SYNTHESIS OF SUBSTITUTED DIAZINES, DIAZOLES, AND CONDENSED THIA- AND OXADIAZOLES

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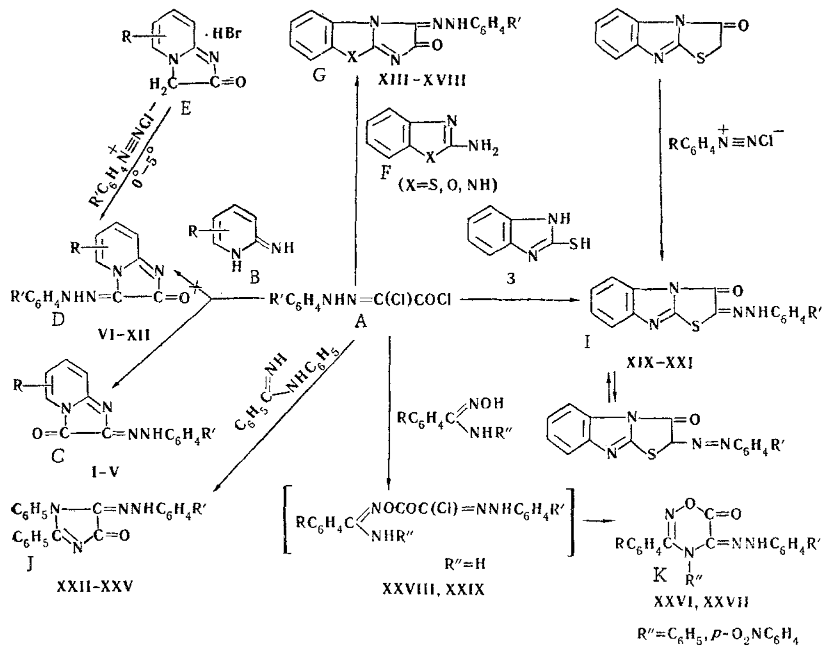
The corresponding 2-arylhydrazono-3-oxoimidazo[1,2-a]pyridines, 3-arylhydrazono-2-oxoimidazo[1,2-a]benzothiazoles, 2-oxoimidazolidino[3,2-a]benzimidazoles, 2-oxoimidazo[1,2-a]benzoxazoles, and 2-arylhydrazono-3-oxothiazolo[2,3-a]benzimidazoles were obtained by the condensation of arylazochloroacetyl chlorides with 2-aminopyridine, 2-aminobenzothiazole, 2-aminobenzoxazole, 2-aminobenzimidazole, and 2-mercaptobenzimidazole. 5-Arylhydrazono-1,2-diphenylimidazole-4-ones and 5-arylhydrazono-3,4-diaryl-1,2,4-oxidiazine-6-ones were synthesized by the reaction of arylazochloroacetyl chlorides with N-phenylbenzamidine and N-phenylamidoxime.

In a continuation of our investigations of cyclization on the basis of arylazochloroacetic acids [1-4] and our search for physiologically active substances, we have studied the cyclization of arylazochloroacetyl chlorides (A) with 2-amino derivatives of pyridine (B) and benzazoles (F), as well as with 2-mercaptobenzimidazole (H), amidines, and amidoximes (see scheme):



In the cyclization of A with B, both 2-arylhydrazones (C) and 3-arylhydrazones (D) of 2,3-dioxoimidazo[1,2-a]pyridine may be formed. However, we isolated only one cyclization product (C) (Table 1) that had properties that were different from those of D (Table 2) obtained by coupling of 2-oxoimidazo[1,2-a]pyridine salts (E) [5] with arenediazonium chlorides.

