

SYNTHESIS AND SOME TRANSFORMATIONS
OF 2,6-DIPHENYL-4-HYDROXYBENZOFURAN

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A 4-oxotetrahydrobenzofuran derivative was obtained from 5-phenylcyclohexane-1,3-dione and phenacyl bromide, and dehydrogenation of the latter gave 2,6-diphenyl-4-hydroxybenzofuran. Some reactions of 2,6-diphenyl-4-hydroxybenzofuran and its derivatives were studied.

The reaction of the sodium derivative of 5-phenylcyclohexane-1,3-dione with phenacyl bromide via a known method [1] gave 2-phenacyl-5-phenylcyclohexane-1,3-dione (I). The latter is cyclized by 20% sulfuric acid to 2,6-diphenyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (II). Dehydrogenation of II by heating with sulfur gives 2,6-diphenyl-4-hydroxybenzofuran (IIIa). The bromination and nitration of hydroxybenzofuran IIIa proceed ambiguously. From the mixture of substances obtained by bromination of IIIa with an equimolar amount of bromine we were able to isolate only 2,6-diphenyl-4-hydroxy-7-bromobenzofuran (IIIb) in low yield. However, bromination with excess bromine gives 2,6-diphenyl-3,5,7-tribromo-4-hydroxybenzofuran (IIIc).

The singlet of a 5-H proton at 7.07 ppm is observed in the PMR spectrum of bromobenzofuran IIIb, and the 3-H signal is overlapped by signals of the phenyl protons. Doublets characteristic for p-disubstituted benzene derivatives and signals of protons of the benzofuran ring are absent in the PMR spectrum of tribromobenzofuran IIIc.

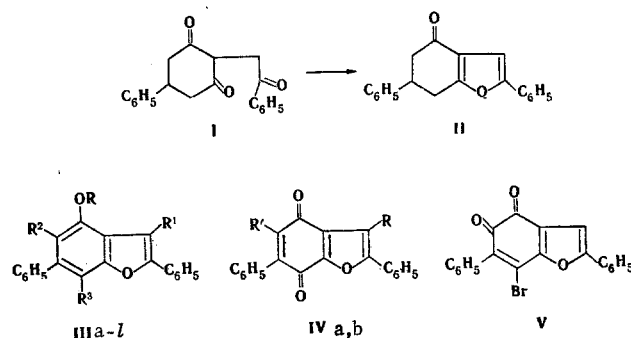
It is interesting to note that only the 3-bromo (IIIe) and 3-nitro (IIIf) derivatives were obtained by bromination and nitration of 2,6-diphenyl-4-acetoxybenzofuran (IIId). 2,6-Diphenyl-3-bromo-4-hydroxybenzofuran (IIIg) and 2,6-diphenyl-3-nitro-4-hydroxybenzofuran (IIIh), respectively, were obtained by hydrolysis of IIIe and IIIf.

Doublets with $J=2$ Hz, which are related to the signals of 5-H protons, are observed in the PMR spectra of hydroxybenzofurans IIIg and IIIh at 7.15 and 7.06 ppm, respectively. The magnitudes of the spin-spin coupling constants (SSCC) indicate that the 7 position of the benzofuran ring is also free. However, the signal of this proton is at weak field because of the effect of the oxygen atom of the furan ring and is overlapped by the multiplet of the phenyl ring. Consequently, both the nitro group in IIIh and the bromo group in IIIg are in the 3 position of the benzofuran ring.

2,6-Diphenyl-3-bromo-4-hydroxy-5,7-dinitrobenzofuran (IIIi) was obtained by nitration of bromo derivative IIIg. The reductive acylation of nitro compound IIIh gives 2,6-diphenyl-3-acetamido-4-hydroxybenzofuran (IIIj).

The oxidation of IIIc with nitric acid by a previously described method [2] gave 2,6-diphenyl-3,5-dibromo-4,7-dioxobenzofuran (IVa), which was reduced to dihydroxy derivative IIIk with sodium hydrosulfite. Oxidation of benzofuran IIIb gave o-quinoline 2,6-diphenyl-4,5-dioxo-7-bromobenzofuran (V). A p-quinone,

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III a $R=R^1=R^2=R^3=H$; b $R=R^1=R^2=H$, $R^3=Br$; c $R=H$, $R^1=R^2=R^3=Br$; d $R=COCH_3$, $R^1=R^2=H$; e $R=COCH_3$, $R^1=Br$, $R^2=R^3=H$; f $R=COCH_3$, $R^1=NO_2$, $R^2=R^3=H$; g $R=R^2=R^3=H$, $R^1=Br$; h $R=R^2=R^3=H$, $R^1=NO_2$; i $R=H$, $R^1=Br$, $R^2=R^3=NO_2$; j $R=R^2=R^3=H$, $R^1=NHCOCH_3$; k $R=H$, $R^1=R^2=Br$, $R^3=OH$; l $R=R^2=H$, $R^1=Br$, $R^3=NH_2$; IV a $R=R^1=Br$; b $R=Br$, $R^1=H$

2,6-diphenyl-3-bromo-4,7-dioxobenzofuran (IVb), is formed by ferric chloride oxidation of 2,6-diphenyl-3-bromo-4-hydroxy-7-aminobenzofuran (III_l), obtained from III_g by the usual method [3] and characterized in the form of the acetyl derivative.

