SYNTHESIS OF 2-BENZYL (AND ISOBUTYL)-5-HYDROXYBENZOPURANS

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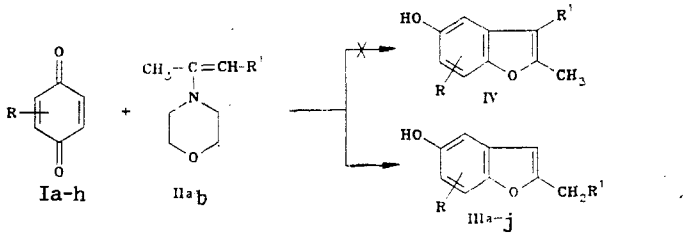
Condensation of p-benzoquinones with methyl benzyl and methyl isobutyl ketone enamines has given the novel 2-benzyl (and isobutyl)-5-hydroxy-benzofurans.

2-Alkyl-5-hydroxybenzofurans are of interest as potentially biologically active compounds [1, 2], but they are difficult to obtain, the syntheses being multistage and giving low yields [3, 4].

We have developed a single-reactor method for the preparation of the novel 2-benzyl (and isobutyl)-5-hydroxybenzofurans (IIIa-j), differing in the substituents in the benzene ring, in yields of 17-76%. The method involves condensing the p-benzoquinones (Ia-h) with the morpholine enamines of methyl benzyl and methyl isobutyl ketones (IIa, b). According to [5], the enamines (IIa, b) are pure compounds, free from contamination with isomers with a terminal double bond. The PMR spectra of (IIa) in $CDCl_3$ and C_6D_5Br showed singlet signals at 5.52 and 1.77 ppm assigned to the vinyl proton and the methyl group, respectively.



Ia, IIIa, i R=H; I b R=2,5-Cl_2, c R=2,3-Cl, d R=2,6-Br_2, e R=2,5-Br_2, f R=C_6H_5, g R=*p*-$NO_2C_6H_4$, h R=SC_6H_5; IIa, IIIa–h R'=C_6H_5; b IIb, IIIi–j R'=$CH(CH_3)_2$; III b R=4,7-Cl_2, c R=6,7-Cl_2, d R=4,6-Br_2, e R=4,7-Br_2, f R=7-C_6H_5, g R=4-(*p*-$NO_2C_6H_4$), h R=6-SC_6H_5, j R=4,6-Br_2

When the reaction was carried out in benzene at 20°C followed by heating in alcoholic hydrogen chloride, the enamines (IIa, b) reacted in an unexpected way to give the benzofurans (IIIa-j) with a free 3-position, instead of the isomeric 2,3-disubstituted benzofurans (IV). The absence from the reaction mixture of the 5-hydroxybenzofurans (IV) was shown by TLC. The 5-hydroxybenzofurans (IV) required for comparison were obtained as described in [6]. According to [7], the sole product of the reaction of the quinone (Ia) with the enamine (IIa) in ether at −70°C is 2-methyl-2-(4-morpholino)-3-phenyl-2,3-dihydro-5-hydroxybenzofuran (V).

We also carried out a stepwise synthesis of the 5-hydroxybenzofuran (IIIg) from the quinone (Ig) and the enamine (IIa), comprising the formation of the dihydrobenzofuran (VI), and deamination of the latter by heating with alcoholic hydrogen chloride. The nature of the substituents in the 2- and 3-positions of the benzofuran ring in compounds (IIIa-j) is therefore determined at the stage of reaction of the benzoquinone with the enamine, rather than at the subsequent stage of aromatization of the dihydrobenzofuran ring. It remains to be supposed that the enamine is converted during the reaction into the sterically less hindered isomer with a terminal C=C bond, which also reacts with the benzoquinone.

The structure of (VI) was confirmed by the presence in the PMR spectrum of signals for the protons of the methylene groups of the morpholine ring at 2.81 and 3.60 ppm,

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TABLE 1. Properties of Compounds (IIIa-j) and (VI)

Compound	Empirical formula	mp,* °C	Chemical shifts, δ, ppm (J, Hz)**						Yield, %
			CH_2CH	$CH_2CH(CH_3)_2$	3-H	4-H	6-H	7-H, d	solvent	
IIIa	$C_{15}H_{12}O_2$	110...112	4,03 d (J=0,7)	—	6,27 q ($J_1=J_2$=0,7)	6,84 d (J=2,5)	6,64 q (J_1=9; J_2=2,5)	7,18 (J=9)	CD_3OD	46
IIIb	$C_{15}H_{10}Cl_2O_2$	103...105	4,22 d	—	6,58 t	—	6,99s	—	$(CD_3)_2CO$	66
IIIc	$C_{15}H_{10}Cl_2O_2$	105...106	4,16 d	—	6,49 t	7,12 s	—	—	$(CD_3)_2CO$	36
IIId	$C_{15}H_{10}Br_2O_2$	111...113	4,06 d	—	6,34 q	—	—	7,57	CD_3OD	60
IIIe	$C_{15}H_{10}Br_2O_2$	123...125	4,12 d	—	6,32 t	—	7,11 s	—	$CDCl_3$	55
IIIf	$C_{21}H_{16}O_2$	116...118	4,09 d	—	6,27 t	6,85...6,90 d (J=2,5)		—	$CDCl_3$	17
IIIg	$C_{21}H_{15}NO_4$	140...144	4,13 d	—	6,58 t	—	6,96 d (J=9)	—***	$(CD_3)_2CO$	87
IIIh	$C_{21}H_{16}SO_2$	76...78	4,08 d	—	6,32 q	6,40 s	—	7,60	$CDCl_3$	30
IIIi	$C_{12}H_{14}O_2$	61...62	—	0,98 d 2,0 m 2,6 q	6,28 q ($J_1=J_2$=0,8)	6,89 d (J=2,5)	6,70 q (J_1=9; J_2=2,5)	7,25 (J=9)	$CDCl_3$	49
IIIj	$C_{12}H_{12}Br_2O_2$	36...38	—	0,96 d 2,09 m 2,60 q	6,35 q	—	—	7,53	$CDCl_3$	54
VI	$C_{25}H_{24}N_2O_5$	233...236	3,28 s	—	3,10 q	—	6,61d	6,74	$(CD_3)_2CO$	88

