SYNTHESIS OF 4,5-DIHYDROXY-7-(2-AMINOPROPYL)- AND 4,5-DIHYDROXY-7-(2-PHENYL-2-AMINOETHYL)BENZOFURAN DERIVATIVES

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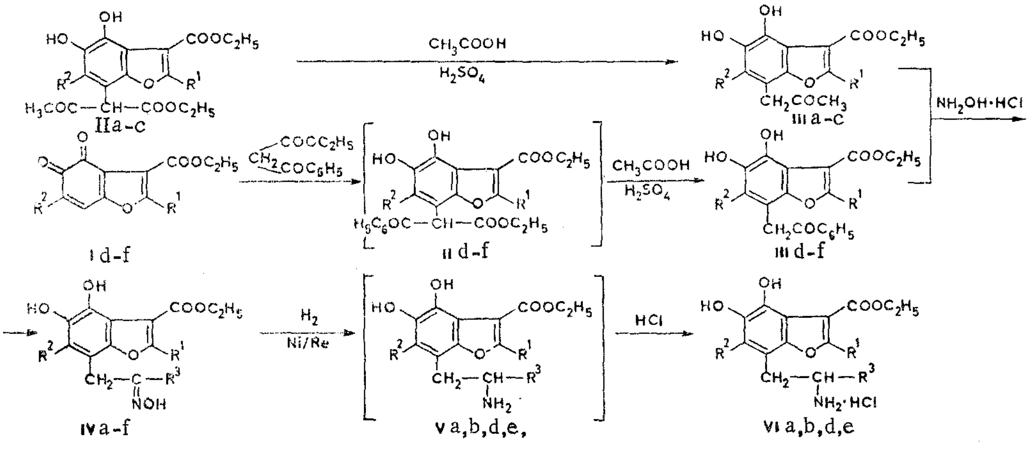
A preparative method for the synthesis of 4,5-dihydroxy-7-acetonyl- and 4,5-dihydroxy-7-phenacylbenzofuran derivatives and their oximes is proposed. Catalytic hydrogenation of the latter gave hydrochlorides of 4,5-dihydroxy-7-(2-aminopropyl)- and 4,5-dihydroxy-7-(2-phenyl-2-aminoethyl)benzofurans.

Some derivatives of catecholamines display high biological activity [1]. In particular, dopamine [2] plays an important role in the transmission of impulses in the central nervous system (CNS) and is a precursor of noradrenaline. In a search for new compounds of this type we turned to 4,5-dihydroxybenzofuran derivatives and to heteroanalogs of catecholamines. We synthesized 4,5-dihydroxy-7-(2-aminopropyl)- and 4,5-dihydroxy-7-(2-phenyl-2-aminoethyl)benzofurans (VIa, b, d, e). However, like dopamine analogs, the compounds obtained did not display biological activity.

4,5-Dihydroxybenzofurans (IIa-c) substituted in the 7 position with an acetoacetic ester residue were previously obtained [3] from o-quinones (Ia-c) of the benzofuran series. 4,5-Dihydroxy-7-acetonylbenzofurans (IIIa-c) were obtained by the action on them of acetic acid in the presence of catalytic amounts of concentrated sulfuric acid.

4,5-Dihydroxy-7-phenacylbenzofurans (IIId-f) (Table 1) were synthesized as a result of condensation of o-quinones Id-f [4] with ethyl benzoylacetate in alcohol in the presence of zinc chloride as the catalyst and treatment of the resulting 4,5-dihydroxybenzofurans IIa-f, which are substituted in the 7 position with an ethyl benzoylacetate residue, with catalytic amounts of concentrated sulfuric acid in acetic acid. The corresponding oximes IVa-f (Table 2) were obtained by the action of hydroxylamine in alcohol on IIIa-f. Catalytic hydrogenation of the oximes over Raney nickel gave amines Va, b, d, e, which were isolated in the form of hydrochlorides VIa, b, d, e (Table 3). It was not possible to isolate the bases, since they are readily oxidized in air.



