REACTIONS OF 4-ETHOXYFLAVYLIUM, 4-ETHOXYCHROMYLIUM, AND 4-ETHOXYFUROCHROMYLIUM SALTS WITH SEVERAL AMINES

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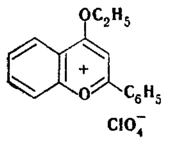
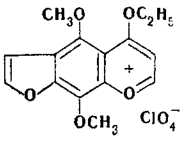
The reactions of 4-ethoxyflavylium, 4-ethoxychromylium, and 4-ethoxyfurochromylium salts in acidic media with several acids were investigated. In the reaction with hydrazine the furochromylium salt forms pyrazole, whereas both α,β-substituted benzopyrylium salts are converted to azines. The reaction of hydroxylamine with the flavylium salt gives a flavone oxime, whereas the reaction with the furochromylium salt gives an isoxazolylbenzofuranol.

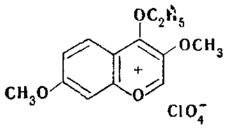
In our preceding papers we reported the syntheses of the previously unknown 4-ethoxyflavylium (I) [1, 2] and 4-ethoxyfurochromylium salts (II) [3]. In order to ascertain the reactivities of I and II and also the newly synthesized 3,7-dimethoxy-4-ethoxychromylium salt (III) we continue [4] our study of their reaction with several amines.



I

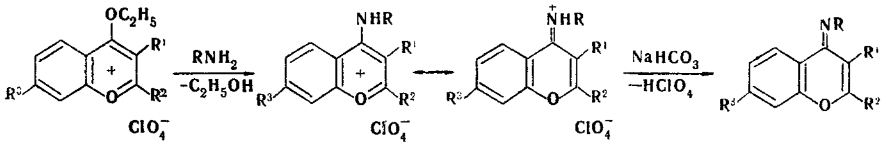


II



III

Regardless of the structure of the salt, the 4-ethoxy group is replaced by an R-amino group in the reactions of I and III with aniline and phenylhydrazine in acetic acid:



IV a-d

Vb,c

IVa $R = C_6H_5$, $R^1 = R^3 = OCH_3$, $R^2 = H$; IV, Vb $R = R^2 = C_6H_5$, $R^1 = R^3 = H$; c $R = NHC_6H_5$, $R^2 = C_6H_5$, $R^1 = R^3 = H$; IV d $R = NHC_6H_5$, $R^1 = R^3 = OCH_3$, $R^2 = H$

When II is refluxed with aniline, the 4-ethoxy group is also replaced by an R-amino group to give perchlorate VI. (See scheme on following page.)

All IVa-d and VI give a negative test for a free hydroxyl group with ferric chloride, and this may be considered to the indirect proof of the retention of the pyran ring.

The IR spectra contain a band at 1620-1640 cm^{-1}, which is characteristic for the pyrylium cation. The structures of the 4-N-phenylflavylium and 4-N-phenylhydrazylflavylium

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TABLE 1. Nitrogen Derivatives of Benzopyrones

Compound	mp, °C*	Empirical formula	Found, %				Calculated, %				IR spectrum, cm^{-1}	Yield, %
			C	H	Cl	N	C	H	Cl	N		
IVa	183	$C_{17}H_{16}ClNO_7$	53,3	4,4	8,8	4,0	53,5	4,2	9,3	3,7	1090, 1230, 1270, 1580, 1595, 1620, 3210	95
IVb	244	$C_{21}H_{16}ClNO_5$	63,5	4,2	9,4	3,8	63,4	4,0	8,9	3,5	1100, 1280, 1580, 1600, 1630	50
IVc	193	$C_{21}H_{17}ClN_2O_5$	60,9	4,3	8,1	6,8	61,1	4,1	8,6	6,8	1555, 1595, 1625, 3250	60
IVd	193	$C_{17}H_{17}ClN_2O_7$	51,5	4,3	9,3	7,3	51,5	4,3	8,9	7,1	1580, 1610, 1630	55
VI	195	$C_{19}H_{16}ClNO_8$	54,3	4,0	8,4	3,3	54,1	3,8	8,4	3,3	1550, 1590, 1620, 1640, 3270	50
VII	141	$C_{13}H_{12}N_2O_4$	59,7	4,5	—	11,0	60,0	4,6	—	10,8	1490, 1540, 1615, 3415	90
VIIIa	293	$C_{30}H_{20}N_2O_2$	82,1	4,6	—	6,6	81,8	4,5	—	6,4	1560, 1605, 1625	100
VIIIb	184	$C_{22}H_{20}N_2O_6$	64,5	4,9	—	7,1	64,7	4,9	—	6,9	1545, 1565, 1605, 1630	100
IX	112	$C_{13}H_{11}NO_5$	60,2	4,2	—	5,4	59,8	4,2	—	5,4	1585, 1625, 3490	65
XI	179	$C_{13}H_{12}ClNO_9$	43,0	3,1	9,9	4,1	43,1	3,3	9,8	3,9	1590, 1615, 1650	47
XII	205	$C_{13}H_{11}NO_5$	59,5	4,0	—	5,7	59,8	4,2	—	5,4	1620, 1645, 3170—3200	90
XIII	232	$C_{20}H_{20}ClNO_5$	61,8	5,1	9,0	3,8	61,6	5,3	9,1	3,6	1090, 1560, 1585, 1620	27

