SYNTHESIS OF SUBSTITUTED 1,3-BENZOXAZIN-4-ONES

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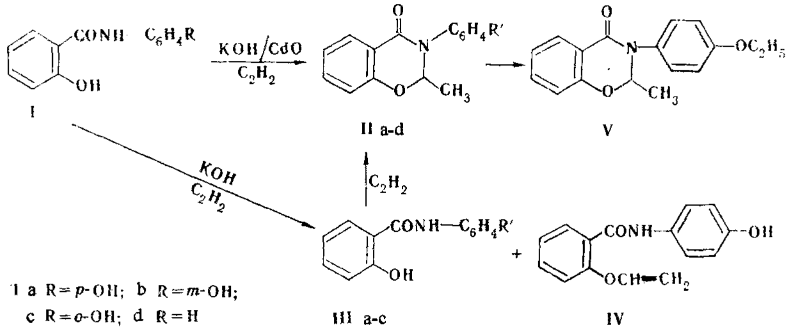
The heterocyclization of 2-hydroxybenzoic acid anilides with acetylene in the presence of a catalyzing mixture of potassium hydroxide with cadmium oxide or cadmium acetate alone gives o-, m-, and p-vinyloxy-substituted 1,3-benzoxazin-4-ones.

We have previously obtained [1] the previously unknown 2-methyl-3-(p-vinyloxyphenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (IIa) from acetylene and 2-hydroxybenzoic acid p-hydroxyanilide (Ia). The present research was devoted to a search for conditions for the synthesis of new vinyl derivatives of the benzoxazine series by the reaction of 2-hydroxybenzoic acid anilides (Ia-d) and 2-hydroxybenzoic acid vinyloxyanilides (III) with acetylene. We also investigated the effect of the position of the hydroxy or vinyloxy group in the benzene ring of the amide fragment of starting anilides Ia-d on the yields of p-, m-, and o-vinyloxyphenyl-substituted 1,3-benzoxazinones IIa-d.

Starting hydroxyanilides Ia-c contain several centers that are capable of nucleophilic addition to acetylene. In this connection, in the reaction with acetylene in the presence of a potassium hydroxide catalyst, which is widely used in reactions of this type, one might have expected the formation of vinylaryl ethers of salicylanilides, the structure of which is determined by the position of the vinyloxy group in the benzene ring of the anilide or acid fragments, as well as the O,O- or O,N-divinyl derivatives of the investigated hydroxyanilides I.

Thus, 2-hydroxybenzoic acid p-vinyloxyanilide (IIIa) and 2-vinyloxybenzoic acid p-hydroxyanilide (IV) are obtained in very low yields in the vinylation of hydroxyanilide Ia in the presence of KOH. p-Vinyloxyaniline and a large amount of resinification products were also isolated from the reaction mixture.



I a R=p-OH; b R=m-OH;
c R=o-OH; d R=H

To solve the problem of the position of the vinyloxy group in ethers III and IV we carried out the alternative synthesis of ether III by the reaction of p-vinyloxyanilide with 2-hydroxybenzoyl chloride and ether IV by the action of 2-vinyloxyphenyl benzoate on p-aminophenol. Their constants were in agreement with the data on the ethers isolated from the reaction mixture in the vinylation of hydroxyanilide Ia with potassium hydroxide, and their IR spectra were completely identical.

Absorption at 1146-1155 cm^{-1} (C—O—C), a broad band at 3300-3380 cm^{-1} (OH and NH), and bands at 1640-1654 cm^{-1} (CO and C=C) appear in the IR spectra of all of the synthesized

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TABLE 1. Characteristics of the Synthesized Compounds (II-V)

Compound	R′	mp or bp (mm), °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	p-OCH=CH$_2$	101—102	72,3	5,4	4,9	$C_{17}H_{15}NO_3$	72,6	5,4	5,0	54
IIb*	m-OCH=CH$_2$	200(4,5)	72,5	5,2	5,0	$C_{17}H_{15}NO_3$	72,6	5,4	5,0	68
IIc*	o-CH=CH$_2$	210(3)	72,4	5,3	4,8	$C_{17}H_{15}NO_3$	72,6	5,4	5,0	60
IId †	H	80—82	75,0	5,4	5,9	$C_{15}H_{13}NO_2$	75,3	5,5	5,9	35
IIIa	p-OCH=CH$_2$	140—142	70,1	5,3	5,3	$C_{15}H_{13}NO_3$	70,6	5,1	5,5	92
IIIb	m-OCH=CH$_2$	120—124	70,9	5,5	5,2	$C_{15}H_{13}NO_3$	70,6	5,1	5,5	90
IIIc	o-OCH=CH$_2$	85—87	70,3	5,3	5,6	$C_{15}H_{13}NO_3$	70,6	5,1	5,5	50
IV	—	153—155	70,7	5,3	5,2	$C_{15}H_{13}NO_3$	70,6	5,1	5,5	11
V	p-OC$_2$H$_5$	134—136	72,2	5,8	5,0	$C_{17}H_{17}NO_3$	72,0	6,0	5,0	90

*The n_D^{20} and d_4^{20} values are presented in the experimental section.

