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SYNTHESIS OF 2-, 6-, AND 7-AMINOMETHYL DERIVATIVES IN THE 4,5-DIHYDROXYBENZOFURAN SERIES

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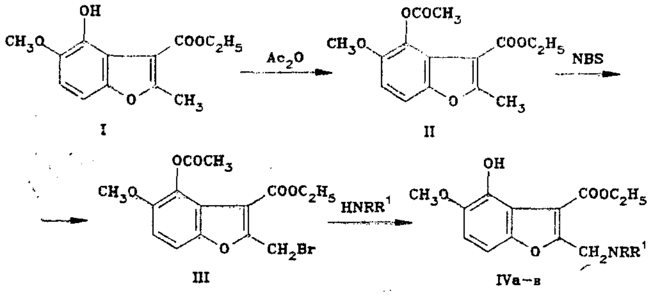
The 2-, 6-, and 7-aminomethyl derivatives have been synthesized from derivatives of 4-hydroxy-5-methoxy- and 4-methoxy-4-hydroxybenzofuran. 2-Methyl-3-carbethoxy-5-methoxy-7-dimethylaminomethylbenzofuran has been converted into the 7-cyanomethyl derivative.

Aminomethyl derivatives of benzofuran are of definite interest in the area of the search for drugs. One of them, viz., 2-phenyl-3-carbethoxy-4-dimethylaminomethyl-5-hydroxybenzofuran hydrochloride (phenykoberan), has found application in the practice of medicine [1]. We recently synthesized derivatives of 4-hydroxy-5-methoxy- and 4-methoxy-5-hydroxybenzofuran [2]. In the present work, we have used them as a basis for obtaining various, primarily the 2-, 6-, and 7-aminomethyl, derivatives.

The bromination of 2-methyl-3-carbethoxy-4-acetoxy-5-methoxybenzofuran (II) by N-bromosuccinimide in the presence of benzoyl peroxide gives 2-bromomethyl derivative III, and 2-dimethylaminomethyl-2-piperidinomethyl-, and 2-isopropylaminomethyl-4-hydroxy-5-methoxybenzofuran (IVa-c) are obtained by reacting the corresponding amines with III. When III is reacted with an excess of the amines, elimination of the acetyl group is observed along with the replacement of bromine by the residue of the amine.



IV a $R=R^1=CH_3$, b $R+R^1=(CH_2)_5$, c $R=H$, $R^1=CH(CH_3)_2$

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*Deceased.

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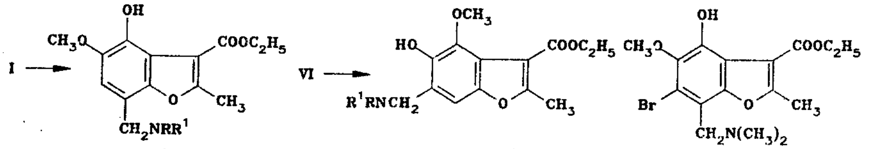
TABLE 1. Carbon-13 Chemical Shifts of Compounds Va, VIIa, and VIII

Compound	δ, ppm in $CDCl_3$							
	$C_{(2)}$	$C_{(3)}$	$C_{(3a)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(7a)}$
Va	162,6	108,8	113,8	138,9	143,0	113,2	111,1	147,7
VIIa	161,5	109,4	119,0	139,7	147,5	120,4	105,4	147,5
VIII	162,6	109,1	113,6	143,1	140,6	112,9	119,2	149.6

The aminomethylation of 2-methyl-3-carbethoxy-4-hydroxy-5-methoxybenzofuran (I) by bis(dimethylamino)methane and a mixture of formalin with piperidine gives 7-aminomethyl derivatives Va and b, and the aminomethylation of isomeric 2-methyl-3-carbethoxy-4-methoxy-5-hydroxybenzofuran (VI) by bis(dimethylamino)methane and dimorpholinomethane gives 6-aminomethyl derivaties VIIa and b.



Va, b VIIa, b VIII

Va, VIIa $R=R^1=CH_3$; Vb $R+R^1=(CH_2)_5$, VIIb $R+R^1=(CH_2)_2O(CH_2)_2$

In order to determine the positions of the substituents in compounds Va, Vb, VIIa and VIIb, we compared the ^{13}C spectra of compounds Va and VIIa and the spectra of VIII, which was previously obtained in [3].

