using a 3*M* excess of sodium ethoxide in absolute ethanol as described in E. These two ethers are listed in Table I, together with the pertinent analytical and physical data.

K. *2,6-Bispyrazinylmethyl diethyl ether* (XVI). The procedure was the same as in E, in which 7.0 g. (0.036 mole) of 2,6-bis(α-chloromethyl)pyrazine (XV) was allowed to react with a 3*M* excess of sodium ethoxide in absolute ethanol. Work-up afforded 2.86 g. (37%) of the bis ether XVI which boiled at 130–133°/20 mm., n_D^{25} 1.4892.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.24; H, 8.25; N, 14.00.

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BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE RESEARCH DIVISION, WYANDOTTE CHEMICALS CORP.]

Chlorination of Alkylpyrazines[1]

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Methyl-, 2,5-dimethyl-, or 2,5-diethylpyrazine, when treated in carbon tetrachloride at 40° with excess chlorine, gave 2-chloro-3-methyl-, 3-chloro-2,5-dimethyl-, and 3-chloro-2,5-diethylpyrazine, respectively, in good yields. A nuclear chlorinated product under these mild conditions was unexpected. The chlorine atom of the alkylchloropyrazines was very reactive towards nucleophilic reagents. Replacement of the halogen was readily effected by reaction of the chloro compounds with alcohols, ammonia, aliphatic amines, and aqueous alkali to give ethers, amines, and hydroxy derivatives.

A chlorination study of alkylpyrazines was begun initially with the objective of preparing α-chloromethylpyrazine. When methylpyrazine in carbon tetrachloride was treated with an excess of elemental chlorine at room temperature and with irradiation from an incandescent lamp a monochloro product was obtained. One might expect a methyl substituted chloro derivative to form under these conditions but the chemical and physical properties of the product indicated that 2-chloro-3-methylpyrazine, a ring substituted compound, had formed instead. Light was later found to have no effect on the reaction. The reaction was applied to the chlorination of 2,5-dimethyl- and 2,5-diethylpyrazine and the products were also ring substituted alkylchloropyrazines.

In addition to the derivatives of the chloro compounds prepared in the course of their identification, several other amino and alkoxy compounds were prepared. When 2-chloro-3-methyl- or 3-chloro-2,5-dimethylpyrazine was heated in an autoclave at about 200° with aqueous ammonia, methylamine, dimethylamine, or ethanolamine the corresponding substituted amines were obtained. To prepare the pyrazyl ethers from 2-chloro-3-methylpyrazine the sodium alkoxides were usually employed. Later we found that simply refluxing a mixture of the chloropyrazine in alcohol with potassium hydroxide was sufficient to afford the corresponding ethers in good yield. By these methods ethers were made from allyl, *n*-butyl and myristyl alcohols and from ethylene glycol. Since ethylene glycol is bifunctional both possible ethers were obtained: the hydroxyethyl ether and the ethylene bispyrazyl ether. 3-Chloro-2,5-dimethylpyrazine presumably reacts in a similar fashion since the corresponding ethyl ether was made in good yield from the chloropyrazine, ethanol and potassium hydroxide.[2]

(1) Presented before the Division of Organic Chemistry at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960.

EXPERIMENTAL[3]

2-Chloro-3-methylpyrazine. To 5.4 l. of carbon tetrachloride heated to 40° in a 12 l. flask equipped with stirrer, Dry Ice-acetone condenser and dropping funnel was added 142 g. (2 moles) of chlorine through a tube ending above the surface of the carbon tetrachloride. This was followed by 94 g. (1 mole) of methylpyrazine added within 5 min. Warming was necessary to maintain the temperature at 40° until an exothermic reaction took place and precipitation of 2-chloro-3-methylpyrazine hydrochloride occurred. Addition of reactants was repeated in this manner (with cooling when necessary) except that the ratio of chlorine to methylpyrazine was adjusted so that final total amounts, 937 g. (13.2 moles) of chlorine and 1128 g. (12 moles) of methylpyrazine, had been added in 6 hr.

