SYNTHESIS OF 2-CARBETHOXY-3-METHYL-4-HYDROXY-6-PHENYLBENZOFURAN DERIVATIVES

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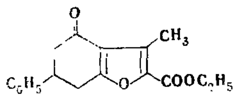
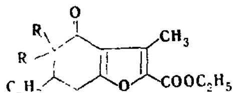
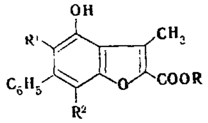
4-Hydroxybenzofuran derivatives were synthesized, and their reactions with bromine and nitric acid were studied.

In connection with the interest in 4-hydroxybenzofurans as intermediates in the synthesis of diverse benzofuran derivatives and the fact that little study had been devoted to the electrophilic substitution reactions of 4-hydroxybenzofuran prior to our research [1], we carried out the synthesis of 2-carbethoxy-3-methyl-4-oxo-6-phenyl-4,5,6,7-tetrahydrobenzofuran (I) by condensation of 5-phenylcyclohexane-1,3-dione with α-chloroacetic ester in the presence of potassium hydroxide, i.e., by the usual method [2]. We established that the bromination of I gives, depending on the reaction conditions and the reagent ratio, either monobromo derivative IIa or gem-dibromo derivative IIb. We also found that bromo derivatives IIa and IIb of tetrahydrobenzofuran are converted in high yields to 4-hydroxybenzofuran-2-carbethoxy-3-methyl-4-hydroxy-6-phenylbenzofuran (IIIa) and 2-carbethoxy-3-methyl-4-hydroxy-5-bromo-6-phenylbenzofuran (IIIb) derivatives on treatment with potassium hydroxide. 2-Carboxy-3-methyl-4-hydroxy-5-bromo-6-phenylbenzofuran (IIIc) was obtained by treatment of IIIb with excess potassium hydroxide. The bromination of 4-hydroxybenzofuran derivative IIIa was studied, and it was found that, depending on the amount of bromine used for the reaction, 5-monobromo derivative IIIb mixed with 2-carbethoxy-3-methyl-4-hydroxy-5,7-dibromo-6-phenylbenzofuran (IIId) or only the 5,7-dibromoderivative (IIId) is formed.

Quinones of the benzofuran series – 2-carbethoxy-3-methyl-4,7-dioxo-5-bromo-6-phenylbenzofuran (IV) and 2-carbethoxy-3-methyl-4,5-dioxo-6-phenyl-7-bromobenzofuran (V) – were obtained by the action of nitric acid on 2-carbethoxy-3-methyl-4-hydroxy-5-bromo-6-phenylbenzofuran (IIIb) and 2-carbethoxy-3-methyl-4-hydroxy-5-7-dibromo-6-phenylbenzofuran (IIId). Quinone V was characterized by the synthesis of phenazine VI. 2-Carbethoxy-3-methyl-4,5-dihydroxy-6-phenyl-7-bromobenzofuran (IIIe) was obtained by reduction of V with sodium hydrosulfite. The nitration of 2-carbethoxy-3-methyl-4-hydroxy-6-phenylbenzofuran (IIIa) proceeds ambiguously. Isomeric mononitro derivatives – 2-carbethoxy-3-methyl-4-hydroxy-5-nitro-6-phenylbenzofuran (IIIf) and 2-carbethoxy-3-methyl-4-hydroxy-6-phenyl-7-nitrobenzofuran (IIIg) – and the 5,7-dinitroderivative (IIIh) were isolated as a result of the reaction.


I


IIa,b


IIIa-i

II a $R=Br$, $R^1=H$; b $R=R^1=Br$; III a $R=C_2H_5$, $R^1=R^2=H$; b $R=C_2H_5$, $R^1=Br$, $R^2=H$; c $R=R^2=H$, $R^1=Br$; d $R=C_2H_5$, $R^1=R^2=Br$; e $R=C_2H_5$, $R^1=OH$, $R^2=Br$; f $R=C_2H_5$, $R^1=NO_2$, $R^2=H$; g $R=C_2H_5$, $R^1=H$, $R^2=NO_2$; h $R=C_2H_5$, $R^1=R^2=NO_2$; i $R=H$ $R^1=Br$, $R^2=NO_2$

The nitration of IIIc gives 2-carboxy-3-methyl-4-hydroxy-5-bromo-6-phenyl-7-nitrobenzofuran (IIIi).

