ALKYL AND 2-HYDROXY DERIVATIVES OF IMIDAZO[4,5-b]PYRAZINE AND THEIR N-OXIDES

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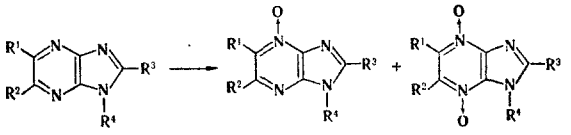
N-Monoxides and N,N-dioxides of some alkyl and hydroxy derivatives of imidazo[4,5-b]pyrazine were synthesized. It was proved that the nitrogen atoms of the pyrazine ring are oxidized; alkylation of N_1 sterically hinders oxidation of N_7. The hydrolytic cleavage of imidazo[4,5-b]pyrazines and their N-oxides was studied.

We have previously shown that imidazo[4,5-b]pyrazines are oxidized by hydrogen peroxide in acetic acid or by peracetic acid solution to N-monoxides and N,N-dioxides, during which the presence of methyl groups in the pyrazine ring promotes the formation of N,N-dioxides. Thus a mixture of N-monoxides and N,N-dioxides IIa and IIIa, with predominance of the former, was obtained in the N-oxidation of Ia, while predominantly N,N-dioxide IIIb was formed from Ib [1].



I a-g II a-g III a-g

I—III a $R^1=R^2=R^4=H$, $R^3=CH_3$; b $R^1=R^2=CH_3$, $R^3=R^4=H$; c $R^1=R^2=R^4=CH_3$, $R^3=H$; d $R^1=R^2=CH_3$, $R^3=H$, $R^4=CH_2C_6H_5$; e $R^1=R^2=CH_3$, $R^3=OH$, $R^4=H$; f $R^1=R^2=R^4=CH_3$, $R^3=OH$; g $R^1=R^2=R^4=H$, $R^3=OH$

In the present research we have studied the N-oxidation of imidazo[4,5-b]pyrazine derivatives Ic-g.

One of the ring nitrogen atoms in 1,5,6-trimethylimidazo[4,5-b]pyrazine (Ic) is preferably oxidized to give N-monoxide IIc, and the oxidation of the second nitrogen atom is difficult. This sort of difficulty in the oxidation of a second ring nitrogen atom was also observed in the case of 1-benzyl-5,6-dimethylimidazo[4,5-b]pyrazine (Id): in addition to the strong spot from N-monoxide IId, a very weak spot with a lower R_f value, which in analogy with the R_f values of other N,N-dioxides of imidazo[4,5-b]pyrazine can be assigned to N,N-dioxide IIId was detected in the reaction solution by thin-layer chromatography (TLC). The same results were also obtained with the corresponding 2-hydroxy derivatives (Ie-f): only N,N-dioxide IIIe was isolated in the oxidation of Ie, and N-monoxide IIe was not detected even by chromatography. In addition, N-monoxide IIf and a very small amount of N,N-dioxide IIIf were obtained in the oxidation of If. 2-Hydroxy derivative Ig, which does not have methyl groups in the 1, 5, and 6 positions, is converted to a mixture of approximately equal amounts of N-monoxide and N,N-dioxide IIg and IIIg on oxidation with peracetic acid. In analogy with the N-oxides of imidazo[4,5-b]quinoxaline [1], it might have been assumed that the nitrogen atoms of the pyrazine ring (N_4 and N_7) undergo oxidation in the investigated imidazo[4,5-b]pyrazine derivatives. As a first approximation, we assigned structures IIc, IId, and IIf to the N-monoxides of N_1-methyl or N_1-benzyl derivatives of imidazo[4,5-b]pyrazine, inasmuch as alkylation or aralkylation of N_1 may sterically hinder the oxidation of N_7. These assumptions were confirmed by hydrolytic cleavage of N-monoxides IIc and IIf and N,N-dioxide IIIb; in this case, the same compound – N-monoxide VI – was obtained from IIc and IIf. The position of the N-oxide group in VI was proved by alternative synthesis of this compound from 2-bromo-3-amino-5,6-dimethylpyrazine (IV). It is known that N-oxidation of 2-halo derivatives of pyrazine

