STRUCTURE AND ISOMERISM OF 2-(3-SUBSTITUTED) QUINOXALINYL-HYDRAZONES OF ISATIN AND ITS HOMOLOGS

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Mono- and dihydrazones, the structures of which were established by means of ^1H and ^{13}C NMR, IR, and electronic absorption spectroscopy, were synthesized by reaction of 3-chloro-2-hydrazino- and 2,3-dihydrazinoquinoxalines with 1H-indole-2,3-dione and its 1-methyl and 1-butyl homologs. Thermal and photochemical conversion of the E,Z isomer to the Z isomer is observed, while the reverse transformation is observed in the case of treatment with alkali.

In the course of research [1] on multidentate chelating agents from a group of mono- and dihydrozones obtained by reaction of 3-chloro-2-hydrazino- and 2,3-dihydrazinoquinoxalines with 1H-indole-2,3-dione and its 1-methyl- and 1-butyl homologs we observed isomerism of the synthesized compounds.

Individual red Ia-IIIa were obtained in good yields in this reaction at 20°C (Table 1). A hypsochromic effect (Table 1) is observed with time when these compounds are dissolved in neutral organic solvents, heated, and irradiated. The absorption band of the stretching vibrations of the carbonyl group in the IR spectra of the resulting yellow forms (Ib-IIIb) is shifted to the low-frequency region from 1700 to 1685 cm^{-1}, while a narrow signal at 13.95 ppm appears in the PMR spectrum (Table 2) in place of a broad signal of an NH proton at ∿11.3 ppm. These compounds also differ markedly with respect to their solubilities: Red Ia-IIIa are readily soluble in dimethyl sulfoxide (DMSO) but considerably less soluble in chloroform, whereas the situation is just the opposite for yellow Ib-IIIb. According to the mass-spectrometric data (identical molecular ions), the pairs of compounds obtained are isomers.

It follows from the above-indicated differences in the IR and PMR spectra that the more stable yellow isomers are stabilized by an N–H(···)O=C intramolecular hydrogen bond and consequently exist in the b form (Z isomers). In series of 1-methylisatin hydrazones deshielding of the NH proton, which participates in an intramolecular H bond, increases on passing from the β-semicarbazone [2] to the β-thiosemicarbazone [3] and to IIb as the electron-acceptor character of the grouping attached to the hydrazone nitrogen atom increases, and a bathochromic shift of the longest-wave band of intramolecular charge transfer (ICT) is observed in the electronic absorption spectra (Table 1).

The *a* form can be assigned to the less stable red isomers. An analysis of the PMR and ^{13}C NMR spectra confirms this structure (E,Z isomers). Thus the proton in the 4 position of the isatin ring is markedly deshielded (to the extent of ∿0.7 ppm as compared with the b isomers) in the PMR spectra of Ia-IIIa due to steric interaction with the hydrazone N atom. This interaction is absent in the Z,Z structure, and this makes it possible to exclude it from consideration. Similar deshielding of 4-H was previously observed for the E isomers of isatin β-guanylhydrazones [4]. Pronounced shielding of quinoxaline 8-H (to the extent of ∿0.7 ppm as compared with the b isomers) as a consequence of replacement of the electron-acceptor sp^2 nitrogen by the electron-donor sp^3 nitrogen in the heteroring is simultaneously observed in the *a* isomers. This replacement leads to characteristic changes in the ^{13}C chemical shifts of the C_9, C_8, C_{10}, and C_6 atoms of the benzene ring of the quinoxaline ring (Table 3), i.e., both the carbon atoms that are directly bonded to this nitrogen atom and those in the ortho and para positions to it. As compared with unsubstituted quinoxaline [5], these changes are, respectively, +4.6, −14.4, −12.4, and −4.5 ppm; this is in qualitative agreement with the changes observed for C_1 and the o- and p-carbon atoms on passing from nitrobenzene

