was extracted into boiling hexane. Partial evaporation of the hexane and cooling in ice yielded the product which was crystallized from hexane. The product obtained in each case was as follows: from **3**, 3,6-dimethoxypyridazine, 74%, m.p. 107–108°, lit.[23] m.p. 108°; from **4**, 3-methoxy-6-methylthiopyridazine, 89%, m.p. 86°, lit.[24] m.p. 87°; from **9**, 3-chloro-6-methoxypyridazine (**3**), 78%, m.p. 90–91°, lit.[17] m.p. 90.5°. From **2**, 3-methoxy-6-methylpyridazine hydrochloride was obtained by addition of dry hydrogen chloride to a solution of the reaction product in hexane, m.p. 130–132°, lit.[25] m.p. 131–132°.

Acknowledgment.—One of the authors (J. H. M. H.) wishes to thank the College Center of the Finger Lakes for a grant that helped support this work and the National Science Foundation Research Participation for College Teachers Program (summer, 1962) at Oregon State University for equipment.

[23] J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

[24] Noboru Takahayashi, *J. Pharm. Soc. Japan*, **75**, 778 (1955).

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Amino Derivatives of Pyrazine N-Oxides[1]

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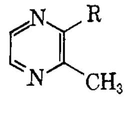
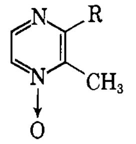
Received December 26, 1963

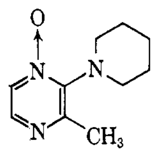
In connection with a program of synthesis of a variety of pyrazine derivatives, we had occasion to prepare several pyrazine N-oxides. The treatment of 2-chloro-3-methylpyrazine[2] (Ia) with hydrogen peroxide afforded the N-oxide IIa,[3] melting at 74–76°, in fair yield. IIa reacted exothermically with piperidine to give a crystalline derivative (IIb) melting at 98–100°. The latter showed a very slight basicity as reflected in the low ionophoretic mobility in 5 *M* acetic acid. The piperidino derivative IIb was smoothly deoxygenated by phosphorus trichloride to give 2-piperidino-3-methylpyrazine (Ib). The properties of the free base and its hydrogen sulfate salt were found to be identical with authentic materials prepared by a different route.[4] This shows that the N-oxide obtained from commercial 2-chloro-3-methylpyrazine has structure IIa and is not derived from 2-chloro-6-methylpyrazine known to be present in significant amount in commercial Ia.[4] Similarly, reaction of the N-oxide IIa with dimethylamine resulted in dimethylamino-3-methylpyrazine N-oxide.



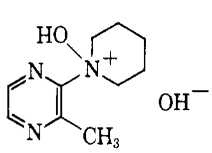
Ia, R = Cl
b, R = 1-piperidyl



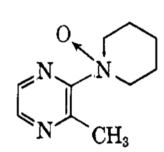
IIa, R = Cl
b, R = 1-piperidyl



III



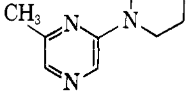
IV



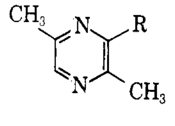
V

When 2-piperidino-3-methylpyrazine was treated with hydrogen peroxide in acetic or formic acid, two products were formed. One of these, obtained in very small yield, melted at 47–49° and showed an ionophoretic mobility similar to IIb. Elemental analyses were in good agreement with values calculated for an N-oxide isomeric with IIb. Since both the ultraviolet and infrared spectra differed widely from that of IIb, structure III was assigned. The bulk of the material obtained from the reaction mixture was a compound much less soluble in ligroin than III and with a high ionophoretic mobility. Elemental analyses were in agreement with a hydrate of a structure isomeric with IIb or III. Aqueous solutions showed a distinctly alkaline reaction. The ultraviolet spectrum was quite different from either IIb or III and was very similar to that of 2-methylpyrazine. It is well known[5,6] that, although the ultraviolet spectra of aniline and benzene differ greatly, the spectrum of the anilinium ion is very much like that of benzene. The structure of the compound in question must then be IV in which the "onium" center prevents participation of the amino nitrogen in resonance with the ring. Dehydration of IV to V by sublimation was not quite complete as the elemental analysis showed a small residual water content. The strong tendency for V to exist as the hydrate IV is characteristic of aliphatic-type N-oxides.[7]