†Crystallized from heptane [mp 78-80°C (from alcohol) [4]].

ethers IIIa-c and IV.

In the PMR spectra of ethers III and IV the chemical shifts of the protons of the vinyl groups and the spin-spin coupling constants (SSCC) (for IIIa: 4.37, 4.68, and 6.62 ppm, and J_{AB} = 1.5, J_{AX} = 5.5, and J_{BX} = 13.5 Hz; for IV: 4.56, 4.87, and 6.65 ppm, and J_{AB} = 2.0, J_{AX} = 5.5, and J_{BX} = 13.5 Hz) are close to one another, and this confirms that the vinyl group in these ethers is attached to the oxygen atom.

We were able to direct the process to favor the synthesis of 1,3-benzoxazin-4-ones IIa-d by the addition of cadmium oxide to the alkaline catalyst. The reaction was carried out in organic solvents (dioxane, dimethoxyethane, DMSO, and benzene) at 195 ± 15°C; in this case para isomer Ia underwent 54% conversion to benzoxazinone IIa, whereas the yield of the benzoxazinone was 43% in the case of catalysis with cadmium acetate [1]. In contrast to anilide Ia, m- and o-hydroxyanilides Ib, c react readily with acetylene in the presence of cadmium acetate to give benzoxazinones IIb, c in up to 60-70% yields. The yields of 1,3-benzoxazinones IIb, c are doubled when a catalyzing mixture of KOH and CdO is used.

The formation of vinyloxyphenyl-substituted 1,3-benzoxazinones that are identical to 1,3-benzoxazinones IIa-c obtained directly from hydroxyanilides Ia-c and acetylene in one step is also observed in the reaction of vinyloxyanilides IIIa-c with acetylene; the yield of benzoxazinone meta isomer IIb is also considerably higher than the yields of the ortho and para isomers in this case.

The higher yield of meta isomer IIb is evidently due to weakening of the electron-donor character of the OH and OCH=CH$_2$ groups in the meta position of the aromatic ring of substituted anilides [2, 3], which leads to an increase in the relative acidity of the secondary amido group and to an increase in the possibility of the occurrence of the reaction at this reaction center. However, an increase in the basic properties of the amido group hinders heterocyclization. Thus as compared with anilides Ia-d, 2-hydroxybenzamide upon reaction with acetylene does not form a benzoxazine system either in the case of catalysis with cadmium acetate or in the presence of potassium hydroxide with cadmium oxide. Heterocyclization of unsubstituted 2-hydroxybenzoic acid anilide Id with acetylene under similar conditions leads to the known 2-methyl-3-phenyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (IId) in 35% yield.

Replacement of cadmium oxide by zinc oxide or the use of only cadmium oxide without the addition of potassium hydroxide does not promote the formation of cyclization products in the reaction of hydroxyanilides Ia-d with acetylene.

As compared with the IR spectra of starting anilides Ia-d, new absorption bands at 3060-3070, 1630-1642, and 945-960 cm^{-1}, which are due to the presence of a CH=CH$_2$ group, appear in the IR spectra of IIa-c, the band at 1670 cm^{-1} (CO) is retained, and the broad absorption bands of NH and OH groups vanish. The chemical shifts of the protons and the SSCC in the PMR spectra of benzoxazines IIa-d are presented in Table 2.

TABLE 2. PMR Spectra of 1,3-Benzoxazinones

Compound	Chemical shifts, ppm							SSCC, Hz			
	H_A	H_B	H_X	2-H	2-CH_3	5-H	C_6H_4*	AB	AX	BX	CH—CH_3
II c	4,25	4,56	6,41	5,67	1,31	7,88	7,11	2,0	6,0	14,0	5,0
II b	4,25	4,62	6,48	5,63	1,32	7,83	6,83	1,5	6,5	14,2	6,0
II a	4,40	4,72	6,60	5,70	1,47	7,91	7,08	1,8	6,6	14,0	6,2
II d	—	—	—	5,67	1,41	7,87	7,21	—	—	—	6,0

*Center of a multiplet.

The hydrogenation of 1,3-benzoxazinone IIa over Raney nickel at room temperature leads to the known ethyl derivative [4]. This additionally proves the presence of a vinyl group in IIa.

It should be noted that vinyloxyanilines, the properties of which are in complete agreement with the data in [5], are always present in small amounts in the reaction mixtures in the formation of benzoxazinones IIa-c. We assume that their formation is possible due to cleavage of the oxazine ring, which, according to the data in [6], is particularly appreciable when KOH is used in the catalytic system. However, we were unable to detect the presence of O,O- or N,O-divinyl derivatives of anilides Ia-c in a single case.

