BROMINATION, NITRATION, AND AZO COUPLING OF SUBSTITUTED 3-ETHOXYCARBONYL-5-HYDROXYBENZOFURANS

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The bromination and nitration of 2-methyl-3-ethoxycarbonyl-5-hydroxybenzofuran (I) leads to 6-bromo and 6-nitro derivatives, while azo coupling results in substitution of the hydrogen in the 4 position. The structures of the compounds obtained were confirmed by IR and PMR spectra.

5-Hydroxybenzofuran derivatives, which were obtained by one of us and co-workers [1-4], are convenient model compounds for the investigation of electrophilic substitution reactions in the benzene ring of 5-hydroxybenzofuran.

It has been shown that mono or dibromo derivatives are formed in the bromination of 2-methyl-3-ethoxycarbonyl-5-hydroxybenzofuran (I) with bromine in chloroform [5]. In the present study, we obtained 2-methyl-3-ethoxycarbonyl-5-hydroxy-6-bromobenzofuran (II) in 85% yield by bromination of I with dioxane dibromide in dioxane. 2-Methyl-3-ethoxycarbonyl-4,6-dibromo-5-hydroxybenzofuran (III) was obtained by subsequent bromination of II with bromine in acetic acid. Bromination of 2-methyl-3-ethoxycarbonyl-5-hydroxy-6,7-dichlorobenzofuran (IV) yielded 2-methyl-3-ethoxycarbonyl-4-bromo-5-hydroxy-6,7-dichlorobenzofuran (V), while 2-phenyl-3-ethoxycarbonyl-4,6-dibromo-5-hydroxybenzofuran (VII) was obtained by the bromination of 2-phenyl-3-ethoxycarbonyl-5-hydroxybenzofuran (VI).

For the first time, we have carried out the nitration of 5-hydroxybenzofuran derivatives containing substituents in the 2 and 3 positions. The nitration of I with nitric acid (sp. gr. 1.42) in chloroform leads to 2-methyl-3-ethoxycarbonyl-4,6-dinitro-5-hydroxybenzofuran (VIII). The action of nitric acid (sp. gr. 1.35) in acetic acid on I gives a mixture of nitration products, from which 2-methyl-3-ethoxycarbonyl-5-hydroxy-6-nitrobenzofuran (IX) was isolated by chromatography with a column filled with aluminum oxide. Only VIII and IX were detected in the residue after column chromatography by means of thin-layer chromatography. The corresponding mononitro derivatives – 2-methyl-3-ethoxycarbonyl-4-nitro-5-hydroxy-6-bromobenzofuran (X) and 2-methyl-3-ethoxycarbonyl-4-nitro-5-hydroxy-6,7-dichlorobenzofuran (XI) – were obtained by the nitration of II and IV with nitric acid (sp. gr. 1.35) in acetic acid.

Two singlets at 7.58 and 7.68 ppm for II and at 7.53 and 8.24 ppm for VIII, which are affiliated with the para $H_{(4)}$ and $H_{(7)}$ protons, are observed in the PMR spectra of II and VIII. The disappearance of the strong-field signals of the aromatic protons that are present in the spectra of II and VIII and the shift of the $H_{(7)}$ signals to favor weaker fields (8.04 and 8.47 ppm) by ~0.3 ppm (which corresponds to the effect of a p-NO_2 group) in the spectra of X and IX are evidence for subsequent substitution of hydrogen in the 4 position of the benzofuran ring. The structure of VI is confirmed by the presence of a proton signal with a chemical shift (7.84 ppm) close to the corresponding low-field signal in the spectra of II, which is structurally similar.