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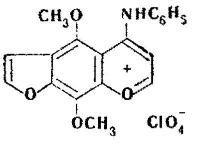
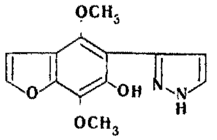
*The compounds were purified by crystallization: IVa-d, VI, XI, and XIII from acetic acid, VII and XII from benzene, VIIIa from dimethylformamide, VIIIb from nitromethane, and IX from octane.



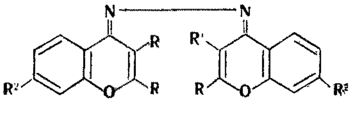
VI

perchlorates were also confirmed by conversion to the corresponding previously described bases (V) [5] by the action of sodium bicarbonate solution.

The difference in the structures of I-III is manifested in their reactions with hydrazine. Furochromylium salt II with free α and β positions reacts with hydrazine to give an almost quantitative yield of pyrazole VII, whereas both the α- and β-substituted benzopyrylium salts (I and III) form chromoneazines (VIIIa,b).



VII



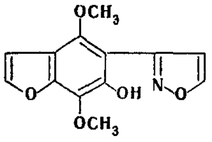
VIII a,b

VIII a R=C_6H_5, R^1=R^2=H; b R=H, R^1=R^2=OCH_3.

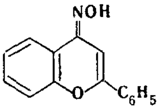
4,7-Dimethoxy-5-[3(5)-pyrazolyl]-6-benzofuranol (VII) was also obtained by alternative synthesis from ω-formylkellinone (synthesized by a modified method [6]) and hydrazine.

The absence in the IR spectra of VIIIa,b of the characteristic absorption band of the OH group and the presence of the absorption band of stretching vibrations of the —C=N group at 1625-1630 cm^{-1} confirm the structure proposed for them. In addition, the 4,4'-azino-2'-diphenyldichromone structure was proved by acid hydrolysis, which gives a flavone.

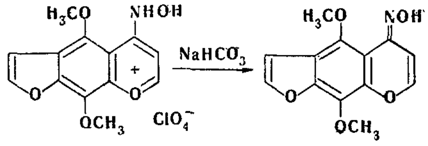
Refluxing II with hydroxylamine in acetic acid gives 4,7-dimethoxy-5-[3(5)-isoxazolyl]-6-benzofuranone (IX), which was also obtained by alternative synthesis from ω-formylkellinone and hydroxylamine. Compound I reacts with hydroxylamine in acetic acid to give flavone oxime X the physical constants of which are in agreement with the literature data [5].



IX



X



XI XII

By changing the conditions of the reaction between the salt and hydroxylamine we were able to isolate, in addition to IX, oxime perchlorate XI, which is converted to the corresponding furochromone oxime (XII) on brief heating with sodium bicarbonate solution. Thus when the ratio of II to hydroxylamine is 1:1.5, careful heating of the mixture gives isoxazole IX in 40% yield and XI in 47% yield.

The IR spectrum of XII contains an absorption band at 1645 cm^{-1}, which is characteristic for the bond in chromone oximes [7].

As in the case of 4-alkoxypyrylium salts [8], in the reaction of salt I with secondary amines the 4-ethoxy group is replaced by an R-amino group to give 4-piperidylflavylium perchlorate (XIII).

EXPERIMENTAL METHOD

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

3,7-Dimethoxy-4-ethoxychromylium Perchlorate (III). A mixture of 0.5 g (2.5 mmole) of 2-hydroxy-4,ω-dimethoxyacetophenone, 6 ml of freshly distilled ethyl orthoformate, and 0.5 ml (5 mmole) of 70% perchloric acid was held at room temperature for 30 min, after which the resulting crystals were removed by filtration to give 0.5 g (59%) of a product with mp 127-128° (from glacial acetic acid). IR spectrum, cm^{-1}: 1100, 1240, 1280, 1470, 1575, 1610, and 1640. Found %: C 46.8; H 4.7; Cl 10.3. $C_{13}H_{15}ClO_8$. Calculated %: C 46.7; H 4.5; Cl 10.6.