I—III a,d $R^1=CH_3$, $R^2=Cl$; b,e $R^1=CH_3$, $R^2=Br$; c,f $R^1=C_6H_5$, $R^2=Br$; IV—VI a $R^1=R^3=CH_3$, $R^2=Cl$; b $R^1=R^3=CH_3$, $R^2=Br$; c $R^1=C_6H_5$, $R^2=Br$, $R^3=CH_3$; d $R^1=CH_3$; $R^2=Cl$, $R^3=C_6H_5$; e $R^1=CH_3$, $R^2=Br$, $R^3=C_6H_5$; f $R^1=R^3=C_6H_5$, $R^2=Br$

The IR spectra of ketones IIIa-f contain intense absorption bands with maxima at 1680-1700 and 1650-1655 cm^{-1}, which were assigned to the C=O stretching vibrations of carbonyl

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TABLE 1. Derivatives of 4,5-Dihydroxy-7-acetonyl- and 4,5-Dihydroxy-7-phenacylbenzofurans (IIIa-f)

Compound	mp,[a] °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	Hal		C	H	Hal	
IIIa	157—158	55,5	4,7	11,0	$C_{15}H_{15}ClO_6$	55,1	4,6	10,8	82
IIIb	159—160	48,3	4,1	21,5	$C_{15}H_{15}BrO_6$	48,5	4,1	21,5	75
IIIc	174—176	55,4	4,0	18,3	$C_{20}H_{17}BrO_6$	55,4	4,0	18,4	88
IIId	177—178	62,0	4,3	9,2	$C_{20}H_{17}ClO_6$	61,8	4,4	9,1	62
IIIe	176—178	55,3	4,0	18,4	$C_{20}H_{17}BrO_6$	55,4	4,0	18,4	48
IIIf	206—208	60,6	3,9	16,0	$C_{25}H_{19}BrO_6$	60,6	3,9	16,1	44

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[a] The compounds were crystallized: IIIa, d, e from acetone, IIIb, f from isopropyl alcohol—acetone (1:1), and IIIc from ethanol.

TABLE 2. 4,5-Dihydroxy-7-acetonyl- and 4,5-Dihydroxy-7-phenacylbenzofuran Oximes (IVa-f)

Compound	mp, °C (from ethanol)	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Hal	N		C	H	Hal	N	
IVa	200—202[a]	52,6	4,5	10,1	3,9	$C_{15}H_{16}ClNO_6$	52,7	4,7	10,4	4,1	88
IVb	199—201	46,5	4,0	20,4	3,5	$C_{15}H_{16}BrNO_6$	46,7	4,2	20,7	3,6	78
IVc	206—207[б]	53,5	4,0	17,4	2,9	$C_{20}H_{18}BrNO_6$	53,6	4,1	17,8	3,1	72
IVd	217—219	59,5	4,5	9,1	3,3	$C_{20}H_{18}ClNO_6$	59,5	4,5	8,8	3,5	74
IVe	207—208	53,7	4,0	17,6	3,1	$C_{20}H_{18}BrNO_6$	53,6	4,1	17,8	3,1	85
IVf	196—198	58,8	4,0	15,8	2,6	$C_{25}H_{20}BrNO_6$	58,8	4,0	15,7	2,7	70

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[a] From acetone. [b] From ethanol—dioxane (1:1).

TABLE 3. 4,5-Dihydroxy-7-(2-aminopropyl)- and 4,5-Dihydroxy-7-(2-phenyl-2-aminoethyl)benzofuran Hydrochlorides (VIa, b, d, e)

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
VIa	258—260	49,4	5,3	19,2	3,5	$C_{15}H_{18}ClNO_5 \cdot HCl$	49,5	5,3	19,5	3,8	63
VIb	240—242	44,1	5,1	8,8	3,7	$C_{15}H_{18}BrNO_5 \cdot HCl$[a]	44,1	4,7	8,7	3,4	48
VId	272—274	56,4	5,2	16,7	3,2	$C_{20}H_{20}ClNO_5 \cdot HCl$	56,4	5,0	16,6	3,3	57
VIe	260—261	50,7	4,5	7,6	2,8	$C_{20}H_{20}BrNO_5 \cdot HCl$[б]	51,0	4,5	7,5	3,0	46

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[a] Found: Br 19.8%. Calculated: Br 19.5%. [b] Found: Br 17.1%. Calculated: Br 17.0%.

and ester groups, respectively (Table 4). The IR spectra of oximes IVa-f contain absorption bands of an ester C=O group (1650-1665 cm^{-1}) and a C=N group (1580-1620 cm^{-1}). The IR spectra of all of the synthesized compounds are characterized by an intense band of stretching vibrations of OH groups at 3250-3490 cm^{-1}.

