SYNTHESIS AND STRUCTURES OF ALKYL(ARYL)BENZAZOLYLAZOKETOXIMES

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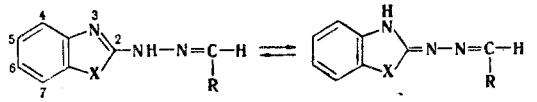
Alkyl(aryl)benzazolylazoketoximes were obtained by nitrosation of the hydrazones of alkyl- and aryl-substituted aldehydes by means of n-amyl nitrite. On the basis of data from IR and PMR spectroscopy it was concluded that the synthesized compounds exist in the oxime form. Their acid ionization constants were determined.

The nitrosation of arylhydrazones with subsequent rearrangement in an alkaline medium leads to the production of arylazoximes [1]. Individual representatives of this class of compounds have been previously described, but information regarding the nitrosation of heterocyclic hydrazones is not available, whereas hetarylazoketoximes, which can be regarded as peculiar oxime analogs of hetarylformazans, are of interest, since the display of a number of properties in common with formazans can be expected from them. The aim of the present research was therefore the synthesis of alkyl(aryl)benzazolylazoketoximes and the study of their structure.

We used 2-benzothiazolyl- and 2-benzimidazolylhydrazones of alkyl- and aryl-substituted aldehydes as the starting hetarylhydrazones:



A B

I-XII

X and R as follows, respect.: I, S, CH_3; II, S, C_6H_5; III, S, $CH(CH_3)_2$; IV, NH, CH_3; V, NH, C_6H_5; VI, NH, $NCH_2C_6H_5$, CH_3; VII, $NCH_2C_6H_5$, C_6H_5; VIII, NCH_2—C_6H_5, $CH(CH_3)_2$; IX, $NCH_2C_6H_5$, $C_6H_4NO_2$-*p*; X, $NCH_2C_6H_5$, $C_6H_4N(CH_3)_2$-*p*; XI, $NCH_2C_6H_5$, C_6H_4OH-*o*; XII, $NCH_2C_6H_5$, C_6H_4OH-*o*

n-Amyl nitrite served as the nitrosating agent. Hydrazones I and IV give methylbenzazolylazoketoximes immediatelyupon nitrosation in benzene or dimethyl sulfoxide (DMSO) (the solvent was selected on the basis of the solubilities of the starting compounds). Alkyl(aryl)benzimidazolylazoketoximes are obtained satisfactorily in an alkaline medium (except for methylbenzimidazolylazoketoxime), viz., in an alcohol solution of sodium ethoxide (hydrazones V-VII) or in alcoholic alkali (V and VII-IX). Benzothiazolylhydrazones II and III and hydrazones X-XII of the benzimidazole series that contain electron-donor groups in the aldehyde fragment in the ortho and para positions of the phenyl substituent do not react under the indicated conditions. The starting compounds were isolated in all cases.

The synthesized compounds are crystalline yellow or brown products that are insoluble in water and moderately soluble in organic solvents. Solutions of benzazolylazoketoximes are more highly colored [λ_{max} = 365-390 nm, ethanol–water (1:1)] than solutions of 1-benzazolyl-3-alkyl(aryl)-5-phenylformazans (λ_{max} = 410-460 nm) [2]. The color of the oximes depends on the character of the heteroring and the substituent attached to the carbon atom, while benzimidazolylformazans are more deeply colored than benzothiazole, and 3-phenylformazans are more deeply colored than 3-methylformazans. Upon conversion from the neutral molecule to the anion hetarylazoketoximes give only a small bathochromic shift (20-40 nm), whereas hetarylformazans are characterized by $\Delta\lambda \geq 100$ nm. In contrast to the aromatic analogs, the alkyl(aryl)azoketoximes, like hetarylformazans, readily undergo complexing with metal ions. We used this property for chromatographic monitoring of the course of the reaction.

