BROMINATION AND NITRATION OF 2(3)-PHENYL-5(6)-HYDROXYBENZOFURANS

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It was established that substituents primarily are incorporated in the benzene ring in the bromination and nitration of 2(3)-phenyl-5(6)-hydroxybenzofurans. The acetoxy derivatives of the same benzofurans are brominated and nitrated only in the free position of the furan ring.

In a previous study of electrophilic substitution reactions it was noted that the shielding effect of the carbethoxy group in 2-methyl-3-carbethoxy-5-hydroxybenzofuran hinders incorporation of a substituent in the 4 position during bromination and nitration. At the same time, in the case of 2-carbomethoxy-5-hydroxybenzofuran the substituents in all electrophilic substitution reactions enter primarily the 4 position [1, 2]. In the present research we studied the electrophilic substitution reactions of 5- and 6-hydroxybenzofurans containing a phenyl substituent in the furan ring [3, 4].

The bromination of 2-phenyl-5-hydroxy- (I), 3-phenyl-5-hydroxy- (II), and 3-phenyl-6-hydroxybenzofuran (III) has been studied under various conditions. 2-Phenyl-4-bromo-5-hydroxybenzofuran (IV) was obtained in 83% yield in the reaction of an equimolar amount of bromine with I. Products IV and 2-phenyl-3,4,6-tribromo-5-hydroxybenzofuran (V) are formed in approximately equal amounts when I is treated with 2 moles of bromine, according to analysis by thin-layer chromatography (TLC). Bromination of II and III with an equimolar amount of bromine gives a mixture of starting II with 2,4-dibromo-3-phenyl-5-hydroxybenzofuran (VI) and a mixture of III with 2,5-dibromo-3-phenyl-6-hydroxybenzofuran (VII), respectively, in a ratio of 1:1. Only dibromo derivatives VI and VII in 71 and 57% yields, respectively, were obtained in the bromination of II and III with 2 moles of bromine.

Thus, a phenyl group in the 3 position does not hinder incorporation of bromine in the 4 position.

Compound I is also nitrated in the 4 position by nitric acid (sp. gr. 1.35) in acetic acid to give 2-phenyl-4-nitro-5-hydroxybenzofuran (VIII) in 65% yield. A mixture of nitration products VIII and 2-phenyl-3,4,6-trinitro-5-hydroxybenzofuran (IX) is formed in the reaction of the same compound with more concentrated acid (sp. gr. 1.42) in chloroform. The nitration of II and III proceeds in a different manner. In the case of the reaction of nitric acid (sp. gr. 1.35) with II, two nitration products in approximately equal amounts – 6-nitro- (X) and 4,6-dinitro-3-phenyl-5-hydroxybenzofuran (XI) – are detected in the reaction mixture by means of TLC. 3-Phenyl-4,6,7-trinitro-5-hydroxybenzofuran (XII) was isolated from the markedly resinified reaction mixture in the nitration of II under more severe conditions. A mixture of nitration products, from which 2,7-dinitro-3-phenyl-6-hydroxybenzofuran (XIII) was isolated by chromatography, is formed in the reaction of III with nitric acid (sp. gr. 1.35) in acetic acid.

Consequently, in the bromination and nitration of hydroxybenzofurans the bromo and nitro groups are incorporated primarily in the benzene ring – in the 4 position of I, in the 2,4 positions during bromination and in the 6 and 4,6 positions during nitration of II, and in the the 2,5 positions during bromination and the 2,7 positions during nitration of III. In contrast to hydroxybenzofuran derivatives I-III, the corresponding acetoxybenzofuran derivatives (XIV-XVI) are brominated and nitrated only in the free positions of the furan ring. 2-Phenyl-3-bromo-5-acetoxy- (XVII), 2-bromo-3-phenyl-5-acetoxy- (XVIII), and 2-bromo-3-phenyl-6-acetoxybenzo-