3,7-Dimethoxy-4-phenylaminochromylium Perchlorate (IVa). A 0.33-g (1 mmole) sample of III was refluxed with 0.19 ml (2 mmole) of aniline for 30 min in acetic acid, after which the mixture was cooled, and the product was precipitated with ether to give 0.36 g (95%) of product. Compounds IVb and VI were similarly obtained by refluxing the reaction mixture for 15 min. The ratio of I and II to phenylhydrazine was 1:1.5 for the preparation of IVc and IVd, and the mixture was refluxed for 40-60 min. Data on the yields and properties of the compounds obtained are presented in Table 1.

ω-Formylkellinone. A hot solution (70°) of 25 g of potassium hydroxide in 200 ml of absolute alcohol was added to 11 g of furochromone, after which the mixture was stirred without further heating for 2-3 h. Glacial acetic acid (60 ml) and 1 liter of distilled water were added, and the mixture was cooled to give 11 g (quantitative yield) of a yellow substance with mp 163-164° (from alcohol). IR spectrum, cm^{-1}: 1550, 1605, 1660, and 3410. Found %: C 59.2; H 4.4. $C_{13}H_{12}O_6$. Calculated %: C 59.1; H 4.5.

4,7-Dimethoxy-5-[3(5)-pyrazolyl]-6-benzofuranol (VII). A) A mixture of 0.76 g (2 mmole) of salt II and 0.13 ml (4 mmole) of hydrazine was refluxed in acetic acid for 40-50 min, after which the solution was cooled and diluted with water, and the product was extracted with ether. The ether extract was dried with sodium carbonate and evaporated to give 0.46 g (90%) of colorless needles.

B) A 0.15-ml sample of hydrazine was added to a solution of 0.52 g of ω-formylkellinone in 10 ml of alcohol, and the mixture was refluxed for 40 min. It was then cooled and diluted with water to give 0.4 g (80%) of product. No melting-point depression was observed for a mixture of this product with VII, and their IR spectra were identical.

4,4'-Azino-3,3',7,7'-tetramethoxydichromone (VIIIb). A mixture of 1 g (3 mmole) of salt III and 0.2 ml (6 mmole) of hydrazine in acetic acid was held at room temperature for 30-40 min, after which 1 g of an unstable yellow substance was removed by filtration. The product was converted to 0.61 g (100%) of orange needles on brief refluxing with sodium bicarbonate solution. 4,4'-Azino-2,2'-diphenyldichromone (VIIIa) (Table 1) was similarly obtained.

4,7-Dimethoxy-5-[3(5)-isoxazolyl]-6-benzofuranol (IX). A) A mixture of 0.74 g (2 mmole) of salt II, 0.26 g (4 mmole) of hydroxylamine hydrochloride, and 0.32 g of sodium acetate was refluxed for 20-30 min, after which the mixture was diluted with water, and 0.34 g (65.4%) of a colorless product was removed by filtration.

B) A reaction mixture consisting of 0.52 g (5 mmole) of ω-formylkellinone in 5 ml of pyridine and 0.14 g of hydroxylamine hydrochloride in 2 ml of water was refluxed for 2-2.5 h, after which it was cooled and diluted with water to give 0.38 g (74.5%) of a colorless product. No melting-point depression was observed for a mixture of this product with IX, and their IR spectra were identical.

Flavone Oxime (X). A mixture of 0.7 g (2 mmole) of salt I, 0.28 g (4 mmole) of hydroxylamine chloride, and 0.35 g of sodium acetate was refluxed in glacial acetic acid for 20-30 min, after which the mixture was diluted with water and extracted with ether. The ether extract was dried with sodium carbonate and evaporated to give 0.34 g (69.4%) of colorless crystals with mp 183° (mp 184° [5]). IR spectrum, cm^{-1}: 1570 and 1645.

5,8-Dimethoxy-6,7-furochromone Oxime Perchlorate (XI). A mixture of 0.37 g (1 mmole) of salt II, 0.1 g (1.5 mmole) of hydroxylamine hydrochloride, and 0.11 g of sodium acetate was heated carefully for 10 min in acetic acid, after which it was cooled and diluted with ether to give 0.17 g (47%) of the yellow perchlorate.

5,8-Dimethoxy-6,7-furochromone Oxime (XII). Brief (3-5 min) heating of 0.72 g of XI with sodium bicarbonate solution gave 0.47 g (90%) of a colorless compound.

4-Piperidylflavylium Perchlorate (XIII). A solution of 0.7 g (2 mmole) of salt I and 0.2 ml of piperidine in alcohol was refluxed for 15 min, after which the mixture was cooled and diluted with ether, and the resulting precipitate was removed by filtration to give 0.21 g (27%) of a yellow substance.

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