HALOGENATION AND NITRATION OF 3-ACYL-5-HYDROXY(ACETOXY)BENZOFURANS

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Depending on the reaction conditions, the bromination of 3-acyl-5-hydroxybenzofurans leads to 4-bromo and 4,6-dibromo derivatives, whereas chlorination leads to replacement of the hydrogen atom in the 4 position. As in the nitration of 3-acyl-5-hydroxybenzofurans with a nitrating mixture, 3-acyl-4,6-dinitro-5-hydroxybenzofurans are formed in the nitration of 3-acyl-5-hydroxybenzofurans with nitric acid.

Previously, in the bromination and nitration of 2(3)-phenyl-5(6)-hydroxybenzofurans it was established that the substituents are incorporated primarily in the benzene ring, whereas the acetoxy derivatives of the same benzofurans are brominated and nitrated in the free position of the furan ring [1].

In the present research we studied the halogenation and nitration of 3-acyl-5-hydroxy- (Ia-c) and 3-acyl-5-acetoxybenzofurans (IIa-c). The latter were obtained in quantitative yields by the action of excess acetic anhydride on 3-acyl-5-hydroxybenzofurans (Ia-c) in the presence of catalytic amounts of sulfuric acid.

4-Bromobenzofurans IIIa-c rather than 6-bromobenzofurans, which were previously obtained in the bromination of 2-methyl-3-ethoxycarbonyl-5-hydroxybenzofurans under the same conditions [2, 3], are formed in the bromination of Ia-c with an equimolar amount of bromine at room temperature in both chloroform and acetic acid. Consequently, in contrast to an ethoxycarbonyl substituent, an acyl substituent in the 3 position does not offer steric hindrance to incorporation of a bromine atom in the 4 position. A similar reaction with excess bromine and heating leads to the corresponding 3-acyl-4,6-dibromo-5-hydroxybenzofurans (IVa-c). The introduction of an electron-acceptor substituent at the hydroxy group of benzofurans decreases the reactivities of the latter. Thus 3-acyl-5-acetoxybenzofurans IIa-c do not undergo bromination under similar conditions.

It has been previously shown [2, 3] that mixtures of chlorination products, from which 4-chlorobenzofuran derivatives could be isolated, are formed in the chlorination of substituted 3-ethoxycarbonyl-5-hydroxybenzofurans with chlorine in chloroform. We have found that exclusively 3-acyl-4-chlorobenzofuran derivatives (Va, b) are formed in the chlorination of Ia, b with sulfuryl chloride at −5 to −10°C.

According to the results of thin-layer chromatography (TLC), mixtures of substances, from which 3-acyl-4,6-dinitro-5-hydroxybenzofurans (VIa-c) were isolated in 61-75% yields by fractional crystallization, are formed by the action of nitric acid (sp. gr. 1.35) in acetic acid on 3-acyl-5-hydroxybenzofurans (Ia-c) at room temperature. However, the corresponding 5-acetoxy derivatives IIa-c do not undergo nitration under similar conditions. Mononitro derivatives could not be isolated by nitration under various conditions of 2,3-dimethyl- and 2,3-diphenyl-5-hydroxybenzofurans [4, 5] and 2-methyl-3-ethoxycarbonyl-5-oxyindole derivatives [6, 7]. It has also been reported that replacement of the hydroxy groups by an O-acetyl group affected the orientation in the nitration of indole derivatives and that only the 6-nitro isomer was obtained in 17% yield in the case of 1,2-dimethyl-3-ethoxycarbonyl-5-acetoxyindole. A nitro compound could not be obtained at all when the acetyl group was replaced by a benzoyl group [6].

