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SYNTHESIS OF 2-CARBETHOXY-3-METHYL-4-HYDROXYBENZOFURAN DERIVATIVES

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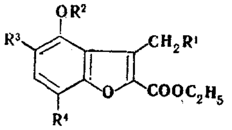
A number of 2-carbethoxy-3-methylbenzofuran derivatives were synthesized. A 5,5-gem-dibromo derivative was obtained in the bromination of 2-carbethoxy-3-methyl-4-oxo-4,5,6,7,tetrahydrobenzofuran. Dehydrobromination of this dibromo derivative gave 2-carbethoxy-3-methyl-4-hydroxy-5-bromobenzofuran. Depending on the structure of the starting compound and the brominating agent, the bromine in the bromination of 2-carbethoxy-3-methyl-4-hydroxy- and 4-acetoxybenzofurans with bromine and N-bromosuccinimide is incorporated either in the methyl group or in 5 and 7 positions of the benzofuran ring. The nitration of 2-carbethoxy-3-methyl-4-hydroxybenzofuran and its bromo derivative leads to 5-nitro- and 5,7-dinitrobenzofuran derivatives. The structures of the synthesized benzofuran derivatives were established by means of the PMR spectra.

In connection with the interest in 4-hydroxybenzofuran derivatives as biologically active compounds [1, 2], we synthesized a number of 2-carbethoxy-3-methyl-4-hydroxybenzofuran derivatives (I).

We used 2-carbethoxy-3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran as the starting compound [3]. To convert this compound to the 4-hydroxy derivative by the method that we proposed in [4] we studied the bromination of 2-carbethoxy-3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran. However, in this case we were able to obtain only a 5,5-gem-dibromo derivative (II), the dehydrobromination of which leads to 2-carbethoxy-3-methyl-4-hydroxy-5-bromobenzofuran (IIIa). Compound IIIa is also formed in the bromination of 2-carbethoxy-3-methyl-4-hydroxybenzofuran [5] with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide. However, in the case of bromination of 2-carbethoxy-3-methyl-4-acetoxybenzofuran (IIIb) under similar conditions the substituent is not incorporated in the benzene ring but rather in the methyl group in the 3 position to give 2-carbethoxy-3-bromomethyl-4- acetoxybenzofuran (IIIc).

The bromination of I with an equimolar amount of bromine leads to the formation of a mixture of substances, from which we were able to isolate only 2-carbethoxy-3-methyl-4-hydroxy-7-bromobenzofuran (IIId). A 5,7-dibromo derivative (IIIe) is formed in high yield by the action of excess bromine on I.



IIIa-h

IIIa $R^1=R^2=R^4=H$, $R^3=Br$; b $R^1=R^3=R^4=H$, $R^2=COCH_3$; c $R^1=Br$, $R^2=COCH_3$, $R^3=R^4=H$; d $R^1=R^2=R^3=H$, $R^4=Br$; e $R^1=R^2=H$, $R^3=R^4=Br$; f $R^1=R^2=R^4=H$, $R^3=NO_2$; g $R^1=R^2=H$, $R^3=R^4=NO_2$; h $R^1=R^2=H$, $R^3=NO_2$, $R^4=Br$

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In addition to signals of protons of methyl and methylene groups, doublet signals of the protons in the 5 (6.65 ppm) and 7 (6.94 ppm) positions and a triplet of the proton in the 6 position (7.22 ppm) are observed in the PMR spectrum of benzofuran I. (We substantiated the assignment of the signals of 4-hydroxybenzofurans in [6].) The doublet signals at 7.16 ppm (IIIa) and 6.56 ppm (IIId) in the spectra of monobromo derivatives IIIa and IIId were assigned to the 7-H and 5-H protons, respectively, on the basis of a comparison with the spectrum of I. With respect to the position and multiplicity of the signals, the spectrum of bromomethyl derivative IIIc is similar to the spectrum of I but differs with respect to the presence of a singlet signal from the protons of the methylene group at 5.05 ppm and the absence of the singlet signal of the protons of the methylene group in the 3 position.