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TABLE 1. Hydrazones I-VII

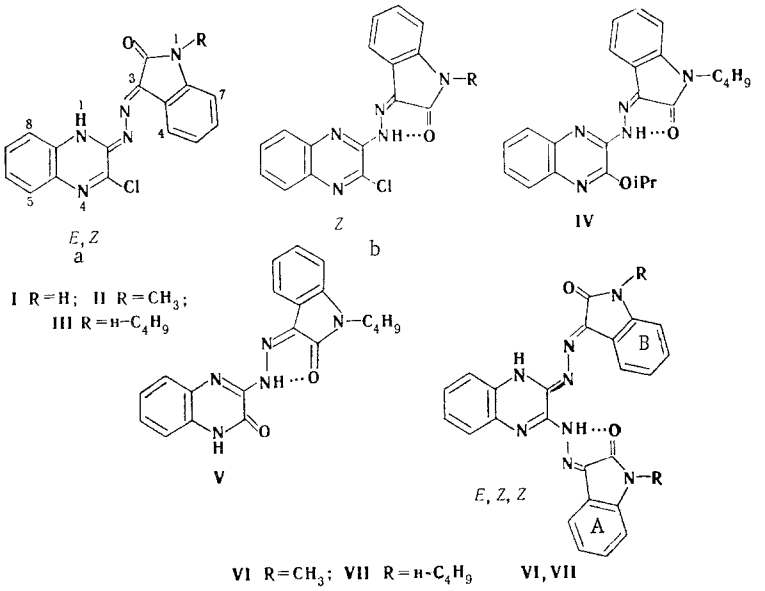
Compound	mp, °C	λ_{max}, nm (log ε)	Found, %				Empirical formula	Calculated, %				M	Yield, %
			C	H	Cl	N		C	H	Cl	N		
Ia[a]	318—319	330 (3,96); 430 i (4,17); 452 i (4,2); 472 (4,22); 492 i (4,15)[b]	59,4	3,1	10,9	21,6	$C_{16}H_{10}ClN_5O$	59,4	3,1	10,9	21,6	323,7	72
IIa[a]	268—269	332 (3,95); 425 i (4,17); 455 i (4,27); 471 (4,29); 490 i (4,22); 522 sh (3,84)[b]	60,5	3,5	10,5	20,7	$C_{17}H_{12}ClN_5O$	60,4	3,6	10,5	20,7	337,8	86
IIIa[c]	138—139	332 (3,92); 430 i (4,16); 453 i (4,26); 472 (4,25); 490 i (4,22); 525 i (3,83)[b]; 335 (3,74); 385 (3,97); 516 (4,54)[d]	63,2	4,8	9,3	18,4	$C_{20}H_{18}ClN_5O$	63,2	4,8	9,3	18,4	379,8	81
Ib	318—319		59,3	3,1	10,9	21,6	—	—	—	—	—	—	60
IIb	268—269	328 i (3,97); 408 (4,46)[b]	60,4	3,6	10,4	20,7	—	—	—	—	—	—	59
IIIb	211—212	328 (3,97); 409 (4,47)[b] 330 i (3,83); 386 (4,09); 515 (4,53)[d]	63,2	4,7	9,3	18,4	—	—	—	—	—	—	40
IV	189—190	306 i (3,76); 409 (4,51)[b]	68,4	6,3	—	17,3	$C_{23}H_{25}N_5O_2$	68,5	6,2	—	17,4	403,5	14
V	298—299	296 i (3,84); 415 (4,46)[b]	66,5	5,3	—	19,3	$C_{20}H_{19}N_5O_2$	66,5	5,3	—	19,4	361,4	14
VI	324—325		65,5	4,2	—	23,5	$C_{26}H_{20}N_8O_2$	65,5	4,2	—	23,5	476,5	77
VII	233—234	328 (4,21); 430 (4,50); 490 i (4,15); 510 i (3,94)[b] 339 (4,20); 389 (4,36); 521 (4,45)[d]	68,6	5,7	—	19,9	$C_{32}H_{32}N_8O_2$	68,5	5,7	—	20,0	560,7	80

[a] This compound becomes more lightly colored in a capillary and melts in the form of isomer b. [b] With ethanol as the solvent. [c] After melting, this compound gradually solidifies, becomes more lightly colored, and remelts at 211°C. [d] The solvent was a mixture of ethanol with a 0.1 N solution of sodium hydroxide.

