ether extract gave unchanged N-methylaniline, then 7.6 g. (43%) of 1-(N-methylanilino)-3-butanone, b.p. 95–96° (1.0 mm.), $n^{25}\text{D}$ 1.5495.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.39; H, 8.67.

The semicarbazone crystallized from ethanol as needles, m.p. 169–171°; lit.[12] b.p. 153–161° (14 mm.) for the ketone and m.p. 163° for the semicarbazone.

Anal. Calcd. for $C_{12}H_{18}N_4O$: C, 61.51; H, 7.74. Found: C, 61.31; H, 7.41.

B.—A mixture of 10.7 g. (0.10 mole) of N-methylaniline, 15.2 g. (0.10 mole) of 1-dimethylamino-3-butanone hydrochloride, and 30 ml. of water was heated on the steam bath for 2 hr., and then worked up as in A. The product was 5.1 g. (30%) of 1-(N-methylanilino)-3-butanone, b.p. 95–96° (1.0 mm.), $n^{25}\text{D}$ 1.5495.

Deuterated 1-(N-Methylanilino)-3-butanone.—A solution of 4.3 g. (0.03 mole) of N-methylaniline hydrochloride in 6 ml. of deuterium oxide was evaporated to dryness *in vacuo* at 25°. This procedure was repeated six times, after which a constant infrared spectrum was obtained. The deuterated salt was heated on the steam bath for 2 hr. with 3.45 g. (0.03 mole) of 1-dimethylamino-3-butanone and 9 ml. of deuterium oxide; then the cooled reaction mixture was extracted with anhydrous ether. Distillation of the ether extract gave a forerun of deuterated N-methylaniline then deuterated 1-(N-methylanilino)-3-butanone, b.p. 81–82° (0.1 mm.), $n^{24}\text{D}$ 1.5475.

Deuterated 1-Anilino-3-butanone.—Treatment of 4.0 g. (0.03 mole) of aniline hydrochloride as above gave deuterated 1-anilino-3-butanone, b.p. 94–95° (2 mm.), $n^{24}\text{D}$ 1.5530.

Self-Deuteration of 1-Dimethylamino-3-butanone.—A mixture of 3.45 g. (0.03 mole) of 1-dimethylamino-3-butanone and 9 ml. of deuterium oxide was heated on the steam bath for 2 hr., and then the cooled mixture was extracted with anhydrous ether. Distillation of the ether gave deuterated 1-dimethylamino-3-butanone, b.p. 60–62° (25 mm.), $n^{25}\text{D}$ 1.4425.

β-(N-Methylanilino)propiophenone (IVa). A.—A mixture of 3.21 g. (0.03 mole) of N-methylaniline, 6.42 g. (0.03 mole) of β-dimethylaminopropiophenone hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, the residue was distributed between ether and water, and the dried (sodium sulfate) ether layer was evaporated finally at 100° (1.0 mm.) Crystallization of the residue from ethanol gave 3.2 g. (45%) of β-(N-methylanilino)-propiophenone as needles, m.p. 60–61°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.41; H, 6.86.

B.—An ice-cold solution of 1.5 g. of sodium hydroxide in 50 ml. of water was added to 6.42 g. (0.03 mole) of β-dimethylaminopropiophenone hydrochloride, and the liberated base was extracted with ether. The ether was washed with water, dried (sodium sulfate), and evaporated. The resulting β-dimethylaminopropiophenone was heated under reflux for 2 hr. with 3.21 g. (0.03 mole) of N-methylaniline, 20 ml. of ethanol, and 10 ml. of water; then the solvent was evaporated *in vacuo*. The residue was taken up in 75 ml. of ice-cold 1 *N* hydrochloric acid, the solution was washed with ether, then was brought to pH 7.5 with sodium hydrogen carbonate. The liberated bases were isolated with ether; the ether was dried (sodium sulfate) and evaporated finally at 100° (1.0 mm.). Crystallization of the residue from ethanol gave 2.2 g. (31%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