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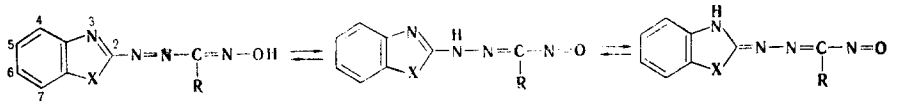
TABLE 1. Spectral Characteristics of Benzazolylhydrazones I and IV-IX

Compound	ν_{NH}, cm^{-1}		Chemical shifts, δ, ppm (dimethyl sulfoxide)					
	CCl_4	$CHCl_3$	4-H, 5-H, 6-H, 7-H	$N_{(3)}H$	$N_{(1)}H$	$-CH_2-$	$=C-H$	Note
I	3450, 3370, 3350	3430, 3340	6,8—7,9 m	11,5 br	—	—	7,75 q	—
IV	3470	3464, 3362	6,7—7,2 m	11,10 br	11,1 br	—	7,35 q	CH_3 2,60 s
V	3474	3469, 3354	6,8—7,5 m	11,5 br	11,5 br	—	8,10 s	C_6H_5 7,2—8,0 m
VI	3470	3460, 3330	6,8—7,5 m	9,8—11,3	—	5,18 s	7,65 q	—
VII	3470	3465, 3330	6,8—7,1 m	11,6 br	—	5,13 s	8,24 d	C_6H_5 7,2—8,0 m
VIII	3470	3465	6,8—7,1 m	9,6—11,3	—	5,13 s	7,44 d	—
IX	3469	3464	6,8—7,2 m	11,5 br	—	5,20 s	8,07 s	—

The existence of three prototropic tautomers of hetarylazoketoximes (the spatial isomers were not taken into account) is possible:



XIII-XIX C D E

X and R as follows, respect.: XIII, S, CH_3; XIV, NH, CH_3; XV, NH, C_6H_5; XVI, $NCH_2C_6H_5$, CH_3; XVII, $NCH_2C_6H_5$, C_6H_5; XVIII, $NCH_2C_6H_5$, $CH(CH_3)_2$; XIX, $NCH_2C_6H_5$, $C_6H_4NO_2$-*p*

To make a choice between the possible tautomers we made a comparative study of the IR and PMR spectra of the starting hydrazones and synthesized products (Tables 1 and 2). In CCl_4 solution all of the hydrazones give spectra with distinct ν_{NH} absorption bands at 3330-3470 cm^{-1}. The structure of benzazolylhydrazones I, VI, and VII was studied in [3], and it was shown that acetaldehyde benzothiazolylhydrazone exists in two forms in equilibrium, viz., amino A (3350, 3370 cm^{-1}) $\rightleftarrows$ imino B (3470 cm^{-1}), whereas 1-benzyl-2-benzimidazolylhydrazones exist in the imino form (ν_{NH} 3470 cm^{-1}). Hydrazones IV, V, VIII, and IX also exist in the imino form, since they have only high-frequency absorption. When carbon tetrachloride is replaced by chloroform, the high-frequency absorption bands in the spectra of the compounds that contain benzimidazole rings are shifted to the low-frequency region, and low-intensity absorption with a maximum at 3330-3360 cm^{-1}, which is absent in the spectra of solutions in CCl_4, appears. In other words, in a more polar solvent the benzimidazolylhydrazones exist in two tautomeric forms in equilibrium (A $\rightleftarrows$ B). The spectra of azoketoximes XIII and XVI-XIX do not contain ν_{NH} bands in the 3330-3470 cm^{-1} region, but absorption bands at 3540-3570 cm^{-1}, which we assigned to the absorption of a free oxime group [4], do appear in the spectra. This constitutes evidence for the existence of the synthesized products in the C form. We were unable to record the spectra of XIV and XV because of their low solubilities in chloroform.

The protons of the benzo ring of benzimidazole give an unsymmetrical multiplet at 6.8-7.2 ppm in the PMR spectra of solutions of benzimidazolylhydrazones IV, V, and VII-IX in dimethyl sulfoxide (DMSO), and this indicates their preferred imine structure, since in the case of benzimidazole, which has an amine structure, the protons of the benzo ring form a spin system that is close to the AA'BB' system and absorb at 7.0-7.9 ppm. The signal of the CH_2 group of the benzyl residue for the imino form is found at 5.1-5.2 ppm. The signal of the cyclic N_3H group gives absorption at 9.6-11.5 ppm. In contrast to the benzimidazolylhydrazones, in the case of benzimidazolylazoketoximes XIV-XVI and XVIII the protons of the benzo ring of benzimidazole absorb at 7.0-8.0 ppm, and the protons of the CH_2 group of the benzyl residue (for XVI and XVIII) absorb in the vicinity of 5.85 ppm; this constitutes evidence for the existence of a benzimidazole fragment in the amino form. In the case of XVII and XIX the chemical shifts of the protons of both the benzene ring of benzimidazole (6.8-8.0 ppm) and of the CH_2 group have somewhat smaller values (5.5 ppm). This difference in the chemical shifts can be explained by the existence for these compounds of mixtures of two forms (C and E) that exist in rapid equilibrium. The protons of the oxime group for XIII-XVI and XVIII give broad absorption at weak field from 9 to 14 ppm. The width of the lines reaches 120-180 Hz. The amplitude of the signals is so small that the position of the signal can be determined only from the integral curve of the spectrum. We were unable to observe signals at weak field for XVII and XIX, which presumably exist in two forms in equilibrium (amino $\rightleftarrows$ imino), possibly because of an even smaller amplitude of the signal. The chemical shifts