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TABLE 1. 2-Arylhydrazono-3-oxoimidazo[1,2-a]pyridines (B)

Comp.	R	R′	Appearance	λ_{max}, nm	mp (dec.) (solvent)	Empirical formula	Found, %		Calc., %		Yield, %
							C	H	C	H	
I	H	o-NO_2	Cherry-green plates	236 282 318 436	273—275 (dioxane-alcoh. 10 : 1)	$C_{13}H_9N_5O_3$*	55,3	3,0	55,1	3,2	71
II	H	o-OCH_3	Dark cherry-red needles	270 340 516	228—230 (alcohol)	$C_{14}H_{12}N_4O_2$†	62,7	4,5	62,7	4,5	42
III	6-CH_3	o-NO_2	Cherry-red needles	348 478	275—276 (dioxane)	$C_{14}H_{11}N_5O_3$	56,6	3,6	56,6	3,7	78
IV	6-CH_3	o-OCH_3	Red needles	250—270 (перегиб) 348 490	240—242 (alcohol)	$C_{15}H_{14}N_4O_2$	64,1	4,9	63,8	5,0	50
V	8-CH_3	o-NO_2	Dark-brown needles	—	252—253 (alcohol-dioxane) 1 : 2)	$C_{14}H_{11}N_5O_3$	56,2	3,9	56,6	3,7	70

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* Found: mol. wt. 292. Calculated: mol. wt. 283.

† Found: mol. wt. 279. Calculated: mol. wt. 268.

TABLE 2. 3-Arylhydrazono-2-oxoimidazo[1,2-a]pyridines (D)

Comp.	R	R′	Appearance	λ_{max}, nm	mp (solvent)	Empirical formula	N, %		yield, %
							found	calc.	
VI	H	o-NO_2	Yellow-orange crystals	258 340 425	277—279 (dioxane - pyridine)	$C_{13}H_9N_5O_3$*	24,4	24,7	94
VII	H	o-OCH_3	Orange plates	257 435	237—239 (alcohol - dioxane, 8 : 1)	$C_{14}H_{12}N_4O_2$	20,9	20,9	87
VIII	H	p-CH_3	Orange plates	—	266—268 (alcohol - dioxane 8 : 1)	$C_{14}H_{12}N_4O$	22,5	22,2	37
IX	H	p-OCH_3	Red needles	—	239—241 (alcohol - dioxane 8 : 1)	$C_{14}H_{12}N_4O_2$	21,2	20,9	51
X	H	n-Cl	Yellow needles	259 425	292—294 (alcohol - dioxane 1 : 1)	$C_{13}H_9ClN_4O$	20,5	20,5	62
XI	6-CH_3	o-NO_2	Red-orange needles	—	266—267 (alcohol - dioxane 1 : 5)	$C_{14}H_{11}N_5O_3$	23,4	23,6	67
XII	8-CH_3	o-NO_2	Orange plates	—	259—260 (alcohol - dioxane 1 : 5)	$C_{14}H_{11}N_5O_3$	23,5	23,6	77

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* Found: mol. wt. 256. Calculated: mol. wt. 283.

The IR spectra of C contain intense absorption bands at 3280-3330 (N−H), 1730-1750 (C=O), and 1650-1670 and 1600-1620 cm^{-1} (C=N). The bands at 1560-1580, 1420-1440, and 1340-1380 cm^{-1} apparently characterize the vibrations of the benzene and pyridine rings, while those at 1510-1540, 1150-1220, 1000-1090, and 750-820 cm^{-1} characterize the vibrations of the imidazole ring [6-8]. The IR spectra of hydrazones D are very similar to the spectra of C, but they have somewhat shifted and less intense frequencies for the C=O bonds (1680-1695 cm^{-1}). The frequencies of the valence vibrations of the N−H bond are less distinct; this may be explained by the presence of an intramolecular hydrogen bond of the N−H · · · O type [7,8] or, in part, by the presence of azo forms. The UV spectra of C have absorption maxima that are shifted to the longer-wave region as compared with D (Tables 1 and 2).