C.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 3.21 g. (0.03 mole) of N-methylaniline, 2.45 g. (0.03 mole) of dimethylamine hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, water was added, and the product was isolated with ether. Evaporation of the dried (sodium sulfate) ether extracts finally at 100° (1.0 mm.) and crystallization of the residue from ethanol gave 3.1 g. (43%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

D.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 3.21 g. (0.03 mole) of N-methylaniline, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr., and then the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml. of 1 *N* hydrochloric acid; the solution was washed with ether, then was brought to pH 7.5 with sodium hydrogen carbonate. The liberated bases were extracted with ether and the dried (sodium sulfate) ether extracts were evaporated finally at 100° (1 mm.). Crystallization of the residue from ethanol gave 4.7 g. (66%) of β-(N-methylanilino)-propiophenone, m.p. and m.m.p. 60–61°.

E.—The same reactants were heated for 5 min. then worked up as before. The product was 4.1 g. (57%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

β-Dimethylaminopropiophenone (Ig). A.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 1.35 g. (0.03 mole) of dimethylamine, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 5 min.; then the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml. of ice-cold 1 *N* hydrochloric acid; the solution was washed with ether and then was brought to pH 14 with ice-cold 3 *N* sodium hydroxide. The product, isolated with ether, was 4.6 g. (86%) of β-dimethylaminopropiophenone, $n^{25}\text{D}$ 1.5240, m.p. 30–32°.

B.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 2.45 g. (0.03 mole) of dimethylamine hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 5 min.; then the solvent was evaporated *in vacuo*. The residue was distributed between ether and ice-water, and the aqueous layer was made basic with ice-cold 3 *N* sodium hydroxide. Isolation with ether gave 4.4 g. (84%) of β-dimethylaminopropiophenone, identical with that obtained in A.

Isomerism in the Direct Chlorination of 2-Methylpyrazine[1a]

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The product of the direct chlorination of 2-methylpyrazine is shown to be a mixture of 2-chloro-3-methylpyrazine and 2-chloro-6-methylpyrazine.

The direct nuclear chlorination of alkylpyrazines recently reported[2,3] has greatly expedited the study of the pyrazine ring system. The alkylchloropyrazines obtained by this method are also available, though less conveniently, by the chlorination of the corresponding alkylhydroxypyrazines with a phosphorus halide. The alkylhydroxypyrazines are obtained *via* the condensation of amino acid amides with α-dicarbonyl compounds.[4] The commercial availability of the three alkylchloropyrazines Ia–c[5] prompted us to prepare a number of dialkylamino derivatives and related compounds for exploratory pharmacological screening.

When commercial Ia was treated with excess piperidine either alone or in the presence of aqueous base the product was shown by gas–liquid chromatography

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[1] (a) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963; (b) Chemistry Department, Manchester College, North Manchester, Ind.

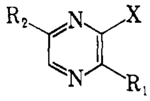
[2] H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

[3] A. Hirschberg and P. E. Spoerri, *ibid.*, **26**, 2356 (1961); see also R. A. Pages and P. E. Spoerri, *ibid.*, **28**, 1702 (1963).

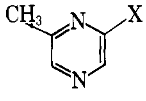
[4] G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).

[5] These compounds were generously supplied by the Wyandotte Chemicals Corp., the method of preparation being as described in ref. 1.

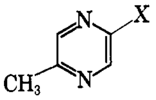
(g.l.c.) to be a mixture of two components in a ratio of about 70:30. With hydrogen chloride, a mixture of bright yellow salts was obtained which could be separated by fractional crystallization. The less soluble, higher melting compound was present in smaller amount. Both had the same per cent composition. The compounds could be separated for analytical purposes by paper ionophoresis, the higher melting compound having the greater mobility. This isomer was also slightly more basic. Its pK_a in water was found to be 3.51 compared to 3.10 for the lower melting isomer. It was assumed that if one of the two compounds had the expected structure Ie then the other must be IIc or IIIc. Expansion or contraction of the pyrazine ring was ruled out on the basis of the similar spectral and chemical properties of the two compounds. Compound IVb was not considered a likely possibility but was nevertheless prepared by treating 2-chloromethylpyrazine[3] (IVa) with piperidine. IVb formed *colorless* salts and could, therefore, be eliminated.