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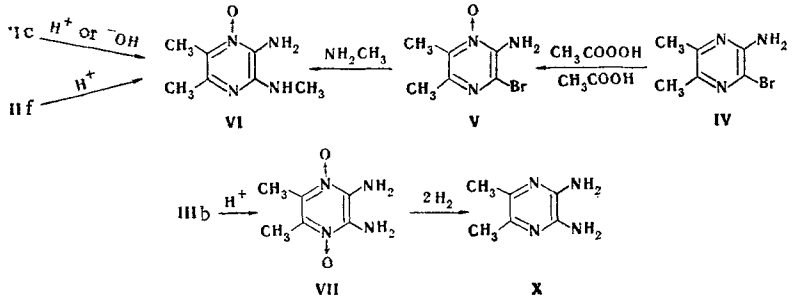
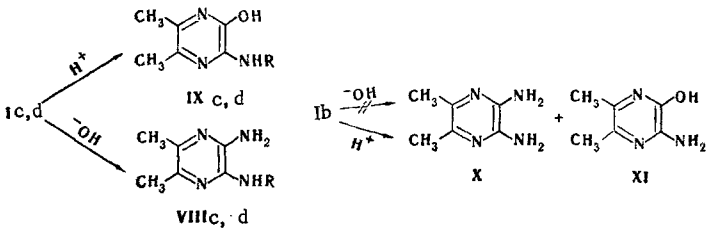
with peracetic acid solution or 30% H_2O_2 in acetic acid gives the corresponding 4-N-monoxides, and oxidation of the cyclic N_1 atom in compounds of this type proceeds only when more powerful oxidizing agents (trifluoroperacetic acid or Caro's acid) are used [2,3]. In conformity with this, oxidation of IV with 7% peracetic acid solution gave 4-N-oxide V, which on treatment with $FeCl_3$ solution gave the color reaction characteristic for heterocyclic N-oxides containing an NH_2 group in the α position relative to the oxidized ring nitrogen atom. 2-Methyl-amino-3-aminopyrazine 4-N-oxide, which was identical to VI, was obtained from V by heating with methylamine.



Hydrolytic cleavage of IIIb gave N,N-dioxide VII, the structure of which was proved by reduction of it to the known 2,3-diamino-5,6-dimethylpyrazine (X) [4]. The imidazole ring is cleaved by heating IIf, IIc, and IIIb in aqueous acid or alkali solutions. It was observed that IIf and IIIb, which contain an "acidic" hydrogen atom, are stable when they are heated in alkalis and are cleaved only in mineral acids, while IIc, in which acidic groupings are absent, undergo hydrolytic cleavage in both acidic and alkaline media. Unoxidized imidazo[4,5-b]pyrazines also behave similarly: Ic and Id are cleaved when they are heated in acids and alkalis, while Ib is cleaved only in acids. The above-indicated peculiarities in the behavior of imidazo[4,5-b]pyrazine derivatives and their N-oxides that contain an unsubstituted hydrogen in the 1 position or a hydroxy group in the 2 position are apparently associated with the formation, in alkaline media, of the corresponding anions, which are more resistant to hydrolytic cleavage.

Only 2,3-diamino derivatives of pyrazine were obtained during opening of the imidazole ring of imidazole ring of imidazo[4,5-b]pyrazine N-oxides, regardless of whether the reaction was carried out in acidic or alkaline media. The nitrogen unoxidized imidazo[4,5-b]pyrazines Ic and Id were also cleaved to 2,3-diamino derivatives VIIIc,d, in alkaline media, but 2-amino-3-hydroxy derivatives IXc,d or (in the case of Ib) a mixture of diamino and aminohydroxy derivatives X and XI were obtained in acidic media. These results are in agreement with the increased stability of the amino group in 2-aminopyrazine 1-N-oxide and 1,4-N,N-dioxide relative to acid hydrolysis [5].

