SYNTHESIS AND TRANSFORMATION OF N-OXIDES OF SOME IMIDAZO[4,5-b]PYRAZINE DERIVATIVES

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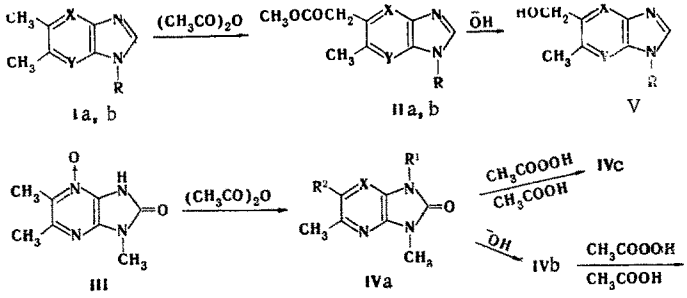
The Böckelheide reaction was accomplished with a number of imidazo[4,5-b]pyrazine N-oxides, and the N-oxidation of the resulting acetoxy(hydroxy)methyl derivatives of imidazo[4,5-b]pyrazine and 6-bromo-1-methylimidazo[4,5-b]pyrazine was studied. The hydrolytic cleavage of 6-bromo-1-methylimidazo[4,5-b]pyrazine and its 4-N-oxide was studied.

In order to synthesize acetoxy(hydroxy)methyl derivatives of imidazo[4,5-b]pyrazine and their N-oxides – analogs of N-oxides of the corresponding quinoxaline derivatives, which have high antibacterial activity [1, 2] – we investigated the possibility of realization of reactions of the Böckelheide type [3] in the imidazo[4,5-b]pyrazine N-oxide series.

We have shown that 1,5,6-trimethylimidazo[4,5-b]pyrazine 4-N-oxide (Ia) is converted to 1,6-dimethyl-5-acetoxymethylimidazo[4,5-b]pyrazine (IIa) on heating with acetic anhydride. Under the same conditions 3-acetyl-5-acetoxymethyl derivative IVa is formed from 2-hydroxy-1,5,6-trimethyl-2,3-dihydroimidazo[4,5-b]pyrazine 4-N-oxide (III). The reaction of 5,6-dimethylimidazo[4,5-b]pyrazine 4,7-N,N'-dioxide (Ib) with acetic anhydride is accompanied by considerable resinification, and only the N-oxide of the 5-acetoxymethyl derivative (IIb) was isolated from the complex mixture of reaction products.



Ia X=NO, Y=N, R=CH_3; Ib X=Y=NO, R=H; IIa X=Y=N, R=CH_3; IIb, V X=N, Y=NO, R=H; IVa X=N, R^1=$COCH_3$, R^2=CH_2OCOCH_3; IVb X=N, R^1=H, R^2=CH_2OH; IVc X=NO, R^1=H, R^2=CH_2OCOCH_3; IVd X=NO, R^1=H, R^2=CH_2OH

The corresponding hydroxymethyl derivatives (IVb and V) were obtained by treatment of IVa and IIb with alkali solutions. The N-oxidation of IVa gives a complex mixture of substances, from which only 2-oxo-1,6-dimethyl-5-acetoxymethyl-2,3-dihydroimidazo[4,5-b]pyrazine N-oxide was isolated in low yield. N-Oxide IVd was also obtained from IVb by N-oxidation. Inasmuch as we have previously shown that the N-oxidation of imidazo[4,5-b]pyrazines that contained a methyl group attached to N_1 gives the corresponding 4-N-oxides [4], structures IVc and IVd were tentatively assigned to the synthesized N-oxides.

In a continuation of our research on N-oxides of imidazo[4,5-b]pyrazine derivatives [4] we studied the N-oxidation of the previously obtained 6-bromo-1-methylimidazo[4,5-b]pyrazine (VI). In contrast to