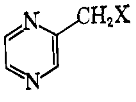
Ia, $R_1 = CH_3$; $R_2 = H$;
X = Cl
b, $R_1 = CH_3$; $R_2 = CH_3$;
X = Cl
c, $R_1 = C_2H_5$; $R_2 = C_2H_5$;
X = Cl
d, $R_1 = CH_3$; $R_2 = H$;
X = OH
e, $R_1 = CH_3$; $R_2 = H$;
X = 1-piperidyl
f, $R_1 = CH_3$; $R_2 = H$;
X = $N(CH_3)_2$



IIIa, X = Cl
b, X = OH
c, X = 1-piperidyl
d, X = $N(CH_3)_2$



IIa, X = Cl
b, X = OH
c, X = 1-piperidyl



IVa, X = Cl
b, X = 1-piperidyl

In order to prepare authentic IIc and/or IIIc the corresponding chloro compounds were desired. Both IIa and IIIa have been prepared by chlorination of the corresponding pyrazinols IIb and IIIb, which were in turn prepared by the condensation of pyruvaldehyde and glycinamide. Karmas and Spoerri[4] report that this reaction gives a separable mixture of 2,5- and 2,6-methylpyrazinols whereas Jones[6] appears to have obtained only the former. In this laboratory, when pyruvaldehyde was used as the bisulfite addition compound[7] the 2,6 isomer (IIIb) was the only compound which could be isolated. The IIIb obtained was easily purified and converted to the chloro compound (IIIa). All of the strong infrared bands of IIIa were found to be present in the spectrum of commercial Ia. With piperidine, IIIa gave a base which afforded a yellow hydrochloride. This salt was found to be identical in all respects with the less abundant higher melting hydrochloride. The identity of the by-product was thus established as the 2,6 isomer (IIIc).

A sample of pure 2-chloro-3-methylpyrazine (Ia) was then prepared from the commercial material by a three-step sequence.[8] Ammonolysis[3] gave a mixture of aminomethylpyrazines. Since the 2,3 isomer is less soluble and higher melting, purification by recrystallization was relatively easy. Treatment of the pure amino compound with nitrous acid then gave pure 2-hydroxy-3-methylpyrazine (Id) which was converted by phosphorus oxychloride to Ia. The infrared spectrum of this material was identical with the spectrum of a sample[9] of pure Ia prepared by the procedure of Karmas and Spoerri. *The only difference between the spectra of pure Ia and commercial Ia was that, in the former, the bands characteristic of IIIa were absent.*[10] Very small amounts of the 2,5 isomer (IIa) would, of course, not be detected by infrared spectroscopy. Hirschberg and Spoerri[3] conclude from ammonolysis studies of their chlorinated methylpyrazine that at least 5% of IIa is present. In addition to 60% of 2-amino-3-methylpyrazine melting at 166–167°, they were able to isolate about 5% of a solid melting at 111–112° which they assumed to be 2-amino-5-methylpyrazine. Since the literature[4,11] records a melting point of 116–118° for the 2,5 isomer and 124–125° and 127–128° for the 2,6 isomer, it is possible that Hirschberg and Spoerri isolated an impure form of the latter compound. Our results would support this conclusion, particularly in view of the similarity in reaction conditions employed by the two groups[2,3] for the chlorination of methylpyrazine.

The reaction of commercial Ia with other primary and secondary amines also gave mixtures which were separable by a combination of fractional distillation of the bases and fractional crystallization of the salts. Since the content of 2,6 isomer generally ranged up to 25–30% it follows that caution must be used in assigning structures to compounds derived from commercial Ia in less than 25–30% yield. Similarly, compounds obtained in yields above 70–75% are likely to contain the 2,6 isomer as an impurity. The techniques which have been found useful for differentiating between the 2,3 and 2,6 isomers in a large number of compounds prepared in our laboratories include the following.