The IR spectra of 2-hydroxy derivatives of imidazo[4,5-b]pyrazine (Ie-g) and their N-oxides (IIf, g, IIIe-g) contain strong bands of amide carbonyls at 1738-1780 cm^{-1} and bands of the stretching vibrations of



associated NH groups at 2260-3130 cm^{-1}; this attests to the existence of these compounds primarily in the oxo form in the crystalline state.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin Elmer 457 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The compounds were chromatographed on paper with an n-butanol–5% acetic (1 : 1) system with development in UV light.

2-Methylamino-3-amino-5,6-dimethylpyrazine (VIIIc). A mixture of 5 g (25 mmole) of IV, 35 ml of isopropyl alcohol, and 50 ml of a 30% aqueous solution of methylamine was heated in an autoclave at 170°

for 8 h, after which it was vacuum evaporated to a small volume, cooled, and filtered to give 3.55 g (94%) of VIIIc with mp 157.5-158.5° (from water) and R_f 0.5 (bright blue-violet spot). Found: C 55.4; H 7.9; N 36.9%. $C_7H_{12}N_4$. Calculated: C 55.3; H 7.9; N 36.8%.

1,5,6-Trimethylimidazo[4,5-b]pyrazine (Ic). A mixture of 1.9 g (12.5 mmole) of VIIIc and 13 ml (82 mmole) of fresly prepared ethyl orthoformate was stirred at 75-80° for 4 h, after which it was cooled and filtered to give 1.4 g (70%) of Ic with mp 193.5-194.5° (from methanol) and R_f 0.58 (dark-violet spot). PMR spectrum (in $CDCl_3$): δ 2.64 (5-CH_3 and 6-CH_3), 3.90 (N−CH_3), 8.12 ppm (2-H). Found: C 59.6; H 6.2; N 34.3%. $C_8H_{10}N_4$. Calculated: C 59.3; H 6.2; N 34.5%.

1-Methyl-2-hydroxy-5,6-dimethylimidazo[4,5-b]pyrazine (If). A 6-g (40 mmole) sample of VIIIc was triturated with 6.66 g (100 mmole) of urea, and the mixture was heated at 160-165° for 2 h. It was cooled to 20°, and the solidified mass was dissolved in 50 ml of 2% NaOH solution. The solution was treated with charcoal and filtered, and the filtrate was acidified to pH 5 with acetic acid and cooled to give 5.6 g (80%) of If with mp 261-262° (from 50% alcohol) and R_f 0.59 (bright blue-violet spot). IR spectrum: 1748 cm^{-1} ($\nu_{C=O}$); 2680-2760, 3120 cm^{-1} (broad, w, ν_{NH}). PMR spectrum (in CF_3COOH): δ 2.79 (5-CH_3 and 6-CH_3), 3.75 ppm (>NCH_3). Found: C 53.5; H 5.7; N 31.5%. $C_8H_{10}N_4O$. Calculated: C 53.9; H 5.7; N 31.5%.

N-Oxidation of Imidazo[4,5-b]pyrazine Derivatives. A) A mixture of 1.5 g (9.2 mmole) of Ic, 6.15 ml of 6.2% peracetic acid (50 mmole), 0.01 g of $Na_4P_2O_7$, and 0.93 g of CH_3COONa was heated at 60-65° for 8 h, after which it was cooled to 2°. The inorganic salts were separated, and the solution was vacuum evaporated at 40-45° to one third of its original volume. Ether was added to the residue, the mixture was cooled, and 1.7 g of a mixture of IIc and IIIc, in which less than 20% IIIc was detected by quantitative paper chromatography, was separated. The mixture was extracted with boiling ether in a Soxhlet apparatus until only one spot (from IIIc) was detected in the residue by paper chromatography. Crystallization of the residue from aqueous alcohol gave an analytically pure sample of IIIc with mp 254° (dec., from aqueous alcohol) and R_f 0.17 (dark-violet spot). Found: C 49.6; H 5.1; N 29.0%. $C_8H_{10}N_4O_2$. Calculated: C 49.4; H 5.2; N 28.9%. The ether extract was evaporated, the residue was dissolved in water, and the solution was extracted with chloroform. Many repetitions of this operation gave N-oxide IIc with mp 252-253° (from methanol) and R_f 0.36 (dark-violet spot). Found: C 53.8; H 6.0; N 32.0%. $C_8H_{10}N_4O$. Calculated: C 54.0; H 5.7; N 31.5%.