After standing overnight the hydrochloride was removed by filtration and washed with carbon tetrachloride. The filter cake was slurried with 500 ml. of water and the mixture was neutralized with 1.2 l. of 35% aqueous sodium hydroxide while the temperature was kept below 40° by cooling. The 2-chloro-3-methylpyrazine precipitated as an oil. It was separated and distilled. Yield: 1029 g. (67%), b.p. 55–65°/15 mm., n_D^{25} 1.5262 (reported[4] b.p. 94–96°/65 mm. and n_D^{25} 1.5302). The compound was unreactive towards hot alcoholic silver nitrate.

3-Chloro-2,5-dimethylpyrazine. This chloro compound was prepared from 2,5-dimethylpyrazine as above. Yield: 87%, b.p. 64°/10 mm.–65°/12 mm., n_D^{25} 1.5237 (reported[4]

(2) H. Gainer, M.S. thesis, Polytechnic Institute of Brooklyn, 1951.

(3) All melting points are uncorrected.

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 74, 1580 (1952).

b.p. 112–113°/70 mm., n_D^{26} 1.5243). The compound was unreactive towards hot alcoholic silver nitrate.

2,5-Diethylpyrazine. This dialkylpyrazine was obtained[5] *via* reaction of 1,2-epoxybutane and ammonia to give 2-hydroxybutylamine which was then simultaneously condensed and dehydrogenated[6] to yield finally 2,5-diethylpyrazine, b.p. 188–189°/760 mm., n_D^{26} 1.4908 (b.p. 185–186°/767 mm.) was reported[7] for 2,5-diethylpyrazine prepared by oxidation of the condensation product of 1-amino-2-butanone with mercuric chloride. This synthesis is similar to the series of reactions recently reported[8] for the preparation of ethylpyrazine.

3-Chloro-2,5-diethylpyrazine. A stream of chlorine was passed over the surface of 500 ml. of stirred carbon tetrachloride heated to 40°. When the solvent was saturated 30 ml. of 2,5-diethylpyrazine was added with stirring and the temperature was maintained at 40°. After about 30 min. the addition of reagents was repeated except that the quantity of 2,5-diethylpyrazine added depended upon the amount of chlorine retained by the reaction mixture. The mole ratio of chlorine to 2,5-diethylpyrazine was 2:1. After 15 min. enough 2,5-diethylpyrazine was added to make the mole ratio of chlorine to 2,5-diethylpyrazine present in the reaction mixture 1.27:1. In this manner was added a total of 205.5 g. (1.5 moles) of 2,5-diethylpyrazine and 140 g. (1.9 moles) of chlorine. Though the temperature was carefully maintained at 40° throughout most of the run by heating or cooling, at one point the temperature rose spontaneously to 60° despite efforts to prevent the rise. The hydrochloride of 3-chloro-2,5-diethylpyrazine did not precipitate.

A mixture of 176 g. of sodium bicarbonate and 250 ml. of water was added with stirring and the mixture was filtered. The organic layer was separated, dried over anhydrous magnesium sulfate and fractionally distilled. Yield: 194 g. (76%) b.p. 81°/5 mm. – 91°/6 mm., n_D^{25} 1.5148.

Anal. Calcd. for $C_8H_{11}ClN_2$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.61; H, 6.42; N, 16.56.

2-Hydroxy-3-methylpyrazine, Method A. For comparison with the product of Method B this compound was prepared from alanineamide and glyoxal.[4] The melting point of the material prepared according to this method was 149.5–150.5° in agreement with the m.p. 151–152° reported by Karmas and Spoerri (reported[9] m.p. 140–142° by the same method).

Method B. A heterogeneous mixture of 360 g. (2.8 moles) of 2-chloro-3-methylpyrazine, 600 g. of potassium hydroxide, and 2.4 l. of water was refluxed for 9 hr. The resultant homogeneous solution was carefully neutralized with concentrated hydrochloric acid and the water was removed by warming *in vacuo*. The dry residue was extracted with hot absolute alcohol. After evaporating the solution to dryness *in vacuo* the residue was recrystallized several times from isopropyl alcohol and finally from absolute alcohol. Yield: 170.5 g. (55%), m.p. 138–145°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.60; H, 5.53; N, 25.38.

A mixed melting point from samples obtained from both Method A and B was 139.5–149°. The comparative infrared spectra for both compounds were essentially identical. A strong absorption band at 6 μ and a medium band at 6.4 μ indicated the presence of an amide group so that the compound probably exists in the keto tautomeric form.[10] The hydroxyl absorption band is absent.

