SYNTHESIS OF 4,5-DIHYDROXYBENZOFURANS AND 4,5-DIHYDROXYINDOLES BY DEHALOGENATION OF HALO DERIVATIVES

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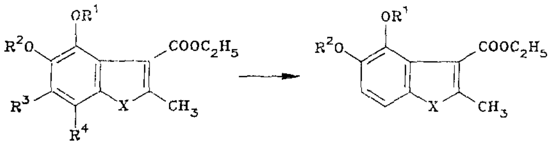
A preparative method for the synthesis of derivatives of 4,5-dihydroxybenzofuran and 4,5-dihydroxyindole by dehalogenation of 4,5-dihydroxy-6-chloro(or bromo) and 4,5-dihydroxy-6,7-dichloro derivatives of benzofuran and indole with heating in aqueous ethanol over Raney nickel has been proposed.

4,5-Dihydroxy derivatives of benzofuran and indole without halo substituents in the benzene ring are practically inaccessible. Derivatives of 4,5-dihydroxyindole form with very low yields when p-benzoquinone is condensed with N-arylaminocrotonic esters [1]. The synthesis of derivatives of 4,5-dihydrobenzofuran from benzoin derivatives is likewise not preparative [2]. 4,5-Dihydroxy derivatives of benzofuran and indole are of interest as starting compounds for the synthesis of biologically active substances; therefore, out task was to develop preparative methods for their synthesis.

Owing to the availability of 6-halo-4,5-benzofuranquinones, 6-halo-, and 6,7-dihalo-4,5-indolequinones, and the possibility of their reduction to the corresponding halo-4,5-dihydroxy derivatives [3-5], we selected the dehalogenation of the 6-halo or 6,7-dihalo derivatives as the main preparative method for the synthesis of 4,5-dihydroxybenzofurans and indoles.

In the case of the dehalogenation of compounds Ia-e, g, and h with the aid of Raney nickel in aqueous ethanol, we obtained a number of derivatives of 4,5-dihydroxybenzofuran (IIa-c) and 4,5-dihydroxyindole (IIe, g,* and h). It should be noted that the bromo derivatives of benzofuran are dehalogenated more rapidly than are the chloro derivatives, while the dehalogenation of the benzofuran derivatives is considerably faster than in the case of the indole derivatives. The use of a large excess of catalyst makes it possible to eliminate the halogen in the indole derivatives as well.



I g IIa-c, e, g, h

I a $X=O$, $R^1=R^2=R^4=H$, $R^3=Br$; b $X=O$, $R^1=R^4=H$, $R^2=CH_3$, $R^3=Br$; c $X=O$, $R^1=R^2=CH_3$, $R^3=Br$, $R^4=H$; d $X=O$, $R^1=R^4=H$, $R^2=CH_3$, $R^3=Cl$; e $X=NCH_3$, $R^1=R^2=H$, $R^3=R^4=Cl$; f $X=NC_6H_5$, $R^1=R^2=R^4=H$, $R^3=Br$; g $X=NC_6H_5$, $R^1=R^4=H$, $R^2=CH_3$, $R^3=Br$; h $X=NC_6H_5$, $R^1=R^2=CH_3$, $R^3=Br$, $R^4=H$; II a $X=O$, $R^1=R^2=H$; b $X=O$, $R^1=H$, $R^2=CH_3$; c $X=O$, $R^1=R^2=CH_3$; e $X=NCH_3$, $R^1=R^2=H$; g $X=NC_6H_5$, $R^1=H$, $R^2=CH_3$; h $X=NC_6H_5$, $R^1=R^2=CH_3$

The preparative method proposed in the present work for the synthesis of derivatives of 4,5-dihydroxybenzofuran and 4,5-dihydroxyindole without halo substituents in the benzene ring was also used to obtain 4-methoxy- 5-hydroxy derivatives of benzofuran and indole, which are inaccessible by the direct methylation of the corresponding dihydroxy derivatives. The

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*Compound IIg was previously obtained [1] by methylating 1-phenyl-2-methyl-3-carbethoxy-4,5-dihydroxyindole.