The mass numbers of the molecular ions in the mass spectra of IIIa-f, IVa-f, and VIa, b, d, e are in agreement with the calculated molecular masses of these compounds.

EXPERIMENTAL

The IR sepctra of mineral oil suspensions of the compounds were recorded with UR-10 and Perkin-Elmer spectrometers. The UV spectra of alcohol solutions were recorded with Hitachi EPS-3T and Perkin-Elmer 575 spectrophotometers. The mass spectra were recorded with a Varian MAT-112 mass spectrometer (70 eV) with direct introduction of the samples into the ion source. The individuality of the substances was monitored on Silufol-254 plates in chloroform; the plates were developed in UV light.

TABLE 4. Spectral Characteristics of IIIa-f and IVa-f

Compound	IR spectrum, ν, cm^{-1}			UV spectrum	
	C=O	C=N	OH	λ_{max}, nm	lg ε
IIIa	1690, 1650	—	3250	205, 250	4,28; 4.10
IIIb	1695, 1650	—	3250	215, 250	4,59; 4,14
IIIc	1700, 1655	—	3410	217, 318	4,61; 4,12
IIId	1690, 1650	—	3470	220, 255	4,56; 4,38
IIIe	1680, 1650	—	3380	214, 244	4,67; 4,48
IIIf	1690, 1650	—	3490	210, 245	4,53; 4,33
IVa	1650	1580	3430	220, 254, 300[a]	4,48; 4,14; 3,66
IVb	1650	1580	3430	217, 250, 300[a]	4,62; 4,15; 3,60
IVc	1660	1620	3470	218, 278, 300	4,60; 4,11; 4,08
IVd	1660	1600	3450	212, 245, 300[a]	4,56; 4,33; 3,56
IVe	1665	1580	3470	213, 245, 300[a]	4,57; 4,25; 3,51
IVf	1650	1600	3470	212, 320	4,58; 4,00

[a] Shoulder.

2-Methyl-3-ethoxycarbonyl-4,5-dihydroxy-6-chloro-7-acetonylbenzofuran (IIIa). A 3.98-g (10 mmole) sample of 2-methyl-3-ethoxycarbonyl-4,5-dihydroxy-6-chloro-7-(1-ethoxycarbonyl-2-oxopropyl)benzofuran (IIa) was dissolved by heating in 150 ml of glacial acetic acid, and the solution was refluxed in the presence of catalytic amounts (0.2 ml) of concentrated sulfuric acid for 6 h. The solution was then poured into 300 ml of water, and the precipitate was removed by filtration, washed with water, and recrystallized from 80% aqueous isopropyl alcohol to give 2.7 g (82%) of IIIa.

Compounds IIIb, c were similarly obtained (Table 1).

2-Phenyl-3-ethoxycarbonyl-4,5-dihydroxy-6-bromo-7-phenacylbenzofuran (IIIf). A mixture of 1.87 g (5 mmole) of 2-phenyl-3-ethoxycarbonyl-4,5-dioxo-4,5-dihydro-6-bromobenzofuran (If), 3.84 g (20 mmole) of ethyl benzoylacetate, and 2.8 g of anhydrous zinc chloride in 50 ml of absolute ethanol was refluxed with stirring for 10-15 min, after which heating was discontinued, and the reaction mass was allowed to cool to room temperature for 1.5 h. The mixture was then treated with 10 ml of a saturated aqueous solution of sodium hydrosulfite and 50 ml of water to decolorize the colored impurities. The precipitated IIf was removed by filtration, washed with water and methanol, dried, and dissolved by heating in 80 ml of glacial acetic acid. The solution was refluxed in the presence of catalytic amounts (0.2 ml) of concentrated sulfuric acid for 6 h, after which the mixture was poured into 150 ml of water, and the precipitate was removed by filtration, washed with water, dried, and recrystallized from isopropyl alcohol—acetone (1:1) to give 1.1 g (44%) of IIIf.