2,5-Dimethyl-3-hydroxypyrazine. This derivative of 3-chloro-2,5-dimethylpyrazine was made in 29% yield by refluxing the chloro compound with 20% aqueous potassium hydroxide according to Baxter and Spring,[11] m.p. 206–207°; (reported[11] m.p. 208–210°).

2-Amino-3-methylpyrazine. A mixture of 240 g. (1.87 moles) of 2-chloro-3-methylpyrazine and 1 l. of 30% aqueous ammonia (16 moles) was heated in an autoclave at 180° for 8 hr. A pressure of 390 p.s.i. developed. The reaction mixture was filtered to obtain the product which was washed with a little alcohol and recrystallized from 600 ml. of absolute alcohol. Yield: 93 g. (46%), m.p. 165–167°.

Anal. Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found: C, 55.19; H, 6.42; N, 38.78.

3-Amino-2,5-dimethylpyrazine. A mixture of 107 g. (0.75 mole) of 3-chloro-2,5-dimethylpyrazine with 300 ml. of 30% aqueous ammonia and 66 g. of anhydrous ammonia (total of 9.3 moles) was heated at 180° in an autoclave for 10 hr. A pressure of 525 p.s.i. developed. The solvents were then removed by evaporation *in vacuo* with heating and the solid residue was extracted with hot benzene. Cooling the benzene precipitated the product which after filtration gave 66 g. of 3-amino-2,5-dimethylpyrazine. Recrystallization of the crude product from 350 ml. of benzene gave finally 57 g. (62%), m.p. 111–112° (reported[12] 112°, prepared from 3 - phenylacetamido - 2,5 - dimethylpyrazine). Karmas and Spoerri[4] have reported the method of preparing amino derivatives of the chloro compounds from the corresponding aqueous amines.

The correspondence of the melting points of the hydroxy and amino compounds with the melting points of the corresponding compounds reported in the literature serves as a proof of structure of the 3-chloro-2,5-dimethylpyrazine.

2-Methyl-3-methylaminopyrazine hydrochloride. A mixture of 64 g. (0.5 mole) of 2-chloro-3-methylpyrazine and 160 ml. (2 moles) of 40% aqueous methylamine was heated in an autoclave at 200° for 6.5 hr. The autoclave was charged with 200 p.s.i. of hydrogen and 600 p.s.i. developed with heating. The homogeneous reaction mixture was evaporated *in vacuo* on the steam bath and the syrupy residue was continuously extracted with ether. After removal of the solvent by warming *in vacuo* the residue was dissolved in 50 ml. of absolute alcohol and acidified with 60 ml. of 8*N* alcoholic hydrogen chloride. A little ether was added to complete the precipitation and the product was filtered. Several recrystallizations from methanol-ether mixture gave 25 g. (31%), m.p. 236–240°. A sample was sublimed at *ca.* 175°/760 mm. for the analysis.

Anal. Calcd. for $C_6H_{10}ClN_3$: C, 45.14; H, 6.31; N, 26.32. Found: C, 44.89; H, 6.05; N, 25.94.

2,5-Dimethyl-3-methylaminopyrazine hydrochloride. A mixture of 49.5 g. (0.35 mole) of 3-chloro-2,5-dimethylpyrazine and 150 ml. of 40% aqueous methylamine (2 moles) was heated in an autoclave at 195–210° for 12 hr. The autoclave was charged with 200 p.s.i. of hydrogen and 700 p.s.i. developed with heating. After removal of most of the solvent by heating *in vacuo* the residue was continuously extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed by warming *in vacuo* and gave a non-crystallizing oil. This residue was dissolved in absolute alcohol and acidified with 8*N* alcoholic hydrogen chloride. The hydrochloride precipitated; the mixture was cooled, treated with ether, filtered and the precipitate was washed with a 1:1 alcohol and ether mixture, then ether alone. Yield, 18.9 g. (29%), m.p. 225–226.5°. Several recrystallizations from absolute alcohol raised the melting point to 228.5–229°.

(5) These preparations were made by Walter F. Schulz, Wyandotte Chemicals Corp., and Ernest Jaul, General Tire and Rubber Co.

(6) W. K. Langdon, U. S. Patent 2,813,869, Nov. 19, 1957.

(7) E. Kolshorn, *Ber.*, **37**, 2474 (1904).