On the basis of our studies and the literature data [7, 8] we assume that the heterocyclization of hydroxyanilides I with acetylene proceeds through a step involving the formation of the N-vinyl derivative of 2-hydroxybenzoic acid anilide, which undergoes rapid recyclization to a benzoxazine system. An attempt to realize the heterocyclization of vinyl ether IV with the aid of the KOH/CdO catalytic system or cadmium acetate alone in the absence of acetylene was unsuccessful. The probability of the reaction of acetylene with the OH group in the ortho position relative to the amido group of anilides I is evidently decreased by its participation in the formation of strong hydrogen bonds with the carbonyl group of the acid fragment. Moreover, it is known that the condensation of amides with the CH_2=CHO group of vinyl ethers proceeds under acid-catalysis conditions [9]. All of this confirms the high reactivity of the N-vinyl product under the conditions of our experiments.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were recorded with a Tesla BS-487 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets and microlayers of the compounds were recorded with a UR-20 spectrometer. The purity of the products was verified by thin-layer chromatography (TLC) on aluminum oxide.

2-Hydroxybenzoic Acid Anilides Ia-d. These compounds were obtained in 80-95% yields by acylation of p-, m-, and o-aminophenols and aniline with salicylyl chloride in the presence of triethylamine. The constants of anilide Id and hydroxyanilides Ia,c were in agreement with the data in [10-12]. m-Hydroxyanilide Ib, with mp 180-183°C (from toluene), was obtained in 64% yield. Found: C 68.3; H 4.6; N 6.0%. $C_{13}H_{11}NO_3$. Calculated: C 68.1; H 4.8; N 6.1%.

2-Methyl-3-(p-vinyloxyphenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (IIa). A) A mixture of 11.5 g (0.05 mole) of hydroxyanilide Ia, 1.4 g (0.025 mole) of KOH, and 1.3 g (0.01 mole) of CdO in 100 ml of dioxane was heated in an autoclave with acetylene under a pressure of 11-12 atm at 200°C for 1-1.5 h, after which it was distilled in vacuo to give 7.6 of benzoxazinone IIa with R_f 0.37 [ether—hexane (2.3:1)].

B) A mixture of 5.7 g (0.025 mole) of anilide Ia and 2.6 g (0.01 mole) of cadmium acetate in dioxane was heated in an autoclave with acetylene at 200°C for 1 h. Workup gave 3 g of benzoxazinone IIa.

Similarly obtained were benzoazinones IIb,c, which, after vacuum distillation, were purified to remove the vinyloxyanilines by TLC by elution of the corresponding spots from aluminum oxide with ether. 2-Methyl-3-(m-vinyloxyphenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (IIb). This compound had n_D^{20} 1.6018, d_4^{20} 1.3112, and R_f 0.46 [ether—hexane (2.3:1)]. 2-Methyl-3-(o-vinyloxyphenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (IIc). This compound had

n_D^{20} 1.5813, d_4^{20} 1.2619, and R_f 0.42 [ether—hexane (2.3:1)].

2-Hydroxybenzoic Acid p-Vinyloxyanilide (IIIa). A 10.4-g (0.066 mole) sample of salicylyl chloride was added dropwise to −10 to −20°C to 8.9 g (0.66 mole) of p-vinyloxyaniline and 6.7 g (0.066 mole) of triethylamine in 10 ml of acetone, and the reaction mixture was poured into a mixture of ice and water. The precipitate was removed by filtration, washed with water, and dried to give 15.7 g of ether IIIa.

Ethers IIIb,c were similarly obtained.

2-Vinyloxybenzoic Acid p-Hydroxyanilide (IV). A 1.2-g (0.005 mole) sample of 2-vinyloxyphenyl benzoate and 0.5 g (0.005 mole) of p-aminophenol in 5-7 ml of ethanol were placed in an ampul, and the ampul was purged with nitrogen and heated at 200-210°C for 14 h. The alcohol was then removed by distillation, and the residue was chromatographed with a column filled with Al_2O_3 [chloroform—ether (1:2)] to give 0.14 g of ether IV.

Reaction of p-Hydroxyanilide Ia with Acetylene in the Presence of KOH. A mixture of 8 g (0.034 mole) of hydroxyanilide Ia, 2.4 g (0.042 mole) of KOH, and 100 ml of benzene was heated in an autoclave with acetylene under a pressure of 11-12 atm at 195-200°C for 1.5 h, after which the benzene solution was separated from the resin and treated with petroleum ether, and the mixture was worked up to give 0.2 g (2.2%) of ether IV with R_f 0.33 [chloroform—ether (1:2)]. Workup of the mother liquor gave 0.15 g (1.7%) of ether IIIa with R_f 0.54 [chloroform—ether (1:2)]. No melting-point depressions were observed for mixtures of ethers IIIa and IV with samples obtained by alternative synthesis, and their IR spectra were identical.

2-Methyl-3-(p-ethoxyphenyl)-2,3-dihydro-4H-dihydro-4H-1,3-benzoxazin-4-one (V). A mixture of 2 g (0.007 mole) of benzoxazinone IIa and 1 g of Raney nickel in 50 ml of absolute ethanol was placed in an autoclave (V = 0.25 liter), hydrogen was fed in from a cylinder, and the autoclave was rotated for 4 h. Workup gave 1.9 g (90%) of benzoxazinone V with mp 134-136°C (heptane) [mp 135-137°C (alcohol) [4]] and R_f 0.26 [hexane—ether (1:2.3)].

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