3-Acyl-4,6-dinitro-5-hydroxybenzofurans (VIa-c) were also obtained in the nitration of 3-acyl-5-acetoxybenzofurans IIa-c under more severe conditions. Hydrolysis of the

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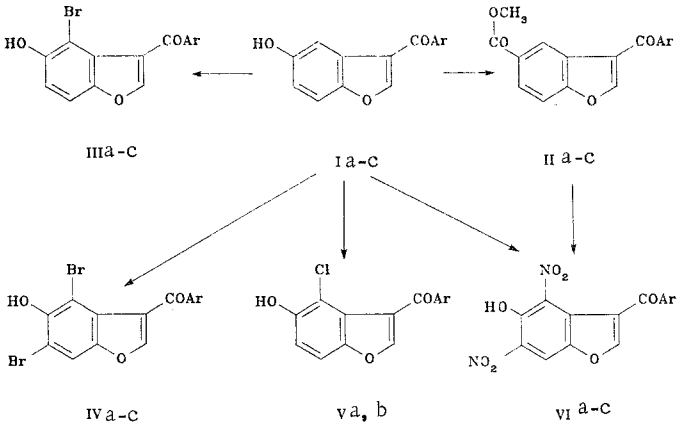
TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp,[a] °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Br (Cl)	N		C	H	Br (Cl)	N	
IIa	83—84	73,2	4,6	—	—	$C_{17}H_{12}O_4$	72,9	4,3	—	—	100
IIb	93—94	73,1	4,7	—	—	$C_{18}H_{14}O_4$	73,5	4,8	—	—	100
IIc	105—106	70,0	4,7	—	—	$C_{18}H_{14}O_5$	69,7	4,6	—	—	100
IIIa	168—170	56,7	3,1	25,2	—	$C_{15}H_9BrO_3$	56,8	2,9	25,2	—	76,3
IIIb	155—157	57,9	3,4	24,2	—	$C_{16}H_{11}BrO_3$	58,0	3,4	24,1	—	72,5
IIIc	147—148	55,3	3,5	23,0	—	$C_{16}H_{11}BrO_4$	55,4	3,2	23,1	—	83,6
IVa	141—142	45,9	2,3	40,1	—	$C_{15}H_8Br_2O_3$	45,5	2,0	40,4	—	91,0
IVb	176—178	46,7	2,5	39,7	—	$C_{16}H_{10}Br_2O_3$	46,9	2,5	39,0	—	68,4
IVc	158—159	45,1	2,4	37,1	—	$C_{16}H_{10}Br_2O_4$	45,1	2,4	37,5	—	74,5
Va	159—160	66,0	2,8	(12,2)	—	$C_{15}H_9ClO_3$	66,1	3,3	(13,0)	—	95,6
Vb	132—133	67,0	3,9	(11,6)	—	$C_{16}H_{11}ClO_3$	67,0	3,9	(12,4)	—	67,3
VIa	209—210	54,9	2,5	—	8,7	$C_{15}H_8O_7N_2$	54,9	2,5	—	8,5	76,6[b] 51,3[c]
VIb	227—228	56,2	3,1	—	7,9	$C_{16}H_{10}O_7N_2$	56,2	2,9	—	8,2	61,4[b] 44,1[c]
VIc	203—204	53,6	2,7	—	7,5	$C_{16}H_{10}O_8N_2$	53,6	2,8	—	7,8	75,4[b] 50[c]

[a]See the experimental section for the crystallization solvents. [b]Obtained from Ia-c. [c]Obtained from IIa-c.

acetoxy group of the benzofurans probably occurs initially under the reaction conditions, after which the resulting 3-acyl-5-hydroxybenzofurans Ia-c undergo nitration.



I—VI a Ar=C_6H_5, b Ar=p-$CH_3C_6H_4$, c Ar=p-$CH_3OC_6H_4$

Thus, as in the case of 5-hydroxyindole derivatives [8], the result of the presence of a strong donor substituent in the benzene ring of benzofurans is that precisely this substituent determines the site of attack by the electrophilic agent: In the chlorination and bromination of 3-acyl-5-hydroxybenzofurans Ia-c the substituents first enter the 4 position and then enter the 6 position, and only 4,6-dinitro derivatives could be obtained in the case of nitration. The inertness of the free 2 position in 3-acyl-5-hydroxybenzofurans Ia-c with respect to electrophilic agents is evidently also associated with the deactivating effect of the electron-acceptor substituent in the 3 position.

The structures of the compounds obtained were confirmed by PMR spectroscopy (Table 2). To assign the signals we used the spectra of 3-(p-methoxybenzoyl)-5-acetoxybenzofuran (IIc). All conclusions regarding the structures of the investigated compounds follow from the multiplicities of the signals in the aromatic part of the spectra.