(8) H. Gainer, *J. Org. Chem.*, **24**, 691 (1959).

(9) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 78 (1949).

(10) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

(11) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 1179 (1947).

(12) G. T. Newbold, F. S. Spring, and W. Sweeney, *J. Chem. Soc.*, 300 (1949).

Anal. Calcd. for $C_7H_{12}ClN_3$: C, 48.42; H, 6.97; N, 24.20. Found: C, 48.51; H, 6.93; N, 24.36.

2-Dimethylamino-3-methylpyrazine hydrochloride. A mixture of 12.8 g. (0.1 mole) of 2-chloro-3-methylpyrazine and 100 ml. (0.55 mole) of 25% aqueous dimethylamine was heated in an autoclave at 200° for 13 hr. The autoclave was charged with 200 p.s.i. of nitrogen and 550 p.s.i. developed with heating. Most of the solvent was removed by heating *in vacuo* and the residue was continuously extracted with ether. After removal of the ether by warming *in vacuo* the residue was dissolved in a little absolute alcohol and the solution was acidified with alcoholic hydrogen chloride. Some ether was added to complete the precipitation. The product was removed by filtration, washed with an alcohol-ether mixture and recrystallized from an alcohol-ether mixture. Yield: 1.2 g. (7%), m.p. 228–230° dec. For the analysis a small sample was sublimed at *ca.* 70°/3 mm., m.p. 224–230° dec.

Anal. Calcd. for $C_7H_{12}ClN_3$: C, 48.42; H, 6.97; N, 24.20; Cl, 20.42. Found: C, 48.09; H, 6.77; N, 24.26; Cl, 20.53.

2,5-Dimethyl-3-dimethylaminopyrazine. A mixture of 106.9 g. (0.75 mole) of 3-chloro-2,5-dimethylpyrazine and 475 ml. (4.2 moles) of 40% aqueous dimethylamine was heated in an autoclave at 200° for 8 hr. A pressure of 400 p.s.i. developed. The reaction mixture was distilled and the fraction collected, b.p. 100–103°/20 mm., was redistilled to yield the product; 42 g. (37%), b.p. 100°/20 mm., and n_D^{25} 1.5338.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79. Found: C, 63.89; H, 8.74; N, 27.52.

2,5-Dimethyl-3-(2-hydroxyethylamino)pyrazine. A mixture of 0.4 ml. (0.003 mole) of 3-chloro-2,5-dimethylpyrazine, 3 ml. (0.05 mole) of ethanolamine and 5 ml. of water was heated in a sealed tube at 180–200° for 24 hr. The homogeneous mixture was extracted continuously with ether and the solvent and excess reagent were removed by heating *in vacuo* on the steam bath. The crystalline residue was recrystallized several times from benzene. Yield: 140 mg., (28%), m.p. 119.5–120.5°.

An infrared spectrum showed bands at 2.95 and 9.45 μ which is indicative of a primary hydroxyl group and the absence of an ether band at 8.9 μ indicates that the possibility of a 3-(2-aminoethoxy) substituent can be eliminated.

Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.67; H, 7.46; N, 26.33.

Allyl 2-(3-methylpyrazyl) ether. A mixture of 30 g. (0.23 mole) of 2-chloro-3-methylpyrazine, 60 ml. (0.9 mole) of allyl alcohol, and 15 g. (0.23 mole) of potassium hydroxide was refluxed for 15.5 hr. To the reaction mixture was added 100 ml. of petroleum ether. The precipitated salt was removed by filtration and the filtrate was fractionally distilled to yield finally the ether; 22 g. (64%), b.p. 61–62°, n_D^{25} 1.5091.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.90; H, 6.71; N, 18.72.

Butyl 2-(3-methylpyrazyl) ether. A solution from 4.6 g. (0.2 g.-atom) of sodium and 175 ml. of 1-butanol prepared by heating the solvent and sodium together was refluxed with 28 g. (0.2 mole) of 2-chloro-3-methylpyrazine for 45 min. The precipitated salt was removed by filtration and the filtrate was fractionally distilled to yield the product, 29 g. (87%), b.p. 98°/14 mm., n_D^{25} 1.4841.

Anal. Calcd. for $C_9H_{14}N_2O$: N, 16.85 Found: N, 17.02.