B) A mixture of 5 g (28 mmole) of If, 188 ml of 6.2% peracetic acid (153 mmole), 0.01 g of $Na_4P_2O_7$, and 2.83 g of CH_3COONa was kept at 20-25° for 6 days, after which the precipitate was removed by filtration, and another small amount of crystalline substance was isolated from the filtrate by extraction with ether. The combined solids were recrystallized from water to give 3.2 g of N-oxide IIf. The aqueous solutions from the recrystallization were extracted with boiling chloroform to give another 1.32 g of IIf. The overall yield of IIf with mp 250-251.5° (from alcohol) and R_f 0.33 (dark-violet spot) was 83%. IR spectrum: 1740 cm^{-1} ($\nu_{C=O}$); 2540-2660, 3080 cm^{-1} (broad, ν_{NH}). PMR spectrum (in CF_3COOH): δ 2.77 (5-CH_3 and 6-CH_3), 3.68 ppm (>NCH_3). Found: C 49.3; H 5.2; N 28.9%. $C_8H_{10}N_4O_2$. Calculated: C 49.5; H 5.2; N 28.9%. The aqueous solutions remaining after extraction with chloroform were evaporated to dryness to give 0.29 g (5%) of IIIf with mp 238-239° (dec., from 80% alcohol) and R_f 0.26 (dark-violet spot). Found: C 45.8; H 4.9; N 27.0%. $C_8H_{10}N_4O_3$. Calculated: C 45.7; H 4.8; N 26.7%.

C) A mixture of 0.5 g (2.8 mmole) of If, 13.5 ml of 8.2% peracetic acid (15 mmole), 0.21 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was heated at 60-65° for 10 h. The solution was then vacuum evaporated at 40° to one third of its original volume, and ether was added to the residue to isolate 0.48 g of a substance that consisted primarily of N-monoxide IIf. Only a weak spot from N,N-dioxide IIIf was detected in it by paper chromatography.

D) A mixture of 8.5 (52 mmole) of Ie, 262 ml of 8.2% peracetic acid (277 mmole), 3.96 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was heated at 65-70° for 9 h, after which the precipitate was removed by filtration, and the solution was vacuum evaporated at 40° to one third of its original volume. An additional amount of a crystalline substance was isolated from the residue by ether. The combined solids were crystallized from water and from aqueous alcohol to give 3.2 g of N,N-dioxide IIIe. The solutions from the recrystallization were vacuum evaporated to dryness, and the residue was crystallized from water to give another 0.9 g of IIIe. The overall yield of IIIe with mp 252° (dec.) and R_f 0.06 (dark-violet spot) was 4.1 g (40%). IR spectrum: 1738, 1758 cm^{-1} ($\nu_{C=O}$); 2260-2640 cm^{-1} (broad, ν_{NH}). PMR spectrum (in DMSO): δ 2.4 ppm (5- and 6-CH_3). Found: C 42.4; H 4.1; N 28.2%. $C_7H_8N_4O_3$. Calculated: C 42.8; H 4.1; N 28.6%.