A. Comparison with material obtained from a chloropyrazine of known structure and purity.

B. Yield of *pure* compound if in the range 40–70%.

C. In four cases examined, the crude bases were readily separated by g.l.c. The larger peak was assigned the 2,3 structure. The bases could then be individually purified and the relative retention times correlated with those obtained for the crude mixture. This method appears to be useful even when conversions are as low as 50–60% (see ref. 8).

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(6) R. G. Jones, U. S. Patent 2,520,088 (August 22, 1950); *Chem. Abstr.*, **44**, 10,740 (1950).

(7) F. Muehlmann and A. R. Day, *J. Am. Chem. Soc.*, **78**, 242 (1956).

(8) Several attempts to purify 2-chloro-3-methylpyrazine by taking advantage of the slightly greater reactivity of the 2,6 isomer toward amines were unsuccessful. Infrared analysis of methylchloropyrazine recovered from reactions in which the commercial material was subjected to partial reaction with various amines showed that the purification achieved was not sufficient to be useful. Somewhat better results were obtained by partial quaternization with dimethyl sulfate but again a pure product could not be obtained.

(9) This material was generously supplied by Dr. Bernard Klein, Veterans Administration Hospital, Bronx, N. Y.

(10) E. A. Wipert (personal communication from Wyandotte Chemicals Corp.) reports that some 2-chloro-6-methylpyrazine can be separated from commercial Ia when its hexane solution is cooled to −20° and that it constitutes about 25% of the total. Separation of the isomers by g.l.c. is extremely difficult. *After an intensive search for adequate columns and conditions, a partial but still very incomplete resolution of isomers was achieved.*

(11) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

TABLE I

Substituent	Salt[a]	M.p., °C.	Recrystn. solvent	Reaction time, hr. (temp., °C.)[b]	Yield, %	Formula	Anal.	C	H	N	Ultraviolet spectra[c] λ_{max}, mμ (log ε)
3-Substituted 2-methylpyrazines											
$NH(CH_3)$	C	53-55	Ether	18 (130)		$C_6H_9N_3$	Calcd.	58.51	7.37	34.12	239 (4.06)
							Found	58.24	7.52	34.32	321 (3.75)
	A	238-240[f]	Ethanol								
						$C_6H_9N_3\cdot HCl$					239 (4.06)
											321 (3.75)
$N(CH_3)_2$[d]	A	142-144	Ethanol-ether	210 (18)	20	$C_7H_{11}N_3\cdot HCl$	Calcd.	48.42	6.97	24.20	
							Found	48.52	7.24	23.98	
1-Piperidyl	A	112-114	2-Propanol-ethyl acetate	96 (reflux)	31	$C_{10}H_{15}N_3\cdot HCl$	Calcd.	56.20	7.55	19.66	239 (3.74)
							Found	56.43	7.40	19.78	257 (3.79)
											317 (3.62)
	B	131-133	2-Propanol-ethyl acetate			$C_{10}H_{15}N_3\cdot H_2SO_4$	Calcd.	43.62	6.23	15.26	
							Found	43.56	6.50	15.10	
1-Pyrrolidinyl	A	197-200	Dichloromethane-ethyl acetate	241 (reflux)	23	$C_9H_{13}N_3\cdot HCl$	Calcd.	54.13	7.07	21.04	255 (4.02)
							Found	54.34	7.33	20.89	336 (3.68)
Morpholino	A	168-172	Acetonitrile	26 (reflux, 25% KOH)	7	$C_9H_{13}N_3O\cdot HCl$	Calcd.	50.11	6.54	19.48	235 (3.75)
							Found	50.25	6.34	19.72	248 (3.77)
											314 (3.64)
1-Piperazinyl	D	160-163	Ethyl acetate-acetonitrile	120 reflux, ethanol)		$C_9H_{14}N\cdot C_7H_8O_3S$	Calcd.	54.83	6.33	15.99	244 (3.78)
							Found	55.01	6.50	15.70	312 (3.70)
6-Substituted 2-methylpyrazines											
$NHCH_3$	C	63-66	[g]	336 (20)		$C_6H_9N_3$	Calcd.	58.51	7.37	34.12	242 (4.38)
							Found	58.33	7.13	34.24	330 (3.76)
$N(CH_3)_2$	A	222-225	Methanol-ether	200 (20)[e]	13	$C_7H_{11}N_3\cdot HCl$	Calcd.	48.42	6.97	24.20	247 (4.04)
							Found	48.20	7.02	24.25	339 (3.68)
1-Piperidyl	A	171-172	Benzene	24 (reflux)	10	$C_{10}H_{15}N_3\cdot HCl$	Calcd.	56.20	7.55	16.59	227 (3.73)
							Found	56.25	7.71	16.57	256 (4.18)
											350 (3.76)
1-Pyrrolidinyl	A	112-113	Dichloromethane-ethyl acetate-ether	18 (reflux)	3	$C_9H_{13}N_3\cdot HCl$	Calcd.	54.13	7.06	21.05	251 (4.15)
							Found	54.28	7.24	20.89	350 (3.80)
Morpholino	A	172-174	Ethyl acetate	26 (reflux, 25% KOH)	<1	$C_9H_{13}N_3O\cdot HCl$	Calcd.	50.11	6.54	19.48	250 (4.04)
							Found	50.34	6.79	19.29	333 (3.70)
1-Piperazinyl	D	198-199	Ethyl acetate	120 (reflux, ethanol)		$C_9H_{14}N_4\cdot C_7H_8O_3S$	Calcd.	54.83	6.33	15.99	246 (4.10)
							Found	54.96	6.62	16.00	327 (3.77)