In addition to a singlet of a proton attached to the $C_{(2)}$ atom (8.1-8.38 ppm), either two doublets (for IIIb, c and Vb, J_{AB} = 9 Hz) or one doublet (for IIIa and Va, J = 9 Hz) stand out in the PMR spectra of IIIa-c and Va, b in the region of signals of aromatic protons. These signals can correspond only to the ortho protons in 6 and 7 positions. Consequently, the halogen is in the 4 position in IIIa-c and Va, b. It follows from an examination of the PMR spectra of nitration products VIa-c that the reaction proceeds with the formation of disubstituted compounds: Only singlet signals at 8.78-9.02 ppm, which belong to the protons attached to the $C_{(2)}$ and $C_{(7)}$ atoms, are observed in the spectra.

TABLE 2. ^{1}H Chemical Shifts of II, III, and V-VII (δ, ppm)

Compound[a]	$C_{(2)}$	$C_{(4)}$	$C_{(6)}$	$C_{(7)}$
IIIa[b]	8,16 s	—	7,12 d	—
IIIb	8,12 s	—	7,10 d	7,50 d
IIIc	8,12 s	—	7,00 d	7,50 d
Va[b]	8,38 s	—	7,08 d	—
Vb	8,33 s	—	7,10 d	7,52 d
VIa	8,80 s	—	—	9,02 s
VIb	8,79 s	—	—	8,99 s
VIc	8,78 s	—	—	8,97 s
VII	8,45 s	7,62 d	6,89 q	7,46 d
IIc[c]	8,47 s	7,92 d	7,12 q	7,64 d

[a]The solvents used to obtain the spectra were $(CD_3)_2CO$ for IIc, IIIa-c, and VIa-c and $(CD_3)_2SO$ for Va, b and VII. [b]For IIIa-c, δ_{OH} = 8.50-8.60 ppm, as compared with 9.95-10.5 ppm for Va, b. [c]For IIc, δ_{OCOCH_3} = 2.28 ppm, $J_{6,7}$ = 9 Hz, and $J_{6,4}$ = 2.5 Hz.

4,6-Dinitro-5-hydroxybenzofuran derivatives VIa-c are formed in the nitration of 3-acyl-5-acetoxybenzofurans; this is confirmed by the absence of signals of an acetoxy group in the PMR spectra.

EXPERIMENTAL

The PMR spectra were recorded with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard. The purity of the isolated substances was verified by thin-layer chromatography (TLC) on Silufol UV-254 plates in a benzene—acetone system (9:1) with development in UV light. The molecular masses of Va, b were confirmed by determination of the molecular ions with a Varian MAT-112 mass spectrometer (70 eV) with direct introduction of the samples into the ion source.

3-Acyl-5-hydroxybenzofurans Ia-c were obtained by the method described in [9].

3-Acyl-5-acetoxybenzofurans (IIa-c). A 10-ml (0.1 mole) sample of acetic anhydride and 0.1 ml of concentrated H_2SO_4 were added to 0.01 mole of Ia-c, and the mixture was maintained at room temperature for 2 h, after which it was poured into 100 ml of water. The resulting precipitate was separated, washed on the filter with water, dried, and crystallized from isopropyl alcohol (Table 1).

3-Acyl-4-bromo-5-hydroxybenzofurans (IIIa-c). A solution of 1.6 g (0.01 mole) of bromine in 10 ml of glacial acetic acid was added gradually with stirring at room temperature to a suspension of 0.01 mole of Ia-c in 20 ml of glacial acetic acid, and the mixture was stirred for 5 h. The product was removed by filtration, washed with water, dried, and recrystallized from isopropyl alcohol (Table 1).

3-Acyl-4,6-dibromo-5-hydroxybenzofurans (IVa-c). A solution of 4.8 g (0.03 mole) of bromine in 15 ml of chloroform was added at room temperature to a suspension of 0.01 mole of benzofuran Ia-c in 25 ml of chloroform, and the mixture was refluxed for 3 h and stirred at room temperature for 3-4 h. The undissolved impurity was removed by filtration, and the filtrate was washed with water and dried with magnesium sulfate. The chloroform was removed by vacuum distillation, and the residue was recrystallized from isopropyl alcohol. Compound IVb was crystallized from carbon tetrachloride (Table 1).