TABLE 3. 3-Arylhydrazono-2-oxoimidazole[1,2-b]benzothiazoles, -imidazole[1,2-b]benzoxazoles, and -imidazolidino[3,2-a]benzimidazoles (G)

Comp.	R′	X	mp (solvent)	λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)	Empirical formula	Found				Calc.				Yield, %
						C, %	H, %	N, %	mol. wt.	C, %	H, %	N, %	mol. wt.	
XIII	o-NO_2	S	304—305 (dioxane)	205 (15,3) 241 (6,7) 282 (5,4) 454 (2)	$C_{15}H_9N_5O_3S$	52,9	2,8	20,7	328	53,1	2,7	20,6	339	53
XIV	p-Cl	S	273—276 (dichloroethane)	—	$C_{15}H_9ClN_4OS$	54,3	2,8	16,8	—	54,8	2,8	17,0	—	73
XV	o-Cl	O	141—143 (benzene–petroleum ether)	205 (42) 244 (14,7) 286 (1,3) 411 (5,5)	$C_{15}H_9ClN_4O_2$	—	—	17,4	—	—	—	17,9	—	50
XVI	p-Cl	O	148—150 (benzene–petroleum ether)	209 (39) 243 (18,5) 284 (15,5) 419 (7,0)	$C_{15}H_9ClN_4O_2$	—	—	17,2	337	—	—	17,9	313	53
XVII	o-Cl	NH	225—227 (alcohol)	—	$C_{15}H_{10}ClN_5O$	—	—	22,8	340	—	—	22,5	312	49
XVIII	p-Cl	NH	180—182 (alcohol)	206 (49,5) 291—301 (19) 394 (14)	$C_{15}H_{10}ClN_5O$	—	—	22,5	—	—	—	22,5	—	56

TABLE 4. 2-Arylhydrazono-3-oxothiazolo[2,3-a]benzimidazoles (I)

Comp.	R′	Appearance	mp*	Empirical formula	Found %			Calc.%			Yield, %
					C	H	N	C	H	N	
XIX	o-NO_2	Shiny orange needles	249—250	$C_{15}H_9N_5O_3S$	53,3	2,6	20,8	53,1	2,7	20,6	47
XX	o-OCH_3	Light-yellow crystals	202—204	$C_{16}H_{12}N_4O_2S$	—	—	17,3	—	—	17,3	52
XXI	n-CH_3	Light-yellow crystals	263 (decomp)	$C_{16}H_{12}N_4OS$	—	—	18,3	—	—	18,2	53

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* From dioxane.

TABLE 5. 5-Arylhydrazono-1,2-diphenylimidazole-4-ones (J)

Comp.	R′	Appearance	λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)	mp*	Empirical formula	Found %			Calc.%			Yield, %
						C	H	N	C	H	N	
XXII	o-NO_2	Shiny orange crystals	—	199—200	$C_{21}H_{15}N_5O_3$†	65,6	4,0	17,9	65,5	3,9	18,2	54
XXIII	o-OCH_3	Dark-brown needles	—	175—178	$C_{22}H_{18}N_4O_2$	—	—	15,0	—	—	15,1	53
XXIV	p-CH_3	Bright-red needles	270 (1,20) 450 (2,24)	200—201	$C_{22}H_{18}N_4O$	74,4	5,0	15,8	74,6	5,1	15,8	57
XXV	p-Cl	Dark-red needles	254 (1,4) 404 (3,0)	213—215	$C_{21}H_{15}ClN_4O$	—	—	14,5	—	—	14,9	83

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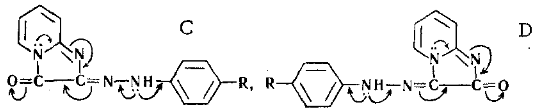
* From alcohol–benzene.

† Found: mol. wt. 392, 379. Calculated: mol. wt. 385.

The differences in the UV spectra of C and D in the case of I and II and VI and VII may be explained by the fact that the electron–donor substituent is in the 2-position in the case of C but in the 1-position of the chromophore chain in the case of D:



In accordance with the Dewar–Knott rule [9, 10], a bathochromic substituent effect is observed in the first case, while a hypsochromic effect is observed in the second case. These regularities are also observed for hydrazones C and D. The above therefore makes it possible to assert that the products of cyclization of A with B have structure C.

