N-OXIDES OF IMIDAZO[4,5-b]QUINOXALINES AND IMIDAZO[4,5-b]PYRAZINES

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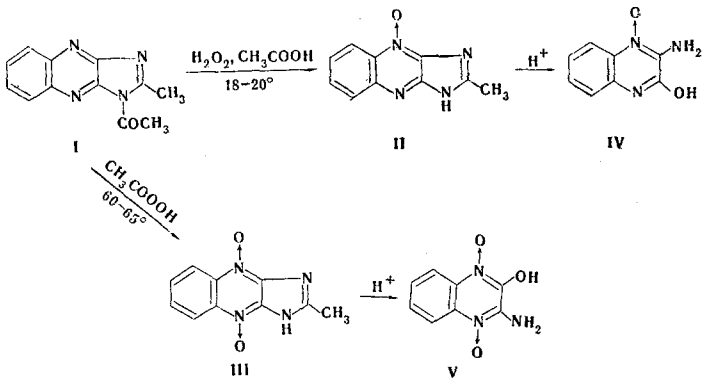
The N-oxides and N,N'-dioxides of methyl derivatives of imidazo[4,5-b]quinoxaline and imidazo[4,5-b]pyrazine were synthesized. The higher reactivity of the 2-methyl group in the N-oxides of 2-methylimidazo[4,5-b]quinoxaline as compared with the corresponding unoxidized derivatives was demonstrated.

In a number of cases, the oxidation of the nitrogen atom in N-heterocyclic compounds leads to the appearance of biological activity that is absent in some unoxidized bases. Thus the high antibacterial activity of the N-oxides of 2-methyl- and 2,3-dimethylquinoxalines and the corresponding hydroxymethyl derivatives has been observed [1,2]. In the present paper we describe the synthesis of the N-oxides of methyl derivatives of imidazo[4,5-b]quinoxaline and imidazo[4,5-b]pyrazine. The N-oxides of these heterocyclic systems have been unknown up until now.

A mixture of N-oxides and N,N'-dioxides of 2-methylimidazo[4,5-b]quinoxaline (II and III), with predominance of the former, is formed in the oxidation of 1-acetyl-2-methylimidazo[4,5-b]quinoxaline (I) with hydrogen peroxide in acetic acid (without heating). When the reaction is carried out at 60-65°C with a solution of peracetic acid in acetic acid as the oxidizing agent, the reaction is shifted to favor the formation of the N,N'-dioxide. Moreover, deacetylation of N_1 occurs in both cases. The structures of II and III were proved by cleavage of the imidazole ring (by heating in dilute mineral acids) and isolation of 3-amino-2-hydroxyquinoxaline 4-oxide (IV) and 2-amino-3-hydroxyquinoxaline 1,4-dioxide (V). Thus it was demonstrated that, just as in purine derivatives, the nitrogens of the aromatic diazine ring in imidazo[4,5-b]-quinoxaline are oxidized more readily than the nitrogen of the imidazole ring.



A mixture of the N-oxide and N,N'-dioxide in a ratio of 2.7:1 is formed in the oxidation of 2-methylimidazo[4,5-b]pyrazine (VIa) with peracetic acid solution. The oxidation of 5,6-dimethylimidazo[4,5-b]-pyrazine (VIb) under the same conditions gives primarily the N,N'-dioxide of VIb; the corresponding N-oxide is isolated in the pure state only when VIb is oxidized with hydrogen peroxide in acetic acid.

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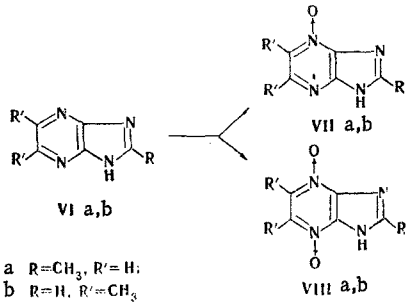
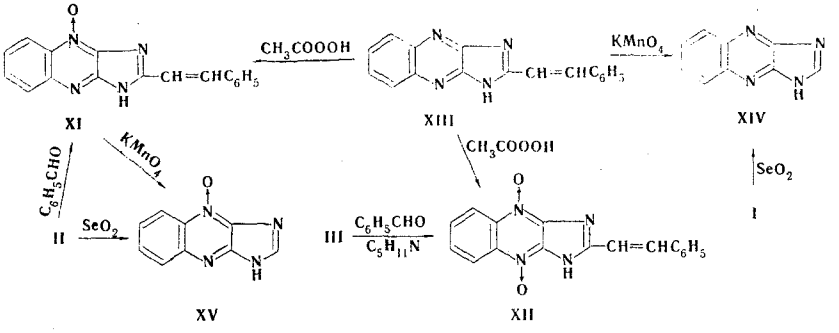