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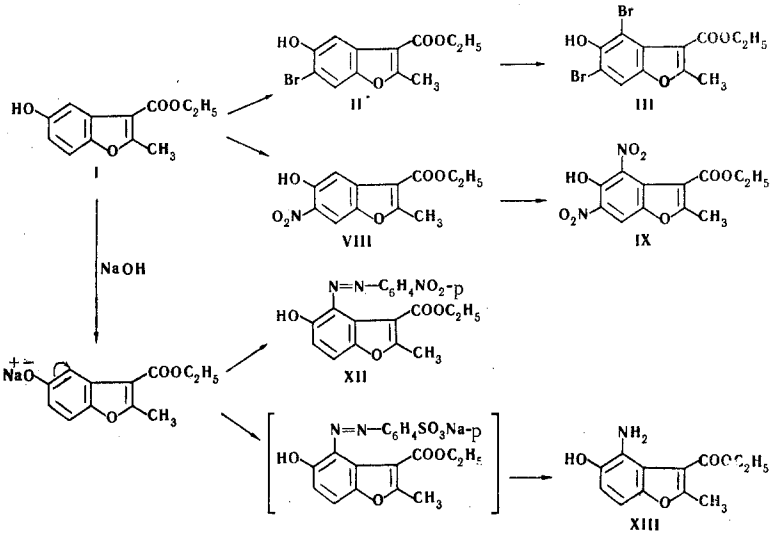
Thus the reagents primarily enter the 6 position in the bromination and nitration of 5-hydroxybenzofuran derivatives with substituents in the 2 and 3 positions, and, when the 6 position is occupied, the reagents enter the 4 position.



The azo coupling of I with p-nitrobenzenediazonium hydrochloride proceeds differently. Even when there are no substituents in the 6 position, this reaction leads to substitution of the hydrogen in the 4 position, i.e., to the formation of 2-methyl-3-ethoxycarbonyl-4-(p-nitrophenylazo)-5-hydroxybenzofuran (XII). Two doublets at 6.87 and 7.47 ppm, which are affiliated with the ortho H-6 and H-7 protons, are observed in the PMR spectrum of this compound. The azo coupling of I with p-diazobenzenesulfonic acid proceeds similarly. In this case, we did not isolate the azo compound, but reduced it with sodium hydrosulfite to 2-methyl-3-ethoxycarbonyl-4-amino-5-hydroxybenzofuran, which was isolated as the hydrochloride (XIII).

2-Methyl-3-ethoxycarbonyl-4,5-dioxo-6-bromobenzofuran (XIV) is obtained along with the nitro derivative (X) by the action of nitric acid in acetic acid on II. 2-Methyl-3-ethoxycarbonyl-4,5-dioxo-6,7-dichlorobenzofuran (XV) was isolated from the reaction of IV in chloroform with nitric acid (sp. gr. 1.42). The structures of XIV and XV were confirmed by the absence in their IR spectra of an absorption band at 3200-3400 cm^{-1} (OH) and by the appearance of an absorption band at 1685 cm^{-1} (C=O).

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard. The solvent for XIII was deuterochloroform, while acetone-d_6 was the solvent for all of the remaining compounds. Thin-layer chromatography on a loose layer of aluminum oxide in a benzene–methanol system (8:2) was used.

2-Methyl-3-ethoxycarbonyl-5-hydroxy-6-bromobenzofuran (II). A total of 5.0 g (0.02 mole) of dioxane dibromide was added in portions with stirring in the course of 1 h at 20-22° to a solution of 4.4 g (0.02 mole) of I in 30 ml of dioxane. The reaction mixture was stirred for another 2-3 h, and the resulting precipitate was removed by filtration and washed with dioxane. The mother liquor was diluted with three volumes of water, and the precipitate was removed by filtration and added to the initial mass to give 5.1 g (85%) of a product with mp 193-194°. Found: C 48.1; H 3.6; Br 27.1%. $C_{12}H_{11}BrO_4$. Calculated: C 48.2; H 3.7; Br 26.7%.

2-Methyl-3-ethoxycarbonyl-4,6-dibromo-5-hydroxybenzofuran (III). A solution of 0.8 g (0.005 mole) of bromine in 5 ml of acetic acid was added with stirring in the course of 40 min at 100° to a solution of 1.5 g (0.005 mole) of II in 40 ml of acetic acid. The reaction solution was heated at 100-120° and stirred for another 16 h, and then cooled to room temperature and filtered. The acetic acid filtrate was diluted with an equal volume of water, and the resulting precipitate was removed by filtration and washed with water to give 1.3 g (79%) of a product with mp 112-114°. This product did not depress the melting point of a sample obtained by a known method [5].