*Compounds (IIIb, e, f) were crystallized from CCl_4, (IIIc, h-j) from petroleum ether, and (IIId) from ethanol.

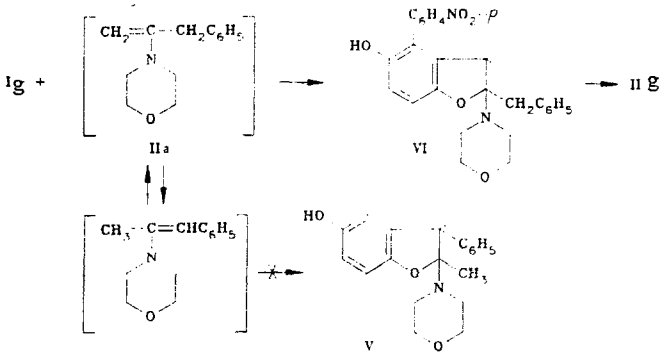
**The coupling constants of (IIIa-h) for the 3-H and 7-H protons and the 2-$CH_2C_6H_5$ group were similar, and for (IIIi, j) the coupling constants for the 3-H and 7-H protons and the 2-$CH_2CH(CH_3)_2$ methylene group were also similar.

***The signal for the 7-H proton overlaps those for the protons of the phenyl substituents (7.31...8.32 ppm).

together with signals for the protons of the methylene group in the 3-position, seen as a quartet for an AB system centered at 3.10 ppm.

In the PMR spectrum of (IIIa) (in CD_3OD), in addition to the signals for the protons in positions 4, 6, and 7, present at 6.84 (d, J = 2.5 Hz), 6.64 (q. d., J_1 = 9.0, J_2 = 2.5 Hz), and 7.18 ppm (d, J = 9.0 Hz), signals were present for the 3-H proton at 6.27 (q, $J_{37} = J_{32}$ = 0.7 Hz) and the methylene group of the 2-substituent at 4.03 ppm (d, J_{23} = 0.7 Hz).

The multiplicity of the signal for 3-H is due to spin coupling with the 7-H proton and the CH_2 proton. Thus, in the double resonance spectrum the signal for the 3-H proton is converted into a doublet (J_{37} = 0.7 Hz) on suppression of the signals for the CH_2 protons, and into a triplet (J_{3,CH_2} = 0.7 Hz) on suppression of the 7-H signal.



The PMR spectra of (IIIb-j) are similar. The assignments of the signals for the protons in these compounds in the spectra are given in Table 1.

EXPERIMENTAL

PMR spectra were obtained on a Varian XL-200 spectrometer, internal standard TMS. The reactions were followed, and the purity of the compounds established by chromatography on Silufol-254 plates in the system benzene—methanol, 9:1, visualized in UV.

The properties of the compounds obtained are shown in Table 1. The elemental analyses of the compounds for C, H, N, S, and Hal were in agreement with the calculated values.

2-Benzyl-5-hydroxybenzofuran (IIIa). To a solution of 61.2 g (300 mmole) of 2-(4-morpholino)-1-phenylprop-1-ene (IIa) in 150 ml of dry benzene was added with stirring at 20°C a solution of 21.6 g (200 mmole) of p-benzoquinone in 65 ml of dry benzene over 30 min. The mixture was stirred for a further 30 min, and the solvent was then removed under reduced pressure. The residue was treated with 150 ml of ethanol and 40 ml of concentrated HCl, and the mixture boiled for 15 min. The solvent was then removed under reduced pressure, the residue dissolved in 500 ml of benzene, and the solution washed with water to pH 7, and dried over magnesium sulfate. It was then chromatographed on a column of silica gel, the benzene eluate evaporated, and the residue recrystallized from a 1:1 mixture of benzene and hexane to give 20.6 g of (IIIa).

Compounds (IIIb-f) and (IIIh-j) were obtained similarly.

2-(4-Morpholino)-2-benzyl-2,3-dihydro-4-(p-nitrophenyl)-5-hydroxybenzofuran (VI). To a solution of 61.2 g (300 mmole) of (IIa) in 150 ml of dry benzene was added with stirring at 20°C a solution of 45.8 g (200 mmole) of p-nitrophenylbenzoquinone (Ig) in 165 ml of dry benzene over 30 min. The solvent was removed under reduced pressure, and the residue recrystallized from DMF to give 76.0 g of (VI).

2-Benzyl-4-(p-nitrophenyl)-5-hydroxybenzofuran (IIIg). To a suspension of 43.2 g (100 mmole) of (VI) in 250 ml of ethanol was added 40 ml of concentrated HCl, and the mixture boiled for 15 min. The resulting solution was evaporated under reduced pressure, and the residue dissolved in chloroform, washed with water, dried over magnesium sulfate, and evaporated. The residue was recrystallized from CCl_4 to give 27.0 g of (IIIg).

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