E) A mixture of 2 g (15 mmole) of Ig, 59 ml of 10.2% peracetic acid (79 mmole), 0.9 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was stirred at 65-70° for 13 h, after which it was cooled, and the precipitate was

removed by filtration. Several recrystallizations of the precipitate from water and then from dilute acetic acid gave 0.5 g (22%) of N-oxide IIg with mp 265° (dec.) and R_f 0.18 (blue-violet spot). IR spectrum: 1715, 1765 cm^{-1} ($\nu_{C=O}$); 2645-2720, 3105 cm^{-1} (broad, ν_{NH}). Found: C 39.7; H 2.7; N 37.1%. $C_5H_4N_4O_2$. Calculated: C 39.5; H 2.7; N 36.5%. The solution remaining from the separation of IIg was extracted with ether to give a solid, from which 0.5 g of N-oxide IIIg with R_f 0.07 (dark-violet spot), which did not melt up to 300°, was obtained after several recrystallizations. IR spectrum: 1790, 1760 cm^{-1} ($\nu_{C=O}$); 2660-2720, 3130 cm^{-1} (broad, ν_{NH}). Found: C 35.4; H 2.5%. $C_5H_4N_4O_3$. Calculated: C 35.7; H 2.4%.

F) A mixture of 2 g (0.8 mmole) of Id, 2.8 ml of 12.2% peracetic acid (4.5 mmole), 0.04 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was heated at 60-65° for 15 h. The same amounts of peracetic acid, CH_3COONa, and $Na_4P_2O_7$ were added, and the mixture was stirred at 60-65° for another 7 h. A strong dark-violet spot from IId, with R_f 0.71 [1], and a very weak dark-violet spot with R_f 0.19, which can be assigned to IIId, were detected by chromatography of the reaction mixture.

2-Bromo-3-amino-5,6-dimethylpyrazine 4-N-Oxide (V). A mixture of 4 g (20 mmole) of IV, 45 ml of 7% peracetic acid (40 mmole), 0.68 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was heated at 60-65° for 2.5 h, after which the precipitated inorganic salts were removed by filtration, and the solution was neutralized to pH 7 and extracted with chloroform. Removal of the chloroform gave 2.82 g (65%) of V with mp 145.5-146° (from acetone–hexane) and R_f 0.5 (dark-violet spot), which gave an intense blue coloration with $FeCl_3$. Found: Br 36.5; N 19.5%. $C_6H_8BrN_3O$. Calculated: Br 36.6; N 19.3%.

2-Methylamino-3-amino-5,6-dimethylpyrazine 4-N-Oxide (VI). A 0.5-g sample of V was heated with 5 ml of 30% aqueous solution of methylamine in 35 ml of isopropyl alcohol in an autoclave at 100° for 7 h and then at 120° for 5 h. It was then cooled and filtered to give 0.1 g of VI. The reaction solution was evaporated to dryness, and the residue was treated with a small amount of water to give another 0.13 g of VI. The overall yield of VI with mp 222-223° (dec., from alcohol) and R_f 0.53 (bright blue-violet spot), which gave an intense blue-green coloration with aqueous $FeCl_3$, was 60%. Found: C 50.4; H 7.2; N 33.3%. $C_7H_{12}N_4O$. Calculated C 50.0; H 7.2; N 33.3%.

Hydrolytic Cleavage of Imidazo[4,5-b]pyrazine Derivatives. A) A 0.2-g (1.2 mmole) sample of Ic was refluxed in 2 ml of 2.5 N NaOH for 4 h, after which the mixture was cooled and filtered to give 0.13 g (69%) of VIIIc, which, according to a mixed-melting-point determination and R_f value, was identical to VIIIc obtained from IV (see above).

B) A 0.5-g (3 mmole) sample of Ic was refluxed in 5 ml of 3 N HCl for 4 h, after which the solution was neutralized to pH 5-6 and extracted with chloroform to give 0.43 g (91%) of IXc with mp 223-224° (from ethyl acetate–methanol) and R_f 0.43 (violet spot). Found: N 27.0%. $C_7H_{11}N_3O$. Calculated: N 27.4%.