The N-oxide and N,N'-dioxide of imidazo[4,5-b]pyrazine can apparently be assigned the VII and VIII structures in analogy with the N-oxides of 2-methylimidazo[4,5-b]quinoxaline described above.

In contrast to 5,6-dimethylimidazo[4,5-b]pyrazine (VIb), its N_1-benzoyl derivative (IX) is oxidized by peracetic acid only to the N-oxide (X).

The NH group in the imidazo[4,5-b]quinoxaline and imidazo[4,5-b]pyrazine N-oxides obtained has more acidic properties than in the corresponding unoxidized bases. Thus VIIIa, VIIIb, and III are soluble in aqueous solutions of sodium bicarbonate (with CO_2 liberation), while VIa, VIb, and 2-methylimidazo-[4,5-b]quinoxaline are soluble only in alkalis.

In a study of the reactivity of the methyl group in N-oxides II and III, it was shown that II and III condense with aromatic aldehydes (particularly with benzaldehyde) in the presence of piperidine to give styryls XI and XII, and it was established that the condensation of aldehydes with II or III proceeds under milder conditions than with the corresponding unoxidized base (I). N-Oxide and N,N'-dioxide XI and XII were also obtained by N-oxidation of styryl XIII. The oxidation of the methyl group in N-oxide II with selenium dioxide also proceeds more readily than with I. However, in both cases, the corresponding carbonyl derivatives were not obtained, but unsubstituted imidazo[4,5-b]quinoxaline (XIV) or its N-oxide (XV) was isolated. The results are evidence that the methyl group in I and II is oxidized to the readily cleaved carboxyl group. The ease of decarboxylation of imidazo[4,5-b]quinoxaline-2-carboxylic acid and its N-oxide is also confirmed by the formation of XIV and XV during the oxidation of styryls XIII or XI with potassium permanganate:



The starting imidazo[4,5-b]quinoxalines and imidazo[4,5-b]pyrazines were synthesized primarily by known methods [3-5]. 2-Methylimidazo[4,5-b]quinoxaline was obtained by deacetylation of I or by condensation of 2,3-diaminoquinoxaline with acetamide.

It was shown that 2,3-diaminoquinoxaline condenses with dimethylformamide to give XIV.

The N-oxides and N,N'-dioxides of imidazo[4,5-b]quinoxalines and imidazo[4,5-b]pyrazines did not display appreciable antibacterial activity.

EXPERIMENTAL

2-Methylimidazo[4,5-b]quinoxaline 4-Oxide (II). A mixture of 100 ml of acetic acid, 22 ml of 30% hydrogen peroxide, and 44 ml of acetic anhydride was held at 18-22° for 18 h; 10 g (44 mmole) of I was then added, and the mixture was stirred at 18-22° for 7 days. The solution was vacuum-evaporated (40-45°) to one fourth of its original volume, and the residue was triturated with alcohol and filtered to give 4.25 g

(48%) of II with mp 273° [dec., from aqueous dimethylformamide (DMF)] and R_f 0.69* (dark violet spot). Found: C 59.8; H 3.9; N 28.1%. $C_{10}H_8N_4O$. Calculated: C 60.0; H 4.0; N 28.0%. A difficult-to-separate mixture of II and III was isolated from the filtrate after the separation of II.

2-Methylimidazo[4,5-b]quinoxaline 4,9-Dioxide (III). A mixture of 200 ml of CH_3COOH, 44 ml of 30% hydrogen peroxide, and 88 ml of acetic anhydride was held at 18-22° for 18 h; 20 g (88 mmole) of I was added, and the mixture was heated with stirring at 60-65° for 20 h. The reaction mixture was worked up as in the preceding experiment to give 6.75 g (35%) of III with mp 259° (dec.), which was purified by isolation of the crystalline sodium salt and subsequent neutralization of an aqueous solution of it. Found: C 55.5; H 3.6; N 25.9%. $C_{10}H_8N_4O_2$. Calculated: C 55.7; H 3.7; N 25.9%. The product had R_f 0.34 (green spot). A difficult-to-separate mixture of II and III was isolated after separation of III from the reaction solution.

