SYNTHESIS AND SOME TRANSFORMATIONS OF HALOGEN-SUBSTITUTED o-QUINONES IN THE BENZOFURAN SERIES*

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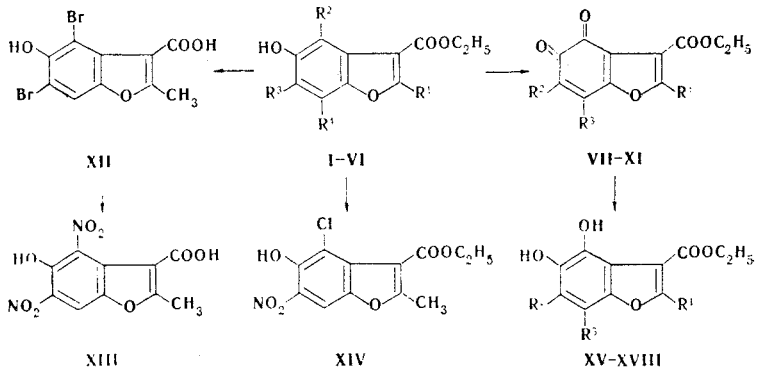
The corresponding 6-halo-substituted o-quinones were obtained by the action of nitric acid on 2-methyl(phenyl)-3-carbethoxy-4,6-dihalo-5-hydroxybenzofurans, whereas 2-methyl-3-carboxy-4,6-dibromo-5-hydroxybenzofuran is converted to the 4,6-dinitro derivative under similar conditions. The action of nitric acid on 2-methyl-3-carbethoxy-4-chloro-5-hydroxybenzofuran leads to replacement of the hydrogen in the 6 position by a nitro group. The reduction of o-quinones to the corresponding dihydroxy derivatives and reactions of quinones with amines are described.

The high antivirus activity of some quinones [2] has generated interest in the synthesis of quinones in the benzofuran series. The main reaction product in the reaction of nitric acid with 2-methyl-3-carbethoxy-5-hydroxy-6-bromobenzofuran is the 4-nitro derivative, but 2-methyl-3-carbethoxy-4,5-dioxo-6-bromobenzofuran-o-quinone is formed in low yield [3]. The synthesis of 6-halo-substituted o-quinones of the benzofuran series by oxidation of 4,6-dihalo-5-hydroxybenzofurans with nitric acid [4] is described in the present paper. To prepare the quinones, we treated solutions of 4,6-dihalo-5-hydroxybenzofurans (I-V) in chloroform with nitric acid at 18-25°C. In this case, we obtained 2-methyl(phenyl)-3-carbethoxy-4,5-dioxo-6-bromo(chloro)benzofurans (VII-XI) in 37-59% yields. Under the same conditions, only 2-methyl-3-carboxy-4,6-dinitro-5-hydroxybenzofuran (XIII)



XII I-VI VII-XI

XIII XIV XV-XVIII

I $R^1=CH_3$, $R^2=R^3=Br$, $R^4=H$; II $R^1=CH_3$, $R^2=R^3=Cl$, $R^4=H$; III $R^1=C_6H_5$, $R^2=R^3=Br$, $R^4=H$; IV $R^1=CH_3$, $R^2=Br$, $R^3=R^4=Cl$; V $R^1=C_6H_5$, $R^2=R^3=Cl$, $R^4=H$; VI $R^1=CH_3$, $R^2=Cl$, $R^3=R^4=H$; VII $R^1=CH_3$, $R^2=Br$, $R^3=H$; VIII $R^1=CH_3$, $R^2=Cl$, $R^3=H$; IX $R^1=C_6H_5$, $R^2=Br$, $R^3=H$; X $R^1=C_6H_5$, $R^2=Cl$, $R^3=H$; XI $R^1=CH_3$, $R^2=R^3=Cl$; XV $R^1=CH_3$, $R^2=Br$, $R^3=H$; XVI $R^1=CH_3$, $R^2=Br$, $R^3=N(CH_3)_2$; XVII $R^1=CH_3$, $R^2=Br$, $R^3=N\langle\rangle O$; XVIII $R^1=C_6H_5$, $R^2=Br$, $R^3=N\langle\rangle O$.