[a] A, hydrochloride; B, sulfate; C, free base; D, *p*-toluenesulfonate. [b] Some reactions were carried out in the presence of aqueous base or inert solvent as indicated. [c] Prepared by dissolving the base or hydrochloride in water (see ref. 12). [d] The compound described in the literature[2] as having this structure is probably the 2,6 isomer (see text). [e] The amine was used as a 25% aqueous solution. [f] Lit.[2] m.p. 236-240°. [g] Purified for analysis by sublimation at 63° (0.04 mm.).

D. When the bases can be separated by paper ionophoresis, the 2,6 isomer has the greater mobility, fluoresces more brightly, and forms a darker iodoplatinate.

E. The hydrochlorides of 2-dialkylamino-3-methylpyrazines show little or no absorption in the 1600-1900-cm.$^{-1}$ region, but occasionally show a *very weak band* at 1620 cm.$^{-1}$. The 2,6 isomers show a medium to strong band at 1620 cm.$^{-1}$ (all Nujol mulls).

F. Both series of dialkylaminomethylpyrazines have a band at 355-375 mμ in 1 *M* hydrochloric acid which is responsible for the yellow color of the salts. In neutral solution, the band shifts to 317-337 mμ for the 2,3 isomers and to 333-350 mμ for the 2,6 isomers. For a given isomeric pair, the 2,6 isomer absorbs at a longer wave length than the 2,3 isomer with respect to this band.[12]

Gainer, *et al.*,[2] described the preparation in 7% yield of 2-dimethylamino-3-methylpyrazine hydrochloride which melted at 224-230°. A repetition of this experiment in our laboratory afforded a mixture of products which was partially separated by fractional distillation.[13] The hydrochlorides of the higher and lower boiling fractions were then prepared and purified to constant melting point. Thus, from one run there was obtained a salt melting at 222-225° and about three times as much of another salt melting at 142-143°. These compounds were assigned the 2,6 and 2,3 structures, respectively, on the basis of D, E, and F. The higher melting product, therefore, has the 2,6 orientation rather than the 2,3 orientation as stated in the literature. It is probable that a number of compounds described as being 2-substituted 3-methylpyrazines contain appreciable quantities of 2,6 isomers[14] (see Table I).

Experimental[15]

Aminolysis of Chloropyrazines.—In the preferred method, a mixture of the chloropyrazine and two or more equivalents of amine was heated in a suitable vessel under conditions commensurate with the reactivity of the components. In earlier experiments water or aqueous alkali was sometimes added, but it is doubtful if the reaction was aided thereby.