TABLE 2. PMR Spectra of I-VII

Compound	t, °C	δ, ppm												
		hydrazone NH	CH_3 (H)	$(CH_2)_2$	CH_2N	quinoxaline					isatin			
						8-H	7-H	6-H	5-H	heteroring NH	4-H	5-H	6-H	7-H
Ia[a]	30	—	10,69 s	—	—	7,68	7,36	7,31	7,81	12,1 br. s	8,49	7,05	7,35	6,90
IIa[b]	60	—	3,30 s	—	—	7,31	7,47	7,23	7,71	—[c]	8,58	7,09	7,36	6,80
IIIa[b]	60	—	0,94 t	1,20—1,78 m	3,72 t	7,32	7,44	7,23	7,69	11,28 br. s	8,59	7,08	7,34	6,83
IIb[b]	60	13,88 s	3,31 s	—	—	8,04	7,69	7,54	7,90	—	7,90	7,14	7,37	6,87
IIIb[b]	60	13,95 s	0,99 t	1,16—1,88 m	3,80 t	8,04	7,70	7,55	7,91	—	7,89	7,12	7,36	6,88
IV[b]	20	13,58 s	0,98 t	1,18—1,88 m	3,80 t	7,72	7,43	7,5	7,95	—	7,92	7,12	7,34	6,88
V[d]	100	13,53 s	0,94 t	1,20—1,84 m	3,78 t	7,65	7,17	7,49	7,10	12,36 br. s	7,65	7,17	7,49	7,10
VI[e]	60	13,75 s				7,40	7,28	7,32	7,76	10,84 br. s	7,86	7,12	7,25	6,82
											9,00	7,10	7,30	6,78
VII[b]	60	13,85				7,46	7,28	7,32	7,76	10,75 br. s	7,86	7,09	7,23	6,84
											9,02	7,09	7,34	6,79

[a] With DMSO as the solvent. [b] With 0.1 M $CDCl_3$ as the solvent. [c] Not observed because of exchange broadening. [d] With 0.1 M d_6-DMSO as the solvent. [e] With 0.05 M $CDCl_3$ as the solvent.



to dimethylaniline, which model replacement of sp^2 nitrogen by sp^3 nitrogen in quinoxaline, viz., +3, −11, and −6 ppm, respectively [6].

One's attention is also directed to the following regularity in the IR absorption spectra: The intensities of the bands of the stretching vibrations of the benzene rings of the *a* isomers at ∿1610 cm^{-1} are approximately twice the intensities of the corresponding bands of the b isomers. The probable contributions to this absorption of $\nu_{C=N}$ bands of stretching vibrations are approximately identical in the possible isomers, so that it is permissible to disregard them in the analysis of the intensities of the bands at ∿1610 cm^{-1}. Thus the coefficient of molar absorption (ε) for the band at 1616 cm^{-1} in the spectrum of IIIb is 440 liters•$mole^{-1}$•cm^{-1}, as compared with 905 liters•$mole^{-1}$•cm^{-1} for the band at 1607 cm^{-1} in the spectrum of IIIa. The increase in the intensities of these bands in the spectra of the *a* isomers is evidently due to replacement in the quinoxaline grouping of the electron-acceptor sp^2 nitrogen atom by the electron-donor sp^3 nitrogen atom. As a result of this replacement, the benzene ring of quinoxaline bears an acceptor and a donor substituent rather than two acceptor substituents. A similar increase in the intensity of the band of stretching vibrations is well known for o-disubstituted benzenes with donor and acceptor substituents [7].

The electronic absorption spectra of the *a* and b isomers dissolved in NaOH—EtOH solutions virtually coincide. Opposite changes in the shielding of 5- and 8-H (Δδ −0.12 and +0.22 ppm, respectively), which indicate equalization of the electronic properties of the nitrogen atoms of the quinoxaline ring, are observed in the PMR spectra of isomer IIIa in 0.05 M KOH—EtOH solutions. The pronounced shielding of 6-H (−0.23 ppm) in the isatin ring constitutes evidence for an increase in the electron-donor properties of the nitrogen atoms of the hydrazone bridge. These data make it possible to assume rearrangement of structure IIIa (the E,Z isomer) during its dissolving in alcoholic alkali, which is associated with the formation of the E-isomeric form of the hydrazone anion, in analogy with the data for β-thiosemicarbazones [2] and β-guanylhydrazones [4] of isatin.

In the synthesis of IIIb by prolonged refluxing in isopropyl alcohol, small amounts of hydrazones IV and V were isolated along with it as a result of nucleophilic substitution of the chlorine atom by iso-Pr and OH groups. Their spectroscopic characteristics (the weak-field chemical shift of the NH proton, the absence of a weak-field chemical shift of isatin 4-H, and the position of the $\nu_{C=O}$ band in the IR spectra and of the intramolecular charge-transfer band in the electronic absorption spectra) indicate that they are b isomers. In this case tautomerization to give the 2(1H)-quinoxaline structure occurs in V; this is confirmed by the sharp increase in the intensity of the band of the stretching vibrations of two C=O groups, the appreciable increase in the intensity of the $\nu_{C=C}$ band at 1616 cm^{-1} (ε = 575 liters•$mole^{-1}$•cm^{-1}) in the IR spectrum, and the considerable shielding of the aromatic protons of the quinoxaline ring (particularly 5-H) in the PMR spectrum.

