HYDROLYSIS OF 2-ARYL-4H-3,1-BENZOXAZIN-4-ONES

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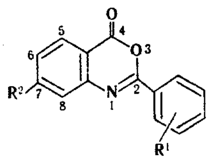
2-Aryl-4H-3,1-benzoxazin-4-ones were subjected to alkaline hydrolysis in O^{18}-enriched water. It was established on the basis of data from mass-spectrometric analysis of the hydrolysis products that the C-2 and C-4 atoms of the benzooxazinone ring undergo nucleophilic attack. The primary direction of attack depends on the nature and position of the substituent.

It is well known that N-acylanthranilic acids are formed in the hydrolysis of 4H-3,1-benzoxazin-4-ones containing a substituent in the 2 position and that the nature of the substituent has a substantial effect on the rate of hydrolysis. Thus 2-methyl-4H-3,1-benzoxazin-4-one is hydrolyzed even by air moisture, whereas 2-phenyl-4H-3,1-benzoxazin-4-one remains unchanged for a long time under the same conditions. The introduction of a nitro group in the para position of the phenyl ring of 2-phenyl-4H-3,1-benzoxazin-4-one accelerates the hydrolysis by a factor of 4.5, whereas introduction of a methoxy group in the same position slows it down by a factor of 1.3 [1].

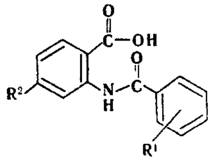
It is evident that substitutents in conjugation with the reaction center will have the greatest effect on the reaction rate. The question of the establishment of the center of nucleophilic attack is therefore the decisive point in the study of the hydrolysis of 4H-3,1-benzoxazin-4-ones.

In [1] it is pointedout that the C-4 atom undergoes nucleophilic attack in the hydrolysis of 2-phenyl-4H-3,1-benzoxazin-4-one and its substituted derivatives in alkaline media. Having proved this in the case of a single compound, Willian and Salvadori extended their conclusion to all substituted 4H-3,1-benzoxazin-4-ones. However, it is difficult to explain their own data on the effect of substituents in the phenyl ring on the rate of hydrolysis starting from this concept.

On the other hand, we have previously made a polarographic study of 2-phenyl-4H-3,1-benzoxazin-4-one and related compounds. It is apparent from this study that the addition of an electron takes place primarily at the C-2 atom of the benzoxazinone ring [2]. The aim of the present research was to ascertain the effect of the nature and position of a substituent on the direction of attack. To solve this problem we subjected substituted 4H-3,-1-benzoxazin-4-ones (Ia-d) to hydrolysis in alkaline media in the presence of water containing an oxygen label (H_2O^{18}).



I a–d



II a–d

I, II a $R^1 = R^2 = H$; b $R^1 = p\text{-}NO_2$, $R^2 = H$; c $R^1 = H$, $R^2 = NO_2$; d $R^1 = o\text{-}NHTs$, $R^2 = H$

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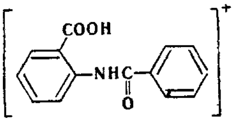
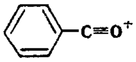
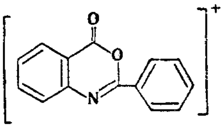
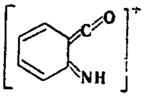
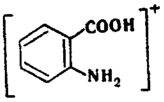
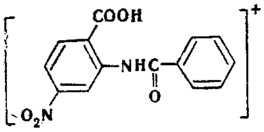
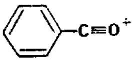
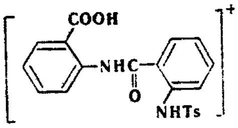
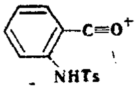
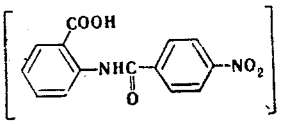
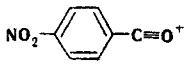
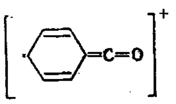
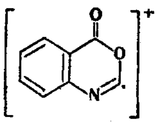
TABLE 1. Mass-Spectrometric Data for the Alkaline Hydrolysis of 2-Aryl-4H-3,1-benzoxazin-4-ones

Compound	Fragment	Mass of the O^{18}-enriched and nonenriched fragment	$\frac{I_{n+2}}{I_n}$ en- richment		$\frac{I_n^{18}}{I_n^{18}+I_n}$	Enrichment, %
			enrichment	nonenrichment		
1	2	3	4	5	6	7
IIa		243/241	0,367	0,018	0,250	100
		107/105	0,064	0,009	0,052	20,8
		225/223	0.208	0,038	0,144	58,8
		121/119	0,106	0,070	0,097	38,7
		139/137	0,205	0,082	0,198	79,1
					P_{C-2}* 21%, P_{C-4}* 79%	
IIb		288/286	0.578	0,024	0.356	100
		152/150	0.189	0,015	0,148	41,6
		106/104	0.198	0,022	0,142	41,8
		148/146	0.378	0,056	0.243	68.4
					P_{C-2} 41%, P_{C-4} 59%	

(TABLE 1. cont.)