2-Methyl-3-ethoxycarbonyl-4-bromo-5-hydroxy-6,7-dichlorobenzofuran (V). A solution of 3.5 g (0.022 mole) of bromine in 25 ml of chloroform was added dropwise with stirring in the course of 3 h at 45-50° to

a suspension of 5.8 g (0.02 mole) of IV in 175 ml of chloroform. The solution was heated at 45-50° for 5 h, cooled to room temperature, and filtered. The filtrate was washed with water and dried. The chloroform was removed by vacuum distillation to give 5.15 g (66%) of a product with mp 96.5-98° (from acetic acid). Found: C 39.1; H 2.5; Br 21.3; Cl 18.9%. $C_{12}H_9BrCl_2O_4$. Calculated: C 39.2; H 2.5; Br 21.7; Cl 19.3%.

2-Phenyl-3-ethoxycarbonyl-4,6-dibromo-5-hydroxybenzofuran (VII). A solution of 8 g (0.025 mole) of bromine in 50 ml of chloroform was added dropwise with stirring in the course of 1 h at 20-22° to a solution of 7.1 g (0.025 mole) of VI in 100 ml of chloroform. The reaction solution was stirred at this temperature for 4-5 h until HBr evolution ceased. The chloroform solution was washed with water and dried. The chloroform was removed by vacuum distillation to give 11.0 g (quantitative) of a product with mp 145.5-146.5° (from alcohol). Found: C 46.3; H 2.6; Br 36.4%. $C_{17}H_{12}Br_2O_4$. Calculated: C 46.4; H 2.8; Br 36.3%.

2-Methyl-3-ethoxycarbonyl-4,6-dinitro-5-hydroxybenzofuran (VIII). A total of 6.5 ml of nitric acid (sp. gr. 1.42) was added to a solution of 1.1 g (0.005 mole) of I in 13 ml of chloroform and the mixture was shaken at 18-25° for 2 min and poured into 50 ml of water. The chloroform layer was separated, washed with water, and dried. The chloroform was evaporated on a rotary evaporator to give 1.15 g (74.5%) of a product with mp 104.5-105.5° (from alcohol) and R_f 0.7. Found: C 46.7; H 3.5; N 9.1%. $C_{12}H_{10}N_2O_8$. Calculated: C 46.5; H 3.3; N 9.0%.

2-Methyl-3-ethoxycarbonyl-5-hydroxy-6-nitrobenzofuran (IX). A solution of 3.4 g (0.06 mole) of nitric acid (sp. gr. 1.35) in 30 ml of acetic acid was added dropwise with stirring in the course of 25 min at 11-13° to a solution of 4.4 g (0.02 mole) of I in 130 ml of acetic acid. The mixture was held at this temperature for 2 h and poured into 400 ml of water. The mixture was then extracted with 800 ml of ether in three portions. The ether solution was washed with water and dried, and the ether was removed by vacuum distillation to give 4.1 g of a mixture of substances with mp 88-92°. Chromatography with a column filled with aluminum oxide with elution by benzene yielded 1.2 g (23%) of IX with mp 142-143° (from alcohol) and R_f 0.9. Found: C 54.2; H 4.2; N 5.3%. $C_{12}H_{11}NO_6$. Calculated: C 54.4; H 4.2; N 5.3%.

2-Methyl-3-ethoxycarbonyl-4-nitro-5-hydroxy-6-bromobenzofuran (X) and 2-Methyl-3-ethoxycarbonyl-4,5-dioxo-6-bromobenzofuran (XIV). A solution of 1.7 g (0.03 mole) of nitric acid (sp. gr. 1.35) in 15 ml of acetic acid was added dropwise with stirring in the course of 25 min at 16-18° to a suspension of 3.2 g (0.011 mole) of II in 65 ml of acetic acid. The mixture was held at this temperature for 2 h. The precipitate was removed by filtration, washed with acetic acid and water, and dried to give 1.9 g of X. The acetic acid mother liquor was diluted with three volumes of water, and the resulting precipitate was removed by filtration, washed with water, and dried to give 1.35 g of a mixture of substances, the recrystallization of which from methanol yielded an additional 0.75 g of X. The overall yield of X with mp 177.5-178° (dec., from methanol) was 2.65 g (72%). Found: C 41.9; H 2.8; Br 23.3; N 3.9%. $C_{12}H_{10}BrNO_6$. Calculated: C 41.9; H 2.9; Br 23.2; N 4.1%. The methanol and acetic acid mother liquors yielded 0.7 g (21%) of XIV with mp 135-137° (dec., from alcohol). Found: C 46.0; H 2.9; Br 25.5%. $C_{12}H_9BrO_5$. Calculated: C 46.0; H 2.9; Br 25.5%.

