

C) A 10-mg sample of ester IVb was heated in a small test tube at 180°C for 10 min, after which it was cooled, 1 ml of ethyl acetate was added, and the contents were analyzed by TLC in system B. Compound IVb (R_f 0.13), IVa (R_f 0.20), and a small amount of V (R_f 0.42) were found in the reaction mixture.

Reactions of Ester IVa in Methanol. A) An ~10 mg sample of IVa was dissolved in 0.25 ml of methanol containing 5% sodium hydroxide, one drop of water was added, and the mixture was allowed to stand at room temperature for 24 h. It was then analyzed by TLC in system B. Ester IVa (R_f 0.20) and a small amount of V (R_f 0.42) were detected in the reaction mixture.

B) An ~10 mg sample of ester IVa was dissolved in 0.25 ml of methanol, a small crystal of p-toluenesulfonic acid was added, and the mixture was refluxed for 5 min. It was then cooled and analyzed by TLC in system B. Only VI (R_f 0.29) was found in the reaction mixture.

Reaction of Methyl 3-Methoxy-3-(2-furyl)propionate (VI) with a Methanol Solution of Sodium Hydroxide. An ~10 mg sample of ester VI was dissolved in 0.25 ml of methanol containing 5% sodium hydroxide, one drop of water was added, and the mixture was heated at 60°C for 5 min. It was then cooled and analyzed by TLC in system B. Only ester V (R_f 0.42) was detected in the reaction mixture.

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SYNTHESIS AND AMINOMETHYLATION OF 4,5-DIHYDROXYBENZOFURAN DERIVATIVES

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Reduction of the corresponding o-quinones of benzofuran gave 4,5-dihydroxybenzofuran derivatives, and methylation of the latter gave 4-hydroxy-5-methoxy and 4,5-dimethoxy derivatives of benzofuran. The aminomethylation of 4-hydroxy-5-methoxy derivatives of benzofuran was studied; a series of 7-aminomethyl derivatives was obtained.

In contrast to 4-hydroxy- and 5-hydroxybenzofuran derivatives, very little study has been devoted to 4,5-dihydroxybenzofuran derivatives. Moreover, they are evidently of interest as analogs of pyrocatechol derivatives.

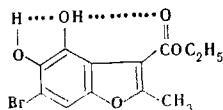
The most convenient method for the synthesis of 4,5-dihydroxybenzofurans is the reduction of benzofuran o-quinones [1, 2]. Another recently described synthesis of 4,5-dihydroxybenzofuran derivatives is not a preparative method [3].

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By reduction of the corresponding quinones with sodium hydrosulfite we obtained the previously known 2-methyl-3-carbethoxy-4,5-dihydroxy-6-bromobenzofuran (Ia) [2] and 2-methyl-3-carbethoxy-4,5-dihydroxy-6-chlorobenzofuran (Ib). Dihydroxy derivatives Ia, b are relatively unstable. Thus only resinous products are formed when aminomethylation is carried out with them. In order to stabilize Ia, b we studied the possibility of protection of the hydroxy groups by methylation.

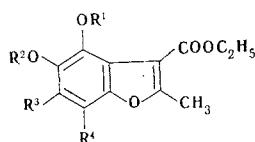
We found that the principal products when Ia, b are treated with excess methyl iodide in the presence of potassium carbonate are monomethoxy derivatives (Ic, d); only dimethoxy derivatives (Ie, f) were obtained by the action of dimethyl sulfate in the presence of a tenfold excess of potassium carbonate.

It is interesting to note that 4-hydroxy-5-methoxy derivatives Ic, d are formed in monomethylation; this was proved by IR and NMR spectroscopy. Two bands, viz., one at 3540 cm^{-1} (narrow) and the other at 3160 cm^{-1} (broad), correspond to OH groups in the IR spectrum of Ia (1% solution in CHCl_3). The positions of the bands do not change substantially (3540 and 3170 cm^{-1}) on passing to dilute solutions (0.02% in CCl_4). The bands were assigned, respectively, to the hydroxy group in the 5 position, linked by an intramolecular hydrogen bond to the oxygen atom of the adjacent hydroxy group in the 4 position, and to this hydroxy group, which participates in an intramolecular bond with the carbonyl group in the 3 position. This assignment is in agreement with the spectrum of pyrocatechol, in which [for a dilute solution (0.02% in CCl_4)] a band at 3575 cm^{-1} (intramolecular OH...OH bond) and a band at 3610 cm^{-1} (free hydroxy group) appear. In the investigated compound the free hydroxy group in the 4 position participates in an intramolecular hydrogen bond of the chelate type and shows up in the form of a band at 3170 cm^{-1} .