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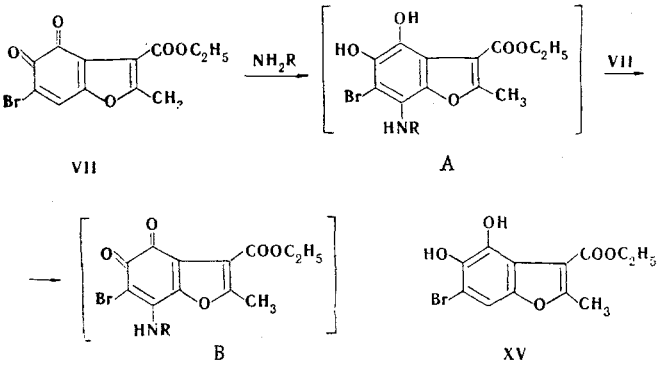
is formed from 2-methyl-3-carboxy-4,6-dibromo-5-hydroxybenzofuran (XII), whereas the corresponding 6-nitro derivative (XIV) is formed from 2-methyl-3-carbethoxy-4-chloro-5-hydroxybenzofuran (VI).

The structure of VII-XI was confirmed by reactions characteristic for quinones. 2-Methyl-3-carbethoxy-4,5-dihydroxy-6-bromobenzofuran (XV) was obtained by reduction of VII with sodium hydrosulfite. The reaction of VII with propyl- or butylamines also gives XV, the formation of which can be explained by redox reactions between the intermediate aminodihydroxy derivative A and starting quinone VII via the scheme



VII A B XV

R*n*-C_3H_7; C_4H_9

We were unable to isolate aminoquinone B when we carried out this reaction. 2-Methyl-(phenyl)-3-carbethoxy-4,5-dihydroxy-6-bromo-7-dimethylamino(morpholino)benzofurans (XVI-XVIII), respectively, were obtained by reaction of secondary amines — dimethylamine and morpholine — with quinones VII-VIII. The aminodihydroxy derivatives formed in the reactions of quinones with amines could not be isolated previously because of their ready oxidizability to aminoquinones during the reaction [5]. In this case the isolation of XVI-XVIII can be explained by their limited solubilities in the solvents selected for the reaction. The structures of the compounds synthesized in this research were confirmed by PMR and IR spectral data.

EXPERIMENTAL METHOD

The PMR spectra were recorded with JHM-4H 100 (100 MHz) and C-60 (60 MHz) spectrometers with tetramethylsilane as the internal standard. The solvent for VII and XV was d_6-acetone, and the solvent for XVI and XVII was d_1-chloroform. The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-10 recording spectrometer.

The starting compounds — 2-methyl(phenyl)-3-carbethoxy-4,6-dibromo(dichloro)-5-hydroxybenzofurans (I-III) and 2-methyl-3-carbethoxy-4-bromo-6,7-dichloro-5-hydroxybenzofuran (IV) — were previously obtained in [3, 4, 6], whereas 2-phenyl-3-carbethoxy-4,6-dichloro-5-hydroxybenzofuran (V) was obtained by chlorination of 2-phenyl-3-carbethoxy-5-hydroxybenzofuran.

2-Phenyl-3-carbethoxy-4,6-dichloro-5-hydroxybenzofuran (V). A solution of 2 g of chlorine in 20 ml of dry chloroform was added dropwise at 8-12° in the course of 30 min to a solution of 3.5 g (0.013 mole) of 2-phenyl-3-carbethoxy-5-hydroxybenzofuran in 45 ml of dry chloroform, after which the mixture was stirred at 10-15° for 5 h. It was then washed with water and dried, and the chloroform was removed by distillation. The residue was recrystallized from carbon tetrachloride to give 1.6 g (37%) of a product with mp 137-138°. Found: C 58.0; H 3.5; Cl 20.2%. $C_{17}H_{12}Cl_2O_4$. Calculated: C 58.1; H 3.5; Cl 20.2%.