2-Methyl-3-ethoxycarbonyl-4-nitro-5-hydroxy-6,7-dichlorobenzofuran (XI). A solution of 0.34 g (0.006 mole) of nitric acid (sp. gr. 1.35) and 3 ml of acetic acid was added dropwise with stirring in the course of 30 min at 16-18° to a suspension of 0.7 g (0.0022 mole) of IV in 10 ml of acetic acid. The reaction mixture was held at this temperature for 1 h. The precipitate was removed by filtration, washed with acetic acid and water, combined with the precipitate obtained during dilution of the mother liquor with three volumes of water, and dried to give 0.75 g (93%) of a product with mp 141.5-142.5° (from methanol). Found: C 43.3; H 2.8; Cl 21.0; N 4.4%. $C_{12}H_{19}Cl_2NO_6$. Calculated: C 43.1; H 2.7; Cl 21.2; N 4.2%.

2-Methyl-3-ethoxycarbonyl-4-(p-nitrophenylazo)-5-hydroxybenzofuran (XII). A solution of p-nitrobenzenediazonium chloride [prepared from 1.8 g (0.013 mole) of p-nitroaniline, 3 ml of concentrated HCl, 19 ml of water, and a saturated aqueous solution of 1 g of sodium nitrite] was added with stirring at 3-5° to a solution of 2.2 g (0.01 mole) of I in 40 ml of dioxane and 40 ml of 5% NaOH. The reaction mass was stirred at 0° for 3 h. The solution was acidified with hydrochloric acid, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from acetic acid. It was then dissolved in chloroform and reprecipitated by the addition of petroleum ether to give 2.2 g (60%) of a product with mp 186-188° (dec.). Found: C 58.8; H 4.3; N 11.5%. $C_{18}H_{15}N_3O_6$. Calculated: C 58.5; H 4.1; N 11.4%.

2-Methyl-3-ethoxycarbonyl-4-amino-5-hydroxybenzofuran Hydrochloride (XIII). A suspension of sodium p-diazobenzenesulfonate [prepared from 1.05 g (0.005 mole) of sulfanilic acid, 0.27 g of anhydrous sodium carbonate, 5 ml of water, a saturated aqueous solution of 0.37 g of sodium nitrite, 1 ml of concentrated HCl, and 6 g of ice] was added with stirring at 0-2° to a solution of 1.1 g (0.005 mole) of I in 20 ml of dioxane

and 20 ml of 5% NaOH. The reaction mass was stirred at 0° for 1-1.5 h, heated to 40-45°, and 2.3 g of sodium hydrosulfite was added. The mixture was stirred at this temperature for 15 min, cooled to room temperature, and diluted with 100 ml of water. The precipitate of the base was removed by filtration, washed with water, dried in a vacuum desiccator (0.7 g yield), and converted to the hydrochloride (XIII) by the usual method. Compound XIII had mp 222-224° (dec.). Found: C 53.3; H 5.2; Cl 13.2; N 5.0%. $C_{12}H_{13}NO_4 \cdot HCl$. Calculated: C 53.0; H 5.2; Cl 13.1; N 5.1%.

2-Methyl-3-ethoxycarbonyl-4,5-dioxo-6,7-dichlorobenzofuran (XV). A total of 3 ml of nitric acid (sp. gr. 1.42) was added to a solution of 0.6 g (0.0021 mole) of IV in 100 ml of chloroform, and the mixture was shaken at 18-25° for 2-3 min and poured into 150 ml of water. The chloroform layer was separated, washed with water, and dried. The chloroform was evaporated, and the residue was recrystallized from alcohol to give 0.2 g (32%) of a product with mp 108.5-109.5° (from alcohol). Found: C 47.6; H 2.9; Cl 23.0%. $C_{12}H_8Cl_2O_5$. Calculated: C 47.5; H 2.7; Cl 23.4%.

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