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The PMR spectrum of IIIa contains two signals at δ 6.98 and 7.27 ppm with a spin–spin coupling constant of 2.0 Hz; these signals are related, respectively, to the 5-H and 7-H protons. The presence in the spectrum of IIIg of a singlet at δ 6.62 ppm, which was assigned to 5-H, indicates incorporation of the nitro group in the 7 position. A signal at 7.09 ppm, which corresponds to the presence of a nitro group in the 5 position, is observed in the spectrum of isomeric IIIf.

In analogy with the spectrum of IIIf, the singlets observed in the spectrum of IIIc and IIIb at 7.05 and 7.02 ppm, respectively, were assigned to the signals of the 7-H proton. Only the multiplet of a phenyl group is present in the PMR spectrum of IIb in the region of aromatic proton signals. In addition to this, multiplets of cyclohexane ring 6-H and 7-H protons are observed at δ 3.35 and 4.08 ppm.

EXPERIMENTAL

The PMR spectra of deuteroacetone solutions of the compounds were recorded with a C-60-HL spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer.

2-Carbethoxy-3-methyl-4-oxo-6-phenyl-4,5,6,7-tetrahydrobenzofuran (I). A 75.6-g (0.4 mole) sample of 5-phenylcyclohexane-1,3-dione and a solution of 55.5 ml of α-chloroacetoacetic ester in 150 ml of methanol were added with stirring to a solution of 22.5 g (0.4 mole) of potassium hydroxide in 75 ml of water, after which the mixture was stirred for 2 h and allowed to stand for 24 h. The solvent was then removed by vacuum distillation, 225 ml of glacial acetic acid was added to the residue, and the mixture was refluxed for 1 h. It was then poured into water, and the resulting precipitate was removed by filtration and dried to give 51.3 g (43%) of I with mp 93-95° (from ethyl acetate). Found: C 72.3; H 6.1%. $C_{18}H_{18}O_4$. Calculated: C 72.5; H 6.1%.

2-Carbethoxy-3-methyl-4-oxo-5-bromo-6-phenyl-4,5,6,7-tetrahydrobenzofuran (IIa). A 16.9-g (0.105 mole) sample of bromine was added dropwise with stirring in the course of 1.5 h to a suspension of 30 g (0.1 mole) of I in 300 ml of ether, after which the mixture was stirred for 1 h. The solid material was removed by filtration, washed with ether, and dried to give 16.6 g (44%) of IIa with mp 150-151.5° (from methanol). Found: C 57.6; H 4.6; Br 21.3%. $C_{18}H_{17}BrO_4$. Calculated: C 57.3; H 4.5; Br 21.2%.

2-Carbethoxy-3-methyl-4-oxo-5,5-dibromo-6-phenyl-6,7-dihydrobenzofuran (IIb). A 24-g (0.15 mole) sample of bromine was added dropwise with stirring in the course of 45 min to a suspension of 15 g (0.05 mole) of I in 150 ml of ether, after which the mixture was stirred for 4 h and allowed to stand overnight. The solid material was removed by filtration, washed with ether, and dried to give 13.5 g (59%) of IIb with mp 157-159° (from acetone). PMR spectrum, δ, ppm: 1.33 t (CH_3 in C_2H_5), 2.55 s (3-CH_3), 4.08 q (6-H), 4.30 (CH_2 in C_2H_5), 3.35 m (7-H), and 7.4 (C_6H_5). Found: C 47.4; H 3.5; Br 34.5%. $C_{18}H_{16}Br_2O_4$. Calculated: C 47.4; H 3.5; Br 35.0%.

2-Carbethoxy-3-methyl-4-hydroxy-6-phenylbenzofuran (IIIa). An 8.5-g (0.0225 mole) sample of IIa was added to a solution of 2.5 g (0.045 mole) of potassium hydroxide in 150 ml of alcohol, and the mixture was refluxed for 2 h. It was then diluted with water, cooled to 20°, and acidified with hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 5.5 g (82.5%) of IIIa with mp 198-200° (from alcohol). PMR spectrum, δ, ppm: 1.38 t (CH_3 in C_2H_5), 2.75 s (3-CH_3), 9.36 (OH), 4.36 q (CH_2 in C_2H_5), 6.98 d (5-H), 7.27 (7-H), and 7.35-7.65 m (C_6H_5). IR spectrum: 3300 cm^{-1} (OH). Found: C 72.6; H 5.5%. $C_{18}H_{16}O_4$. Calculated: C 72.9; H 5.4%.