The signals in the ^{13}C spectrum of unsubstituted benzofuran for the $C_{(3)}$, $C_{(3a)}$, $C_{(4)}$, $C_{(5)}$, $C_{(6)}$, and $C_{(7)}$ atoms and for the $C_{(2)}$ and $C_{(7a)}$ atoms are known to be observed in the 106-127 and 145-155 ppm ranges, respectively [4]. An evaluation of the chemical shifts of the aromatic carbon atoms with the use of the increments of the substituents for benzene [5] reveals that in the spectrum of VIII the $C_{(4)}$ and $C_{(5)}$ signals should fall in the weaker-field group along with the signals of the $C_{(2)}$ and $C_{(7a)}$ atoms. To assign the signals having similar chemical shifts and the same multiplicity, we also took into account the dependence of the values of the spin–spin coupling constants of the carbon atoms of benzofuran with the protons of the substituents on the number of bonds [6]. On the basis of all the considerations just enumerated, the signals at 162.6 162.6 (q, $^2J_{C_{(2)}, 2\text{-}CH_3} = 7.5$ Hz, 109.1 (q, $^3J_{C_{(3)}, 2\text{-}CH_3} = 2.5$ Hz), 112.9 (t, $^3J_{C_{(7a)}, 7\text{-}CH_2} = 4.5$ Hz) 119.2 (t, $^2J_{C_7, 7\text{-}CH_2} = 6$ Hz), and 149.6 (t, $^3J_{C_{(7a)}, 7\text{-}CH_2} = 4.5$) were assigned to the $C_{(2)}$, $C_{(3)}$, $C_{(6)}$, $C_{(7)}$, and $C_{(7a)}$ atoms, respectively. It should be noted that the spectrum ot compound VIII in $CDCL_3$ displays additional splitting of the signals of $C_{(4)}$ ($^2J_{C_{(4)}, 4\text{-}OH} = 4$ Hz), as well as of $C_{(3a)}$ and $C_{(5)}$ ($^3J_{C_{(3a)}, 4\text{-}OH} = {^3J_{C_{(5)}, 4\text{-}OH}} = 2.5$ Hz), by the proton of the OH group, which participates in a chelating hydrogen bond with the oxygen atom of the carbethoxy group at $C_{(3)}$ [3]. This splitting is absent in the spectrum of VIII in CD_3OD, where at singlet at 112.9, the signlet at 142.5, and the quartet at 139.4 ppm ($^3J_{C_{(5)}, 5\text{-}OCH_3} = 4$ Hz) belong to the $C_{(3a)}$, $C_{(4)}$, and $C_{(5)}$ atoms.

The spectrum of compound Va is similar in many ways to the spectrum of VIII. Here we also observe additional splitting of the signals of the $C_{(3a)}$, $C_{(4)}$, and $C_{(5)}$ atoms due to the proton of the hydroxyl group, which vanishes in the spectrum recorded in CD_3OD. The chemical shifts of the signals of most of the carbon atoms of the benzene fragment change only slightly upon the transition from Va to VIII (Table 1). The multiplicity* of these signals is consistent exclusively with placement of the aminomethyl group at $C_{(7)}$. The signal of $C_{(3a)}$ is a singlet, the signal of $C_{(4)}$ is a doublet ($J_{C_{(4)}, 6\text{-}H} = 8$ Hz), the signal of $C_{(5)}$ is a quartet ($^3J_{C_{(5)}, 5\text{-}OCH_3} = 4$, $^2J_{C_{(5)}, 6\text{-}H} = 4$ Hz), the signal of $C_{(6)}$ is a doublet of triplets ($^1J_{C_{(6)}, 6\text{-}H} = 158$, $^3J_{C_{(6)}, 7\text{-}CH_2} = 5$ Hz), the signal of $C_{(7)}$ is a sextet ($^2J_{C_{(7)}, 7\text{-}CH_2}$ =

