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SYNTHESIS AND TRANSFORMATIONS OF 2-BROMOMETHYL DERIVATIVES OF 4,5-DIHYDROXYBENZOFURAN

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4,5-Diacetoxy- and 4-acetoxy-5-methoxy derivatives were obtained by the acylation of 2-methyl-3-carboethoxy-4,5-dihydroxy-6-chlorobenzofurans and 2-methyl-3-carboethoxy-4-hydroxy-5-methoxy-6-chlorobenzofurans (and their 6-bromo analogs). The bromination of these derivatives by N-bromosuccinimide gave the corresponding 2-bromomethyl derivatives. The reaction of these 2-bromomethyl derivatives with primary and secondary amines, sodium acetoacetic and sodium malonic esters gave 2-aminomethyl derivatives and derivatives of acetoaetic and malonic esters.

The present work is a continuation of a study of 4,5-dihydroxybenzofurans [1] and is devoted to the synthesis and transformation of their 2-bromomethyl derivatives. 4- and 5-Acetoxy derivatives of benzofuran, in contrast to the corresponding hydroxy- and methoxy derivatives, are brominated not in the benzene ring but rather in the furan ring or in the furan ring methyl group [2-4]. Thus, we initially carried out the acetylation of 2-methyl-3-carboethoxy-4,5-dihydroxy-6-chlorobenzofuran and 2-methyl-3-carboethoxy-4-hydroxy-5-methoxy-6-chlorobenzofuran and their 6-bromo analogs in order to obtain the 2-bromomethyl derivatives. The subsequent bromination of acetoxy derivatives Ia-d with N-bromosuccinimide in the presence of benzoyl peroxide gave high yields of 2-bromomethyl-3-carboethoxy-4,5-diacetoxy-6-chlorobenzoburan (IIa), its 6-bromo anlog (IIb), 2-bromomethyl-3-carboethoxy-4-acetoxy-5-methoxy-6-chlorobenzofuran (IIc) and its 6-bromo analog (IId).

TABLE 1. Chemical Shifts of Ia-d, Ia, b, d, and VI in CD_3COCD_3 (σ, ppm)[a]

Compound[b]	7-H (s)	4(5)-OCOCH$_3$	5-OCH$_3$	2-CH$_3$, 2-CH$_2$Br (s)
Ia	7,65	2,32 2,36	—	2,70
Ib	7,77	2,30 2,35	—	2,70
Ic	7,52	2,36	3,83	2,70
Id	7,63	2,36	2,82	2,67
IIa	8,10	2,33 2,40	—	5,00
IIb	8,20	2,34 2,40	—	5,00
IId	7,82	2,38	3,84	5,00
VI[c]	7,47		3,86	—

[a]The spectra of IIa and IIb were taken in $(CD_3)_2SO$. [b]The signals of the protons of 3-$CO_2C_2H_5$ groups are seen and a triplet and quartet at 1.36-1.42 and 4.33-4.65 ppm, respectively. [c]The signals of the 4-OH and 2-CHO protons are present as singlets at 10.8 and 10.4 ppm, respectively.

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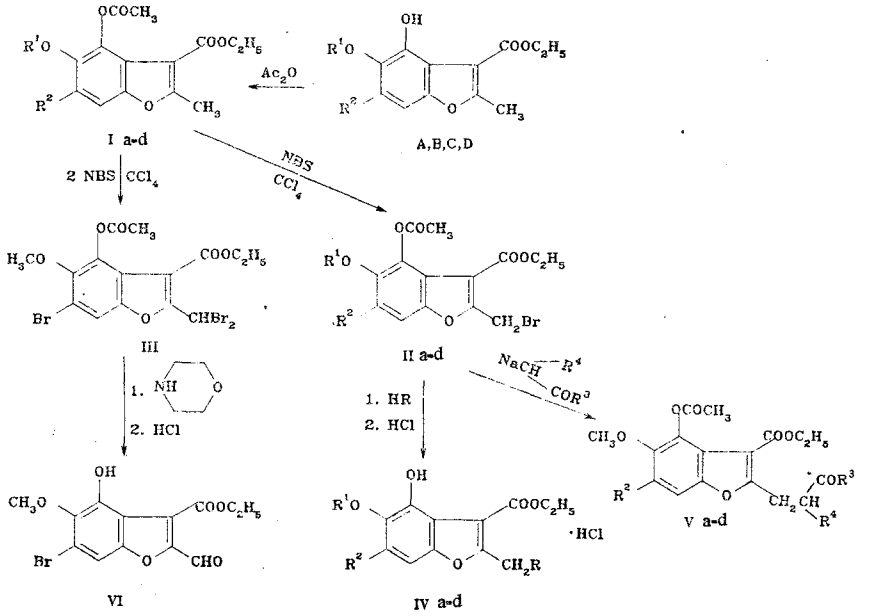
The structures of these bromomethyl derivatives were demonstrated by PMR spectroscopy (see Table 1). The spectra of IIa, b, and d lack signals at 2.67-2.70 ppm which are characteristic for methyl groups at C-2 of the starting acetoxy derivatives Ia-d, while methylene group signals at 5.0 ppm are noted.