Conversion of II and III to 3-Amino-2-hydroxyquinoxaline 4-Oxide (IV) and 2-Amino-3-hydroxyquinoxaline 1,4-Dioxide (V). A. A suspension of 0.5 g (2.5 mmole) of II in 10 ml of 2.5 N hydrochloric acid was heated at 100° for 1 h. The solution was treated with activated charcoal and neutralized with ammonia to give 0.33 g (75%) of IV with mp 313° (dec.). The IR spectrum, the melting point, R_f value (0.47, violet spot), and color reaction with $FeCl_3$ (blue-green) were in complete agreement with the characteristics of a sample of IV obtained via the method in [6].

B. The reaction with III was carried out similarly: 0.5 g (2.3 mmole) of III gave 0.37 g (83%) of V, which was identical with respect to its melting point [307° (dec.)], IR spectrum, R_f value (0.18, violet spot), and color reaction with $FeCl_3$ (brown) to V obtained by the method in [6].

N-Oxidation of 2-Methylimidazo[4,5-b]pyrazine (VIa). A 0.4-g sample of anhydrous CH_3COONa, 0.01 g of $Na_4P_2O_7$, and 0.72 g (5.4 mmole) of VIa were added successively to 2.6 ml of an 8.5% solution of peracetic acid in acetic acid, and the mixture was stirred at 55-60° for 21 h. The precipitate was removed by filtration, and ether was added to the filtrate to precipitate an additional amount of a mixture of reaction products. The combined precipitates were crystallized from aqueous alcohol to give 0.19 g (21%) of 2-methylimidazo[4,5-b]pyrazine 4,7-dioxide (VIIIa) with mp 273-273.5°. Found: C 43.4; H 3.8; N 33.9%. $C_6H_6N_4O_2$. Calculated: C 43.4; H 3.6; N 33.7%. PMR spectrum† (D_2O): singlet at 1.48 ppm (2-CH_3 group), singlet at 7.06 ppm (pyrazine ring protons).

The solution remaining after the recrystallization of VIIIa was evaporated to dryness, and the residue was suspended in $CHCl_3$ and applied to a column filled with 12 g of silica gel. Acetone eluted 0.47 g (58.2%) of VIIa; VIIa did not melt up to 300° (it was purified by crystallization from aqueous alcohol). Found: C 48.5; H 4.0; N 37.2%. $C_6H_6N_4O$. Calculated: C 47.9; H 4.0; N 37.3%. PMR spectrum (in D_2O): singlet at 1.48 ppm (2-CH_3 group), singlet at 7.05 ppm (pyrazine ring protons).

N-Oxidation of 5,6-Dimethylimidazo[4,5-b]pyrazine (VIb). A. A 0.7-g sample of anhydrous CH_3COONa, 0.01 g of $Na_4P_2O_7$, and 2 g (13 mmole) of VIb were added successively to 45 ml of a solution of peracetic acid (10%), and the mixture was stirred at 60-65° for 6 h. The mixture was then worked up as in the preceding experiment to give 1.15 g (47%) of VIIIb with mp 272° (from water, dec.). Found: C 42.1; H 5.3%. $C_7H_8N_4O_2 \cdot H_2O$. Calculated: C 42.4; H 5.1%.

B. A 1.3-g (8.8 mmole) sample of VIb in a mixture of 50 ml of glacial acetic acid and 5 ml of 30% hydrogen peroxide was stirred at 75-80° for 9 h. The solution was evaporated to one fourth of its original volume and treated with methanol–ether to give 1.03 g of a mixture of VIIb and VIIIb. Several crystallizations from aqueous alcohol gave 0.5 g (35%) of VIIb with mp 272.5-273° (dec.). Found: C 51.6; H 4.9; N 34.3%. $C_7H_8N_3O$. Calculated: C 51.2; H 4.9; N 34.2%.