We obtained dihydrazones VI and VII in the reaction with 2,3-dihydrazinoquinoxaline at room temperature in acetic acid. According to the PMR and ^{13}C NMR spectra, these compounds

TABLE 3. ^{13}C NMR Spectra of Hydrazones III, IV, and VII

Compound	Isatin								Quinoxaline								N—CH_2	2-CH_2	3-CH_2	4-CH_3	OCH	$(CH_3)_2$
	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(2)	C(3)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)						
IIIa	175,37	165,82	129,41	123,22	132,27	108,56	147,35	117,67	144,98	133,48	128,81	124,42	131,14	115,49	147,87	130,86	39,89	29,74	20,22	13,69	—	—
IIIb	161,93	143,93	121,77	122,98	130,60	109,05	142,40	120,13	135,67	137,03	128,04	127,60	130,61	127,72	140,75	138,87	39,66	29,73	20,21	13,65	—	—
IV	161,92	140,11	121,69	122,77	130,14	108,91	142,15	120,15	134,69	147,71	127,39	126,72	126,72	126,45	137,57	137,97	39,47	29,73	20,22	13,76	70,71	21,97
VII	161,62[b]	144,49	121,92	122,81	130,48	108,85	142,66	120,53	—	—	—	—	—	—	—	—	39,89		20,81	—	—	—
	174,99[a]	166,19	129,91	123,40	131,55	108,3	146,07	117,45	144,25	135,44	127,64	124,60	130,48	115,81	134,14	128,58	39,59	29,76	20,23	13,71	—	—

[a]The A ring. [b]The B ring.

have a mixed E,Z configuration of the hydrazone fragments. The additive character of the intramolecular charge-transfer (ICT) band in their electronic absorption spectra (λ_{max} = 430 nm) as compared with the ICT bands of monohydrazones I-III (λ_{max} = 409 and 472 nm) is also in agreement with this conclusion. As in the IR spectra of the E,Z isomers of the monohydrazones, the intensity of the band of $\nu_{C=C}$ stretching vibrations is increased in the IR spectra of the dihydrazones. Thus $\nu_{C=C}$ is found at 1608 cm^{-1} with ε = 1110 liters·$mole^{-1}$·cm^{-1} in the spectrum of VII, and this confirms the presence of a benzene ring with electron-donor and electron-acceptor substituents in the ortho position.

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ and KBr pellets were recorded with a UR-20 spectrometer. The electronic spectra were obtained with a Unicam-100A spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard. The assignment of the ^{13}C NMR spectra was made on the basis of an analysis of the spectra obtained in the case of complete noise and selective decoupling and without decoupling of the protons, as well as a comparison with the spectra of model compounds. The mass spectra were obtained with an AEI-702 spectrometer with direct introduction of the samples into the ionization region at an ionizing-electron energy of 70 eV; the temperature of the system for vaporization of the samples was 120-180°C. The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates.

1-Butyl-1H-indole-2,3-dione. A 14.7-g (0.1 mole) sample of isatin was mixed with 16 g (0.4 mole) of finely ground NaOH and 20.7 g (0.15 mole) of finely ground K_2CO_3, 3.22 g (0.01 mole) of Bu_4NBr, 68.5 g (0.5 mole) of BuBr, and 100 ml of benzene, and the mixture was refluxed with stirring for 5 h. It was then cooled and filtered, and the solvent was removed by distillation to dryness. Distillation of the residue gave an orange oil with bp 155-160°C (5 mm), which solidified on cooling. Recrystallization from 80% ethanol gave orange crystals. The yield of product with mp 41-42°C [11] was 13.5 g (66%).

3-Chloro-2(1H)-quinoxalinone (E,Z)-[1,3-Dihydro-2(2H)-indolon-3-idene]hydrazone (Ia). A 0.1-g sample of concentrated H_2SO_4 was added dropwide with stirring to a solution of 1.47 g (0.01 mole) of isatin and 1.94 g (0.01 mole) of 3-chloro-2-hydrazinoquinoxaline [8] in 50 ml of DMSO, and the mixture was maintained at room temperature for 6 h. It was then diluted to 300 ml of water, and the aqueous mixture was neutralized to pH 6-7 with Na_2CO_3. The precipitate was removed by filtration, washed with water, dried, and recrystallized from ethanol to give dark-red needles (2.33 g) that were soluble in dimethylformamide (DMF), DMSO, and acetic acid, less soluble in chloroform, alcohols, and benzene, and insoluble in water.