A singlet related to the 5-H proton is observed in the PMR spectrum of acetyl derivative III_l, i.e., the acetamido group occupies the 7 position of the benzofuran ring.

The p-quinoid structure of IVa is preferable, inasmuch as the experimental value of the dipole moment of quinone IVa (0.57 D) lies considerably closer to the value calculated via an additive scheme for the p-quinone (1.7 D) and differs considerably from the value (4.1 D) corresponding to the ortho structure.

EXPERIMENTAL

The PMR spectra of the substances were recorded with a JNM-4H-60 spectrometer (60 MHz) with tetramethylsilane in deuteroacetone as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The dipole moments were determined with a DP-1 dielectric meter in benzene at 25°.

2-Phenacyl-5-phenylcyclohexane-1,3-dione (I). A 47-g (0.25 mole) sample of 5-phenylcyclohexane-1,3-dione and a solution of 50 g (0.25 mole) of phenacyl bromide in 130 ml of methanol were added with stirring to a solution of 14.0 g (0.25 mole) of potassium hydroxide in 54 ml of water, after which the mixture was stirred for 2 h and then allowed to stand for 24 h. The methanol was then removed by vacuum distillation, and the residue was extracted with 6% alkali solution. The alkaline extracts were cooled to 0° and acidified with dilute hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 28 g (37%) of I with mp 157.5–158.5° (from ethyl acetate). Found: C 78.6; H 5.9%. $C_{20}H_{18}O_3$. Calculated: C 78.4; H 5.9%.

2,6-Diphenyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (II). A total of 70 ml of 20% sulfuric acid solution was added to a solution of 46 g (0.15 mole) of I in 100 ml of dioxane, and the mixture was refluxed with vigorous stirring for 15 h, after which 8.5 ml of concentrated H_2SO_4 was added, and the mixture was refluxed for another 5 h. It was then poured into 500 ml of ice water, and the resulting precipitate was removed by filtration, washed with water, and dried to give 32.8 g (75.5%) of benzofuran II with mp 114–116° (from isopropyl alcohol). Found: C 83.0; H 5.8%. $C_{20}H_{16}O_2$. Calculated: C 83.3; H 5.6%.

2,6-Diphenyl-4-hydroxybenzofuran (IIIa). A mixture of 32.5 g (0.11 mole) of II and 7.25 g (0.22 mole) of sulfur was heated at 190° for 2 h and at 220° for 18 h, after which it was cooled to 20° and recrystallized from carbon tetrachloride to give 25.25 g (78%) of IIIa with mp 158–159°. Found: C 83.7; H 5.2%. $C_{20}H_{14}O_2$. Calculated: C 83.8; H 4.9%. IR spectrum: 3230 cm^{-1} (OH); no absorption band was present at 1670–1720 cm^{-1} (CO).

2,6-Diphenyl-7-bromo-4-hydroxybenzofuran (IIIb). A solution of 8 g (0.05 mole) of bromine in 50 ml of chloroform was added dropwise with stirring in the course of 1.5 h at 5° to a suspension of 14.3 g (0.05 mole) of hydroxybenzofuran IIIa in 100 ml of chloroform, after which the mixture was stirred at 20° for another 3 h. It was then washed with water, dried with magnesium sulfate, and subjected to column chromatography with elution by chloroform–hexane (1:1) to give 5 g (27%) of bromobenzofuran IIIb with mp 110–111° (from hexane). Found: C 65.5; H 3.7; Br 21.5%. $C_{20}H_{13}BrO_2$. Calculated: C 65.8; H 3.6; Br 21.9%.

2,6-Diphenyl-3,5,7-tribromo-4-hydroxybenzofuran (IIIc). A solution of 40 g (0.025 mole) of bromine in 100 ml of acetic acid was added dropwise with stirring in the course of 2 h at 20° to a solution of 15 g (0.052 mole) of benzofuran IIIa in 350 ml of acetic acid, after which the mixture was stirred for another 4 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 27 g (98%) of tribromo derivative IIIc with mp 154–156° (from acetic acid). Found: C 46.0; H 2.2; Br 45.8%. $C_{20}H_{11}Br_3O_2$. Calculated: C 45.9; H 2.1; Br 45.8%.

