents in the peri position relative to the carbonyl group and on their steric influence on the carbonyl group. The oximation reaction can be used both for determining the reactivities of the carbonyl groups in benzo-γ-pyrone and 2-phenylbenzo-γ-pyrone compounds in the determination of the structure and also for the quantitative estimation of some of them.

EXPERIMENTAL

The substances for analysis were dried in vacuum (residual pressure 10^{-2} mm Hg) over P_2O_5 for 5 h. The purity of the substances was determined by thin-layer chromatography using plates of the Silufol type and the following solvent systems: 1) chloroform; 2) chloroform–methanol (49:1).

Method of Determination. A weighed sample of substance (0.002 mole/liter [sic]) was placed in a 25-ml measuring flask and was dissolved in methanol freed from carbonyl compounds, and the volume of liquid in the flask was made up to the mark with methanol. Then 5 ml of the resulting solution was transferred to a flask with a ground-in stopper, 5 ml of reagent (3.5 g of hydroxylamine hydrochloride and 0.4 g of diethylamine in 100 ml of methanol) was added, and the mixture was kept for predetermined times at temperatures of 30, 40, and 50°C. Samples were taken and were cooled to 0°C (in an ice bath) over 5 min. The excess of reagent was titrated with a 0.05 N solution of hydrogen chloride in methanol in the presence of a 0.3% solution of Thymol Blue in methanol as indicator.

The concentration of the substance under investigation (M) was calculated from the difference in the number of milliliters consumed in the titration of a control sample and in the experiment with the weighed sample of substance. The rate constants of the reaction were calculated by means of the first-order equation [9, 13]. Using the constants obtained, graphs were plotted of the dependence of the logarithms of the rate constants of the reaction for the compounds investigated on the reciprocal temperature (Fig. 1). The activation energies for the compounds investigated were calculated from the tangents of the angles of slope of the straight lines in the Arrhenius coordinates [9].

SUMMARY

The rate constants of the oximation reaction of more than 20 compounds belonging to the group of carbonyl-containing derivatives of 1-mono- and 1,3-diphenylpropanes have been determined, and their activation energies have been calculated.

On the basis of the results of the investigation of the kinetics of the oximation reaction, it has been established that this reaction depends on the structure and composition of the substituents in the γ-pyrone nucleus of compounds containing such a nucleus on the degree of oxidation (reduction) of the propane fragment in the case of 2-phenylbenzo-γ-pyrone, and also on the temperature.

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