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TABLE 1. Proton-Magnetic-Resonance Spectra of Compounds Ie, g, k, *l*, IIa-c, e, g, and k

Compound	4-OH 5-OH	5-$OCH_2C_6H_5$ 1-C_6H_5	6-H 7-H	3-$COOCH_2CH_3$	4-OCH_3 5-OCH_3	2-CH_3
Ie	7,69 (c)	—	—	1,43 (t) 4,44 (q)	—	2,74 (s)
Ig	—	7,72—7,46 (m)	6,54 (s)	1,44 (t) 4,46 (q)	3,82 (s)	2,50 (s)
Ik	—	7,38—7,59 (m) 5,03 (m)	7,57 (s)	1,40 (t) 4,40 (q)	3,96 (s)	2,35 (s)
Il	—	7,35—7,66 (m) 5,03 (s)	6,93 (s)	1,41 (t) 4,39 (q)	4,00 (s)	2,41 (s)
IIa	7,15 (c)	—	6,84 (s) (2H)	1,45 (t) 4,47 (q)	—	2,70 (s)
IIb*	—	—	7,0 (d) 7,03(d)	1,46 (t) 4,46 (q)	3,91 (s)	2,38 (s)
IIc*	—	—	7,11 (d) 7,91 (d)	1,43 (t) 4,40 (q)	3,91 (s) 3,89 (s)	2,64 (s)
IIe	—	—	6,75 (d) 6,79 (d)	1,45 (t) 4,32 (q)	—	2,66 (s)
IIg	—	7,42—7,69 (m)	6,87 (d) 6,29 (d)	1,43 (t) 4,45 (q)	3,80 (s)	2,50 (s)
IIk	—	—	7,12 (d) 6,90 (d)	1,40 (t) 4,37 (q)	3,81 (s)	2,40 (s)

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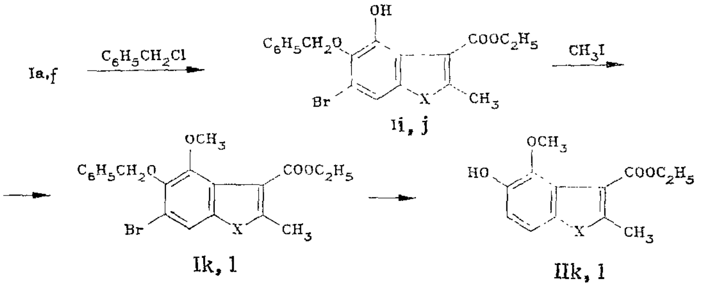
*The spectra were recorded in $CDCl_3$

benzylation of Ia and it gives the corresponding 5-benzyloxy derivatives Ii and Ij, whose methylation affords 4-methoxy-5-benzyloxy derivatives Ik and I*l*. When Raney nickel acts on Ik and I*l* under the conditions indicated, benzylation takes place along with debromination, and 2-methyl-3-carbethoxy-4-methoxy-5-hydroxybenzofuran (IIk) and 1-phenyl-2-methyl-3-carbethoxy-4-methoxy-5-hydroxyindole (IIm), respectively, form.



I i X=O; j X=NC_6H_5; k X=O; l X=NC_6H_5; II kX=O; l X=NC_6H_5

The PMR spectra of compounds IIb, c, e, g, and k in the 6.54-7.7-ppm region do not show singlet signals characteristic of protons in position 7 of the original halo derivatives I, but they do show doublet signals at 6.29-7.91 ppm, which are assigned to protons in positions 6 and 7. The signals of the 6-H and 7-H protons in the spectrum of compound IIa are displayed in the form of a singlet at 6.84 ppm (2H).

EXPERIMENTAL

The PMR spectra were obtained on a Varian XL-100 spectrometer in acetone-d_6 with TMS as an internal reference.

The course of the reactions was monitored chromatographically on Silufol-254 in a 9:1 benzene—methanol solvent system with development in UV light.

<u>1,2-Dimethyl-3-carbethoxy-4,5-dihydroxy-6,7-dichloroindole (Ie).</u> A suspension of 3.16 g (0.01mole) of 1,2-dimethyl-3-carbethoxy-4,5-dioxo-6,7-dichloroindole [4] in 65 ml of methanol is given an addition of a solution of 2.1 g (0.02 mole) of sodium hydrosulfite in 9 ml of water with stirring at room temperature, and the mixture is stirred for 1 h. The precipitate is filtered out, washed with methanol and water, and dried. This gives 2.8 g of Ie.

The characteristics and yields of the compounds obtained are given in Tables 1 and 2.