2,6-Diphenyl-4-acetoxybenzofuran (IIId). A mixture of 7.35 g (0.025 mole) of IIIa, 2.6 g (0.025 mole) of acetic anhydride, and 2.4 g (0.03 mole) of dry pyridine was heated at 100° for 5 h, after which it was poured into water, and the resulting precipitate was removed by filtration to give 8 g (97.5%) of acetoxybenzofuran IIId with mp 136–137° (from alcohol). Found: C 80.0; H 5.0%. $C_{22}H_{16}O_3$. Calculated: C 80.4; H 4.9%.

2,6-Diphenyl-3-bromo-4-acetoxybenzofuran (IIIe). This compound was obtained by the method used to prepare IIIc. Reaction of 2.6 g (0.008 mole) of acetoxybenzofuran IIId, 40 ml of acetic acid, and 1.7 g (0.011 mole) of bromine in 20 ml of acetic acid gave 3 g (95%) of IIIe with mp 185–186° (from acetic acid). Found: C 64.9; H 3.7; Br 19.4%. $C_{22}H_{15}BrO_3$. Calculated: C 64.9; H 3.7; Br 19.6%.

2,6-Diphenyl-3-nitro-4-acetoxybenzofuran (IIIf). A solution of 1.6 g (0.025 mole) of nitric acid (sp. gr. 1.35) in 10 ml of acetic acid was added dropwise with stirring in the course of 30 min at 10–15° to a suspension of 4.1 g (0.0125 mole) of IIId in 50 ml of acetic acid, where the resulting solution was stirred at 20° for 5 h. It was then poured into water, and the resulting precipitate was removed by filtration, washed with water, and dried. After chromatography with a column filled with silica gel, the benzene eluate yielded 4 g (86%) of nitro compound IIIf with mp 123–124.5° (from isopropyl alcohol). Found: C 71.0; H 4.3; N 3.6%. $C_{22}H_{15}NO_5$. Calculated: C 70.8; H 4.0; N 3.7%.

2,6-Diphenyl-3-bromo-4-hydroxybenzofuran (IIIg). A total of 12 ml of a hot 10% alcohol solution of potassium hydroxide was added to 2.35 g (0.006 mole) of IIIe, and the resulting solution was diluted with 100 ml of water, cooled to 5–10°, and acidified with dilute hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 2.1 g (95%) of IIIg with mp 145–146° (from alcohol). Found: C 65.8; H 3.8; Br 21.7%. $C_{20}H_{13}BrO_2$. Calculated: C 65.8; H 3.6; Br 21.9%.

2,6-Diphenyl-3-nitro-4-hydroxybenzofuran (IIIh). This compound was obtained by the method used to prepare IIIg. Reaction of 3.7 g (0.001 mole) of IIIf and 20 ml of a 10% alcohol solution of potassium hydroxide gave 2.1 g (63.5%) of a product with mp 160–161.5° (from alcohol). Found: C 72.2; H 3.9%. $C_{20}H_{13}NO_4$. Calculated: C 72.5; H 3.9%.

2,6-Diphenyl-3-bromo-4-hydroxy-5,7-dinitrobenzofuran (IIIi). A solution of 3.45 g (0.06 mole) of nitric acid (sp. gr. 1.35) in 20 ml of acetic acid was added dropwise with stirring at 10–15° to a suspension of 3.65 g (0.01 mole) of IIIg in 40 ml of acetic acid, during which the light-colored solid dissolved, and a brown solid precipitated. At the end of the addition of the nitric acid, the mixture was stirred at 18–20° for 2 h, after which the precipitate was removed by filtration, washed with water, and dried to give 4.5 g (98%) of IIIi with mp 218–219° (dec., from alcohol). Found: C 52.6; H 2.6; Br 17.1; N 6.3%. $C_{20}H_{12}BrN_2O_6$. Calculated: C 52.8; H 2.4; Br 17.5; N 6.2%.

2,6-Diphenyl-3-acetamido-4-hydroxybenzofuran (IIIj). A 1-g (0.015 mole) sample of zinc dust was added in portions with stirring to a refluxing solution of 0.85 g (0.0026 mole) of nitrohydroxybenzofuran IIIh, 0.3 g (0.0026 mole) of acetic anhydride, and 0.3 g (0.0031 mole) of sodium acetate in 85 ml of glacial acetic acid. At the end of the addition, the mixture was stirred and refluxed for 1 h. The resulting solution was filtered hot, the filtrate was cooled to 20°, and the resulting precipitate was removed by filtration to give 0.75 g (95%) of IIIj with mp 279–280° (from alcohol). Found: C 77.0; H 5.0%. $C_{22}H_{17}NO_3$. Calculated: C 77.0; H 5.0%.