2-Carbethoxy-3-methyl-4-hydroxy-5-bromo-6-phenylbenzofuran (IIIb). This compound was obtained by the method used to prepare IIIa. Reaction of 4.6 g (0.01 mole) of IIb and 1.2 g (0.02 mole) of potassium hydroxide in 100 ml of alcohol gave 2.5 g (66.5%) of IIIb with mp 146-148° (from alcohol). PMR spectrum, δ, ppm: 1.39 t (CH_3 in C_2H_5), 2.73 s (3-CH_3), 7.02 (7-H), 9.68 broad s (OH), and 4.34 q (CH_2 in C_2H_5). IR spectrum: 3500 cm^{-1} (OH). Found: C 57.6; H 3.8; Br 21.2%. $C_{18}H_{15}BrO_4$. Calculated: C 57.6; H 4.0; Br 21.3%.

2-Carboxy-3-methyl-4-hydroxy-5-bromo-6-phenylbenzofuran (IIIc). This compound was obtained by the method used to prepare IIIa. Reaction of 4.6 g (0.01 mole) of IIb and 2.4 g (0.04 mole) of potassium hydroxide in 100 ml of alcohol gave 2.2 g (63.5%) of IIIc with mp 218-220° (dec., from methanol). PMR spectrum, δ, ppm: 2.75 s (3-CH_3), 7.05 (7-H), 7.42 m (C_6H_5). Found: C 55.5; H 3.3; Br 22.7%. $C_{16}H_{11}BrO_4$. Calculated: C 55.4; H 3.2; Br 23.0%.

2-Carbethoxy-3-methyl-4-hydroxy-5,7-dibromo-6-phenylbenzofuran (IIId). A solution of 9.6 g (0.06 mole) of bromine in 15 ml of acetic acid was added dropwise with stirring in the course of 1 h to a suspension of 5.9 g (0.02 mole) of IIIa in 85 ml of acetic acid, after which the mixture was stirred for 3 h. The solid material was removed by filtration, washed with water, and dried to give 8.0 g (88%) of IIId with mp 171-172° (from methanol). Found: C 47.7%; H.3.0%. $C_{18}H_{14}Br_2O_4$. Calculated: C 47.6; H 3.1%.

2-Carbethoxy-3-methyl-4-hydroxy-5-bromo-6-phenylbenzofuran (IIIb) and 2-Carbethoxy-3-methyl-4-hydroxy-5,7-dibromobenzofuran (IIId). A solution of 1.62 g (0.011 mole) of bromine in 5 ml of acetic acid was added dropwise with stirring to a suspension of 2.96 g (0.01 mole) of IIIa in 30 ml of acetic acid, after which the mixture was stirred for another hour. The solid material was removed by filtration, washed with water, dried, and chromatographed with a column filled with silica gel. Workup of the benzene eluate gave 1.0 g (26.8%) of IIIb with mp 146-148° (no melting-point depression was observed for a mixture of this product with IIIb obtained from the preceding experiment) and 1.5 g (33%) of IIId with mp 171-172° (no melting-point depression was observed for a mixture of this product with IIId obtained from the preceding experiment).