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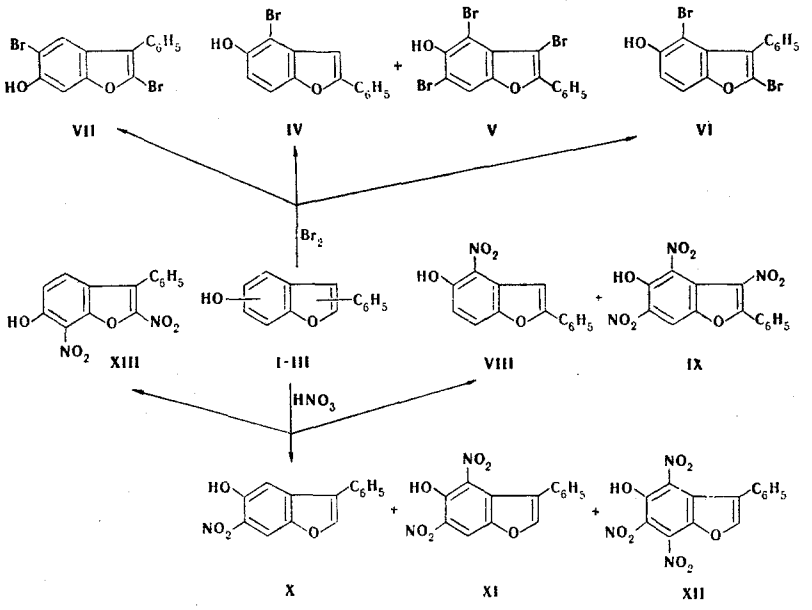

furan (XIX) are obtained in quantitative yields in the bromination of XIV-XVI with an equivalent amount of bromine. The nitration of XV and XVI with nitric acid (sp. gr. 1.35) in acetic acid is accompanied by pronounced resinification of the reaction mixture, from which 2-nitro-3-phenyl-5-acetoxy-(XX) and 2-nitro-3-phenyl-6-acetoxybenzofuran (XXI) were isolated by chromatography.

The structures of the compounds were confirmed by PMR spectroscopy. The presence in the PMR spectra of IV and VIII of two doublets with J=9.0 Hz, which corresponds to coupling of ortho protons, proves that substitution takes place in the 4 position. The singlet at δ 7.85 ppm in the spectrum of V is related to the 7H proton. On the basis of a comparison with the spectrum of starting III, the two singlets at δ 7.67 and 7.17 ppm in the spectrum of VII were assigned to the 4H and 7H signals, respectively. The singlet of a proton with δ 8.87 ppm in the spectrum of product IX corresponds to the 7H proton, inasmuch as this shift is in good agreement with the shift due to the contribution of the p- and o-NO_2 groups (8.68_{calc}–8.87_{exp}) [5].

The presence in the spectrum of product X of three singlets at 7.50, 8.33, and 8.38 ppm is possible only when the nitro group is in the 6 position of the ring. When a second nitro group is introduced in XI, the 4H signal at 7.50 ppm vanishes, and the singlet at 8.38 ppm does not change, whereas the 7H signal (δ 8.68 ppm) is shifted to weak field by 0.3 ppm as compared with the spectrum of X. The latter shift corresponds to the shift of the para proton due to the nitro group [5]. On the basis of a comparison of the spectra of XII, X, and XI, the singlet at δ 8.38 ppm was assigned to 2H. Two doublets with an ortho spin–spin coupling constant (SSCC) of 9 Hz are observed in the spectrum of XIII at weak field, and this corresponds to substitution of the 2 and 7 positions. A quartet with J_1=9.0 Hz and J_2=2.5 Hz, which was assigned to the 5H proton for XIX and XXI and to the 6H proton for XVII, XVIII, and XX, is observed in the PMR spectra of acetyl derivatives XVII-XXI at 7.0-7.3 ppm. Thus acetoxybenzofurans are brominated and nitrated in the furan ring of the molecules.