3-Chloro-2(1H)-quinoxalinone (E,Z)-[1,3-Dihydro-1-methyl-2-(2H)-indolon-3-idene]hydrazone (IIa) and 3-Chloro-2(1H)-quinoxalinone (E,Z)-[1-Butyl-1,3-dihydro-2(1H)-indolon-3-idene]hydrazone (IIIa). These compounds were similarly obtained.

(Z)-2-[(1,3-Dihydro-2(2H)-indolon-3-indene)hydrazino]-3-chloroquinoxaline (Ib). A 1.62-g (0.05 mole) sample of Ia was dissolved in 100 ml of DMSO, and the solution was heated at 100°C for 4 h. A total of 70 ml of the solvent was removed by vacuum distillation, and the residue was diluted with water. The precipitate was removed by filtration, washed with water, dried, and dissolved in 50 ml of $CHCl_3$. The solution was applied to a column filled with SiO_2 in $CHCl_3$ and eluted with CCl_4—$CHCl_3$—Me_2CO (10:5:1). The first yellow zone was collected, and the adsorbed material was recrystallized from benzene to give bright-yellow needles (0.97 g).

(Z)-2-[(1,3-Dihydro-1-methyl-2(2H)-indolon-3-idene)hydrazino]-3-chloroquinoxaline (IIb). A 0.1-g sample of concentrated H_2SO_4 was added to a solution of 1.94 g (0.01 mole) of 3-chloro-2-hydrazinoquinoxaline and 1.61 g (0.01 mole) of 1-methyl-1H-indol-2,3-dione [10] in 130 ml of ethanol, and the mixture was refluxed for 3 h. It was then cooled, and the precipitate was removed by filtration and suspended in water. The suspension was neutralized to pH 6-7 with 10% NaOH solution, and the solid material was removed by filtration, washed with water, dried, and recrystallized from ethanol to give yellow needles (2 g) that were quite soluble in chloroform, less soluble in DMF, DMSO, benzene, and alcohols, and insoluble in water.

(Z)-3-[1-Butyl-1,3-dihydro-2(2H)-indolon-3-idene)hydrazino]-2(1H)-quinoxalinone (V). A 0.1-g sample of concentrated H_2SO_4 was added dropwise to a solution of 1.94 g (0.01 mole) of 3-chloro-2-hydrazinoquinoxaline and 2.03 g (0.01 mole) of 1-butyl-1H-indole-2,3-dione in 150 ml of isopropyl alcohol, and the mixture was refluxed for 10 h. It was then cooled and diluted

to 400 ml with water. The aqueous mixture was neutralized to pH 6-7 with Na_2CO_3, and the precipitate was removed by filtration, dried, and dissolved by heating in 100 ml of benzene. The benzene solution was filtered, and the benzene-insoluble material was recrystallized from 100 ml of ethanol to give lemon-yellow plates of V (0.5 g).

The benzene filtrate was applied to a column filled with SiO_2 and eluted with benzene. The first yellow zone after evaporation of the benzene was recrystallized from heptane to give 0.58 g of (Z)-2-[(1-butyl-1,3-dihydro-2(2H)-indolon-3-idene)hydrazino]-3-isopropoxyquinoxaline (IV) as bright-yellow needles that were quite soluble in many organic solvents.

The second yellow zone after evaporation of the solvent was recrystallized from hexane—benzene (5:1) to give 1.52 g of (Z)-2-[1-butyl-1,3-dihydro-2(2H)-indolon-3-idene)hydrazino]-3-chloroquinoxaline (IIIb) as yellow needles that were quite soluble in organic solvents.

2-[(1,3-Dihydro-1-methyl-2(2H)-indolon-3-idene)hydrazino]-2(1H)-quinoxalinone (E,Z,Z)-[1,3-Dihydro-1-methyl-2(2H)-indolon-3-idene]hydrazone (VI). A 1.9-g (0.01 mole) sample of 2,3-dihydrazinoquinoxaline [9] and 3.22 g (0.02 mole) of 1-methyl-1H-indole-2,3-dione were dissolved in 100 ml of acetic acid by heating and stirring on a water bath. The solution was cooled to room temperature and stirred at this temperature for 3 h. The red precipitate was removed by filtration and recrystallized from acetic acid to give 3.66 g of dark-red needles that were soluble in DMSO, DMF, and chloroform, less soluble in benzene and alcohols, and insoluble in water.

3-[1-Butyl-1,3-dihydro-2(2H)-indolon-3-idene)hydrazino]-2(1H)-quinoxalinone (E,Z,Z)-[1-Butyl-1,3-dihydro-2(2H)indolon-3-indene]hydrazone (VII). This compound was obtained as blood-red needles by a method similar to that used to prepare VI.

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