2-Carbethoxy-3-methyl-4,7-dioxo-5-bromo-6-phenylbenzofuran (IV) and 2-Carbethoxy-3-methyl-4,5-dioxo-6-phenyl-7-bromobenzofuran (V). A solution of 1.35 g (0.012 mole) of nitric acid (sp. gr. 1.35) in 5 ml of acetic acid was added dropwise with stirring in the course of 30-40 min to a suspension of 3.42 g (0.0075 mole) of IIId in 50 ml of acetic acid, and the resulting solution was stirred for 1 h. It was then diluted with water, and the resulting precipitate was removed by filtration, washed with water, dried, and chromatographed with a column filled with silica gel. Workup of the benzene eluate gave 0.45 g (15.5%) of IV with mp 140-141° (from alcohol). Found: C 55.7; H 3.4; Br 19.8%. $C_{18}H_{13}BrO_5$. Calculated: C 55.6; H 3.4; Br 20.5%. The benzene eluate also yielded 0.7 g (24%) of V with mp 126-128° (from 70% alcohol). Found: C 55.4; H 3.4; Br 20.3%. $C_{18}H_{13}BrO_5$. Calculated: C 55.6; H 3.4; Br 20.5%. Phenazine VI had mp 281-283° (from CH_3COOH). Found: C 62.2; H 3.8; Br 17.3; N 5.9%. $C_{24}H_{17}BrN_2O_3$. Calculated: C 62.5; H 3.7; Br 17.3; N 6.0%. Absorption bands at 3200-3300 cm^{-1} (OH) were absent in the IR spectra of IV and V, but two absorption bands were present at 1680-1730 cm^{-1} (CO) in the spectra of each of the compounds.

2-Carbethoxy-3-methyl-4,7-dioxo-5-bromo-6-phenylbenzofuran (IV). A solution of 0.34 g (0.003 mole) of nitric acid (sp. gr. 1.35) in 5 ml of acetic acid was added dropwise with stirring to a solution of 0.6 g (0.0016 mole) of IIIb in 20 ml of acetic acid, after which the resulting solution was diluted with water, and the precipitate was removed by filtration, dried, and chromatographed with a column filled with silica gel. Workup of the benzene eluate yielded 0.25 g (40%) of IV with mp 140-141° (from alcohol). No melting-point depression was observed for a mixture of this product with IV obtained from the preceding experiment.

2-Carbethoxy-3-methyl-4,5-dihydroxy-6-phenyl-7-bromobenzofuran (IIIe). A solution of 1.4 g (0.0036 mole) of VI in 50 ml of ethyl acetate was shaken with a solution of 1.5 g of sodium hydrosulfite in 20 ml of water, after which the ethyl acetate solution was washed with water, dried over magnesium sulfate, and evaporated to give 1.4 g (quantitative yield) of IIIe with mp 165° (dec., from benzene). Found: C 55.1; H 3.9; Br 20.6%. $C_{18}H_{15}BrO_5$. Calculated: C 55.3; H 3.9; Br 20.4%. IR spectrum: 3420 cm^{-1} (OH).

2-Carbethoxy-3-methyl-4-hydroxy-5-nitro-6-phenylbenzofuran (IIIf), 2-Carbethoxy-3-methyl-4-hydroxy-6-phenyl-7-nitrobenzofuran (IIIg), and 2-Carbethoxy-3-methyl-4-hydroxy-5,7-dinitro-6-phenylbenzofuran (IIIh). A solution of 1.35 g (0.012 mole) of nitric acid (sp. gr. 1.35) in 5 ml of acetic acid was added dropwise with stirring in the course of 45 min to a suspension of 2.96 g (0.01 mole) of IIIa in 25 ml of acetic acid, after which the mixture was stirred for 1 h. The solid material was removed by filtration to give 1.2 g (35%) of IIIg with mp 222° (dec., from CH_3COOH). PMR spectrum, δ, ppm: 1.34 t (CH_3 in C_2H_5), 2.72 s (3-CH_3), 6.62 (5-H), 11.65 (OH), 4.4 q (CH_2 in C_2H_5), and 7.42 m (C_6H_5). Found: C 63.3; H 4.5; N 3.8%. $C_{18}H_{15}NO_6$. Calculated: C 63.3; H 4.4; N 4.1%. The filtrates were diluted with water, and the resulting precipitate was removed by filtration and recrystallized from acetic acid to give 0.84 g (21%) of IIIh with mp 192-193° (dec.). Found: C 56.0; H 3.6; N 6.8%. $C_{18}H_{14}N_2O_8$. Calculated: C 56.0; H 3.6; N 6.8%. The acetic acid mother liquor from the crystallization of IIIh was diluted with water, and the precipitate was removed by filtration, washed with water, dried, and chromatographed with a column filled with silica gel. Workup of the benzene eluate yielded 0.5 g (13%) of IIIg and 0.41 g (13%) of IIIf with mp 140-142° (from alcohol). PMR spectrum, δ, ppm: 1.4 t (CH_3 in C_2H_5), 2.74 s (3-CH_3), 7.09 (7-H), 4.46 q (CH_2 in C_2H_5), 4.36 m (C_6H_5). Found: C 62.9; H 4.3; N 3.9%. $C_{18}H_{15}NO_6$. Calculated: C 63.3; H 4.4; N 4.1%.