The spectrum of Ic does not contain a band at 3540 cm^{-1} , but the second broad band at 3140 cm^{-1} (1% solution in CDCl_3) and at 3180 cm^{-1} (0.02% solution in CCl_4) is retained. Thus it may be assumed that the hydroxy group in the 5 position is methylated. This conclusion is in agreement with data from the ^1H and ^{13}C NMR spectra. Thus in the ^1H spectrum of Ia the signal of a hydroxy group is observed at 10.8 ppm, which is characteristic for an OH group that participates in a chelate hydrogen bond [4]. This is also indicated by the ^{13}C NMR data. The signal of the carbon atom in the C=O group of Ia, c, e is observed at, respectively, 166.5, 166.3, and 162.9 ppm. The shift of the signal in the spectrum of benzofurans Ia, c to the weak-field region as compared with Ie is evidently due to participation of the C=O group in a hydrogen bond with the hydroxy group in the 4 position [5].

4-Hydroxy-5-methoxy derivatives of benzofuran were subjected to aminomethylation. A series of 7-aminomethyl derivatives (Ig-n) was obtained by the action of dialkylaminomethanes or formaldehyde and amines.



Ia-n

Ia $\text{R}^1=\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^3=\text{Br}$; b $\text{R}^1=\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^3=\text{Cl}$; c $\text{R}^1=\text{R}^4=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Br}$; d $\text{R}^1=\text{R}^4=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Cl}$; e $\text{R}^1=\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Br}$, $\text{R}^4=\text{H}$; f $\text{R}^1=\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Cl}$, $\text{R}^4=\text{H}$; g $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Br}$, $\text{R}^4=\text{CH}_2\text{N}-\text{CH}_2-$ $\text{O}-\text{HCl}$; h $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Br}$, $\text{R}^4=\text{CH}_2\text{N}-\text{CH}_2-$ $\text{O}-\text{HCl}$; i $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Br}$, $\text{R}^4=\text{CH}_2\text{N}-\text{CH}_2-$ $\text{N}-\text{CH}_3 \cdot 2\text{HCl}$; j $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Cl}$, $\text{R}^4=\text{CH}_2\text{NHC(CH}_3)_2\text{-HCl}$; k $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Br}$, $\text{R}^4=\text{CH}_2\text{N(CH}_3)_2$; l $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Cl}$, $\text{R}^4=\text{CH}_2\text{N(CH}_3)_2$; m $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Cl}$, $\text{R}^4=\text{CH}_2\text{N}-\text{CH}_2-$ O ; n $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{R}^3=\text{Cl}$, $\text{R}^4=\text{CH}_2\text{N}-\text{CH}_2-$ O .

TABLE 1. Characteristics of Ib-n

Compound	mp, ^a °C	Found, %					Empirical formula	Calc., %					Yield, %
		C	H	Br	Cl	N		C	H	Br	Cl	N	
Ib	182-184	53.2	4.4	—	12.7	—	C ₁₂ H ₁₁ ClO ₅	53.2	4.1	—	13.1	—	88
Ic	159-161	47.0	3.8	24.5	—	—	C ₁₃ H ₁₃ BrO ₅	47.4	4.0	24.3	—	—	75
Id	168-169	55.0	4.8	—	12.3	—	C ₁₃ H ₁₃ ClO ₅	54.8	4.6	—	12.5	—	84
Ie	57-58.5	49.0	4.3	23.2	—	—	C ₁₄ H ₁₅ BrO ₅	49.0	4.4	23.3	—	—	76
If	50-51	56.2	5.2	—	11.9	—	C ₁₄ H ₁₅ ClO ₅	56.3	5.1	—	11.9	—	75
Ig	194-196 ^b	49.3	5.3	17.1	7.6	3.0	C ₁₉ H ₂₅ BrClNO ₅	49.3	5.4	17.3	7.7	3.0	25
Ih	210-211 ^b	46.4	4.6	16.8	7.4	3.0	C ₁₈ H ₂₃ BrClNO ₆	46.5	5.0	17.2	7.6	3.0	25
Ii	175-177 ^b	44.4	5.6	15.4	13.7	5.4	C ₁₉ H ₂₇ BrCl ₂ N ₂ O ₅	44.4	5.3	15.5	13.8	5.4	40
Ij	199-200 ^b	52.5	5.9	—	17.7	3.6	C ₁₇ H ₂₉ Cl ₂ NO ₅	52.1	5.9	—	18.1	3.6	35
Ik	116-118	49.4	5.4	20.5	—	3.2	C ₁₆ H ₂₀ BrNO ₅	49.8	5.2	20.7	—	3.6	83
Il	132-134	56.2	5.8	—	10.3	4.1	C ₁₆ H ₂₀ ClNO ₅	56.2	5.9	—	10.4	4.1	76
Im	161-163	56.6	5.7	—	9.3	3.8	C ₁₈ H ₂₂ ClNO ₅	56.3	5.8	—	9.2	3.6	50
In	147-149	59.9	6.4	—	9.4	3.5	C ₁₉ H ₂₄ ClNO ₅	59.8	6.3	—	9.3	3.4	41

^aThe compounds were recrystallized: Ib from ethyl acetate, Ie and If from methanol, Ic, Id, and Ik-In from acetone, and Ij from alcohol. Compounds Ik-n were isolated in the base form, while Ig-j were isolated in the form of hydrochlorides. ^bDecomposition.