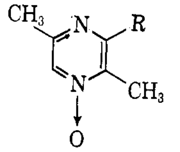
The oxidation of 2-piperidino-6-methylpyrazine (VI) with hydrogen peroxide in formic acid gave a much more complicated reaction mixture than in the case of the isomeric Ib. However, on the basis of ionophoretic data it is clear that the compound to which structure III has been assigned did not arise from VI, conceivably present as a contaminant in starting material Ib.



VI



VIIa, R = Cl
b, R = N(CH$_3$)$_2$



VIIIa, R = Cl
b, R = N(CH$_3$)$_2$

In the 2,5-dimethylpyrazine series, 2-chloro-3,6-dimethylpyrazine (VIIa) was converted to the oxide VIIIa[8] and the latter to the dimethylamino derivative VIIIb. The ultraviolet spectrum of VIIIb was very similar to that of IIb but unlike that of III. In boiling acetic anhydride, VIIIb was converted to the ester IXa which was not isolated but was saponified directly to the alcohol IXb. Structure Xc is excluded because this compound was prepared as described below and shown

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[1] Presented at the 144th Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

[2] Wyandotte Chemicals Corp., Wyandotte, Mich.

[3] B. Klein, N. E. Hetman, and M. E. O'Donnell, *J. Org. Chem.*, **28**, 1682 (1963).

[4] W. B. Lutz, S. Lazarus, S. Klutchko, and R. I. Meltzer, *ibid.*, **29**, 415 (1964).

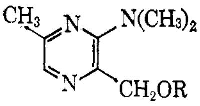
[5] G. W. H. Cheeseman, *J. Chem. Soc.*, 269 (1960).

[6] D. J. Brown, E. Hoerger, and S. F. Mason, *ibid.*, 4053 (1955).

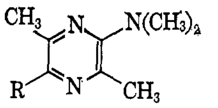
[7] N. V. Sidgewick, "The Organic Chemistry of Nitrogen," New Ed., Oxford University Press, London, 1933, p. 166.

[8] R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1859 (1948).

to be quite unlike IXb. Furthermore, Klein[9] has shown that in the pyrazine series, rearrangement of an N-oxide will not occur unless a methyl group is *ortho* to the oxide function. The treatment of VIIIb with phosphorus oxychloride in benzene afforded 2-dimethylamino-5-chloro-3,6-dimethylpyrazine Xa in good yield. It was subsequently discovered that the same compound could also be obtained by the direct chlorination of VIIb in chloroform.



IXa, R = acetyl
b, R = H



Xa, R = Cl
b, R = OCH_3
c, R = OH
d, R = $N(CH_3)_2$

The chlorine atom of Xa was found to be relatively unreactive, but, under forcing conditions, nucleophilic substitution products could be obtained. With sodium methoxide, a 23% yield of the methyl ether Xb was obtained as the hydrochloride and, with dimethylamine, 2,5-bis(dimethylamino)-3,6-dimethylpyrazine (Xd) was obtained in 32% yield as the dihydrochloride. The hydrochloride of Xb lost methyl chloride at the melting point to give 2-dimethylamino-3,6-dimethyl-5-hydroxypyrazine (Xc). On a preparative scale, the demethylation could be carried out with concentrated hydrochloric acid. The ultraviolet spectrum of Xc showed a continuous shift in basic, neutral, and acidic aqueous media in accord with its expected amphoteric properties.