TABLE 1. Characteristics of IV-VIII and XVII-XIX

Compound	mp, °C*	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
IV	138—140	$C_{14}H_9BrO_2$	58,2	3,1	58,2	3,1	83
V	162—164	$C_{14}H_7Br_3O_2$	38,0	1,7	37,6	1,6	45
VI	190—192 (2 mm)†	$C_{14}H_8Br_2O_2$	45,7	2,2	45,7	2,2	71
VII	147—149	$C_{14}H_8Br_2O_2$	45,6	2,3	45,7	2,2	57
XVII	117—118	$C_{16}H_{11}BrO_3$	58,1	3,5	58,0	3,3	100
XVIII	60—61	$C_{16}H_{11}BrO_3$	58,0	3,3	58,0	3,3	100
XIX	102—103	$C_{16}H_{11}BrO_3$	58,0	3,3	58,0	3,3	100

*Crystallization solvents: benzene–petroleum ether (1 : 1) for IV, and methanol for V, VII, and XVII-XIX.

† Boiling point.

TABLE 2. Characteristics of VIII-XIII, XX, and XXI

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
VIII	130—133	$C_{14}H_9NO_4$	65,6	3,5	5,4	65,9	3,5	5,5	65
IX	253—254	$C_{14}H_7N_3O_8$	48,9	2,7	12,0	48,7	2,1	12,2	33,7
X	138—140	$C_{14}H_9NO_4$	65,9	3,4	—	65,9	3,5	—	35
XI	178—179	$C_{14}H_8N_2O_6$	56,0	2,7	—	56,0	2,7	—	33,4
XII	280—281	$C_{14}H_7N_3O_8$	48,7	2,2	—	48,7	2,0	—	41
XIII	194—195	$C_{14}H_8N_2O_6$	55,9	2,7	9,3	56,0	2,7	9,3	22,4
XX	125—126	$C_{16}H_{11}NO_5$	64,6	3,9	4,3	64,6	3,7	4,7	30,3
XXI	131—132	$C_{16}H_{11}NO_5$	64,5	3,8	4,6	64,6	3,7	4,7	18,5

*Crystallization solvents: 50% acetic acid for VIII and X, acetic acid for IX and XII, methanol for XI, XX, and XXI, and ethyl acetate for XIII.

TABLE 3. PMR Spectral Data (δ, ppm) for I-XIII and XVII-XXI

Compound	2H	3H	4H	5H	6H	7H	C_6H_5	CH_3CO
I		7,12	7,10		6,88	7,39	7,30—8,19	
II	7,93		7,30		6,92	7,40	7,24—7,68	
III	7,88		7,66	6,92		7,03	7,28—7,60	
IV		7,18			7,00	7,43	7,33—7,95	
V						7,85	8,02—8,55	
VI					7,02	7,37	7,40—7,70	
VII			7,67			7,17	7,42—7,57	
VIII		7,45			7,10	7,95	7,25—8,27	
IX						8,87	7,65	
X	8,38		7,50			8,33	7,38—7,75	
XI	8,38					8,68	7,37	
XII	8,38						7,40	
XIII			7,90	7,33			7,60	
XVII			7,45		7,18	7,60	7,23—8,25	2,28
XVIII			7,30—7,62		7,10	7,30—7,62	7,30—7,62	2,23
XIX			7,63	7,07		7,39	7,40—7,68	2,25
XX			7,36		7,58	7,87	7,40—7,60	2,25
XXI			7,72	7,30		7,45	7,40—7,68	2,25

EXPERIMENTAL

The PMR spectra of deuteroacetone solutions of the compounds were recorded with a JNM-4H-100 JEOL spectrometer with tetramethylsilane as the internal standard.

2-Phenyl-5-hydroxybenzofuran (I), 3-Phenyl-5-hydroxybenzofuran (II), and 3-Phenyl-6-hydroxybenzofuran (III). These compounds were obtained in quantitative yields from the methoxy derivatives [6, 7] by the method described for other examples in [2].

