PYRAZINES AND THEIR N-OXIDES

II. 2-Aminopyrazine N-Oxide*

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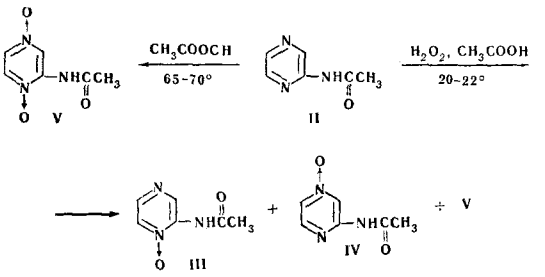
Two isomeric mono-N-oxides of 2-aminopyrazine and the 1,4-di-N-oxide have been synthesized. A marked fall in the capacity of these compounds for nucleophilic exchange reactions and for rearrangements in acid and alkaline media has been found, which distinguishes them from the corresponding N-oxides of 2-aminoquinoxaline.

Continuing our investigations of the chemical and biological properties of N-oxides of the pyrazine and quinoxaline series, we undertook the synthesis of N-oxides of 2-aminopyrazines. It has been shown previously that when 2-acetylaminoquinoxaline (I) is oxidized with perhydrol in acetic acid or with a 10% solution of peracetic acid (in a ratio of 1 mole : 1 mole) at 20–25° C, the main products are the 1- and 4-mono-N-oxides of compound I, together with a small amount of the 1,4-di-N-oxide of I [1].

When 2-acetylaminopyrazine (II) was oxidized under the same conditions, a mixture of substances was obtained in which the following were detected by paper chromatography in the butanol-5% acetic acid system: the initial compound II, the product of its saponification, 2-aminopyrazine, and two substances with R_f 0.17–0.18 (dark violet spot in UV) and with R_f 0.45–0.46 (violet spot in UV). The compound with R_f 0.45–0.46 was isolated from the reaction mixture and freed from contamination with the compound having R_f 0.17–0.18 by repeated recrystallization. Its elementary composition corresponded to a mono-N-oxide of compound II, and its melting point did not change on repeated crystallizations. In spite of all these data indicating the uniformity of the reaction product obtained, a consideration of the PMR spectrum showed that it was not an individual substance. It was natural to assume that this compound was a eutectic mixture of the two isomeric mono-N-oxides of compound II. The formation of such a type of difficultly-separable mixtures of isomeric mono-N-oxides has been observed previously in the oxidation of 2-methylpyrazine [2]. After a preliminary selection of the system by thin-layer chromatography on plates, the mixture of the products of the oxidation of compound II was separated by sorption chromatography on Al_2O_3. In this way we in fact isolated in the pure state the 1-N-oxide of compound II (III) (24–25%), the 4-N-oxide of compound II (IV) (21–22%) and a substance V with R_f 0.17–0.18 (8.1%), the elementary composition of which corresponded to the 1,4-di-N-oxide of compound II.



The structure of the mono-N-oxides III and IV so obtained were established by their conversion into the corresponding mono-N-oxides of 2-aminopyrazine VI and VII and by a consideration of their PMR spectra. The PMR spectra were measured on a JNM4H100 spectrometer (working frequency 100 MHz) in D_2O using dioxane as internal standard. The chemical shifts are given relative to tetramethylsilane (TMS) in the σ scale (dioxane relative to TMS—3.7 ppm). The spectrum of each of the N-oxides VI and VII considered exhibited three signals corresponding to the signals of the protons of the ring of a pyrazine or its N-oxide [3]. In the spectrum of compound VI, the H_6 signal was represented by a doublet at 7.76 ppm with a spin-spin coupling constant $J_{6,5} = 4.3$ Hz. The H_3 signal was represented by a peak at 8.23 ppm feebly split through meta spin-spin coupling with H_5 ($J_{5,3}$ 0.6 Hz), and H_5 appeared in the 8.02 ppm region in the form of a quartet due to interaction with H_6 and H_3. In the spectrum of compound VII, the H_6 and H_3 signals appeared in the form of doublets at 7.94 ppm and 7.65 ppm, respectively ($J_{6,5} = 4.3$ Hz; $J_{3,5} = 1.5$ Hz). The H_5 signal appeared in the 7.54 ppm region in the form of a quartet. Thus, the presence in the molecule of compound VII of a $N_{(4)} \rightarrow O$ group was shown by the value of the meta spin-spin coupling constant $J_{3,5}$ of 0.6 Hz to 1.5 Hz, which corresponded to the results of other authors [4].

On the basis of the information obtained in a consideration of the PMR spectra, compound VI was assigned the structure of the 1-N-oxide of 2-aminopyrazine and compound VII that of the 4-N-oxide of 2-aminopyrazine. This conclusion was confirmed by the fact that solutions of the mono-N-oxide VI gave with $FeCl_3$ the deep blue coloration that is characteristic for N-oxides of nitrogen-containing aromatic heterocycles in which the $N \rightarrow O$ and NH_2 groups are adjacent to one another. As was to be expected, compound VII did not give a color reaction with $FeCl_3$.