The dibromomethyl derivative III was obtained by the bromination of acetoxybenzofuran Id by a twofold excess of N-bromosuccinimide.

The reaction of 2-bromomethyl derivatives IIb-d with primary and secondary amines gave 2-aminomethyl derivatives which were isolated as hydrochloride salts IVa-d. In all cases, the elimination of the acetyl groups was seen in addition to the formation of the aminomethyl derivatives.

The action of sodium acetoacetic ester and sodium malonic ester on IIc and IId gave the corresponding alkylation products Va-c. Product Vb was converted into 1-(3-carboethoyl-4-acetoxy-5-methoxy-6-bromobenzofur-2-yl)-3-butanone (Vd).

The consecutive treatment of dibromomethyl derivative III by morpholine and hydrochloric acid leads to 2-formyl-3-carboethoxy-4-hydroxy-5-methoxy-6-bromobenzofuran (VI).



I, II a $R^1=COCH_3$, $R^2=Cl$; б $R^1=COCH_3$, $R^2=Br$; в $R^1=CH_3$, $R^2=Cl$; г $R^1=CH_3$, $R^2=Br$; A $R^1=H$, $R^2=Cl$; B $R^1=H$, $R^2=Br$; C $R^1=CH_3$, $R^2=Cl$; D $R^1=CH_3$, $R^2=Br$; IV a $R^1=H$, $R^2=Br$, R = morpholino; б $R^1=CH_3$, $R^2=Cl$, R = morpholino; в $R^1=CH_3$, $R^2=Br$, R = morpholino; г $R^1=CH_3$, $R^2=Br$, R=NHPr-*i*; V a $R^2=Cl$, $R^3=CH_3$, $R^4=COOC_2H_5$; б $R^2=Br$, $R^3=CH_3$, $R^4=COOC_2H_5$; в $R^2=Br$; $R^3=OC_2H_5$, $R^4=COOC_2H_5$; г $R^2=Br$, $R^3=CH_3$, $R^4=H$

EXPERIMENTAL

The PMR spectra were taken on a Varian XL-100 spectrometer with TMS as internal standard. The characteristics and yields of all the compounds obtained are given in Tables 1 and 2.

2-Methyl-3-carboethoxy-4,5-diacetoxy-6-chlorobenzofuran (Ia). A mixture of 4.0 g (0.015 mole) 2-methyl-3-carboethoxy-4,5-dihydroxy-6-chlorobenzofuran, 20 ml acetic anhydride, and 2 drops piperidine was heated at reflux for 5 h and then treated with 200 ml water. The precipitate was filtered off, washed with water and dried to yield 4.75 g (91%) Ia.

Compounds Ib-d were obtained by analogy.

2-Bromomethyl-3-carboethoxy-4,5-diacetoxy-6-chlorobenzofuran (IIa). A mixture of 1.8 g (5 mmoles) Ia, 0.9 g (5 mmoles) N-bromosuccinimide, and 0.01 g benzoyl peroxide in 4 ml carbon tetrachloride was heated at reflux for 3 h. The hot reaction mixture was filtered and the mother liquor was evaporated in vacuum. The residue was recrystallized from ethanol to yield 1.7 g (78%) IIa.

Compounds IIb-d were obtained by analogy.

2,2-Dibromomethyl-3-carboethoxy-4-acetoxy-5-methoxy-6-bromobenzofuran (III). A mixture of 15.0 g (0.04 mole) 2-methyl-3-carboethoxy-4-acetoxy-5-methoxy-6-bromobenzofuran (Id), 15.0