TABLE 2. Characteristics of Compounds Obtained

Compound	mp, °C*	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Br(Cl)	N		C	H	Br(Cl)	N	
Ie	231—232	48,7	4,2	(22,3)	4,4	$C_{13}H_{13}Cl_2NO_4$	49,1	4,1	(22,3)	4,4	88
If	225—227	55,3	4,2	20,5	3,6	$C_{18}H_{16}BrNO_4$	55,4	4,1	20,5	3,6	82
Ig	233—235	57,0	4,8	19,7	3,3	$C_{19}H_{14}BrNO_4$	56,5	4,5	19,8	3,5	69
Ih	117—119	57,8	4,8	19,0	3,3	$C_{20}H_{20}BrNO_4$	57,4	4,8	19,1	3,3	28
Ii	144—146	56,4	4,2	19,6	—	$C_{19}H_{17}BrO_5$	56,3	4,2	19,7	—	32
Ij	211—213	62,4	4,9		2,8	$C_{25}H_{22}BrNO_4$	62,5	4,6	16,6	2,9	26
Ik	69,5—71	57,3	4,7	19,2	—	$C_{20}H_{19}BrO_5$	57,3	4,6	19,1	—	81
Il	100—102	63,2	5,2	16,1	2,6	$C_{26}H_{24}BrNO_4$	63,2	4,9	16,2	2,8	68
IIa	195—197	61,2	4,9	—	—	$C_{12}H_{12}O_5$	61,0	5,1	—	—	67
IIb	140—142	62,3	5,6	—	—	$C_{13}H_{14}O_5$	62,4	5,6	—	—	92
IIc	180†	63,6	6,1	—	—	$C_{14}H_{16}O_5$	63,6	6,1	—	—	86
IIe	184—186	62,4	6,0	—	5,6	$C_{13}H_{15}NO_4$	62,6	6,1	—	5,6	67
IIg	179—181‡	70,2	6,0	—	4,3	$C_{19}H_{19}NO_4$	70,1	5,9	—	4,3	96
IIh	93—95	70,7	6,2	—	4,1	$C_{20}H_{21}NO_4$	70,8	6,2	—	4,1	31
IIk	116—118	62,3	5,6	—	—	$C_{13}H_{14}O_5$	62,4	5,8	—	—	88
IIl	202—204	70,0	5,7	—	4,3	$C_{19}H_{19}NO_4$	70,1	5,9	—	4,3	78

*Compounds Ie, g, and IIe were recrystallized from acetone, If was recrystallized from ethyl acetate, Ih, i, *l*, IIb, g, k, and *l* were recrystallized from benzene, Ik was recrystallized from petroleum ether, and IIh was recrystallized from

†bp at 8 mm Hg.

‡According to the data in [1], mp 181°C.

1-Phenyl-2-methyl-3-carbethoxy-4,5-dihydroxy-6-bromoindole (If). A suspension of 5 g (0.013 mole) of 1-phenyl-2-methyl-3-carbethoxy-4,5-dioxo-6-bromoindole [5] in 250 ml of methanol is given in addition of 40 ml of concentrated hydrochloric acid and 35 g (0.535 mole) of zinc fillings at the boiling point with stirring over the course of 40 min, and then the mixture is boiled for 15 min. The reaction mass is filtered, and the deposit on the filter is washed with 100 ml of dioxane. The combined filtrates are diluted with 1 liter of water. The precipitate is filtered out, washed with water, and dried. This gives 4.1 g of If.

General Procedure of the Alkylation of Ia, f, i, and j. A solution of 0.1 mole of the hydroxy derivative in 500 ml of acetone is given an addition of 0.1 mole of anhydrous potassium carbonate, the mixture is boiled for 1 h, then given an addition of 0.1 mole of methyl iodide or benzyl chloride,* and boiled until the TCL spot of the original compound disappears. The reaction mixture is filtered, the filtrate is evaporated, and the residue is recrystallized. This gives compounds Ig-*l*.

General Procedure for the Dehalogenation of Compounds Ia-e, g, h, k, and *l*. A suspension of 10 g of the halo derivative in 500 ml of 50% aqueous ethanol is given an addition of 50.0 g of freshly prepared Raney nickel (W-7) (100 g for halo derivatives Id, e, g, h, and *l*), and the mixture is boiled for 2-3 h (15-30 h in the case of compounds Id, e, g, h, and *l*) until the TLC spot of the original compound disappears. The reaction mixture is filtered, and the catalyst on the filter is washed with hot ethanol. The combined filtrates are evaporated, and the residue is recrystallized.† This gives compounds IIa, c, e, g, h, k, and *l*.

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*For the synthesis of Ih 0.5 mole of anhydrous potassium carbonate and 0.2 mole of methyl iodide are taken.

†Compound IIc is vacuum-distilled.