Experimental[10]

2-Chloro-3-methylpyrazine 4-Oxide (IIa).—A solution of partially purified commercial 2-chloro-3-methylpyrazine[4] in 300 ml. of acetic acid was treated with 400 ml. of 30% hydrogen peroxide at 65–70° for 8 hr. After standing at room temperature overnight most of the acetic acid and excess hydrogen peroxide were removed on a rotary evaporator at 25° (1 mm.). Water (200 ml.) was added to the residue and similarly removed. The residue was again dissolved in water containing ice and the pH was adjusted to 8 with potassium carbonate. The separated white solid was taken up in chloroform, and the solution was dried over potassium carbonate. The residue, after removal of chloroform, was triturated with petroleum ether (b.p. 30–60°). The resulting crystals on recrystallization from 1:9 benzene–ligroin (b.p. 65–70°) gave a 37% yield of product melting at 74–76°, lit.[3] m.p. 69–71.5°; $\lambda_{\max}^{1\,N\,\mathrm{HCl}}$ 223 mμ (log ϵ 4.15) and 265 (4.03).

Anal. Calcd. for $C_5H_5ClN_2O$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.58; H, 3.64; N, 19.58.

2-Piperidino-3-methylpyrazine 4-Oxide (IIb) **and 2-Dimethylamino-3-methylpyrazine 4-Oxide.**—A mixture of 2-chloro-3-methylpyrazine 4-oxide, 5.9 g. (0.041 mole), and 100 ml. of piperidine was kept at reflux for 8 hr. The mixture was cooled, piperidine hydrochloride was removed by filtration, and the solvent was removed on a rotary evaporator. The yellow residue was dissolved in 25 ml. of warm benzene, decolorized with charcoal, and diluted with 50 ml. of petroleum ether. White crystals separated on cooling. The product weighed 6.4 g. (81%), m.p. 98–100°. Recrystallization from ligroin afforded analytically pure material with the same melting point.

2-Dimethylamino-3-methylpyrazine 4-oxide was prepared by keeping a solution of 14.5 g. of the chloro N-oxide IIa in 50 ml. of dimethylamine in a sealed tube for 2 days at room temperature. Work-up similar to the above afforded 13.1 g. (86%) of white crystals, m.p. 87–90°. Recrystallization from ligroin gave analytically pure material melting at 89–91°; $\lambda_{\max}^{1\,N\,\mathrm{HCl}}$ 217 mμ (log ϵ 3.83), 256 (4.29), and 365 (3.80).

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.33; H, 8.10; N, 21.64.

Deoxygenation of 2-Piperidino-3-methylpyrazine 4-Oxide (IIb).—To 15 ml. of phosphorus trichloride was added 0.5 g. of 2-piperidino-3-methylpyrazine 4-oxide. A vigorous exothermic reaction ensued, but no attempt to control the temperature was made. After 15 min., excess phosphorus trichloride was removed *in vacuo* and the residue was treated with 15% potassium carbonate. The colorless oil which separated was extracted with 100 ml. of ether. The extract was washed with 15 ml. of water and dried over magnesium sulfate. The filtered solution was then evaporated to give 0.4 g. (89%) of a colorless oil. A Beilstein test for halogen was negative and the infrared spectrum was identical with the spectrum of 2-piperidino-3-methylpyrazine.[4]

The sulfate prepared from this base melted at 132–134°, as did a mixture with authentic sulfate.[4] The infrared spectra were also identical.

1-Hydroxy-1-(3-methyl-2-pyrazinyl)piperidinium Hydroxide (IV).—A mixture of 20.1 g. (0.11 mole) of 2-methyl-3-piperidinopyrazine, 14 ml. (0.22 mole) of 30% hydrogen peroxide, and 45 ml. of formic acid was allowed to stand at room temperature for 4 days. An additional 7 ml. of hydrogen peroxide was added on the third day. The mixture was made strongly basic with 10 *M* potassium hydroxide and extracted with chloroform. The extract was dried over potassium carbonate and concentrated on a rotating evaporator. The resulting pasty solid was treated with ligroin (b.p. 65–70°). The insoluble portion was washed with ligroin to give 18 g. (84%) of a white solid, m.p. 70–86°. After recrystallization from ethyl acetate and exposure to moist air, the product melted at 94–97°; $\lambda_{\max}^{1\,N\,\mathrm{HCl}}$ 263 mμ (log ϵ 3.81), 266 (3.81), and 291 (3.06).

Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.84; H, 8.11; N, 19.89. Found: C, 56.67; H, 8.25; N, 19.75.

2-Piperidino-3-methylpyrazine 1-Oxide (III).—Evaporation of the ligroin filtrate from the above preparation gave a white crystalline solid, m.p. 50–52°. After sublimation at 0.02 mm., the product weighed 0.2 g. (1%) and melted at 47–49°; $\lambda_{\max}^{1\,N\,\mathrm{HCl}}$ 221 mμ (log ϵ 3.81), 295 (3.53), and 325 (3.53); $\lambda_{\min}^{1\,N\,\mathrm{HCl}}$ 308 mμ (log ϵ 3.40). The material exhibited no tendency to hydrate, and had a very low ionophoretic mobility; the infrared and ultraviolet spectra were found to be quite different from that of the isomeric IIb.

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.04; H, 8.11; N, 21.69.

Preparation of 2-Dimethylamino-3-hydroxymethyl-6-methylpyrazine Hydrochloride (**IXb**).—A solution of 8.0 g. (0.048 mole) of 2-dimethylamino-3,6-dimethylpyrazine 4-oxide in 25 ml. acetic anhydride was maintained at reflux for 2 hr. and stripped of acetic anhydride; the crude ester was dissolved in 200 ml. of methanol. The solution was treated with 80 ml. of 10 *M* potassium hydroxide and maintained at reflux for 15 min. Water (200 ml.) was added and traces of dark, undissolved material were removed by filtration. Removal of most of the methanol gave more dark tar which was removed by decantation. Potassium carbonate, 100 g., was then added and the resulting oil was extracted with 1 l. of ether. The ether solution was treated with charcoal and anhydrous potassium carbonate and filtered. The light yellow filtrate was treated with hydrogen chloride to give a greenish, tacky salt which soon crystallized. The ether was decanted and the residue was washed several times with ether to give 3.5 g. of hygroscopic yellow solid.

Recrystallization from 25 ml. of 2-propanol afforded 1.5 g. (15%) of light yellow green solid, m.p. 135–138°.

An analytical sample was prepared by recrystallization from 2-propanol; m.p. 141–142°; $\lambda_{\max}$ (hydrochloride in water) 239 mμ (log ϵ 3.74), 260 (3.01), and 318 (3.91).

Anal. Calcd. for $C_8H_{13}N_3O \cdot HCl$: C, 47.17; H, 6.93; N, 20.63. Found: C, 47.43; H, 7.11; N, 20.70.

2-Dimethylamino-5-chloro-3,6-dimethylpyrazine Hydrochloride (Xa). Method A.—Chlorine was bubbled into a stirred solution of 15.1 g. (0.1 mole) of 2-dimethylamino-3,6-dimethyl-

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[9] B. Klein, J. Berkowitz, and N. E. Hetman, *J. Org. Chem.*, **26**, 126 (1961).

[10] Infrared spectra were run on a Baird 455 spectrograph, and ultraviolet spectra were run on a Beckman DK-1. Melting points were taken in capillaries using Anschutz thermometers in a Hershberg apparatus and are therefore corrected. Ionophoreses were run in 5 *M* acetic acid on Whatman No. 1 paper at *ca.* 30 v./cm. N.m.r. spectra were run on a Varian A-60 with tetramethylsilane as standard.

pyrazine[11] in 200 ml. of chloroform. The temperature rose to near the boiling point, and the color became yellow, then yellow-brown, and finally light yellow again. The chlorine was passed in at a moderate rate for a total of 0.5 hr. Most of the chloroform was removed and 150 ml. of ether was added. The light yellow hygroscopic solid that separated was filtered and washed with ether.