TABLE 2. Spectral Characteristics of Alkyl(aryl)benzazolylazoketoximes XIII-XIX

Compound	λ_{max}, nm (log ε) [ethanol–water (1:1)]	ν_{OH}, cm^{-1} ($CHCl_3$)	Chemical shifts, δ, ppm (dimethyl sulfoxide)					pK$_a$ †
			4-H, 5-H, 6-H, 7-H	$N_{(1)}H$	$-CH_2-$	OH	Note	
XIII	365 (3.28)	3560	7.3—8.2 (m)	—	—	11.7—13.6	—	8.45
XIV	372 (4.24)	—	7.0—7.9 (m)	11.5—14.0	—	11.5—14.0	—	9.01
XV	380 (4.23)	—	7.0—7.8 (m)	11.5—14.0	—	11.5—14.0	—	8.74
XVI*	375 (4.30)	3562	7.3—8.0 (m)	—	5.87 s	—	CH_3 1.15 s	8.94
XVII	386 (4.24)	3550	6.8—8.0 (m)	—	5.50 s	—	—	8.79
XVIII*	381 (4.34)	3569	7.3—8.0 (m)	—	5.81 s	8.9—12.9	CH_3 1.15 d	9.42
XIX	388 (4.00)	3543	6.8—8.0 (m)	—	5.50 s	—	—	7.96

*The PMR spectra were obtained from solutions in d_6-dimethyl sulfoxide.
†With an accuracy of ±0.02.

found for the NOH protons are in good agreement with the literature values for aromatic oximes [4, 5].

Thus, according to the data from the IR and PMR spectra of solutions in chloroform and DMSO, XIII-XVI and XVIII exist in the oxime form (C), while XVII and XIX exist in two forms in equilibrium (oxime ⇄ nitroso, C ⇄ E).

The ionization constants were determined for alkyl(aryl)benzazolylazoketoximes by a spectrophotometric method (Table 2). All of the compounds are weak acids, the pK$_a$ of which range from 7.96 to 9.42. The ionization constants obtained are of the same order of magnitude as those presented in the literature for monooximes of the aromatic series [6]. The introduction of a heteroring in the molecule increases the lability of the proton of the oxime group. For example, p-nitrophenylphenylazoketoxime has pK$_a$ 9.54, while p-nitrophenyl-1-benzylbenzimidazolylazoketoxime has pK$_a$ 7.96. The transition from a benzothiazole ring to a benzimidazole ring for benzazolylazoketoximes is characterized by a slight difference in the pK$_a$ values (pK$_a$ 8.45 for XIII, and pK$_a$ 9.01 for XIV), while the acidities of formazans differ by approximately three orders of magnitude [pK$_a$ = 9.1 for 1-(2-benzothiazolyl)-3-methyl-5-phenylformazan, and pK$_a$ = 12.5 for 1-(benzyl-2-benzimidazolyl)-3-methyl-5-phenylformazan [2]].

EXPERIMENTAL

The IR spectra of saturated solutions of the compounds in CCl_4 (l = 5 cm) and $CHCl_3$ (l= 2 cm) were recorded with a UR-20 spectrometer with an LiF prism. The PMR spectra of solutions in DMSO and d_6-DMSO were recorded with a Perkin–Elmer R12B spectrometer relative to tetramethylsilane. The chemical shifts were determined with respect to the spectra recorded at a sample temperature of 35°C. The spectrophotometric measurements of aqueous ethanol (1:1) solutions of the compounds ($2 \cdot 10^{-5}$ mole/liter) were made with a Beckmann Acta-6 spectrophotometer. The ionization constants of 50% alcohol buffer solutions of the reagents (10^{-4} mole/liter) were determined; an ammonia–acetate buffer was used. The pH values of the solutions were determined with a pH-121 pH meter with a glass electrode. The compositions of the reaction mixtures and the purity of the reaction products were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in ethyl acetate.