2-Carboxy-3-methyl-4-hydroxy-5-bromo-6-phenyl-7-nitrobenzofuran (IIIi). A solution of 0.86 g (0.0078 mole) of nitric acid (sp. gr. 1.35) in 10 ml of acetic acid was added dropwise with stirring to a suspension of 1.24 g (0.0036 mole) of IIIc in 50 ml of acetic acid, and the resulting solution was stirred for 1 h. It was then diluted with water, and the precipitate was removed by filtration, washed with water, and dried to give 1.0 g (71%) of IIIi with mp 210° (dec., from alcohol). Found: C 49.2; H 2.4; Br 19.8; N 3.5%. $C_{16}H_{10}BrNO_6$. Calculated: C 49.0; H 2.6; Br 20.4; N 3.6%.

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4-(5-METHOXY-2-OXAZOLYL)NAPHTHALIC ANHYDRIDE AND PRODUCTS OF ITS CONDENSATION WITH AROMATIC AMINES

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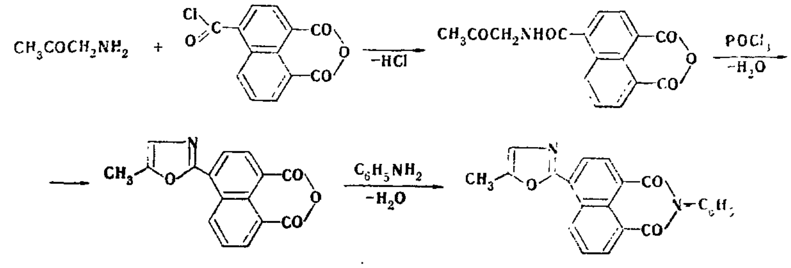
4-(5-Methyl-2-oxoazolyl)naphthalic anhydride was synthesized by condensation of 4-chloroformylnaphthalic anhydride with aminoacetone and subsequent cyclization of the resulting amide. Luminescing methyl-substituted N-phenylnaphthalimide and 1,8-naphthoylene-1',2'-benzimidazole were obtained by condensation of this product with aniline and o-phenylenediamine, respectively. The relationship between the structures of the products and their electronic absorption and luminescence spectra was investigated.

We have previously described 2,5-diaryl-substituted oxazoles with a peri-anhydride grouping that makes it possible to obtain organic luminophores with luminescences of various colors [1, 2]. In a continuation of our research we synthesized 4-(5-methyl-2-oxazolyl)naphthalic anhydride (I) by condensation of 4-chloroformylnaphthalic anhydride [3] with aminoacetone [4] and subsequent dehydration of the resulting amide.



I

III

Shortening of the conjugation chain in I as compared with 4-(5-phenyl-2-oxazolyl)naphthalic anhydride (II) [2] gives rise to a hypsochromic effect in the absorption and a hypsofluoric effect in the luminescence (Table 1). It is remarkable that the absolute photoluminescence quantum yield (η) in toluene increases. This is especially interesting since 2-(1-naphthyl)-5-methyloxazole, in contrast to 2-(1-naphthyl)-5-phenyloxazole, which luminescences intensely in toluene, has only weak luminescence [5]. The luminescence properties of I are possibly due to a considerable extent to donor–acceptor interaction, although weak, of the methyl group and the anhydride grouping.

Phenylimide III, which differs little from the starting anhydride with respect to its spectral-luminescence characteristics but is sensitive to a change in the pH of the medium, was obtained by heating methyloxazolylnaphthalic anhydride with aniline.

The formation of a mixture of isomeric 4- and 5-substituted 1,8-naphthoylene-1',2'-benzimidazoles (IV and V) is possible in the reaction of oxazolylnaphthalic anhydride with o-phenylenediamine. Unsubstituted

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