Recrystallization was effected by dissolving the solid in 150 ml. of hot acetonitrile and adding ether until turbid. Crystals quickly separated and were filtered and washed with 1:1 acetonitrile–ether. The almost white crystals weighed 8.8 g., m.p. 155–157°; $\lambda_{\max}$ (hydrochloride in ethanol) 260 mμ (log ϵ 4.05) and 332 (3.76). A second crop weighed 1.5 g., m.p. 150–153°, to give a total of 10.2 g. (45.9%).[12]

Anal. Calcd. for $C_8H_{12}ClN_3{\cdot}HCl$: C, 43.26; H, 5.90; N, 18.92. Found: C, 43.17; H, 6.16; N, 18.64.

In another run using prolonged reaction time and increased rate of chlorine addition, a sparingly soluble, weakly basic polychlorination reaction product was obtained in 20% yield. Two recrystallizations from 2-propanol afforded material of constant melting point (113–115°). The analysis corresponded fairly closely to a tetrachloro derivative. Only three halogens could be replaced by silver nitrate in ethanol. N.m.r. studies showed proton resonances at 2.63 and 3.08 p.p.m., with the integrated intensities being in the proportion 1:2, respectively. The above data are consistent with a compound in which three of the chlorines are located on one methyl group and one chlorine is on the ring.

Anal. Calcd. for $C_8H_9Cl_4N$: C, 33.25; H, 3.14; N, 49.08. Found: C, 33.54; H, 3.38; N, 48.60.

2-Dimethylamino-5-chloro-3,6-dimethylpyrazine Hydrochloride (Xa). Method B.—A solution of 5.1 g. (0.03 mole) af 2-dimethylamino-3,6-dimethylpyrazine 4-oxide,[13] 100 ml. of benzene, and 15 ml. of phosphorus oxychloride was maintained at reflux for 15 min. The reddish solution was freed of benzene and most of the excess phosphorous oxychloride. On the addition of 200 ml. of ether to the viscous residue, tan crystals gradually formed. The solid was filtered, washed with 20 ml. of ether, and dried in a vacuum desiccator to give 2.5 g. (37.5%) of white crystals, m.p. 149–152°.

Recrystallization from acetonitrile–ether afforded an analytical sample melting at 153–154°. The infrared spectrum was identical with that of the product obtained by direct chlorination.

2-Dimethylamino-5-methoxy-3,6-dimethylpyrazine Hydrochloride (Xb).—A solution of 0.06 mole of sodium methoxide and 5.55 g. (0.0297 mole) of 2-dimethylamino-5-chloro-3,6-dimethylpyrazine in 50 ml. of methanol was heated in a Carius tube at 125° for 18 hr. Sodium chloride was removed by filtration and the solvent was removed on a rotary evaporator. Water was added and the separated oil was extracted into ether. The dried ($MgSO_4$) yellow-green solution was treated with dry hydrogen chloride to give a yellow, partly crystalline solid. This was filtered and washed with 20 ml. of ether to give 4.4 g. of a hygroscopic solid.

Recrystallization from 25 ml. of hot ethyl acetate gave 1.5 g. (23.3%) of light yellow crystals melting at 128° with bubbling and resolidification and remelting at 232–234°. Further recrystallization from ethyl acetate gave a product which melted at 154–156° and resolidified and remelted at 232–234°.

Anal. Calcd. for $C_9H_{15}N_3O{\cdot}HCl$: C, 49.65; H, 7.41; N, 19.30. Found: C, 49.67; H, 7.67; N, 19.17.

2-Dimethylamino-5-hydroxy-3,6-dimethylpyrazine Hydrochloride (Xc).—A solution of 8.0 g. (0.0398 mole) of 2-dimethylamino-5-methoxy-3,6-dimethylpyrazine hydrochloride in 100 ml. of concentrated hydrochloric acid was maintained at reflux for 3 hr. and evaporated to dryness on a rotary evaporator. The remaining crude brown solid was sublimed at 140° (0.01 mm.) to give 4.5 g. (56%) of orange sublimate, m.p. 225–230°.

