IMIDAZO[1,2-*a*]QUINOXALINE AND ITS TRANSFORMATIONS

II.* 7-SUBSTITUTED IMIDAZO[1,2-*a*]QUINOXALINE

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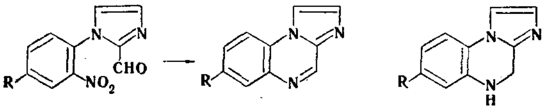
7-Substituted imidazo[1,2-*a*]quinoxalines were synthesized. Transformations of compounds of this series – quaternization, reduction to 4,5-dihydro derivatives, and behavior toward oxidizing agents – were studied.

Continuing our study of the imidazo[1,2-*a*]quinoxaline (IIa) system, we have synthesized 7-methyl-, 7-methoxy-, and 7-bromo-substituted compounds of this heterocycle (IIb-d, Table 1). For this, N-(o-nitroaryl)-2-formylimidazoles (Ib-d) were subjected to the action of sodium dithionite in ammonia.

The cyclization proceeds smoothly to give good yields. The formation of a 4-amino substituted compound, which occurred in the preparation of the simplest representative of the series (IIa), was not observed in this case. Thus substituent R has a substantial effect on the course of the process. It also has an effect on the behavior of II towards sodium amide: IIb-d could not be aminated under the conditions described for IIa.



I a-d II a-d III a,b

I, II a R=H; b R=CH_3; c R=CH_3O; d R=Br; III a R=H; R=OH

Heterocyclic compounds IIa-d have low basicities and therefore form quaternary salts with difficulty; only the methiodides were obtained in low yields. According to calculations of the electron density distribution by the Hückel MO method [1], one should assume that both alkylation and protonation proceed in the 3 position.

Like phenanthrene and phenanthridine, the middle ring of which has low aromaticity and is readily hydrogenated at the 9-10 bond, IIa adds hydrogen to the C = N bond of the quinoxaline ring when it is heated with hydriodic acid in the presence of phosphorus. The IR spectrum of the compound confirms the structure of the hydrogenation product; it contains an absorption band at 3430 cm^{-1}, which is characteristic for the stretching vibration of the NH bond, and two absorption bands at 2990 and 2830 cm^{-1}, which can be ascribed, respectively, to the asymmetrical and symmetrical stretching vibrations of the CH_2 group [3]. When 7-methoxy derivative IIc is heated with hydriodic acid, the methoxy group is dealkylated, and the ring is reduced to give IIIb. For comparison, we note that quinoxalines are also readily reduced to the dihydro derivatives which, however, rarely can be isolated [4].

Like phenanthridine, IIa-d are stable with respect to oxidizing agents and do not change on reaction with aqueous and aqueous alkaline solutions of potassium permanganate and solutions of potassium dichromate in glacial acetic acid and sulfuric acid, both in the cold and on heating on a boiling-water bath. The starting compounds can be isolated from the reaction mixtures practically without any loss.

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*See [1] for communication I.

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TABLE 1. 7-Substituted Imidazo[1,2-*a*]quinoxalines (IIb-d)

Comp.	R	mp, °C	pK_a*	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IIb	CH_3	184	4,71	$C_{11}H_9N_3$	72,3	5,2	23,3	72,1	4,9	23,0	93
IIc	CH_3O	167	4,73	$C_{11}H_9N_3O$	66,5	4,6	21,3	66,3	4,5	21,1	92
IId	Br	229	4,62	$C_{10}H_6BrN_3$†	48,7	2,6	17,0	48,4	2,4	16,9	73

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*In 50% aqueous alcohol at 20°C; the pK_a value for IIa was 4.60.

† Found,%: Br 31.9. Calculated,%: Br 32.3.