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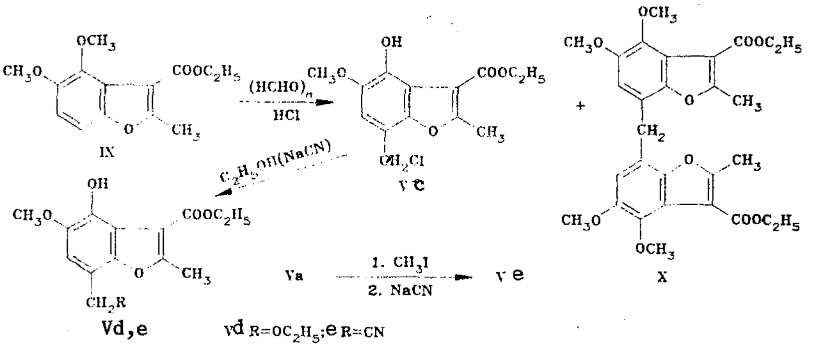
*The splitting of the signals in CD_3OD is given.

4.5, $^{2}J_{C_{(7)},6\text{-}H}$ = 1.5 Hz;, and the signal of $C_{(7a)}$ is a sextet ($^{3}J_{C_{(7a)},6\text{-}H}$ = 11.5, $^{3}J_{C_{(7a)},7\text{-}CH_2}$ 4.5 Hz). The spectrum of compound VIIa differs significantly from the spectrum of Va with respect to the values of the chemical shifts (Table 1) and especially with respect to the character of the multiplicity of the signals of the carbon atom of the benzene fragment, which can be unequivocally attributed only to the presence of an aminomethyl substiuent in position 6 in compound VIIa. The splitting of the signals of $C_{(7)}$, $C_{(3a)}$, and $C_{(5)}$, which are observed, respectively, in the form of a doublet ($^{2}J_{C_{(7a)},7\text{-}H}$ = 3 Hz) at 147.5, a doublet ($^{3}J_{C_{(3a)},7\text{-}H}$ = 5.5 Hz) at 119, and a quartet ($^{3}J_{C_{(5)},6\text{-}CH_2}$ = 4, $^{3}J_{C_{(5)},7\text{-}H}$ = 8 Hz) at 147.5 ppm, are the most characteristic from this point of view.

We also carried out the chloromethylation of 2-methyl-3-carbethoxy-4,5-dimethoxybenzofuran (IX) and obtained 7-chloromethylated derivative Vc and bis(benzofurnanyl)methane derivative X. Demethylation of the methoxy group in position 4 by hydrogen chloride was observed during the reaction.



According to the literature data, the chloromethylation of derivatives of 4-methoxy- and 5-methoxybenzofuran produces derivatives of bis(benzofuranyl)methane exclusively [7].

Compound Vc reacts with nucleophilic reagents, viz., ethanol and sodium cyanide. These reactions result in the formation of 2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-ethoxymethylbenzofuran (Vd) and 2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-cyanomethylbenzofuran (Ve) with high yields.

We also obtained 7-cyanomethylbenzofuran derivative Ve from 7-dimethylaminomethyl derivative Va. Compound Va reacts with methyl iodide in dioxane to form a methiodide, which is converted without isolation under the action of sodium cyanide into compound Ve.

The structures of the compounds synthesized were confirmed by the data from ^{1}H NMR spectra (Table 3).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on Varian XL-200 and XL-100 spectrometers, respectively, in $CDCl_3$ with TMS as an internal reference. The course of the reaction was monitored chromatographically on Silufol-254 plates in a 9:1 benzene—methanol system with development in UV light.

The characteristics and yields of the compounds obtained are presented in Tables 1-3.

2-Methyl-3-carbethoxy-4-acetoxy-5-methoxybenzofuran (II). A mixture of 2.5 g (10 mmole) of methoxybenzofuran I, 10 ml of acetic anhydride, and 0.01 ml of concentrated H_2SO_4 was heated at 60°C with stirring for 2.5 h. The reaction mixture was diluted by 100 ml of water, and the precipitate was filtered out, washed with water, and dried. This gave 2.15 g (73.6%) of II.