The cyclizations of A with 2-aminobenzazoles (F) and 2-mercaptobenzimidazole (H) [11, 12] led to the formation of G and I (Tables 3 and 4). We proved the structures of G by means of the IR spectra of I and alternative synthesis.

Compounds similar to I were recently obtained in [13-15]. The IR spectra of the cyclization products G contain intense frequencies of the valence vibrations of the N–H (3250-3320 cm^{-1}), C=O (1730-1750 cm^{-1}), and C=N (1585-1610 cm^{-1}). The frequencies of the valence vibrations at 1440-1550, 1250-1370, and 1040-1165 cm^{-1} apparently characterize the vibrations of the imidazo[1,2-b]benzothiazole, benzoxazole, benzimidazole, and benzene rings [6-8]. On the basis of these data, we assume that the products of cyclization of arylazochloroacetyl chlorides with 2-aminobenzazoles (F) have the arylhydrazone structure (G). As for compounds I, we cannot draw an unambiguous conclusion regarding their hydrazone structure (see [15]). The IR spectra of XIX and XXI contain distinct absorption bands at 1720-1740 (C=O) and 1600-1620 cm^{-1} (C=N), and low-intensity bands at 3200-3250 cm^{-1} (N–H). In addition to C=O (1730 cm^{-1}), C=N (1610 cm^{-1}), and N–H (3300 cm^{-1}) frequencies, the IR spectra of XX also contains absorption frequencies at 2850-2950 (C–H) and 1565-1580 cm^{-1} (N=N), which indicates their possible azo structure.

The condensation of acid chlorides A with N-phenylbenzamidine in benzene in the presence of triethylamine via the method in [16] yielded 5-arylhydrazono-1,2-diphenylimidazole-4-ones (J) (Table 5). The structures of J were confirmed by the IR spectra, which contain frequencies of the valence vibrations of the C=O (1735-1750 cm^{-1}) and C=N (1620-1670 cm^{-1}) bonds. The bands at 1545-1560, 1430-1460, and 1330-1380 cm^{-1} apparently characterize the vibrations of the imidazole and benzene rings. The frequencies of the N–H valence vibrations (3290-3320 cm^{-1}) are of low intensity, which may be explained by the presence of intramolecular hydrogen bonding of the N–H · · · O type in the solid state [7, 8].

The cyclization of acid chlorides A with amidoximes proceeds peculiarly. In the case of N-phenyl-substituted benzamidoxime, the cyclization proceeds with the formation of 5-arylhydrazono-3,4-diphenyl-1,2,4-oxidiazin-6-ones (K). The cyclization with unsubstituted phenylamidoxime stops at the O-acylation step (absence of frequencies of valence vibrations of the OH group at 3400-3500 cm^{-1}) (see [17]). The O-acyl product cannot be cyclized to K, either by prolonged heating (16 h) under the conditions used to obtain it, or by refluxing in m-xylene with pyridine. This can be explained by the high lability of the hydrogen atom in the case of the N-phenyl substituent. The structures of K were proved by the IR spectra, which contain frequencies of the valence vibrations of the N–H (3320-3340 cm^{-1}), C=O (1720-1750 cm^{-1}), and C=N (1615-1625 cm^{-1}) bonds. The absorption bands at 1410-1440, 1240-1280, and 940-970 cm^{-1} are related to the vibrations of the oxadiazine ring [7, 8].

EXPERIMENTAL

2-(o-Nitrophenylhydrazono)-3-oxoimidazo[1,2-a]pyridine (I). A solution of 1.3 g (0.05 mole) of o-nitrophenylazoacetyl chloride in 40 ml of dry benzene was added dropwise with stirring at 40-50° in the course of 10 min to a solution of 0.6 g (0.06 mole) of α-aminopyridine, 2.5 ml of triethylamine, and 1 ml of pyridine in 15 ml of benzene. The mixture gradually took on an intense raspberry color, and triethylamine and pyridine hydrochlorides began to precipitate from the solution. The reaction mass was refluxed on a water bath for 3-7 h and cooled. The resulting precipitate was filtered, dried, washed with water, and crystallized from dioxane–alcohol (10 : 1). An additional 0.1-0.2 g of I could be obtained from the filtrate after evaporation to dryness to give a total yield of 1 g.