1-Benzyl-5,6-dimethylimidazo[4,5-b]pyrazine (IX). The potassium salt of VIb was obtained from 1 g (6.8 mmole) of VIb, 0.55 g (10 mmole) of KOH, and 4 ml of anhydrous alcohol and was placed in 15 ml of anhydrous dimethylformamide and added to a solution of 0.9 ml (8 mmole) of benzyl chloride. The mixture was stirred at 22° for 1 h, and the potassium chloride formed was separated by filtration. The filtrate was

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*All of the compounds were chromatographed with n-butyl alcohol–5% acetic acid (1 : 1) on Leningrad Factory No. 2 paper. The spots were developed in UV light.

† The PMR spectra were recorded with a JNM-4H-100 spectrometer, and the shifts are presented on the δ scale. The internal standard for the spectra of compounds in D_2O was tert-butyl alcohol [$\delta_{(CH_3)}$ 1.26 ppm], while tetramethylsilane was the internal standard for the spectra of compounds in $CDCl_3$.

evaporated to dryness, and the residue was treated with ether to precipitate 1.17 g (73%) of IX with mp 146-147.5° (from methanol–ether). Found: C 71.0; H 6.1; N 23.6%. $C_{14}H_{14}N_4$. Calculated: C 70.6; H 5.9; N 23.3%. PMR spectrum ($CDCl_3$): slightly split singlet at 2.62 ppm (5- and 6-CH_3 groups), singlet at 5.40 ppm (benzyl CH_2), and singlet at 8.10 ppm (H_2).

1-Benzyl-5,6-dimethylimidazo[4,5-b]pyrazine N-Oxide (X). A 1-g (4.2 mmole) sample of IX was oxidized with a solution of 1.35 ml of 30% hydrogen peroxide in 13.5 ml of acetic acid (3 h at 75-80°), after which the same amounts of acetic acid and hydrogen peroxide were added, and the mixture was heated for another 12 h. This operation was repeated (heating for 7 h). The reaction solution was vacuum-evaporated (at 40-45°) to a small volume and treated with methanol–ether to give 0.61 g (57%) of X with mp 220-221° (from methanol). Found: C 66.5; H 5.3; N 22.0%. $C_{14}H_{14}N_4O$. Calculated: C 66.1; H 5.6; N 22.0%. PMR spectrum ($CDCl_3$): singlets at 2.65 and 2.60 ppm (5- and 6-CH_3 groups), singlet at 5.42 ppm (benzyl CH_2), and singlet at 7.97 ppm (H_2).

2-Styrylimidazo[4,5-b]quinoxaline 4-Oxide (XI). A. A 1.3-g (4.8 mmole) sample of XIII was added to 30 ml of 10% solution of peracetic acid that had been previously stirred with 0.45 g of anhydrous CH_3COONa and 0.01 g of $Na_4P_2O_7$, and the mixture was heated at 50-55° for 20 h to give 0.37 g (27%) of XIII with mp 258° (dec., from CH_3COOH) and R_f 0.64 (light green spot). Found: C 70.5; H 4.5; N 19.1%. $C_{17}H_{12}N_4O$. Calculated: C 70.8; H 4.2; N 19.4%.

B. A mixture of 0.25 g (1.2 mmole) of II, 1.25 ml of benzaldehyde, and 0.13 ml of piperidine was heated at 110° for 5 h to give 0.25 g (70%) of XI with mp 258°; the product was identical to the XI obtained by the oxidation of XIII (see the preceding experiment).

2-Styrylimidazo[4,5-b]quinoxaline 4,9-Dioxide (XII). A. Compound XIII [1.6 g (5.9 mmole)] was oxidized with a solution of 10% peracetic acid (45 ml plus 0.6 g of anhydrous CH_3COONa plus 0.01 g of $Na_4P_2O_7$) at 65-70° for 29 h to give 1.2 g (67%) of XII with mp 253° (dec., from acetic acid) and R_f 0.30 (dark yellow spot). Found: C 66.9; H 4.2; N 18.5%. $C_{17}H_{12}N_4O_2$. Calculated: C 67.1; H 4.0; N 18.4%.

B. A suspension of 0.25 g (1.1 mmole) of III in 1.25 ml of benzaldehyde and 0.13 ml of piperidine was heated at 110° for 8 h to give 0.2 g (57%) of XII with mp 253°. The product was identical to the XII obtained by the oxidation of XIII (see the preceding experiment).