TABLE 2. Characteristics of Compounds Prepared

Compound	mp, deg C (from ethanol)	Found, %				Chemical formula	Calculated, %				Yield, %
		C	H	Br	Cl		C	H	Br	Cl	
Ia	146,5—148,5	54,0	4,0	—	9,8	$C_{16}H_{15}ClO_7$	54,2	4,3	—	10,0	91
Ib	138—140[a]	48,2	3,9	19,7	—	$C_{16}H_{15}BrO_7$	48,1	3,8	20,0	—	94
Ic	91—93	55,4	4,5	—	11,0	$C_{15}H_{15}ClO_6$	55,1	4,6	—	10,8	98
Id	91—93	48,9	4,1	20,9	—	$C_{15}H_{15}BrO_6$	48,5	4,1	21,5	—	92
IIa	140—142	44,9	3,3	18,0	8,0	$C_{16}H_{14}BrClO_7$	44,3	3,2	18,4	8,2	78
IIb	136—138	40,6	3,2	33,2	—	$C_{16}H_{14}Br_2O_7$	40,2	3,0	33,4	—	54
IIc	105—107	44,4	3,6	20,0	8,9	$C_{15}H_{14}BrClO_6$	44,4	3,5	19,7	8,7	84
IId	115,5—117	40,4	3,4	35,6	—	$C_{15}H_{14}Br_2O_6$	40,0	3,1	35,5	—	87
III	127—129	34,1	2,4	45,2	—	$C_{15}H_{13}BrO_6$	34,1	2,5	45,3	—	58
IVa	234—236[a]	44,2	4,7	17,8	7,9	$C_{19}H_{19}BrClNO_6$[b]	44,0	4,4	18,3	8,1	27
IVb	222—223[a]	50,0	5,2	—	17,4	$C_{17}H_{21}Cl_2NO_6$[c]	50,3	5,2	—	17,4	28
IVc	230—231[a]	45,3	4,8	18,1	8,0	$C_{17}H_{21}BrClNO_6$	45,3	4,7	17,7	7,9	42
IVd	204,5—206[a]	45,5	5,0	18,9	8,4	$C_{16}H_{21}BrClNO_6$[e]	45,4	5,0	19,0	8,4	30
Va	110—111	55,3	5,0		—	$C_{21}H_{23}ClO_9$	55,4	5,1		—	9
Vb	177—179	50,3	4,4	15,8	—	$C_{21}H_{23}BrO_9$	50,5	4,6	16,0	—	40
Vc	199—200[d]	49,9	4,5	15,2	—	$C_{22}H_{25}BrO_{10}$	49,9	4,8	15,1	—	16
Vd	169—171	50,4	4,4	19,2	—	$C_{18}H_{19}BrO_7$	50,6	4,5	18,7	—	35
VI	178—180	45,6	3,3	23,4	—	$C_{13}H_{11}BrO_6$	45,5	3,2	23,3	—	24

[a]With decomposition. [b]Found: N, 3.2%. Calculated: N, 3.2%. [c]Found: N, 3.2%. Calculated: N, 3.4%. [d]Found: N, 3.1%. Calculated: N, 3.2%. [e]From ethyl acetate.

g (0.08 mole) N-bromosuccinimide, and 0.01 g benzoyl peroxide in 30 ml carbon tetrachloride was heated at reflux for 30 h. The hot reaction mixture was filtered and the mother liquor was evaporated under vacuum. The residue was recrystallized from ethanol to yield 12.3 g (58%) III.

Hydrochloride salt of 2-morpholinomethyl-3-carboethoxy-4,5-dihydroxy-6-bromobenzofuran (IVa). A sample of 1.2 g (0.012 mole) morpholine was added to a solution of 1.45 g (3 mmole) Ib in 20 ml benzene and left for 18 h at room temperature. The reaction mass was extracted with three 50-ml portions of water. The organic layer was separated and evaporated under vacuum. The residue was dissolved in 20 ml acetone and concentrated hydrochloric acid was until to reduce the pH to 3. The hydrochloride precipitate formed was filtered off, washed with acetone and dried to yield 0.35 g (27%) IVa.

Compounds IVb-d were obtained by analogy.

1-(3-Carboethoxy-4-acetoxy-5-methoxy-6-chlorobenzofur-2-yl)-2-carboethoxy-3-butanone (Va). A mixture of 0.55 g (4 mmoles) acetoacetic ester and 0.6 g (4 mmoles) anhydrous potassium carbonate in 10 ml acetone was heated at reflux for 15 min. Then a solution of 1.55 g (4 mmoles) IIc in 25 ml acetone was added and, after 5 h heating at reflux, 250 ml water was added. The mixture was extracted with three 50-ml portions of chloroform. The chloroform was evaporated and the residue recrystallized from ethanol to yield 0.15 g (9%) Va.

Compounds Vb and Vc were obtained by analogy.