2-Methyl(phenyl)-3-carbethoxy-4,5-dioxo-6-bromo(chloro)benzofurans (VII-XI). A 12.5-ml sample of nitric acid (sp. gr. 1.42) was added to a solution of 5.0 g (0.013 mole) of 2-methyl-3-carbethoxy-4,6-dibromo-5-hydroxybenzofuran (I) in 50 ml of chloroform, after which the mixture was shaken at 18-25° for 2-3 min. It was then poured into 100 ml water, and the chloroform layer was separated, washed with water, and dried. The chloroform was evaporated, and the residue was recrystallized. The yields and physical constants of VII-XI are presented in Table 1. PMR spectrum for VII, δ: 8.00 (7-H, s), 4.25 ($3-CH_2$, q), 2.56 ($2-CH_3$, s), and 1.35 ppm ($3-CH_3$, t).

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C (from ethyl acetate)	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	Cl (Br)	C	H	Cl (Br)	
VII	135—137 (dec.)*	$C_{12}H_9BrO_5$	46,0	2,9	25,5	46,0	2,9	(25,5)	37
VIII	141—143 (dec.)	$C_{12}H_9ClO_5$	53,6	3,3	13,0	53,6	3,4	13,2	59
IX	137—139 (w. dec)	$C_{17}H_{11}BrO_5$	54,4	3,1	21,1	54,4	3,0	(21,3)	47
X	132—133	$C_{17}H_{11}ClO_5$	61,9	3,3	10,4	61,7	3,4	10,7	57
XI	108,5—109,5*	$C_{12}H_8Cl_2O_5$	47,6	2,9	23,0	47,5	2,7	23,4	49
XVI	98—100 (dec.)	$C_{14}H_{16}BrNO_5$	46,8	4,4	4,1	47,0	4,5	(3,9)	55
XVII	158—160 (dec.)	$C_{16}H_{18}BrNO_6$	48,1	4,6	3,6	48,0	4,5	(3,5)	31
XVIII	191—193 (dec.)	$C_{21}H_{20}BrNO_6$	54,2	4,4	3,4	54,5	4,4	(3,0)	48

*From alcohol.

2-Methyl-3-carboxy-4,6-dibromo-5-hydroxybenzofuran (XII). An 11.4-g (0.03 mole) sample of 2-methyl-3-carbethoxy-4,6-dibromo-5-hydroxybenzofuran (I) was added to a solution of 3.6 g of sodium hydroxide in 60 ml of alcohol, and the mixture was refluxed on a water bath for 30 min. It was then cooled to room temperature and poured into 200 ml of water. The aqueous solution was cooled and acidified with hydrochloric acid, and the resulting precipitate was removed by filtration, washed with water, and dried to give 9.9 g (94.5%) of a product with mp 192-193.5° (with decomposition, from acetic acid). Found: C 34.6; H 1.8; Br 45.4%. $C_{10}H_6Br_2O_4$. Calculated: C 34.3; H 1.7; Br 45.7%.

2-Methyl-3-carboxy-4,6-dinitro-5-hydroxybenzofuran (XIII). A 0.83-ml sample of nitric acid (sp. gr. 1.4) was added dropwise with stirring at 18-20° in the course of 15 min to a suspension of 3.5 g (0.01 mole) of 2-methyl-3-carboxy-4,6-dibromo-5-hydroxybenzofuran (XII) in 20 ml of glacial acetic acid, after which the resulting solution was stirred at 40-45° for 2 h. It was then cooled to 20°, and the resulting precipitate was removed by filtration, washed with acetic acid, and dried to give 0.8 g (29%) of a product with mp 229-230° (with decomposition, from acetic acid). Found: C 42.7; H 2.3; N 9.6%. $C_{10}H_6N_2O_8$. Calculated: C 42.6; H 2.1; N 9.9%.