1	2	3	4	5	6	7
IIc		288/286	0,566	0,025	0,351	100
		107/105	0,264	0,209	0,055	15,8
					P_{C-2} 16%, P_{C-4} 84%	
IId		412/410	0,383	0,098	0,207	100
		276/274	0,098	0,081	0,017	9,1
					P_{C-2} 9%, P_{C-4} 91%	

*The P_{C-2} value is the probability of attack at the C-2 atom, and P_{C-4} indicates the probability of attack at the C-4 atom.

The primary direction of nucleophilic attack was established on the basis of a comparison of the mass spectra of the products obtained by hydrolysis in ordinary water and heavy-oxygen water.

In order to isolate the peaks of ions that are least subject to rearrangements and superimpositions of peaks of ions with the same mass but different structures, we made a preliminary study of the fragmentation of N-aroylanthranilic acids (IIa-d) under the influence of electron impact. The ions of acyl residues formed as a result of cleavage of the amide bond with retention of the charge on the acyl group proved to be the most informative ions.

The enrichment in the labeled samples was determined as the ratio of the intensities of the ion current of the O^{18}-labeled acyl ion to the total ion current of a given fragment:

$$\frac{I_n^{18}}{I_n^{18}+I_n}.$$

The intensity (I_n^{18}) of the peak of the O^{18}-labeled ion was determined with allowance for a correction for rearranged ions and isotopic superimpositions on the n+2 peak (I_{n+2}) on the part of the n-th peak (I_n):

$$I_n^{18}=I_{n+2}-cI_n,$$

where $c = I^*_{n+2}/I^*_n$ is the ratio of the intensities of the analogous n+2 and n peaks in the spectrum with ordinary water. The total enrichment was determined from the molecular ion peak. The percentage enrichment of the individual fragments was calculated with respect to the total enrichment, which was assumed to be 100%. The results of the mass-spectrometric analysis are presented in Table 1.

It is apparent from Table 1 that both reaction centers undergo attack in the hydrolysis of 2-phenyl-4H-3,1-benzoxazin-4-one, but the probability of attack at the C-2 atom is lower by a factor of four than the probability of attack at the C-4 atom. The introduction of an electron-acceptor group in the 7 position (Ic) increases the electropositivity of the C-4 atom and raises the probability of attack at it to 84%. The same electron-acceptor group introduced in the para position of the phenyl ring (Ib) changes the direction of attack: the probability of attack at the C-2 atom increases to 41%. Compound Id has a tosylamino substituent, the electron-donor properties of which are increased substantially in alkaline media by detachment of a proton. This lowers the probability of attack at the C-2 atom conjugated with the tosylamino group to 9%. One cannot exclude the possibility that the intramolecular hydrogen bond peculiar to this compound also affects the direction of attack.

EXPERIMENTAL

The mass spectra were obtained with an MS-702 spectrometer. The accelerating voltage was 10 kV, the ionizing-electron energy was 70 eV, and the temperature of the sample vaporization block was 120°. The spectra were recorded with the aid of a source with direct introduction of the sample into the ionization region. The percentage enrichments of the fragments presented in Table 1 have a confidence interval of ± 1%.

2-Phenyl-4H-3,1-benzoxazin-4-one and its substituted derivatives were obtained by reaction of the aroyl chloride with the appropriate anthranilic acid in pyridine [3,4]. 2-(2-Tosylaminophenyl)-4H-3,1-benzoxazin-4-one was obtained by reaction of anthranilic acid with p-toluenesulfonyl chloride in refluxing pyridine [5].

Hydrolysis of 2-Aryl-4H-3,1-benzoxazin-4-ones in O^{18}-Enriched Water. A 1 sodium hydroxide solution enriched with O^{18} was obtained by dissolving sodium metal in 30% heavy-oxygen water. A 50-mg sample of 2-aryl-4H-3,1-benzoxazin-4-one was added to 2.5 cm^3 of the sodium hydroxide solution, and the mixture was allowed to stand at 50° until the solid has dissolved almost completely. The mixture was filtered, and the N-aroylanthranilic acid was isolated from the filtrate by acidification with hydrochloric acid. Hydrolysis with a nonenriched sodium hydroxide solution was carried out under similar conditions.

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REACTIONS OF 1,5-DIKETONES. XX*. SEMICYCLIC 1,5-DIKETONES IN THE FISCHER REACTION

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Monophenylhydrazones involving both the phenacyl carbonyl group and the ring carbonyl group are formed as intermediates in the reaction of semicyclic 1,5-diketones of the 2-(phenacylobenzyl)cyclohexanone type with phenylhydrazine in acid media. The former undergo subsequent conversion to the corresponding substituted indoles, whereas the latter are converted to substituted 1H-2,3,3a,4-tetrahydropyrido[3,2,1-j,k]carbazoles; in addition, the corresponding 5,6,7,8-tetrahydroquinoline derivatives are also partially formed.

The Fischer reaction in the 1,5-diketone series is unknown, although the reactions of 1,5-diketone derivatives with phenylhydrazine in acidic media have been described [2,3]. We made a detailed study of the behavior of semicyclic 1,5-diketones Ia-d with respect to phenylhydrazine. Judging from the structure of the isolated compounds, the process can be represented by the scheme

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*See [1] for communication XIX.

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