TABLE 2

R′	R	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
CH_2OH	CH_3	164 165	$C_{11}H_{11}N_3O_3$	57,0	4,9	—	56,7	4,7	—	66
CH_2OH	CH_3O	181	$C_{11}H_{11}N_3O_4$	53,1	4,3	17,0	53,0	4,4	16,9	79
CH_2OH	Br	185	$C_{10}H_8BrN_3O_3$*	40,5	3,0	—	40,3	2,7	—	54
CHO	CH_3	123	$C_{11}H_9N_3O_3$	57,2	4,0	18,3	57,1	3,9	18,2	78
CHO	CH_3O	110	$C_{11}H_9N_3O_4$	53,6	4,0	17,2	53,4	3,6	17,0	82
CHO	Br	116	$C_{10}H_6BrN_3O_3$ †	40,7	2,2	14,4	40,5	2,0	14,2	80
CH=NOH	H	215	$C_{10}H_8N_4O_3$	51,6	3,8	23,9	51,7	3,5	24,1	78

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*Found,%: Br 26.7. Calculated,%: Br 26.9.

† Found,%: Br 26.7. Calculated,%: Br 27.0.

EXPERIMENTAL

2-Hydroxymethyl-1-(o-nitroaryl)imidazoles (Table 2). These compounds were obtained by the action of 32% formaldehyde solution on 1-(o-nitroaryl)imidazoles [5]. The hydroxymethylation of 1-(2,4-dinitrophenyl)imidazole [6] does not occur under the previously described conditions [5]. A broad low-intensity absorption band at 3100-3200 cm^{-1}, which is related to the vibrations of the CH_2OH group involved in a hydrogen bond, is present in the IR spectra of the 2-hydroxymethyl derivatives.

2-Formyl-1-(o-nitroaryl)imidazoles (Table 2). These compounds were obtained by the method in [2]. Absorption bands at 1680-1700 cm^{-1} (CHO) are observed in the IR spectra of these compounds.

Experiments on the Amination of IIb-d. When the reaction was carried out under the conditions described for IIa [1], only the starting compounds were isolated (40-60%). Heating the reaction mixture to 230° caused decomposition of the starting materials.

Imidazo[1,2-*a*]quinoxaline Methiodide. A 3.55-g (25 mmole) sample of methyl iodide was added gradually to a solution of 0.85 g (5 mmole) of IIa in 10 ml of alcohol, and the mixture was refluxed for 3 h, after which it was cooled to precipitate 0.6 g (38%) of pale-yellow needles with mp 268° (from alcohol). Found,%: I 40.5. $C_{11}H_{10}IN_3$. Calculated,%: I 40.8.

7-Methoxyimidazo[1,2-*a*]quinoxaline Methiodide. This compound was obtained in 28% yield as light-brown needles with mp 264° (from alcohol). Found,%: N 12.4. $C_{12}H_{12}IN_3O$. Calculated,%: N 12.3.

4,5-Dihydroimidazo[1,2-*a*]quinoxaline (IIIa). A solution of 0.34 g (2 mmole) of IIa in 4 ml of hydriodic acid (sp. gr. 1.7) was refluxed for 6 h in the presence of 0.15 g of red phosphorus. The hot solution was filtered, and the filtrate was cooled, diluted with water, and neutralized with sodium carbonate solution. The resulting light-yellow oil was extracted with chloroform and chromatographed on aluminum oxide. The first fraction was worked up to give 0.15 g (44%) of colorless needles with mp 114° (from benzene–petroleum ether) that darkened gradually in air because of oxidation to IIa. Found,%: C 69.9; H 5.6; N 24.7. $C_{10}H_9N_3$. Calculated,%: C 70.2; H 5.3; N 24.6. UV spectrum: λ_{max} 313 nm (log ε 4.05); λ_{min} 276 nm (log ε 3.53).

7-Hydroxy-4,5-dihydroimidazo[1,2-*a*]quinoxaline (IIIb). A solution of 0.5 g of hydriodic acid (sp. gr. 1.7) was refluxed for 6 h, cooled, and neutralized with sodium carbonate. The precipitate was removed by filtration and washed with water to give 0.28 g (60%) of colorless crystals with mp 285° (from alcohol). Found,%: C 64.5; H 4.5; N 22.9. $C_{10}H_9N_3O$. Calculated,%: C 64.2; H 4.8; N 22.5.

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