2-Methyl-3-carbethoxy-4-chloro-5-hydroxy-6-nitrobenzofuran (XIV). A solution of 1.25-ml [1.7 g (0.027 mole)] of nitric acid (sp. gr. 1.35) in 15 ml of acetic acid was added dropwise at 14-16° to a solution of 2.55 g (0.01 mole) of 2-methyl-3-carbethoxy-4-chloro-5-hydroxybenzofuran (VI) in 35 ml of acetic acid,* after which the mixture was stirred for 30 min. The mixture was then stirred for another 2 h, and the resulting precipitate was removed by filtration and washed with water. The filtrate was diluted with water, and the resulting precipitate was removed by filtration and combined with the precipitate isolated from the reaction mixture to give 2.05 g (65%) of a product with mp 152-154° (from ethyl acetate). Found: C 48.3; H 3.3; Cl 11.7; N 4.7%. $C_{12}H_{10}ClNO_6$. Calculated: C 48.1; H 3.4; Cl 11.8; N 4.7%.

2-Methyl-3-carbethoxy-4,5-dihydroxy-6-bromobenzofuran (XV). A) A solution of 1.5 g (5 mmole) of 2-methyl-3-carbethoxy-4,5-dioxo-6-bromobenzofuran (VII) in 20 ml of ethyl acetate was shaken in a separatory funnel with a solution of 2.1 g of sodium hydrosulfite in 15 ml of water. The resulting precipitate was removed by filtration, the solution was evaporated with a rotary evaporator at 30-40°, and the residue was added to the initially formed precipitate to give 1.4 g (93%) of a product with mp 187-188.5° (from ethyl acetate). IR spectrum: 3540; 3520 cm^{-1} (OH). PMR spectrum: δ 7.15 (7-H, s), 4.49 (3-CH_2, q), 2.68 (2-CH_3, s), and 1.44 ppm (3-CH_3, t). Found: C 45.8; H 3.6; Br 25.6%. $C_{12}H_{11}BrO_5$. Calculated: C 45.7; H 3.5; Br 25.4%.

B) A 0.2-ml sample of propylamine was added to a solution of 0.6 g (2 mmole) of VII in 10 ml of ethyl acetate, and the resulting solution was refluxed for 10 min. It was then cooled, and the resulting precipitate was removed by filtration to give 0.3 g (95%) of a product with mp 187-188° (from ethyl acetate). No melting-point depression was observed for a mixture of this product with the product of the preceding experiment (A).

2-Methyl(phenyl)-3-carbethoxy-4,5-dihydroxy-6-bromo-7-dimethylamino(morpholino)benzofurans (XVI-XVIII). A solution of 2 g (0.045 mole) of dimethylamine in 5 ml of ethyl acetate

*The reaction proceeds similarly in chloroform.

was added to a solution of 0.8 g (2.5 mmole) of 2-methyl-3-carbethoxy-4,5-dioxo-6-bromobenzofuran (VII) in 15 ml of ethyl acetate. The precipitate that formed 10-15 min later was removed by filtration, washed with ethyl acetate, and dried. The yields and physical constants of XVI-XVIII are presented in Table 1. IR spectrum of XVI: 3470 cm^{-1} (OH). PMR spectrum of XVI: δ 4.43 (3-CH_2, q), 2.68 [7-$N(CH_3)_2$, s], and 1.42 ppm (3-CH_3, t). IR spectrum for XVII: 3490 cm^{-1} (OH). PMR spectrum: δ 4.44 (3-CH_2, q), 3.85, 3.20 (multiplets of the morpholine group), and 1.43 ppm (3-CH_3, t).

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