When commercial 2-chloro-3-methylpyrazine was the starting material the isomeric products were separated by fractional recrystallization of a suitable salt (or the free base if crystalline) aided in some cases by prior fractional distillation of the crude mixed bases. Partial separations are possible by the latter method since at water pump pressure (*ca.* 15 mm.) the 2,6 iso-

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[12] The spectra obtained for neutral solutions were obtained by dissolving the hydrochlorides in water and making the necessary dilution. The salts are so extensively dissociated that the addition of sodium hydroxide had a negligible effect on the spectrum.

[13] In all cases so far examined the boiling point of the 2,6 isomer is slightly higher than that of the 2,3 isomer.

[14] J. Behun, P. Kan, P. Gibson, C. Lenk, and E. Fujiwara, *J. Org. Chem.*, **26**, 4981 (1961).

[15] Infrared spectra were run on a Baird 455 spectrograph, ultraviolet spectra were run on a Beckman DK-1, and gas-liquid chromatography was performed on a Perkin-Elmer 254 and a Research Specialties 600. Melting points were taken in capillaries using Anschutz thermometers in a Hershberg apparatus. Ionophoreses were run in 5 *M* acetic acid on Whatman No. 1 paper at *ca.* 30 v./cm.

mers usually boil about 5–10° higher than the 2,3 isomers. The difficulty of separating the isomers is reflected in the low yields reported in some cases.

2-Piperidino-3-methylpyrazine Hydrochloride and 2-Piperidino-6-methylpyrazine Hydrochloride.—A mixture of 10 g. (0.078 mole) of commercial 2-chloro-3-methylpyrazine, 15.4 ml. (0.16 mole) of piperidine, and 15 ml. of water was maintained at reflux for 4 days. The reaction mixture was made strongly basic and extracted with ether. The ether layer was separated, dried over potassium carbonate, and evaporated on a rotating evaporator at *ca.* 1 mm. Two 5-ml. portions of toluene were successively added and evaporated leaving 12.5 g. (90%) of the mixed bases. A solution of the mixed bases in 100 ml. of ethyl acetate was then treated with *ca.* 0.07 mole of hydrogen chloride in 90 ml. of ether in five roughly equal portions, the precipitated solids being removed by filtration after each addition. The first fraction, 3.7 g. (22.5%) of a yellow solid melting at 164–166°, was mostly the 2,6 isomer. The other fractions all melted in the range 98–112° and were combined to give a total of 9.2 g. (56%) of crude 2,3 isomer. Recrystallization from dichloromethane–ether afforded 5.0 g. (31%) of yellow crystals, m.p. 112–114°.

The first (high melting) fraction was recrystallized from acetonitrile–benzene to give 1.6 g. (10%) of yellow crystals, m.p. 169–171°. An additional recrystallization from benzene raised the melting point to 170–172°.

2-Methylamino-3-methylpyrazine.—A mixture of 64.3 g. (0.5 mole) of commercial 2-chloro-3-methylpyrazine and 60 ml. of liquid dimethylamine was heated for 18 hr. at 130° in a steel bomb. Excess dimethylamine was vented from the bomb and the residue dissolved in 100 ml. of water. Potassium carbonate (52 g.) was then added and the solution extracted with 800 ml. of ether. The extract was dried over potassium carbonate and concentrated on a steam bath. Distillation at 0.25 mm. gave only a single fraction boiling at 65° which weighed 41.1 g. (67%) and which partly crystallized. The solid was separated by filtration and washed with ether. This was compared with the total distillate by means of g.l.c. on Apiezon L at 137°. The distillate exhibited two fairly well-resolved peaks with retention times of 9.0 and 11.5 min. with areas under the curves corresponding to approximately 84% and 16%, respectively, of the weight of the material. Since the solid had a retention time of 9.3 min. under the same conditions, it is concluded that it is the 2,3 isomer. Conversion to the hydrochloride gave a white solid melting at 238–240° in close agreement with that reported by Gainer, *et al.*[2]