The nitration of benzofuran I with nitric acid proceeds unambiguously. 2-Carbethoxy-3-methyl-4-hydroxy-5-nitrobenzofuran (IIIf) and 2-carbethoxy-3-methyl-4-hydroxy-5,7-dinitrobenzofuran (IIIg) were isolated from the mixture of reaction products.

The doublet signals at 7.21 (7-H) and 8.19 ppm (6-H) in the PMR spectrum of 5-nitro derivative IIIf are in good agreement with the contribution of the magnetic anisotropies of o- and m-oriented nitro groups. The chemical shift of the 6-H proton (9.01 ppm) in the PMR spectrum of dinitro derivative IIIg is due to the overall effect of two o-nitro groups.

The same compound, viz., 2-carbethoxy-3-methyl-4-hydroxy-5-nitro-7-bromobenzofuran (IIIh), was obtained by the action of nitric acid on bromo derivatives IIId and IIIe. Thus, in the first case the free 5 position underwent nitration, whereas in the second case the bromine atom in the 5 position was replaced by a nitro group.

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

2-Carbethoxy-3-methyl-4-oxo-5,5-dibromo-6,7-dihydrobenzofuran (II). A solution of 9.6 g (60 mmole) of bromine in 20 ml of CCl_4 was added dropwise with stirring in the course of an hour at 40°C to a solution of 6.66 g (30 mmole) of 2-carbethoxy-3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran in 90 ml of CCl_4, and the mixture was stirred for 1 h. The resulting solution was washed with water, dried over magnesium sulfate, and evaporated. The residue was recrystallined from hexane to give 7.0 g of dibromo derivative II. The characteristics of the compounds obtained are presented in Table 1.

2-Carbethoxy-3-methyl-4-hydroxy-5-bromobenzofuran (IIIa). A) A 7.0-g (18.5 mmole) sample of dibromo derivative II was added to a solution of 1.04 g (18.5 mmole) of potassium hydroxide in 30 ml of alcohol, and the mixture was refluxed for 2 h. It was then cooled to 10°C, diluted with 100 ml of water, and the aqueous solution was acidified to pH 5 with hydrochloric acid. The precipitate was removed by filtration, washed with water, dried, and recrystallized from hexane to give 3.0 g (54%) of IIIa.

B) A 5.4-g (30 mmole) sample of N-bromosuccinimide (NBS) and 0.01 g benzoyl peroxide were added to a solution of 6.6 g (30 mmole) of benzofuran I in 100 ml of CCl_4, and the mixture was refluxed for 1 h. The resulting solution was filtered and evaporated, and the

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C[a]	PMR spectrum, δ, ppm[b]						Found, %				Empirical formula	Calc., %				Yield, %
		5-H	6-H	7-H	CH_2 in C_2H_5	CH_3 in C_2H_5	3-CH_3	C	H	Br	N		C	H	Br	N	
I		6,65	7,22	6,94	4,35	1,35	2,73										
II	85—87	—	3,2		4,39	1,36	2,53	37,9	3,3	42,0	—	$C_{12}H_{12}Br_2O_4$	37,9	3,2	42,0	—	61,5
IIIa	118—120	—	7,51	7,16	4,38	1,34	2,68	48,0	3,9	27,1	—	$C_{12}H_{11}BrO_4$	48,2	3,7	26,7	—	89,5
IIIb	70—72							64,1	5,3	—	—	$C_{14}H_{14}O_5$	64,1	5,4	—	—	93,5
IIIc	106—108	7,52—7,57	7,18	7,52—7,57	4,45	1,43	5,05[c]	49,5	4,0	22,9	—	$C_{14}H_{13}BrO_5$	49,3	3,8	23,4	—	82,0
IIId	213—214	6,56	7,26	—	4,36	1,40	2,67	47,7	3,9	27,2	—	$C_{12}H_{11}BrO_4$	48,2	3,7	26,7	—	27,5
IIIe	170—172	—	7,59	—	4,39	1,42	2,70	38,2	2,6	41,8	—	$C_{12}H_{10}Br_2O_4$	38,1	2,7	42,3	—	74,0
IIIf	157—158	—	8,19	7,21	4,40	1,39	2,75	54,1	4,1	—	5,1	$C_{12}H_{11}NO_6$	54,3	4,2	—	5,3	19,0
IIIg	191—193	—	9,01	—	4,44	1,41	2,78	46,8	3,7	—	9,0	$C_{12}H_{10}N_2O_8$	46,5	3,3	—	9,0	10,0
IIIh	127—129	—	8,31	—	4,42	1,39	2,72	41,7	3,1	23,1	3,9	$C_{12}H_{10}BrNO_6$	41,9	2,9	23,2	4,1	48.5