C) A 0.2-g (0.84 mmole) sample of Id was refluxed in 2 ml of 2.5 N NaOH for 2 h, after which it was worked up to give 0.18 g (94%) of VIIId with mp 144.5-145.5° (from ethyl acetate) and R_f 0.89 (bright-violet spot). Found: 24.4%. $C_{13}H_{16}N_4$. Calculated: N 27.4%.

D) A 1-g (4.2 mmole) sample of Id was refluxed in 10 ml of 20% HCl for 1.5 h, after which the solution was neutralized to pH 7 and cooled. The precipitate (0.87 g) was removed and crystallized repeatedly from methanol to give pure 2-benzylamino-3-hydroxy-5,6-dimethylpyrazine (IXd) with mp 171.5-172° (from methanol) and R_f 0.81 (bright-blue spot). Found: C 67.5; H 6.7; N 17.8%. $C_{13}H_{15}N_3O$. Calculated: C 68.0; H 6.6; N 18.3%.

E) A 0.5-g (3.4 mmole) sample of Ib was refluxed in 5 ml of 3 N HCl for 4 h, after which it was cooled to 20°, and the precipitated hydrochloride of X was removed by filtration. The precipitate was dissolved in water, and the solution was made alkaline to pH 8 and extracted with chloroform to give 0.15 g (32%) of X, which, according to the R_f value (0.34, blue-violet spot) and a mixed-melting-point determination, was identical to X obtained by the method in [2]. The acid solution remaining after the separation of the hydrochloride of X was cooled to 2°, and the resulting precipitate was removed by filtration and dissolved in water. The solution was neutralized to pH 7 and filtered to give 0.12 g (26%) of XI, which according to the R_f value (0.22, violet spot) and a mixed-melting-point determination, was identical to XI obtained by the method in [6].

Hydrolytic Cleavage of Imidazo[4,5-b]pyrazine N-Oxides. A) A 0.4-g (2 mmole) sample of IIf was refluxed in 4 ml of 60% H_2SO_4 for 1 h and 15 min, after which it was poured over ice, and the resulting solution was neutralized and extracted with chloroform to give 0.16 g (46%) of VI, which, according to its R_f value, its color reaction with $FeCl_3$, and a mixed-melting-point determination was identical to VI obtained

from V (see above). Starting IIf was detected chromatographically in the aqueous solution after extraction with chloroform.

B) A 0.2-g (1.1 mmole) sample of IIc was refluxed in 2 ml of 30% H_2SO_4 for 2 h, after which the mixture was worked up as in method A to give 0.1 g (55%) of VI.

C) A 0.4-g (2.2 mmole) sample of IIc was refluxed in 4 ml of 2.5 N NaOH for 1 h, after which the mixture was cooled and filtered to give 0.35 g (93%) of VI.

D) A 0.5-g (2.8 mmole) sample of IIIb was refluxed in 5 ml of 60% H_2SO_4 for 30 min, after which the mixture was worked up as in method A and extracted with chloroform to give 0.27 g (57%) of VII with mp 257-258° (dec., from methanol) and R_f 0.12 (blue-violet spot) that gave an intense coloration with $FeCl_3$ solution. Found: C 43.0; H 5.9%. $C_9H_9N_3O_3$. Calculated: C 42.5; H 5.9%.

Reduction of 2,3-Diamino-5,6-dimethylpyrazine 1,4-N,N-Dioxode (VII). A 0.3-g (1.8 mmole) sample of VII was hydrogenated in 5 ml of anhydrous alcohol at 20-25° in the presence of Raney nickel until 3.6 mmole of hydrogen had been absorbed. The catalyst was separated, and the solution was vacuum evaporated to dryness to give 0.24 g (96%) of X with mp 212.5-213.5, which, according to the R_f value and mixed-melting-point determination, was identical to X obtained by the method in [2].

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