1-(3-Carboethoxy-4-acetoxy-5-methoxy-6-bromobenzofur-2-yl)-3-butanone (Vd). A mixture of 0.5 g (1 mmole) Vb, 15 ml acetic acid, and 5 ml concentrated hydrochloric acid was heated at reflux for 5 h and then cooled to 0-5°C. The precipitate formed was filtered off and recrystallized from ethanol to yield 0.15 g (35%) Vd.

2-Formyl-3-carboethoxy-4-hydroxy-5-methoxy-6-bromobenzofuran (VI). A sample of 5.0 g (0.06 mole) morpholine was added to 5.0 g (9 mmoles) III, stirred, and then left standing at 20°C for 20 h. The crystals were filtered off and washed with morpholine and then, water and recrystallized from acetone. The product obtained (0.9 g) was suspended in 50 ml water and 2 ml 1:1 diluted hydrochloric acid was added and then heated for 20 min at 70-80°C. The mixture was cooled to 20°C. The crystals were filtered off, washed with water, and dried with water to yield 0.82 g (24%) VI. Thiosemicarbazone, mp 240-242°C (from acetic acid). Found: C, 40.4; H, 3.6; Br, 19.1; N, 10.2%. Calculated for $C_{14}H_{14}BrNO_5$: C, 40.4; H, 3.4; Br, 19.2; N, 10.1%.

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SYNTHESIS OF 2-AMINO-1-ACETYL-5,5-DIMETHYL-3-CYANO-4,5,6,7-TETRAHYDROPYRROLO-[2,3-c]PYRAN AND ITS ACETYLATION

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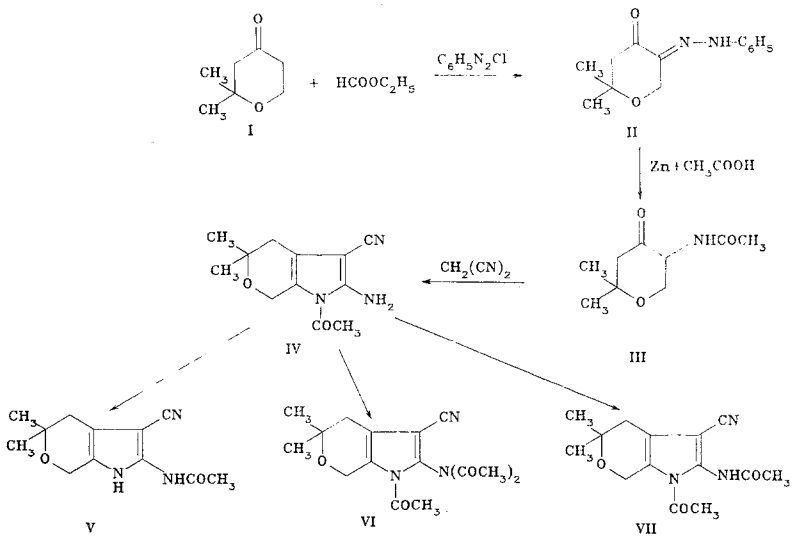
2,2-Dimethyltetrahydropyran-4-one was used to obtain 2-amino-1-acetyl-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran and its acetyl derivatives.

The condensed system of pyran and pyrrole may be considered as an analog of indole whose structure is the basis for many compounds with high biological activity.

There is only one example of the synthesis of pyranopyrroles. This system was obtained by Carr et al. [1] in the synthesis of porphyrins.

We have prepared this condensed system using 2,2-dimethyltetrahydropyran-4-one (I) [2]. The reaction of ketone I with ethyl formate and with phenyldiazonium chloride gave the 5-monophenylhydrazone of 2,2-dimethyltetrahydropyran-4,5-dione (II). This dione was reduced by zinc dust in acetic acid to give 5-acetamido-2,2-dimethyltetrahydropyran-4-one (III). The condensation of ketoamide III with malononitrile gave 2-aminol-1-acetyl-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (IV). Heating IV in acetic acid or pyridine gave 2-acetylamino-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (V). This transformation is apparently related to intramolecular migration of the acetyl group. The triacetyl derivative VI was obtained by heating aminonitrile IV with acetic anhydride at reflux. On the other hand, the acetylation of aminonitrile IV by acetic anhydride in benzene leads to the diacetyl derivative VII.



The PMR spectrum of aminonitrile IV shows a singlet at 2.35 ppm which is related to the protons in the spectrum of amidonitrile V are at higher field (2.25 ppm) than in the spectrum of aminonitrile IV. The signals for the acetyl group protons of triacetyl derivative VI are

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