Ethylene glycol bis-2-(3-methylpyrazyl) ether and 2-hydroxyethyl 2-(3-methylpyrazyl) ether. To a solution prepared from 13.3 g. (0.33 mole) of powdered sodium hydroxide and 62 g. (1.0 mole) of hot ethylene glycol was added 125 ml. of toluene. This mixture was refluxed 1.5 hr. while water was removed as an azeotrope with toluene. In this manner, 6.5 ml. of water was collected. The mixture was cooled and treated dropwise at 85° with a solution of 43 g. (0.33 mole) of 2-chloro-3-methylpyrazine in 50 ml. of toluene. After heating an additional 45 min. at 100° the mixture was cooled and filtered. The filtrate was fractionally distilled giving two fractions. One fraction was a liquid and corresponded to 2-hydroxyethyl 2-(3-methylpyrazyl) ether; 16 g., b.p. 100–106°/2 mm., n_D^{25} 1.5297.

Anal. Calcd. for $C_7H_{10}N_2O_2$: N, 18.17. Found: N, 18.31.

The second fraction, b.p. 150°/3 mm., crystallized in the condenser during its distillation and after recrystallization from 25% aqueous methyl alcohol had m.p. 84–85°. This fraction was considered to be the disubstituted ether, ethylene glycol bis-2-(3-methylpyrazyl) ether.

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: N, 22.75 Found: N, 22.63.

Myristyl 2-(3-methylpyrazyl) ether. A mixture of 45 g. (0.2 mole) of myristyl, alcohol, 8 g. (0.2 mole) of powdered sodium hydroxide, and 100 ml. of xylene was refluxed while removing some of the water formed. To this mixture was added 26 g. (0.2 mole) of 2-chloro-3-methylpyrazine and the mixture was refluxed again for 2.5 hr. Most of the xylene was then distilled, the precipitated salt removed by filtration and the filtrate was fractionally distilled. Yield: 41 g. (70%), b.p. 175–179°/2 mm., n_D^{25} 1.4775.

Anal. Calcd. for $C_{19}H_{34}N_2O$: N, 9.14. Found: N, 9.21.

DISCUSSION

The method of preparation of alkylmonochloropyrazines in our laboratories makes readily available these chloropyrazines and many interesting pyrazine compounds derived from them.

2-Chloro-3-methyl- and 3-chloro-2,5-dimethylpyrazine are known compounds. 3-Chloro-2,5-diethylpyrazine was not previously reported. 2-Chloro-3-methylpyrazine was first described by Karmas and Spoerri[4] who prepared it from the reaction between 2-hydroxy-3-methylpyrazine and phosphorus oxychloride. There are several syntheses of 3-chloro-2,5-dimethylpyrazine previously described; they are the reactions of phosphorus oxychloride with either diketodimethylpiperazine,[11] the mono-*N*-oxide of 2,5-dimethylpyrazine[13,14] or with 2,5-dimethyl-3-hydroxypyrazine.[4] Larson and Spoerri more recently described a synthesis of 2-chloromethyl-5-methylpyrazine by the reaction of 2,5-dimethylpyrazine with chlorine in carbon tetrachloride.[15]

Since these are the conditions in which we obtain 3-chloro-2,5-dimethylpyrazine, Larson and Spoerri probably obtained the ring substituted chloro compound instead of the formulated chloromethyl derivative. Hirschberg and Spoerri[16] have since prepared authentic α-chloromethylpyrazine and 2-chloromethyl-5-methylpyrazine as unstable undistillable oils.

Our assignments of structures were based on comparisons of derivatives of the chloropyrazines with compounds of unequivocal structure as well as on physical data. 2-Chloro-3-methylpyrazine was

(13) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

(14) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2949 (1951).

(15) C. W. Larson, Ph.D. Dissertation, Polytechnic Inst. of Brooklyn, 1949.

(16) A. Hirschberg, Ph.D. Dissertation, Polytechnic Inst. of Brooklyn, 1960.

hydrolyzed with aqueous alkali to 2-hydroxy-3-methylpyrazine.