In order to obtain the di-N-oxide of compound II, the latter was subjected to oxidation under more se-

*For part I, see [5].

vere conditions, namely with an excess of peracetic acid solution at 65–70° C. The yield of the pure di-N-oxide of compound II was 50% of theoretical. It was identical with substance V formed as an impurity in the synthesis of the mono-N-oxides III and IV. Hydrolysis of the acetyl group of compound V formed the 1, 4-di-N-oxide of 2-aminopyrazine (VIII), which gave with $FeCl_3$ a color reaction which is unusual for N-oxides of heterocyclic o-amino derivatives: violet-red instead of blue-green or blue. The structure of this compound was confirmed by the PMR spectrum, which exhibited three signals from the protons of the ring: H_3, at 8.07 ppm (doublet, $J_{3,5} = 2.5$ Hz); H_5, at 7.67 ppm (quartet, $J_{5,6} = 6$ Hz, $J_{5,3} = 2.5$ Hz); and H_6, at 8.17 ppm (doublet, $J_{6,5} = 6$ Hz).

It has been shown previously that when the 4-N-oxide and the 1, 4-di-N-oxide of 2-aminoquinoxaline are heated with dilute hydrochloric acid, they first undergo a rearrangement giving 2-amino-3-hydroxyquinoxaline and the 1-N-oxide of 2-amino-3-hydroxyquinoxaline while, on further heating under the same conditions, hydrolysis of the amino group takes place with the formation of 2, 3-dihydroxyquinoxaline and the 1-N-oxide of 2, 3-dihydroxyquinoxaline, respectively [1]. Attempts to effect the analogous reactions with the corresponding N-oxides of pyrazine showed the considerable stability of these compounds. Thus, after the di-N-oxide VIII had been boiled in 2.5 N hydrochloric acid for 10 hr it was recovered almost unchanged. Under analogous conditions, the mono-N-oxides VI and VII were likewise scarcely changed; the bulk of the starting materials was recovered and the solution was found to contain some deoxidation product, 2-aminopyrazine, and small amounts of two unknown substances appearing on paper chromatograms in the form of very weak spots (in all cases, the paper chromatography was carried out in the butanol–5% acetic acid system). Alkaline solutions of the di-N-oxide VIII rapidly darkened on gentle heating, and chromatography of the reaction solution on paper showed the presence of an extremely complex mixture of products, which indicated far-reaching conversion leading to the decomposition of the molecule and the polymerization of the fragments formed. So far as concerns the mono-N-oxides VI and VII, they were stable in an alkaline medium and underwent practically no change on being boiled with 2.5 N NaOH for 1 hr 30 min. In contrast to this, an analog of the mono-N-oxide VI—the 1-N-oxide of 2-aminoquinoxaline—was readily converted, by being heated in dilute alkali, into the corresponding hydroxy derivative—the 1-N-oxide of 2-hydroxyquinoxaline [1].

Thus, while previously we observed only some lowering of the reactivity of the α-methyl groups of the N-oxides of methylpyrazines [5] in condensation reactions as compared with the α-methyl groups of the N-oxides of the corresponding quinoxaline derivatives, in a study of the rearrangements of the N-oxides of 2-aminopyrazine in the presence of mineral acids and of the hydrolysis reactions of the amino group, a marked lowering of the reactivity of the pyrazine N-oxides to nucleophilic substitutions and to oxidation-reduction reactions was found. The considerably higher reactivity of the N-oxides of 2-aminoquinoxaline in relation to nucleophilic substitutions, in comparison with the corresponding pyrazine derivatives, may be connected with the greater capacity for polarization of these compounds at the moment of reaction thanks to the presence of the condensed benzene ring.