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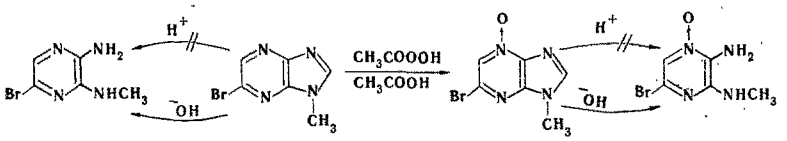
5,6-dimethylimidazo[4,5-b]pyrazine and its 2-hydroxy derivative, which form the corresponding 4,7-N,N'-dioxide relatively easily, the N-oxidation of VI proceeds with great difficulty and is accompanied by side processes. As a result of this reaction we isolated 6-bromo-1-methylimidazo[4,5-b]pyrazine N-oxide, to which structure VII was assigned, inasmuch as the N_4 atom is the most likely center of N-oxidation in VI. A shift of the signal of the 5-H proton to strong field by 0.32 ppm as compared with the 5-H signal in the spectrum of starting VI [5] is observed in the PMR spectrum of N-oxide VII, and this is characteristic for the α protons of heteroaromatic N-oxides [6, 7]. The hydrolytic cleavage of VII gave 6-bromo-3-amino-2-methylaminopyrazine 4-N-oxide (VIII), which gives the deep-blue coloration with $FeCl_3$ solution that is characteristic for N-oxides of aromatic heterocycles in which the amino group is in the α position with respect to the oxidized ring nitrogen atom [8].

It is interesting to note that, in contrast to the methyl and hydroxy derivatives of imidazo[4,5-b]pyrazine, which relatively readily undergo hydrolytic cleavage on heating with mineral acids [4], VI and its N-oxide (VII) display considerable stability on heating in acids and are cleaved to the corresponding pyrazine derivatives (IX or, respectively, VIII) only on heating in alkalis.



IX VI VII VIII

Some of the imidazo[4,5-b]pyrazines and their N-oxides have shown weak activity in vitro with respect to tuberculosis mycobacteria and pathogenic fungi.

EXPERIMENTAL METHOD

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra of acetic acid solutions were recorded with a JNM 4H-100 spectrometer with tetramethylsilane as the internal standard. Paper chromatography was carried out with a butanol–5% acetic acid (1 : 1) system and with development in UV light.

1,6-Dimethyl-5-acetoxymethylimidazo[4,5-b]pyrazine (IIa). A 0.44-g (2.5 mmole) sample of N-oxide Ia was heated in 4.4 ml of acetic anhydride at 100° for 3 h, after which the acetic anhydride was removed by distillation, and the residue was extracted with ether to give 0.27 g (50%) of acetoxy derivative IIa with mp 119-120° (from ether–methanol). Found: C 54.7; H 5.5; N 25.3%. $C_{10}H_{12}N_4O_2$. Calculated: C 54.6; H 5.5; N 25.4%.

2-Oxo-1,6-dimethyl-3-acetyl-5-acetoxymethyl-2,3-dihydroimidazo[4,5-b]pyrazine (IVa). A 1.65-g (8.5 mmole) sample of N-oxide III was refluxed in 33 ml of acetic anhydride for 25 min, after which the mixture was worked up as described above to give 0.76 g (32%) of acetoxy derivative IVa with mp 144.5-145° (from alcohol) and R_f 0.67 (bright-violet spot). IR spectrum, cm^{-1}: 1735 (broad) and 1758 (C = O). PMR spectrum, δ, ppm: 2.3 (6-CH_3), 2.84 ($COCH_3$), 2.92 (CH_3COO), 3.67 (N-CH_3), and 5.52 (CH_2). Found: C 51.8; H 5.2; N 20.2%. $C_{12}H_{14}N_4O_4$. Calculated: C 51.9; H 5.1; N 20.2%.

6-Methyl-5-acetoxymethylimidazo[4,5-b]pyrazine 7-N-Oxide (IIb). A 4.67-g (26 mmole) sample of N,N'-dioxide Ib was heated in 23 ml of acetic anhydride at 100° for 2 h, after which the acetic anhydride was removed by distillation, and the oily residue was applied to a polyethylene column filled with silica gel, and ethyl acetate–methanol (9 : 1) was passed through the column. After the mixture of solvents had risen to the top of the column, the silica gel was cut into 10 sections. Each section was extracted with methanol. Monitoring was accomplished by means of paper chromatography, and the methanol solutions from sections 6-9 were combined. The solvent was removed to give 1.5 g (29%) of 5-acetoxymethyl derivative IIb with mp 265-266° (dec., from methanol). IR spectrum, cm^{-1}: 1750 (ester C = O) and 3000-3150 (NH). PMR spectrum, δ, ppm: 3.41 (CH_2), 2.93 (CH_3COO), and 2.37 (6-CH_3). Found: C 48.5; H 4.7; N 25.0%. $C_9H_{10}N_4O_3$. Calculated: C 48.6; H 4.6; N 25.2%.