Compounds II-V were similarly obtained. They were soluble in organic solvents and also in mineral acids and alkalies.

8-Methyl-3-(o-nitrophenylhydrazono)-2-oxoimidazo[1,2-a]pyridine (XII). A diazonium solution obtained from 0.2 g of o-nitroaniline, 2.5 ml of 12% hydrochloric acid, and 0.1 g of sodium nitrite in 5 ml of water was added dropwise to a cooled (to 0-2°) solution of 0.35 g (0.0015 mole) of 8-methyl-2-oxoimidazo-[1,2-a]pyridine hydrobromide [5] and 7 g of sodium acetate in 20 ml of water. The mixture was stirred at 0-2° for 5 h, 50 ml of water was added, and the resulting precipitate was filtered, washed with water, and dried. Recrystallization from dioxane–alcohol (5 : 1) gave 0.35 g of XII.

Products VI-XI were similarly obtained, with the only difference that the medium was pyridine–water (1 : 10), and the amount of sodium acetate was halved.

3-(o-Nitrophenylhydrazono)-2-oxoimidazo[1,2-b]benzothiazole (XIII). Triethylamine (0.85 ml) was added to a solution of 0.46 g (0.003 mole) of 2-aminobenzothiazole in 10 ml of dry chloroform and, with periodic shaking, a solution of 0.8 g (0.003 mole) of o-nitrophenylazochloroacetyl chloride in 10 ml of dry chloroform was added dropwise to the resulting mixture. In the process, the colorless solution changed from yellow to yellow-orange, and slow precipitation was observed. The mixture was heated on a water bath for 6 h and cooled. The resulting precipitate was filtered, dried, washed thoroughly with water, and crystallized from dioxane to give 0.55 g of product. Compound XIV was similarly obtained.

3-(p-Chlorophenylhydrazono)-2-oxoimidazo[1,2-b]benzoxazole (XVI). A solution of 0.63 g (0.0025 mole) of p-chlorophenylazochloroacetyl chloride was added dropwise to a stirred solution of 0.34 g (0.0025 mole) of 2-aminobenzoxazole in 10 ml of benzene–dioxane (1 : 1) and 1 ml of triethylamine. The color of the solution changed from yellow to bright-red, and a precipitate formed. The mixture was heated on a water bath for 2 h, and the solvent was evaporated to dryness. The residue was washed with water, dried, and repeatedly reprecipitated from benzene solution by the addition of petroleum ether to give 0.42 g of product.

Compound XV was similarly obtained. Products XV and XVI were quite soluble in most organic solvents.

3-(p-Chlorophenylhydrazono)-2-oxoimidazolidinyl[3,2-a]benzimidazole (XVIII). A solution of 0.5 g (0.002 mole) of p-chlorophenylazochloroacetyl chloride in 10 ml of benzene–dioxane (1 : 1) was added dropwise to a suspension of 0.26 g (0.002 mole) of 2-aminobenzimidazole in 10 ml of benzene–dioxane (1 : 1) and 0.7 ml of triethylamine. The color of the solution changed from yellow to bright-red. The mixture was heated on a water bath for 3 h, and the solvent was evaporated. The residue was washed with water and dried. Recrystallization from alcohol gave 0.35 g (56%) of yellow-orange crystals with mp 180-182° that were readily soluble in benzene, dioxane, and acetone and slightly soluble in alcohol. Compound XVII was similarly obtained.