2-(o-Hydroxystyryl)imidazo[4,5-b]quinoxaline (XVII). A mixture of 1 g (4.4 mmole) of I, 1.5 ml of salicylaldehyde, and 0.5 ml of piperidine was heated at 160-165° for 3 h to give 1.15 g (90%) of XVII with mp 253.5° (dec.). The product was insoluble in the usual organic solvents and was purified by repeated treatment with boiling acetic acid. Found: C 70.5; H 4.3; N 19.4%. $C_{17}H_{12}N_4O$. Calculated: C 70.8; H 4.2; N 19.4%.

2-(o-Hydroxystyryl)imidazo[4,5-b]quinoxaline 4-Oxide (XVIII). A mixture of 0.7 g (3.5 mmole) of II, 3.5 ml of salicylaldehyde, and 0.35 ml of piperidine was heated at 100-110° for 3 h to give 0.68 g (64%) of XVIII with mp 343° (dec.). The product was purified by the method used to purify XVII. Found: C 66.9; H 4.3; N 18.7%. $C_{17}H_{12}N_4O_2$. Calculated: C 67.1; H 4.0; N 18.4%.

Oxidation of I and II with Selenium Dioxide. A. A mixture of 0.5 g (2.3 mmole) of I and 0.26 g of SeO_2 in 5 ml of piperidine was refluxed for 5 h. The solid material was removed by filtration, and the solution was vacuum-evaporated to dryness. The residue was dissolved in 2.5 N NaOH, and the solution was filtered. The filtrate was neutralized with hydrochloric acid and salted out with sodium chloride to give 0.28 g (75%) of imidazo[4,5-b]quinoxaline (XIV) with mp 285-286° (from water); the product was identical to XIV obtained by the method in [3] with respect to its melting point and R_f value (0.73, violet spot).

B. A mixture of 2 g (10 mmole) of II and 1.2 g of SeO_2 in 20 ml of piperidine was refluxed for 1.5 h. The solid material was removed by filtration and treated with aqueous $NaHCO_3$. The reaction solution was vacuum-evaporated to dryness, and the residue was also treated with $NaHCO_3$. The combined alkaline solutions were neutralized with hydrochloric acid and salted out with sodium chloride to give 0.93 g (50%) of XV with mp 260.5° (dec., from acetic acid) and R_f 0.56 (dark violet spot). Found: C 57.7; H 3.4; N 30.0%. $C_9H_6N_4O$. Calculated: C 58.0; H 4.2; N 30.1%.

Oxidation of Styryls XIII and XI with Potassium Permanganate. A. Aqueous $KMnO_4$ was added to a suspension of 1 g (3.7 mmole) of XIII [4] in 200 ml of acetone at 20° until the permanganate was no longer decolorized. The mixture was filtered, and the solid was extracted several times with water (heated to 40°). The wash waters and solution were combined and vacuum-evaporated at 35-40° to a small volume. The solution was neutralized with hydrochloric acid and salted out with NaCl. The precipitate was removed

by filtration to give 0.32 g (51%) of XIV with mp 285-286° (from water); the product was identical to the XIV obtained via the method in [3] and to that isolated from the oxidation of I with selenium dioxide (see above).

B. A 1-g (3.5 mmole) sample of XI was similarly oxidized to give 0.28 g (43%) of XV with mp 260° (dec.); the product was identical to the XV isolated from the oxidation of II with selenium dioxide (see above).

Reaction of 2,3-Diaminoquinoxaline with Dimethylformamide. A suspension of 1.5 g (9.4 mmole) of 2,3-diaminoquinoxaline in 30 ml of dimethylformamide was refluxed for 10 h, and the resulting solution was vacuum-evaporated to dryness. The residue was treated with 2.5 N NaOH. The alkaline solution was neutralized and salted out with sodium chloride to give 1.2 g (75%) of XIV; the product was identical to the XIV obtained by the oxidation of I with selenium dioxide and to that obtained by the oxidation of XIII with potassium permanganate (see above).

2-Methylimidazo[4,5-b]quinoxaline. A mixture of 0.8 g (5 mmole) of 2,3-diaminoquinoxaline and 0.89 g (15 mmole) of acetamide was heated at 160-165° for 5 h. The solid melt was triturated with 2.5 N NaOH, and the mixture was neutralized and salted out to give 0.53 g (58%) of 2-methylimidazo[4,5-b]quinoxaline with mp 322° and R_f 0.78 (rose spot). The product was identical to the compound obtained by the method in [3].

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