TABLE 2. ¹H Chemical Shifts (δ , ppm) of Ia, c, e

Compound	7- <i>H</i>	4,5-OH 4,5-OC ₂ H ₅	2-CH ₃	3-COOCH ₂ CH ₃
Ia	7.3	9.1 10.6	2.66	1.38 t 4.4 q
Ib	7.15	3.8	2.6	1.38 t 4.45 q
Ic	7.7	3.8 3.85	2.6	1.35 t 4.3 q

EXPERIMENTAL

The PMR spectra of solutions in DMSO were obtained with a Varian XL-100 spectrometer. The IR spectra were recorded with a Perkin-Elmer 457 spectrometer with tetramethylsilane as the internal standard.

2-Methyl-3-carbethoxy-4,5-dihydroxy-6-chlorobenzofuran (Ib). A solution of 24.0 g (0.137 mole) of sodium hydrosulfite in 300 ml of water was added with stirring at 18-20°C to a suspension of 14.8 g (0.055 mole) of 2-methyl-3-carbethoxy-4,5-dioxo-6-chlorobenzofuran in 300 ml of ethyl acetate, and the precipitate was removed by filtration, washed with water, and dried to give 14.0 g of Ib.

The characteristics and yields of the compounds obtained are presented in Tables 1 and 2.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromobenzofuran (Ic). A 6.7-g (0.05 mole) sample of anhydrous potassium carbonate was added to a refluxing solution of 7.5 g (0.024 mole) of 2-methyl-3-carbethoxy-4,5-dihydroxy-6-bromobenzofuran (Ia) in 750 ml of acetone, and the mixture was refluxed for 40 min. A 7.1-g (0.05 mole) sample of methyl iodide was added, and refluxing was continued for 14 h. The mixture was filtered, the solvent was evaporated, and the residue was recrystallized from acetone to give 5.6 g of Ia.

The acetone mother liquor was evaporated, and the residue was chromatographed with a column filled with silica gel by elution with benzene to give 0.55 g of Ie.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-chlorobenzofuran (Id). This compound was obtained by a method similar to that used to prepare Ic, e. The reaction of 19.3 g (0.07 mole) of Ib, 860 ml of acetone, 20 g (0.144 mole) of anhydrous potassium carbonate, and 21.8 g (0.153 mole) of methyl iodide gave 16.9 g of Id and 1.8 g of If as a side product.

2-Methyl-3-carbethoxy-4,5-dimethoxy-6-bromobenzofuran (Ie). A 31.5-g (0.23 mole) sample of anhydrous potassium carbonate was added to a refluxing solution of 7.2 g (0.023 mole) of Ia in 200 ml of acetone, the mixture was refluxed for 30 min, 12.1 g (0.096 mole) of dimethyl sulfate was added, and refluxing was continued for 14 h. The mixture was filtered, the solvent was evaporated, and the residue was recrystallized from methanol to give 5.95 g of Ie.

2-Methyl-3-carbethoxy-4,5-dimethoxy-6-chlorobenzofuran (If). This compound was obtained by a method similar to that used to prepare Ie. The reaction of 6.2 g (0.023 mole) of Ib, 200 ml of acetone, 31.5 g (0.23 mole) of anhydrous potassium carbonate, and 12.1 g (0.096 mole) of dimethyl sulfate gave 5.1 g of If.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromo-7-piperidinomethylbenzofuran Hydrochloride (Ig). A mixture of 3.3 g of (0.01 mole) of 2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromobenzofuran (Ic), 1.72 g (0.021 mole) of piperidine, 0.3 g (0.01 mole) of formalin, and 20 ml of dioxane was refluxed for 10 h, after which it was diluted with water. The precipitate was removed by filtration, washed with water, and dried. The hydrochloride was isolated in the usual way to give 1.15 g of Id. Compounds II, j, n were similarly obtained.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromo-7-morpholinomethylbenzofuran Hydrochloride (Ih). A mixture of 3.3 g (0.01 mole) of Ic, 20 g (0.1 mole) of dimorpholinomethane, and 50 ml of dioxane was refluxed for 10 h, after which it was diluted with water. The precipitate was removed by filtration, washed with water, and dried. The hydrochloride was isolated in the usual way to give 1.7 g of Ih. Compounds Ik-m were similarly obtained.

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