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EXPERIMENTAL

Oxidation of 2-acetylaminopyrazine II. 1) A mixture of 3 g (0.022 mole) of **II**, 15 ml of glacial acetic acid, 3.09 ml of acetic anhydride, and 3.72 ml (0.033 mole) of 30% H_2O_2 was kept at room temperature for 48 hr. The amount of H_2O_2 consumed was 1.0132 g (0.03 mole). The H_2O_2 that had not reacted was decomposed with an aqueous solution of Na_2SO_3 (1.7 g) at a temperature not exceeding 20° C. The resulting solution was evaporated to dryness and the dried residue was extracted with hot $CHCl_3$. After the chloroform had been distilled off, the solid residue (3.02 g) was recrystallized from 96% ethanol to give 2 g of a mixture of the 1-N-oxide of 2-acetylaminopyrazine (**III**) and the 4-N-oxide of 2-acetylaminopyrazine (**IV**) together with a small amount of the 1,4-di-N-oxide of 2-acetylaminopyrazine (**V**). The following compounds were found in the ethanolic mother liquor on paper chromatography in the butanol–5% acetic acid system (spots revealed in UV light): **II**, R_f 0.62–0.63, dark violet spot; 2-aminopyrazine, R_f 0.56–0.57, bright violet spot; and **V**, R_f 0.17–0.18 and the 1,4-di-N-oxide of 2-aminopyrazine (**VIII**), R_f 0.07 (dark violet spots). The mixture of N-oxides (2 g) was separated on a column containing 200 g of Al_2O_3. The substance was added in the form of a suspension in chloroform. The process was followed by thin-layer chromatography on plates of Al_2O_3 in the ethyl acetate–5% methanol system. Elution was first carried out with chloroform, until dark violet spots with R_f 0.79–0.80 were found on the chromatographic plates. These chloroform fractions yielded 0.8 g of **III**, yield 24.5%, mp 220–221° C (from 96% ethanol). Found, %: C 47.17; H 4.58; N 27.47. Calculated for $C_6H_7N_3O_2$, %: C 47.1; H 4.61; N 27.45. Then elution was continued with ethyl acetate. After the ethyl acetate had been distilled off, these fractions yielded 0.6 g (21.5%) of **IV**, mp 256–257° C (from 96% ethanol), R_f 0.56–0.57, dark violet spot in UV light on a plate covered with Al_2O_3. Found, %: C 47.52; H 4.50; N 27.59. Calculated for $C_6H_7N_3O_2$, %: C 47.1; H 4.61; N 27.45. The last fractions, eluted with methanol, yielded 0.3 g (8.1%) of **V**.

2) A mixture of 2 g (0.015 mole) of **II**, 39 ml (0.045 mole) of 8.5% peracetic acid, 0.589 g of CH_3COONa, and 0.001 g of $Na_4P_2O_7$ was heated at 65–70° C for 18 hr. The amount of peracetic acid that reacted was 2.07 g (0.027 mole). The acid that had not reacted was decomposed with a saturated aqueous solution of Na_2SO_3 (3 g) at a temperature not above 20° C. The reaction mixture was evaporated to dryness. The dry residue was extracted with hot $CHCl_3$. After the evaporation of the $CHCl_3$, the solid residue (2.32 g) was recrystallized from 96% ethanol to give 1.12 g (45.4%) of **V**, mp 215.5–216° C (decomp., from 96% ethanol). Found, %: C 42.64; H 4.21; N 25.06. Calculated for $C_6H_7N_3O_3$, %: C 42.6; H 4.17; N 24.85.

2-Aminopyrazine 1-N-oxide (VI). A mixture of 0.4 g (0.003 mole) of **III** and 1.54 ml (0.004 mole) of 2.5 N HCl was heated at 105° C for 10 min. The acid solution was neutralized with saturated aqueous sodium hydrogen carbonate to pH 7 and was evaporated to dryness in vacuum. The dry residue was extracted with hot $CHCl_3$. Evaporation of the $CHCl_3$ yielded 0.22 g (76%) of **VI**, mp 186–187° C (from absolute ethanol), giving an intense blue coloration with aqueous $FeCl_3$; R_f 0.31–0.32 on paper chromatography (violet spot in UV light). Found, %: C 43.45; H 4.66; N 37.20. Calculated for $C_4H_5N_3O$, %: C 43.2; H 4.54; N 37.78.

2-Aminopyrazine 4-N-oxide (VII). Compound **IV** was saponified under the same conditions as **III**. After the evaporation of the $CHCl_3$

in vacuum, 69% of **VII** with mp 177.5–178° C (from ethanol) was obtained; it gave no coloration with aqueous $FeCl_3$; R_f 0.27–0.28 on paper chromatography (light blue spot with a dark center in UV light). Found, %: C 43.30; H 4.70; N 37.38%. Calculated for $C_4H_5N_3O_2$, %: C 43.2; H 4.54; N 37.78%.

2-Aminopyrazine 1,4-di-N-oxide (VIII). A mixture of 0.6 g (0.0036 mole) of **V** and 2.4 ml (0.006 mole) of 2.5 N HCl was heated at 100–105° C for 10 min. Then it was cooled and brought to pH 4.5–5 with 2.5 N NaOH, and 0.38 g of **VIII** (84.5%) was filtered off; mp 265–266° C (decomp., from 96% ethanol), R_f 0.07 on paper chromatography (dark violet spot in UV light), forming a violet-red coloration with aqueous $FeCl_3$. Found, %: C 37.54; H 3.98; N 32.71%. Calculated for $C_4H_5N_3O_2$, %: C 37.75; H 3.97; N 33.05%.

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