Compounds IIId, e were similarly obtained (Table 1).

2-Methyl-3-ethoxycarbonyl-4,5-dihydroxy-6-chloro-7-acetonylbenzofuran Oxime (IVa). A 3.26-g (10 mmole) sample of IIIa was dissolved by heating in 100 ml of absolute alcohol, 0.9 g (13 mmole) of hydroxylamine hydrochloride and 1.64 g (20 mmole) of fused sodium acetate were added, and the reaction mass was refluxed for 5 h. It was then diluted with 100 ml of water, and the precipitate was removed by filtration and washed with water and alcohol to give 3.03 g (88%) of IVa.

Compounds IVb-f were similarly obtained (Table 2).

2-Methyl-3-ethoxycarbonyl-4,5-dihydroxy-6-chloro-7-(2-aminopropyl)benzofuran Hydrochloride (VIa). A 1.7-g (5 mmole) sample of oxime IVa was hydrogenated in a mixture of dioxane (100 ml) with alcohol (100 ml) over Raney nickel (0.5 g) for 12 h at normal pressure at 50°C. The reaction solution was filtered to remove the catalyst into a flask containing ether saturated with hydrogen chloride. The solvent was concentrated *in vacuo* at a small volume (2-3 ml), and 7-10 ml of acetone was added to the residue. The resulting crystals were removed by filtration, washed with acetone, and dried to give 1.13 g (63%) of VIa.

Compounds VIb, d, e were similarly obtained (Table 3).

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PYRYLOCYANINES.

18.* UNSYMMETRICAL FLAVYLOCYANINES ON THE BASIS OF METHOXY-SUBSTITUTED 4-METHYLFLAVYLIUM SALTS

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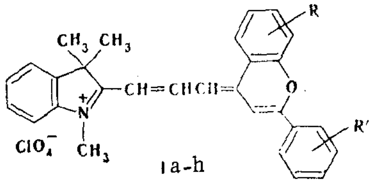
Unsymmetrical flavyloindotrimethylidynecyanines in which a methoxy group is located alternately in the 5, 6, 7, 8, 2', 3', and 4' positions of the flavylium ring were synthesized. An increase in the electron-donor character of the heterocyclic residue generally leads to a bathochromic shift of the absorption bands of the dyes and a decrease in the widths of these bands and the ratios of the intensities of the short-wave and long-wave maxima in them.

Previously in the case of a number of unsymmetrical polymethine dyes that differ with respect to the structure of one of the heterocyclic residues it was shown that the form of their long-wave absorption bands changes as the electronic asymmetry of the dye changes [2]. The indicated principle should be observed more distinctly in the case of unsymmetrical dyes with a monotypic structure, the electronic asymmetry of which changes only under the influence of the introduction of substituents into one of the heteroresidues. With this in mind, in the present research we synthesized a number of substituted derivatives of flavyloindotrimethylidynecyanine (Ia), which contain a methoxy group in various positions of the flavylium residue (Ib-h). Dyes Ib-h were obtained by condensation of the corresponding substituted 4-methylflavylium salts [1] with 1,3,3-trimethyl-2-formylmethyleneindoline in acetic anhydride.



Ia-h

b $R=5\text{-}OCH_3$; c $R=6\text{-}OCH_3$; d $R=7\text{-}OCH_3$; e $R=8\text{-}OCH_3$; f $R'=2'\text{-}OCH_3$; g $R'=3'\text{-}OCH_3$; h $R'=4'\text{-}OCH_3$ (unindicated R, R'=H)

The spectral characteristics of solutions of dyes Ia-h in methylene chloride and acetonitrile are compared in Table 1. In the case of long-wave absorption bands that have two maxima we present the positions of these maxima and their extinctions, as well as the average positions of the bands (M^{-1}) (obtained by the method of moments), their deviations (D_M), the oscillator forces (f), the widths (σ), and the coefficients of asymmetry (γ_1), excess (γ_2), and fine structure (F). When one compares the average positions of the absorption bands, it is apparent that in both the slightly polar methylene chloride and the strongly polar acetonitrile the dyes obtained (except for Ie) are more deeply colored than unsubstituted dye Ia. The introduction of a methoxy group in the 8 position (dye Ie) has virtu-

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*See [1] for communication 17.

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