The characteristics of the compounds obtained are presented in Tables 1-3.

Isobutyraldehyde 1-Benzyl-2-benzimidazolylhydrazone (VIII). A 9-g (0.04 mole) sample of 1-benzyl-2-benzimidazolylhydrazine was dissolved by heating in 80 ml of isopropyl alcohol, 4.5 ml (0.05 mole) of isobutyraldehyde was added, and the mixture was refluxed for 5 min. It was then cooled, and the light-lilac-colored precipitate was removed by filtration and recrystallized from isopropyl alcohol.

Hydrazones IV, IX, and X were similarly obtained.

Methylbenzothiazolylazoketoxime (XIII). A 7-ml (0.06 mole) sample of freshly prepared amyl nitrite was added in portions to a benzene solution of 6 g (0.03 mole) of acetaldehyde 2-benzothiazolylhydrazone, and the mixture was heated up to 50°C in the course of 15 min, after which it was maintained at 20°C for 2 h. The benzene was removed by distillation, and the precipitate was recrystallized from ethanol.

TABLE 3. Benzimidazolylhydrazones IV and VIII-X and Alkyl-(aryl)benzazolylazoketoximes XIII-XIX

Compound	mp, °C	R_f	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IV	200	0,53	62,6	6,2	—	$C_9H_{10}N_4$	62,1	5,8	—	90
VIII	195	0,82	74,2	7,1	19,6	$C_{18}H_{20}N_4$	74,0	6,9	19,2	70
IX	245	0,83	66,0	4,4	—	$C_{21}H_{17}N_5O$	65,6	4,7	—	70
X	210	0,90	74,1	7,0	—	$C_{23}H_{23}N_5$	73,8	6,8	—	60
XIII	215	0,87	49,3	3,8	25,5	$C_9H_8N_4OS$*	49,1	3,6	25,5	80
XIV	221—222	0,52	53,1	4,7	33,9	$C_9H_9N_5O$	53,2	4,4	34,5	60
XV	200	0,71	63,5	4,5	26,2	$C_{14}H_{11}N_5O$	63,4	4,2	26,4	30
XVI	190	0,51	65,5	5,2	23,5	$C_{16}H_{15}N_5O$	65,5	5,1	23,9	30
XVII	165—166	0,62	70,8	4,9	19,4	$C_{21}H_{17}N_5O$	71,0	4,8	19,7	40
XVIII	176	0,64	67,2	6,0	21,5	$C_{18}H_{19}N_5O$	67,3	5,9	21,8	60
XIX	158	0,73	63,3	4,3	21,1	$C_{21}H_{16}N_6O_3$	63,0	4,0	21,0	30

*Found: S 11.7%. Calculated: S 11.6%.

Compound XIV was similarly obtained.

Phenyl-1-benzyl-2-benzimidazolylazoketoxime (XVII). A 3.2-g (0.01 mole) sample of benzaldehyde 1-benzyl-2-benzimidazolylhydrazone was dissolved by heating in an alcohol solution of sodium ethoxide (2 g of sodium in 80 ml of absolute ethanol), 2 ml (0.02 mole) of amyl nitrite was added, and the mixture was heated to 50-60°C in the course of 1 h. The mixture was evaporated to half its original volume, ice was added, and the mixture was neutralized carefully with stirring with acetic acid to pH 7. The precipitate was removed by filtration, washed with water, and recrystallized from ethanol.

Compounds XV and XVI were similarly obtained.

Isopropyl-1-benzyl-2-benzimidazolylazoketoxime (XVIII). A 2.9-g (0.01 mole) sample of isobutyraldehyde 1-benzyl-2-benzimidazolylhydrazone was dissolved by heating in alcoholic alkali, and 2 ml (0.02 mole) of amyl nitrite was added to the solution at 20°C. After 24 h, the solution was acidified to pH 7 with acetic acid and evaporated to half its original volume. Water (100 ml) was added, and the resulting brown precipitate was removed by filtration and recrystallized from ethanol.

Compound XIX was similarly obtained.

The synthesis of the following hydrazones has been described: II [7], III [10], V [8], VI and VII [9], and XI and XII [11].

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