2,6-Diphenyl-3,5-dibromo-4,7-dioxobenzofuran (IVa). A solution of 7.1 g (0.11 mole) of nitric acid (sp. gr. 1.35) in 60 ml of acetic acid was added dropwise at 20° in the course of 2 h with stirring to a suspension of 20.4 g (0.029 mole) of IIIc in 175 ml of acetic acid, during which the yellow solid dissolved. At the end of the addition of the nitric acid, the mixture was stirred for 3 h. The precipitate was removed by filtration, washed with water, and dried to give 0.8 g of IVa with mp 194–195° (from acetone). A precipitate was isolated from the acetic acid mother liquor and chromatographed with a column filled with aluminum oxide and elution with benzene to give another 1.2 g of IVa with mp 194–195°. The overall yield was 2 g (11%). Found: C 52.2; H 2.2; Br 35.3%. $C_{20}H_{10}Br_2O_3$. Calculated: C 52.4; H 2.2; Br 34.9%. Absorption bands at 3200–3400 cm^{-1} (OH) were absent in the IR spectrum, but the split absorption band characteristic for a quinone was present at 1670–1680 cm^{-1} (CO).

2,6-Diphenyl-3,5-dibromo-4,7-dihydroxybenzofuran (IIIk). A solution of 2.5 g (0.0055 mole) of quinone IVa in 150 ml of ethyl acetate was shaken with a solution of 2.1 g of sodium hydrosulfite in 15 ml of water, after which the ethyl acetate solution was washed with water, dried over magnesium sulfate, and evaporated to give 1.5 g (60%) of dihydroxybenzofuran IIIk. The diacetyl derivative had mp 206-208° (from acetic acid). Found: C 53.0; H 3.0%. $C_{24}H_{16}Br_2O_5$. Calculated: C 53.0; H 3.0%.

2,6-Diphenyl-3-bromo-4-hydroxy-7-aminobenzofuran (IIIl). A suspension of sodium p-diazobenzene-sulfonate, prepared from 1.82 g (0.0086 mole) of sulfanilic acid, 0.56 g of anhydrous sodium carbonate, 11 ml of water, a saturated aqueous solution of 0.79 g of sodium nitrite, 2.25 ml of concentrated HCl, and 13 g of ice, was added with stirring at 0-2° to a solution of 3.9 g (0.011 mole) of IIIg in 43 ml of dioxane and 15 ml of 15% solution of sodium hydroxide. The mixture was then stirred at 0° for 2 h, after which it was heated to 60°, and 5 g of sodium hydrosulfite was added. The mixture was then stirred at the same temperature for 30 min, after which it was cooled to 18-20° and diluted with 200 ml of water. The precipitated substance was extracted with ether and converted in a usual way to 2.55 g (56%) of the hydrochloride of IIIl. The acetyl derivative had mp 213-214° [benzene-heptane (1:1)]. Found: C 62.8; H 4.0; Br 18.5%. $C_{22}H_{16}BrNO_3$. Calculated: C 62.6; H 3.8; Br 18.9%.

2,6-Diphenyl-3-bromo-4,7-dioxobenzofuran (IVb). A solution of 1.25 g (0.003 mole) of the hydrochloride of IIIl in 50 ml of methanol and one to two drops of concentrated HCl was heated to 30°, and a solution of 4 g (0.015 mole) of ferric chloride in 3 ml of methanol and 1.5 ml of concentrated HCl was added with stirring. The mixture was then heated at 60° for 2 h, after which it was cooled to 18-20° and stirred at this temperature for 3 h. It was then diluted with 250 ml of water, and the resultant precipitate was removed by filtration and washed with hot alcohol to give 1 g (90%) of quinone IVb with mp 184-185° (from alcohol). Found: C 63.3; H 3.0; Br 20.0%. $C_{20}H_{11}BrO_3$. Calculated: C 63.3; H 2.9; Br 21.0%.

2,6-Diphenyl-4,5-dioxo-7-bromobenzofuran (V). This compound was obtained by the method used to prepare IVa. Reaction of 0.91 g (0.0025 mole) of IIIb in 10 ml of acetic acid with 0.32 ml of the nitric acid (sp. gr. 1.35) gave 0.5 g (52.5%) of V with mp > 220°. Found: C 63.5; H 3.0; Br 20.0%. $C_{20}H_{11}BrO_3$. Calculated: C 63.3; H 2.9; Br 21.0%.

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