2-Hydroxy-3-methylpyrazine was also prepared from alanineamide and glyoxal[4] and was shown to be identical with the compound prepared by alkaline hydrolysis of 2-chloro-3-methylpyrazine. 2-Hydroxy-3-methylpyrazine probably exists in the tautomeric keto form as shown by infrared spectra. If the chloro derivative had given hydroxymethylpyrazine upon hydrolysis then a tautomeric keto form would not be possible. These reactions verified that the chlorine atom of the chlorinated pyrazine was therefore a ring substituent and was not on the alkyl group.

Both NMR spectroscopy and the dipole moment of 2-chloro-3-methylpyrazine furnished additional confirmation of structure.[17] The NMR spectrum showed peaks with chemical shifts (relative to benzene) of $\delta = +4.9$ and $\delta = 1.25$ (parts per million) and intensity ratio 3:2 in agreement with the values expected for ring substitution. The low dipole moment of the compound (1.33 D in benzene at 25°) is nearly the same as that (1.35 D) calculated for 2-chloro-3-methylpyrazine from bond moments. The calculated moments of 2-chloro-5-methyl-, 2-chloro-6-methyl-, and α-chloromethylpyrazine, which are all the other possibilities, are 1.90, 1.73, and 1.85, respectively.

To prove the structure of 3-chloro-2,5-dimethylpyrazine it was treated with aqueous alkali and aqueous ammonia to obtain 2,5-dimethyl-3-hydroxy- and 3-amino-2,5-dimethylpyrazine, respectively. The melting points of these derivatives compared favorably with those reported in the literature for the same compounds made by unequivocal methods.[11,12]

The pyrazines were previously not known to react readily with electrophilic reagents. To prepare monochloropyrazine from pyrazine and chlorine a vapor phase reaction at 365° and the presence of sulfur dioxide was necessary. These conditions are more conducive to free radical attack of chlorine rather than polar reaction. A plausible explanation of this lack of reactivity towards electrophilic reaction hinged on the influence of the hetero atoms on the aromatic ring. Because of the inductive effect of the two nitrogen atoms in addition to a resonance effect, the carbon atoms of pyrazine should be relatively positive.[18] The experimental conditions involved in electrophilic substitutions causes the pyrazine ring to be converted into the pyrazinium ion. The inductive effect is then enhanced by the resultant positive ionic charge. The positively charged nitrogen atom is ordinarily meta directing and should deactivate the ring.

A reaction of an alkylpyrazine with excess chlorine in carbon tetrachloride at 40° to yield the monoalkylchloropyrazine is one which is occurring under very mild conditions and this was quite unexpected. If the reagents, alkylpyrazine and excess chlorine, were mixed in carbon tetrachloride directly the reaction was marked by an induction period followed by an exothermic reaction difficult to control. Irradiation from an incandescent or an ultraviolet lamp had no effect upon the induction period or the yield of product when 2-chloro-3-methylpyrazine was prepared in this manner. The difficulty of an uncontrollable exothermic reaction was mitigated by addition of the alkylpyrazine and chlorine initially in the molar ratio of two to one portionwise to preheated carbon tetrachloride.

The first step in the chlorination of methylpyrazine is probably the formation of a methylpyrazine perchloride. An excess of chlorine is essential to the reaction. If one mole or less of chlorine was used the reaction invariably failed. Examples of addition compounds of the alkylpyrazines or other six-membered nitrogen heterocyclics with halogens are well known.[19]

Of the two nitrogen atoms of methylpyrazine the one closest to the methyl group most likely forms salts and influences orientation during electrophilic substitution. The base strength of the nitrogen atom closest to the methyl group probably is greater than that of the more remote nitrogen atom. The ionization constant of 2-methylpyridine is 5.4×10^{-8} and that of pyridine at the same temperature is 1.3×10^{-9}.[20] Methylpyrazine (pK, 12.5) is likewise a stronger base than pyrazine (pK, 12.9).[21] Carbon atoms three and five are relatively electronegative because of the inductive effect of the positively charged nitrogen atom in the perchloride of methylpyrazine. An additional increase in electronegativity of carbon atom three may be due to the presence of the adjacent methyl group. The second step in the chlorination then involves the three position.

It should be emphasized that these considerations apply only to the orientation of the substituting chlorine atom. They do not explain the ease of ring chlorination of a heterocyclic compound under such mild conditions.

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WYANDOTTE, MICH.

(17) These physical measurements were done by Dr. Max T. Rogers, Michigan State University, East Lansing, who kindly supplied us with these results.

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