2-(o-Nitrophenylhydrazono)-3-oxothiazolo[3,2-a]benzimidazole (XIX). A solution of 0.65 g (0.0025 mole) of o-nitrophenylazochloroacetyl chloride in 10 ml of benzene–dioxane (1 : 1) was added in the course of 15 min with stirring to a solution of 0.4 g (0.0025 mole) of 2-mercaptobenzimidazole in 10 ml of benzene–dioxane (1 : 1) and 0.65 g (0.006 mole) of triethylamine. The color of the mixture gradually changed from light-yellow to bright-red; it was refluxed on water bath for 3 h, and the solvent was evaporated. The residue was washed thoroughly with water, dried, and crystallized from dioxane to give 0.4 g of product.

Products XX and XXI were similarly obtained. They were soluble on heating in organic solvents. Compounds XIX and XXI were also obtained by alternative synthesis from anhydro-2-benzimidazolylthioacetic acid and diazotized amines by the method in [13-15]. The products obtained by the different methods did not depress one another's melting points.

5-(o-Nitrophenylhydrazono)-1,2-diphenylimidazol-4-one (XXII). A solution of 0.65 g (0.002 mole) of o-nitrophenylazochloroacetyl chloride in 10 ml of benzene was added in the course of 15 min to a solution of 0.49 g (0.002 mole) of N-phenylbenzamidine and 0.52 g (0.004 mole) of triethylamine in 10 ml of dry benzene. The reaction proceeded with spontaneous heating, and the mixture gradually took on an intense red color. The mixture was refluxed on a water bath for 4 h and cooled. The resulting precipitate was filtered, dried, washed thoroughly with water, and crystallized from benzene or alcohol to give 0.5 g (54%) of product. Compounds XXIII-XXV were similarly obtained.

5-(o-Nitrophenylhydrazono)-3,4-diphenyl-1,2,4-oxadiazin-6-one (XXVI). A solution of 0.66 g (0.0025 mole) of o-nitrophenylazochloroacetyl chloride in 5 ml of benzene was added dropwise to a solution of 0.53 g (0.0025 mole) of phenylbenzamidoxime and 0.52 g (0.005 mole) of triethylamine in 10 ml of dry benzene. The reaction proceeds with spontaneous heating, and the mixture gradually took on an intense red color. The mixture was refluxed on a water bath for 7 h, and the solvent was removed by distillation. The residue was treated with water, dried, and crystallized from alcohol to give 0.7 g (70%) of a product with mp 214-216°. λ_{max} 252 nm (ε 12,200) and 270 nm (ε 4000) (in alcohol). Found %: C 62.4; H 3.8; N 17.4; mol. wt. 385. $C_{21}H_{15}N_5O_4$. Calculated %: C 62.8; H 3.8; N 17.5; mol. wt. 401.

5-(o-Nitrophenylhydrazono)-3-(p-nitrophenyl)-4-phenyl-1,2,4-oxadiazin-6-one (XXVII). This was similarly obtained in 57% yield and had mp 260-261° (from alcohol). Found %: N 19.1. $C_{21}H_{14}N_6O_6$. Calculated %: N 18.8.

O-(o-Nitrophenylazochloroacetyl)benzamidoxime (XXVIII). This was similarly obtained in 93% yield after condensation for 16 h and had mp 182-184° (from alcohol). Found %: N 19.5, 19.6. $C_{15}H_{12}ClN_5O_4$. Calculated %: N 19.4.

O-(p-Chlorophenylazochloroacetyl)benzamidoxime (XXIX). This was similarly obtained in 75% yield and had mp 210-211° (from alcohol). Found %: N 16.1, 16.0. $C_{15}H_{12}Cl_2N_4O_2$. Calculated %: N 16.0.

The starting compound was isolated in an attempt to cyclize XXIX by heating in refluxing m-xylene with pyridine for 2 h.

The UV spectra of C, D, J, and K in alcohol were recorded with an SF-4 spectrophotometer, while the UV spectra of G were recorded with a Unicam Sp-700 spectrophotometer. The IR spectra of KBr pellets (1:100) were recorded with a UR-10 spectrometer.

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