2-Oxo-1,6-dimethyl-5-hydroxymethyl-2,3-dihydroimidazo[4,5-b]pyrazine (IVb). A 0.25-g (0.9 mmole) sample of IVa was mintained in 1.5 ml of 2.5 N NaOH solution at 5-10° until it dissolved, after which the solution was filtered. A 2.5 N solution of HCl was added to the filtrate to pH 1, after which it was cooled and filtered to give 0.08 g of hydroxymethyl derivative IVb. The solution was then extracted with chloroform to give another 0.07 g of IVb for an overall yield of 0.15 g (88%) of a product with mp 251-252° (from

methanol). PMR spectrum, δ, ppm: 2.72 (6-CH_3), 3.72 (N−CH_3), and 5.22 (CH_2). Found C 49.6; H 5.0; N 28.7%. $C_{10}H_{12}N_4O_3$. Calculated: C 49.4; H 5.2; N 28.9%.

6-Methyl-5-hydroxymethylimidazo[4,5-b]pyrazine 7-N-Oxide (V). A 0.18-g (0.8 mmole) sample of 5-acetoxymethyl derivative IIb was refluxed in 2 ml of 2.5 N NaOH solution for 10 min, after which the solution was cooled, acidified to pH 2 with 2.5 N HCl solution, and worked up to give 0.14 g (96%) of a product with mp 276-277° (dec., from water). Found: C 46.7; H 4.7; N 31.2%. $C_7H_8N_4O_2$. Calculated: C 46.7; H 4.5; N 31.1%.

N-Oxidation of IVa. A mixture of 2.06 g (7.4 mmole) of acetoxy derivative IVa, 29.6 ml (40 mmole) of 10.3% peracetic acid, 0.45 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was heated at 70-82° for 20 h, after which it was filtered, and the filtrate was evaporated to one-third of its original volume. Ether was added to the condensed filtrate, and the precipitated inorganic salts were separated. The solution was air-evaporated, and the residue was recrystallized repeatedly from anhydrous alcohol to give 0.16 g (8.4%) of N-oxide IVc with mp 207-208° (dec.). IR spectrum, cm^{-1}: 1728 and 1743 (amide and ester C=O) and 3040-3200 (NH). Found: C 47.9; H 4.9%. $C_{10}H_{12}N_4O_4$. Calculated: C 47.6; H 4.8%.

N-Oxidation of IVb. A mixture of 0.43 g (1.8 mmole) of IVb, 8.3 ml (11 mmole) of 10.3% peracetic acid, 0.125 g of CH_3COONa, and 0.01 g of $Na_4P_2O_7$ was heated at 65-82° for 1 h, after which it was filtered and the filtrate was vacuum evaporated to one-third of its initial volume (at 40-50°). Ether was added to the residue, and the mixture was cooled and worked up to give 0.2 g (41%) of N-oxide IVd with mp 247-248° (dec., from alcohol). IR spectrum, cm^{-1}: 1730 (amide C=O), 2300-2700 (broad), and 3410 (NH and OH). Found: C 45.8; H 4.8; N 26.9%. $C_8H_{10}N_4O_3$. Calculated: C 45.6; H 4.8; N 26.8%.

6-Bromo-1-methylimidazo[4,5-b]pyrazine 4-N-Oxide (VII). A 3-g (14 mmole) sample of bromo derivative VI was heated with 51 ml (72 mmole) of 10.8% peracetic acid, 0.78 g of sodium acetate, and 0.01 g of $Na_4P_2O_7$ at 75-80° for 20 h, after which the mixture was filtered, and the filtrate was evaporated at 30°. The residue was treated with a mixture of methanol and ether to give 0.46 g (14%) of N-oxide VII with mp 265-266° (dec., from methanol). PMR spectrum (in $CDCl_3$), δ, ppm: 3.93 (N−CH_3), 8.01 (2-H), and 8.29 (5-H). Found: C 31.4; H 2.2; N 24.3%. $C_6H_5BrN_4O$. Calculated: C 31.5; H 2.2; N 24.5%.

Hydrolytic Cleavage of 6-Bromo-1-methylimidazo[4,5-b]pyrazine (VI). A 0.1-g (0.47 mmole) sample of VI was heated in 1.5 ml of 2.5 N NaOH solution at 50-60° for 4 h, after which it was cooled and filtered to give 0.06 g (63%) of pyrazine IX, which, with respect to its melting point and R_f value, was identical to IX previously obtained by a different method [5].

Hydrolytic Cleavage of N-Oxide VII. The hydrolytic cleavage of VII was carried out as described above to give 0.41 g (86%) of 6-bromo-3-amino-2-methylaminopyrazine 4-N-oxide (VIII) with mp 217-218° (dec., from alcohol). Found: Br 36.0; N 25.4%. $C_5H_7BrN_4O$. Calculated: Br 36.4; N 25.6%.

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