2-Hydroxy-3-methylpyrazine and 2-Chloro-3-methylpyrazine.—To a magnetically stirred solution of 2.0 g. (0.0183 mole) of 2-amino-3-methylpyrazine[3] in a mixture of 6.3 ml. of sulfuric acid and 17 ml. of acetic acid cooled to 0°, was added 2.3 g. (33.5 mmoles) of sodium nitrite in small portions during 10 min. The mixture was then stirred at 0° for an additional 1.5 hr. and permitted to warm to room temperature during 18 hr. with continuous stirring. The mixture was diluted with water, made basic with 10 *M* potassium hydroxide, and adjusted to pH 6 with hydrochloric acid. The solvent was then removed by evaporation at reduced pressure on a rotary evaporator and the residue purified by sublimation at 0.05 mm. (130°). The product, 1.8 g., melted at 139–148°. Recrystallization from ethyl acetate gave 1.35 g. (64%) of pale yellow crystals, m.p. 149–152°. The literature[4,16] records m.p. 151–152° and 150–152°.

Conversion to 2-chloro-3-methylpyrazine was carried out by the Karmas–Spoerri procedure.[4] Although the ultraviolet spectra of the 2,3 and 2,6 isomers were almost identical, the infrared spectra were quite different. The principal differences are listed, all bands being medium to very strong in intensity: 2,6 isomer (cm.$^{-1}$), 1260, 1178, 1015, 895, 740 (carbon disulfide solution); 2,3 isomer (cm.$^{-1}$), 1210, 1195, 1090, 1070, 855 (neat).

2-Hydroxy-6-methylpyrazine.—To 24 g. (0.1 mole) of commercial 30% aqueous pyruvaldehyde was added 19 g. (0.1 mole) of sodium metabisulfite (equivalent to 0.2 mole of sodium bisulfite) and the mixture stirred for 1 hr. at room temperature. The addition compound was precipitated as a gummy solid on addition of 60 ml. of methanol and 20 ml. of ethanol.

This solid was dissolved in 10 ml. of water and 5.5 g. (0.05 mole) of glycineamide hydrochloride was added. The pH was then adjusted to 8 with 10 *M* potassium hydroxide and the mixture maintained at 60–80° for 2 hr. The pH was adjusted to 10 and kept at 50–60° (spontaneous heating) for 30 min. The mixture was cooled and adjusted to pH 6 with concentrated hydrochloric acid, cooled to 0°, and filtered to give 3.2 g. (58%) of solid, m.p. 247° dec. Recrystallization from 35 ml. of water afforded 1.1 g. (20%) of light tan platelets, m.p. 246–248°, lit.[4] m.p. 250–251°.

2-Chloro-6-methylpyrazine.—A mixture of 1.1 g. of 2-hydroxy-6-methylpyrazine, 4 ml. of phosphorus oxychloride and a small drop of dimethylformamide was maintained at reflux for 40 min. The brown mixture was cooled, poured into 100 ml. of ice and water, and shaken vigorously. The mixture was then extracted twice with 25-ml. portions of ether and the extract washed with water and saturated sodium sulfate solution. After drying over calcium chloride the ether was removed by distillation through a short column packed with glass helices. Removal of the last traces of solvent at 15 mm. left 1.0 g. (78%) of a colorless crystalline residue, m.p. 49–51°, lit.[4] m.p. 50–51°.

2-Piperidino-6-methylpyrazine from Pure 2-Chloro-6-methylpyrazine.—A solution of 1.0 g. of the above chloro compound and 5 ml. of piperidine was maintained at reflux for 30 min. The cooled mixture was diluted with 10 ml. of ether, the precipitated piperidine hydrochloride removed by filtration, and the filtrate concentrated to a brown oil. Two small portions of toluene were added and evaporated. The residual oil was taken up in 10 ml. of ethyl acetate and the solution was treated with excess hydrogen chloride to give 0.57 g. (41%) of yellow solid, m.p. 168–169°. The melting point was raised to 169–172° by sublimation at 90° (0.05 mm.). On admixture of this material with the high melting by-product from the piperidinolysis of commercial 2-chloro-3-methylpyrazine, the melting point was 169–172°. The infrared spectra and ionophoretic mobilities of the substances were identical.

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(16) M. E. Hultquist, U. S. Patent 2,805,223; *Chem. Abstr.*, **52**, 2931 (1958).