Recrystallization from 100 ml. of ethyl acetate gave 3.2 g. of a light orange solid, m.p. 235–240°; $\lambda_{\max}^{H_2O}$ 230 mμ (log ϵ 3.94) and 323 (3.76). Infrared absorption of a mull showed strong bands at 1636 and 1684 cm.$^{-1}$, indicating that the material exists largely as a lactam.

Anal. Calcd. for $C_8H_{13}N_3O{\cdot}HCl$: C, 47.17; H, 6.93; N, 17.41. Found: C, 47.28; H, 7.01; N, 17.40.

2,5-Bis(dimethylamino)-3,6-dimethylpyrazine Dihydrochloride (Xd).—A mixture of 11.1 g. (0.05 mole) of 2-dimethylamino-5-chloro-3,6-dimethylpyrazine and 50 ml. of liquid dimethylamine was heated in a steel bomb for 18 hr. at 200°. The solvent was removed. The oily residue was treated with 50 ml. of water and 100 ml. of 50% potassium carbonate and extracted with 800 ml. of ether. The dried (K_2CO_3) solution was filtered and the ether was evaporated to give 3.4 g. of a light yellow oil. This was dissolved in 35 ml. of 2-propanol and treated with dry hydrogen chloride. The light yellow solid was filtered and washed with 2-propanol and ether to give 4.2 g. (32%) of white solid, m.p. 173–175° dec.

Recrystallization from ethanol–ether (1:1) afforded 3.9 g. of analytically pure material, m.p. 176–178°; $\lambda_{\max}$ (hydrochloride in ethanol) 263 mμ (log ϵ 4.03) and 337 (3.77).

Anal. Calcd. for $C_{10}H_{18}N_4.2HCl$: C, 44.95; H, 7.55; N, 20.97. Found: C, 45.06; H, 7.84; N, 20.74.

Acknowledgment.—We wish to acknowledge the services of the Analytical and Physical Chemistry Section, under the supervision of Mr. Arnold D. Lewis, for physical analytical data. In particular we want to thank Mr. Thomas Wilderman, Mrs. Unni Zeek, and Miss Awilda Calenti for microanalyses; Mrs. Barbara Kane, Mr. Robert Puchalski, and Mr. Joseph Brooks for infrared and ultraviolet spectra and interpretations; and Miss Marianne Garofalo for gas–liquid chromatograms. The technical assistance of Mr. Jerry Cetenko and Mr. George Conrad is also gratefully acknowledged.

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(11) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

(12) A 70% crude yield was subsequently obtained by using a solution of chlorine (slight excess) in chloroform and maintaining the temperature at 35°.

(13) Prepared similarly to IIb, this material melted at 89–91°; $\lambda_{\max}^{1\,N\ HCl}$ 212 mμ, (log ϵ 3.89), 252 (4.30), and 358 (3.78). *Anal.* Calcd. for $C_7H_{11}N_3O$: C, 54.88; H, 7.24; N, 27.43. Found: C, 55.00; H, 7.53; N, 27.54.

6-Cyano-1,2,5,6-tetrahydropyridines in the Preparation of 1,2-Dihydropyridines. Tautomerism of the Dienes

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Received December 6, 1963

In the study of a 1,2-dihydropyridine for use in the synthesis of a β-benzomorphan, rearrangements leading to both a *cis*- and *trans*-2,3-dialkyldihydropyridine were encountered.[1] It was demonstrated that the *cis*-dialkylimonium salt was formed by stepwise migration of double bonds, whereas the *trans* isomer probably resulted from a concerted rearrangement of the ammonium salt. This note presents other examples of stepwise rearrangements in 1,2-dihydropyridine systems together with another example of control of the 2,3-dialkyl steric relationship. Perhaps of more general interest is a description of the use of the cyano as a protecting group in the preparation of 1,2-dihydropyridine bases by both the Grignard and borohydride reagents.

Recent work with the borohydride reagent on N-alkylpyridines suggests that, after the initial dihydro stage is reached, further reduction depends on the tautomerism of an α,β double bond to the imonium form and that unless this transformation is inhibited

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(1) E. M. Fry, *J. Org. Chem.*, **28**, 1869 (1963).