2-Phenyl-5-acetoxybenzofuran (XIV). A solution of 5 g of I in 30 ml of acetic anhydride and 0.3 ml of triethylamine was refluxed for 1 h, after which the bulk of the acetic anhydride was removed by vacuum distillation. The residual mixture was poured into water, and the resulting precipitate was separated to give XIV, with mp 154-155° (from alcohol), in quantitative yield. Found: C 76.3; H 4.8%. $C_{16}H_{13}O_3$. Calculated: C 76.2; H 4.8%.

3-Phenyl-5-acetoxy- (XV) and 3-Phenyl-6-acetoxybenzofuran (XVI). These compounds were similarly obtained. Compound XV, with mp 55-56° (from methanol), was obtained in quantitative yield. Found: C 76.0; H 4.8%. $C_{16}H_{13}O_3$. Calculated: C 76.2; H 4.8%. Compound XVI, with mp 77-78° (from aqueous methanol), was also obtained in quantitative yield. Found: C 76.3; H 4.8%. $C_{16}H_{13}O_3$. Calculated: C 76.2; H 4.8%.

General Method for the Preparation of IV-VII (Table 1). A solution of bromine in 8 ml of glacial acetic acid was added gradually at 20° to a suspension of 0.01 mole of benzofuran in 20 ml of glacial acetic acid, after which the mixture was stirred for 2 h. It was then poured into water, and the resulting precipitate was separated and chromatographed on a column filled with silica gel with elution by chloroform. The eluate was evaporated, and the residue was recrystallized. Compound IV was obtained by the action of 1 mole of bromine per mole of starting compound, whereas V-VII were obtained by the action of 2 moles of bromine per mole of starting compound.

General Method for the Preparation of the XVII-XIX (Table 1). A solution of 0.01 mole of bromine in 3 ml of carbon tetrachloride was added gradually at 20° to a solution of 0.01 mole of benzofuran in 7 ml of carbon tetrachloride, after which the mixture was stirred for 2 h. The solvent was then removed by vacuum distillation, and the residue was recrystallized.

General Method for the Preparation of VIII, X, XI, XIII, XX, and XXI (Table 2). A solution of 0.03 mole of nitric acid (sp. gr. 1.35) in 15 ml of acetic acid was added dropwise with stirring at 15° to a suspension of 0.01 mole of benzofuran in 65 ml of glacial acetic acid, after which the mixture was allowed to stand at this temperature for 1 h. It was then poured into water, and the resulting precipitate was separated and chromatographed on a column filled with silica gel (elution with chloroform). The eluate was evaporated, and the residue was recrystallized.

General Method for the Preparation of IX and XII (Table 2). A 6.5-ml sample of nitric acid (sp. gr. 1.42) was added to a solution of 5 mmole of the benzofuran in 34 ml of chloroform, after which the mixture was shaken at room temperature for 5 min and poured into 50 ml of water. The chloroform layer was separated, washed with water, and chromatographed on a column filled with silica gel (elution of the reaction product with chloroform). The eluate was evaporated, and the residue was recrystallized.

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3,4-DIAMINOCOUMARINS*

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A number of 3,4-diaminocoumarins was obtained by hydrogenation of 3-nitro-4-aminocoumarins. It was established that these compounds exist in the coumarin form, and monoacetylation of the 3-NH_2 group does not shift the tautomeric equilibrium.

Substances having various kinds of biological activity are found among 3- and 4-aminocoumarin derivatives [2-4]. The tautomerism and stereochemistry of these compounds have also been studied [5-7]. However, 3,4-diaminocoumarins, from which one might expect the manifestation of properties of both 3- and 4-aminocoumarins, as well as a novel combination of these properties, have not yet been investigated in this respect.

We have synthesized a number of 3,4-diaminocoumarins (Ia-j) by hydrogenation of the corresponding 3-nitro-aminocoumarin (IIa-j), the synthesis of which we previously described in [7], over $Pd/BaSO_4$.

*See [1] for a previous communication.

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