2-Bromomethyl-3-carbethoxy-4-acetoxy-5-methoxybenzofuran (III). A mixture of 5.45 g (19 mmole) of acetoxybenzofuran II, 3.4 g (19 mmmole) of N-bromosuccinimide, 11 ml of carbon tetrachloride, and 1 mg of benzoyl peroxide was boiled for 10 h. The hot reaction mixture was filtered, the mother solution was evaporated to dryness, and the residue was recrystallized from ethanol. This gave 6.1 g (88%) of compound III.

2-Dimethylaminomethyl-3-carbethoxy-4-hydroxy-5-methoxybenzofuran (IVa). A solution of 1.85 g (5 mmole) of derivative III in 15 ml of dry benzene was given an addition of a solution of 0.68 g (15 mmole) of dimethylamine in 10 ml of benzene with stirring. The reaction

TABLE 2. Characteristics of Compounds II, III, IVa-c, Va-e, VIIa, VIIb, and X

Compound	mp,* °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl(Br)	N		C	H	Cl(Br)	N	
II	129—131	61,9	5,5	—	—	$C_{15}H_{16}O_6$	61,6	5,5	—	—	73,6
III	96—97	48,4	4,1	(21,5)	—	$C_{15}H_{15}BrO_6$	48,5	4,1	(21,5)	—	88,0
IVa	170—173 †	54,4	6,2	10,8	4,2	$C_{15}H_{20}ClNO_5$	54,6	6,1	10,8	4,2	51,0
IVb	181—182 †	58,7	6,6	9,3	3,9	$C_{18}H_{24}ClNO_5$	58,5	6,5	9,6	3,8	60,0
IVc	180—182 †	56,0	6,3	9,9	4,0	$C_{16}H_{22}ClNO_5$	55,9	6,4	10,3	4,0	45,0
Va	205—207 †	55,8	6,7	10,3	3,7	$C_{16}H_{22}ClNO_5$	55,9	6,4	10,3	4,0	69,5
Vb	220—221 †	59,7	6,9	9,4	3,8	$C_{19}H_{26}ClNO_5$	59,5	6,8	9,2	3,7	49,5
Vc	126—128	56,9	5,0	11,3	—	$C_{14}H_{15}ClO_5$	56,3	5,1	11,8	—	16,8
Vd	85—86	62,8	6,3	—	—	$C_{16}H_{20}O_6$	62,3	6,5	—	—	87,5
Ve	174—176	62,3	5,3	—	4,8	$C_{15}H_{15}NO_5$	62,3	5,2	—	4,8	77,0
VIIa	175—176 †	55,7	6,4	10,0	3,9	$C_{16}H_{22}ClNO_5$	55,9	6,4	10,3	4,0	48,0
VIIb	136—138	61,5	6,6	—	3,9	$C_{18}H_{23}NO_6$	61,9	6,6	—	4,0	25,0
X	257—259	64,2	5,7	—	—	$C_{29}H_{32}O_{10}$	64,4	6,0	—	—	18,5

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*Compounds II, III, Va, Vb, and VIIb were recrystallized from ethanol; IVa-c, Ve, and VIIa were recrystallized from acetone; Vc and Vd were recrystallized from hexane; X was recrystallized from ethyl acetate. Compounds IV_{a-c}, Va, Vb, and VIIa were characterized in the form of the hydrochlorides, and VIIb was characterized in the form of the base.

†Decomposition.

TABLE 3. Proton Chemical Shifts of Compounds III, Vc, Vd, and Ve

Compound	δ, ppm, in $CDCl_3$				
	2-CH_3, 2-CH_2Br, s	3-$COOC_2H_5$	5-OCH_3, s	6-H	7-H, 7-CH_2Cl, 7-CH_2CN, 7-$CH_2OC_2H_5$
III	4,82	4,40 q 1,42 t	3,87	7,33 d, 7,10 d (J_{ortho}=8 Hz)	
Vc	2,73	4,42 q 1,45 t	3,92	6,94 s	4,79 s
Vd	2,70	4,42 q 1,44 t	3,92	6,95 s	4,66 s, 3,55 q, 1,25 t
Ve	2,72	4,42 q 1,45 t	3,92	6,92 s	3,87 s

mixture was left to stand for 24 h at 20°C and then washed with water (two 50-ml portions, and the benzene) layer was separated, dried over magnesium sulfate, and evaporated to dryness. The residue was dissolved in 20 ml of acetone and given an addition of concentrated hydrochloric acid to pH 3. The precipitate isolated was filtered, washed with acetone, and dried. This gave 0.84 g (51%) of the hydrochloride of IVa.