3-Acyl-4-chloro-5-hydroxybenzofurans (Va, b). A solution of 1.35 g (0.01 mole) of sulfuryl chloride in 3 ml of chloroform was added gradually at −5-10°C to a suspension of 0.01 mole of benzofuran Ia, b in 30 ml of chloroform, and the mixture was stirred at this temperature for 2 h. The cooling bath was removed, and the reaction mixture was allowed to stand at room temperature for 15-18 h. The reaction product was removed by filtration, the chloroform was removed by distillation, and the residue was combined with the crystals that precipitated from the reaction mixture. This mixture was recrystallized from carbon tetrachloride (Table 1).

3-Acyl-4,6-dinitro-5-hydroxybenzofurans (VIa-c). A) A solution of 0.03 mole of nitric acid was added gradually with stirring at room temperature to a suspension of 0.01 mole of benzofuran Ia-c in 20 ml of glacial acetic acid, and the mixture was stirred for 5 h. The precipitate was removed by filtration, washed on the filter with water, and recrystallized from ethyl acetate (Table 1).

B) A cooled (to 0-5°C) nitrating mixture, prepared from 1 ml of concentrated nitric acid and 1.4 ml of concentrated sulfuric acid, was added dropwise at 10-15°C to a solution of 0.01 mole of IIa-c in 20 ml of glacial acetic acid, and the mixture was stirred at room temperature for 5 h. The resulting precipitate was removed by filtration, washed on the filter with water, dried, and recrystallized from ethyl acetate (Table 1).

No melting-point depression was observed for a mixture of samples obtained by methods A and B.

LITERATURE CITED

1. A. N. Grinev, S. A. Zotova, and T. F. Vlasova, Khim. Geterotsikl. Soedin., No. 3, 311 (1976).
2. C. A. Qiza and R. L. Hinman, J. Org. Chem., 29, 1453 (1964).
3. A. N. Grinev, N. V. Arkhangel'skaya, G. Ya. Uretskaya, and T. F. Vlasova, Khim. Geterotsikl. Soedin., No. 6, 738 (1975).
4. R. Royer, J.-F. Rossignol, P. Demerseman, and N. Platzer, Bull. Soc. Chim. Fr., No. 1, 163 (1972).
5. O. H. Hishmat and A. H. Abdel'Pahman, Ann. Chem., 733, 120 (1970).
6. E. A. Zinchenko, L. G. Yudin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 12, 1646 (1973).
7. V. Kucklander, Arch. Pharm., 304, 602 (1971).
8. V. A. Budylin, L. G. Yudin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 9, 1181 (1980).
9. T. I. Mukhanova, F. A. Trofimov, N. G. Tsyshkova, A. N. Grinev, and K. S. Shadurskii, Khim.-farm. Zh., No. 9, 14 (1967).

SYNTHESIS OF NEW UNCONDENSED BIHETEROCYCLIC COMPOUNDS — 2,2-DIMETHYLTETRAHYDROPYRAN DERIVATIVES

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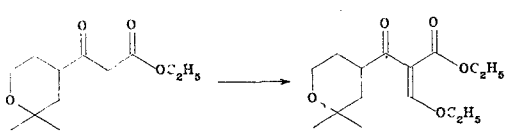
A method for the synthesis of α-ethoxymethylene-β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate is proposed. New uncondensed biheterocyclic compounds were obtained on the basis of the latter. A fundamental difference in the behavior of this system with 1,2-, 1,3-, and 1,4-binucleophiles is demonstrated.

The synthesis of ethoxymethylene derivatives in order to use them in heterocyclization reactions to give uncondensed biheterocycles was a continuation of research on β-keto esters of the tetrahydropyran series.

An ethoxymethylene derivative of a β-keto ester was obtained by the method in [1] on the basis of ethyl β-(2,2-dimethyltetrahydro-4-pyranyl)-β-oxopropionate [2].



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