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[a] Compounds II and IIIa were crystallized from hexane, while I and IIIb-h were crystallized from alcohol. [b] In d_6-DMSO (IIIa-e) and in d_6-acetone (I and IIIf-h). [c] 3-CH_2Br.

residue was recrystallized from hexane to give 8.0 g of IIIa. No melting-point depression was observed for a mixture of this product with the substance obtained in the preceding experiment.

2-Carbethoxy-3-methyl-4-acetoxybenzofuran (IIIb). A mixture of 6.6 g (30 mmole) of I, 26 ml of acetic anhydride, and 0.1 ml of triethylamine was refluxed for 2 h, 100 ml of water was added, and the precipitate was removed by filtration, washed with water, dried, and recrystallized from alcohol to give 7.35 g of IIIb.

2-Carbethoxy-3-bromomethyl-4-acetoxybenzofuran (IIIc). A 0.89-g (5 mmole) sample of NBS and 0.02 g of benzoyl peroxide were added to a solution of 1.31 g (5 mmole) of IIb in 40 ml of CCl_4, and the mixture was refluxed for 6 h. The solution was filtered and evaporated, and the residue was recrystallized from alcohol to give 1.4 g of IIIc.

2-Carbethoxy-3-methyl-4-hydroxy-7-bromobenzofuran (IIId). A solution of 7 g of bromine in 10 ml of chloroform was added dropwise with stirring at 20°C to a solution of 9.6 g (43.5 mmole) of I in 35 ml of chloroform, and stirring was continued for 1 h. The precipitate was removed by filtration, dried, and recrystallized from chloroform to give 4.0 g of IIId.

2-Carbethoxy-3-methyl-4-hydroxy-5,7-dibromobenzofuran (IIIe). A solution of 4.8 g (30 mmole) of bromine in 5 ml of acetic acid was added dropwise with stirring at 20°C to a solution of 2.2 g (10 mmole) of benzofuran I in 50 ml of acetic acid, and the mixture was stirred for 2 h. The precipitate was removed by filtration, washed with water, dried, and recrystallized from alcohol to give 2.8 g of IIIe.

2-Carbethoxy-3-methyl-4-hydroxy-5-nitrobenzofuran (IIIf) and 2-Carbethoxy-3-methyl-4-hydroxy-5,7-dinitrobenzofuran (IIIg). A solution of 1.7 ml of nitric acid (sp. gr. 1.35) in 5 ml of acetic acid was added dropwise with stirring at 15°C in the course of 30 min to a solution of 4.4 g (20 mmole) of benzofuran I in 25 ml of acetic acid, and stirring was continued for 2 h. The solution was diluted with 150 ml of water, and the liberated substance was extracted with benzene. The benzene extracts were washed with water and dried over magnesium sulfate. Workup of the benzene eluate obtained after chromatography with a column filled with silica gel yielded successively 1.0 g of IIIf and 0.6 g of IIIg.

2-Carbethoxy-3-methyl-4-hydroxy-5-nitro-7-bromobenzofuran (IIIh). A) A solution of 1.0 g (9 mmole) of nitric acid (sp. gr. 135) in 5 ml of acetic acid was added dropwise with stirring at 20°C to a suspension of 1.75 g (6 mmole) of IIId in 15 ml of acetic acid, and stirring was continued for 1 h. The precipitate was removed by filtration, washed with water, and dried. Workup of the benzene eluate after chromatography with a column filled with silica gel yielded 1.0 g of IIIh.

B) For this experiment we used 4.4 g (12 mmole) of IIIe, 2.0 g (18 mmole) of nitric acid (sp. gr. 1.35), and 60 ml of acetic acid. The reaction and the isolation of the substance were accomplished under the conditions of the preceding experiment. Workup gave 0.7 g of IIIh. No melting-point depression was observed for a mixture of this product with a sample of the product obtained in the preceding experiment.

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