Compounds IV and IVc were obtained in a similar manner.

2-Methyl-3-carbethoxy-4-hydroxy-t-methoxy-7-dimethylaminomethylbenzofuran (Va). A solution of 15.0 g (60 mmole) of methoxybenzofuran I in 250 ml of dioxane was given an addition of 24.5 g (240 mmole) of bis(dimethylamino)methane and boiled for 20 h. The reaction mixture was diluted with 1 liter of water, and the precipitate formed was filtered out, washed with water, dried, and recrystallized from acetone. The base obtained was dissolved in 100 ml of acetone, and the pH was adjusted to 3 with concentrated hydrochloric acid. The precipitate formed was filtered out, washed with acetone, and dried. This gave 14.3 g (69.5%) of the hydrochloride of compound Va.

Compounds VIIa and VIIb were obtained in a similar manner from 2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-piperidinomethylbenzofuran (VI).

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-piperidinomethylbenzofuran (Vb). A solution of 2.75 g (11 mmole) of compound I in 50 ml of dioxane was given an addition of 1.72 g (21 mmole of piperidine and 0.7 ml of formalin and boiled for 25 h. The reaction mixture was diluted with 200 ml of water, and the precipitate isolated was filtered out, washed with water, and dried. The precipitate was dissolved in 20 ml of acetone, the pH was adjusted to 3 with concentrated hydrochloric acid, and the precipitated substance was filtered out, washed with acetone, and dried. This gave 2.1 g (49.5%) of the hydrochloride of compound **Vb**.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-chloromethylbenzofuran (Vc) and Bis(2-methyl-3-carbethoxy-4,5-dimethoxybenzofuran-7-yl)methane (X). A solution of 2.64 g (10 mmole) of dimethoxybenzofuran IX in 10 ml of dry benzene was saturated with dry hydrogen chloride and given an addition of 0.4 g (13 mmole) of paraformaldehyde at 5°C with stirring. The passage of hydrogen chloride through the reaction mixture was continued for 1 h at 5-10°C. The precipitate formed was filtered out, washed with 30 ml of benzene, and dried. This gave 1.0 g (18.5%) of compound X. The mother solution was washed with water (five 100 ml portions), and the benzene layer was separated, dried, and evaporated to dryness. The residue was recrystallized from hexane. This gave 0.5 g (16.8%) of Vc.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-ethoxymethylbenzofuran (Vd). A solution of 1.0 g (3 mmole) of chloromethyl derivative Vc in 30 ml of ethanol was boiled for 2 h. The alcohol was evaporated to dryness, and the residue was recrystallized from hexane. This gave 0.9 g (87.5%) of Vd.

2-Methyl-3-carbethoxy-4-hydroxy-5-methoxy-7-cyanomethylbenzofuran (Ve). A. A solution of 1.48 g (5 mmole of Vc in 30 ml of dioxane was given an addition of a solution of 0.245 g (4 mmole) of sodium cyanide in 3 ml of water, and the mixture was boiled for 14 h. The reaction solution was diluted with 200 ml of water, and the precipitate formed was filtered out, washed with water, dried, and recrystallized from acetone. This gave 0.9 g (63%) of compound Ve.

B. A solution of 6.6 g (21 mmole) of Va in 40 ml of dioxane was given an addition of 6.1 g (42 mmole) of methyl iodide with stirring. The precipitated methiodide was filtered out, washed with dioxane, dissolved in 75 ml of dioxane, and given an addition of a solution of 1.03 g (21 mmole) of sodium cyanide in 7.5 ml of water. The mixture was boiled for 3.5 h. Then the reaction mixture was diluted with water (300 ml), and the precipitate formed was filtered out, washed with water, dried, and recrystallized from acetone. This gave 4.8 g (77%) of Ve. A mixed sample with the product obtained according to method A does not display any melting-point depression.

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