Studies on Pyrazines. 6 (1). A Facile Separation Method for a Mixture of the Isomeric 2-Amino-3,5, and 6-methylpyrazines

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This paper describes a facile separation method for a mixture of the isomeric aminomethylpyrazines by two-stage processes. Thus the mixture of aminomethylpyrazines was converted into that of the aminobromomethylpyrazines, which could be separated by chromotography on silica gel. Each of the bromopyrazines was hydrogenated to regenerate the original aminopyrazine as a pure form.

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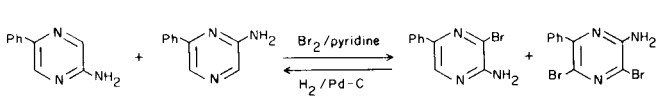
The isomeric 2-amino-5- and 6-alkyl or arylpyrazines (2) are generally prepared, in one or more preparative steps, by condensation of the corresponding glyoxal with 1,2-diamines, α-amino amides, or α-amino amidines (3). In many literatures (4-11) this condensation reaction was emphasized as leading to an exclusive formation of either isomer (12). On the other hand, a few examples in which a mixture of both isomers was obtained by the condensation have been known (13-17). In the latter case, purification of aminopyrazine by recrystallization is wasteful, and isolation of the minor component is difficult by ordinary separation methods (18). In this connection, we previously found (17) that a mixture of 2-amino-5-phenyl- and 2-amino-6-phenylpyrazines prepared by condensation of phenylglyoxal with α-aminoacetamidine could be separated in excellent yields by conversion into easily separable monobromo and dibromopyrazines, respectively, followed by catalystic debromination (Scheme I).

Scheme I



This paper reports the successful application of this procedure to separation of a mixture containing not only 2-amino-5-methyl- and 2-amino-6-methylpyrazines (**1** and **2**) but also 2-amino-3-methylpyrazine (**3**).

As a first approach, the bromination of each aminomethylpyrazine was investigated in detail. Aminopyrazines **1** and **3** as authentic samples were prepared by known methods (9, 19a), but they were both contaminated with a small amount of the other isomer **2**. On the other hand, the aminopyrazine **2** was obtained by decarboxylation of 3-amino-5-methylpyrazinecarboxylic acid which was prepared as an unexpectedly major product by Hofmann degradation of 5-methylpyrazine-2,3-dicarboxamide (Scheme II) according to the procedure of Gabriel and Sonn (20) for the preparation of 3-aminopyrazinecarboxylic acid.

Scheme II

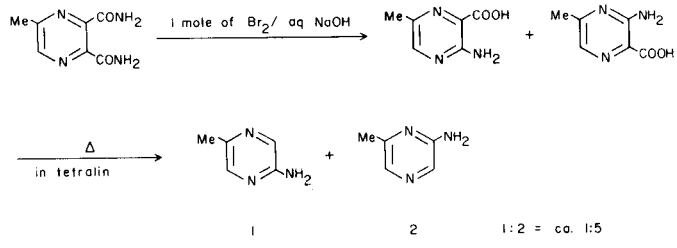


Table I

Preparation of Aminobromomethylpyrazines

Starting material	Product	Substituents	Yield, % (Yield, %) (a)	M.p., °C	Tlc (f), R_f
1	**4**	2-amino-3-bromo-5-methyl	74 (44)	64-65 (d)	0.55
1	**7**	2-amino-6-bromo-5-methyl	(b)	156-157 (d)	0.35
2	**5**	2-amino-3,5-dibromo-6-methyl	91 (91)	178-180 (e)	0.71
2	**8**	2-amino-5-bromo-6-methyl	(c)	144-145 (d)	0.34
3	**6**	2-amino-5-bromo-3-methyl	84 (73)	106-108 (d)	0.33

(a) The yield when the bromination reaction was exposed to light. (b) By-product compound, the precise yield cannot be determined. (c) Yield cannot be accurately determined because this compound is the intermediate of 5. (d) Recrystallized from cyclohexane and (e) benzene. (f) The tlc was performed on a Merck Kieselgel $60F_{254}$ sheet, eluted with benzene:ether (1:1).

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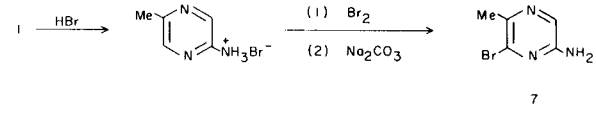
The amino substituent attached to the pyrazine ring facilitates bromination on the ortho and para positions (3). As expected, the bromination of aminopyrazines **1,2** and **3** proceeded readily by treatment with bromine in the presence of pyridine at room temperature to produce the corresponding brominated compounds **4,5**, and **6**, respectively (Table I). As the solvent, chloroform was better to increase the yield than acetic acid which was often used in the earlier procedure (21-23). A more important condition to optimize the yield of aminobromopyrazine is that the bromination reaction be carried out in the dark. If the reaction is exposed to light, the yields of **6** and particularly **4** are reduced remarkably compared to those in the dark. On the contrary, the yield of dibromopyrazine **5** was unchanged on exposure to light. On the other hand, when pyridine as an acceptor for hydrogen bromide which formed in the progress of the reaction was absent, the bromination did not proceed throroughly but an unexpected material was also produced. This behavior was significantly exemplified by the bromination of **1**, thus, which led to a formation of 2-amino-6-bromo-5-methylpyrazine (**7**) as well as the brominated pyrazine **4** together with the unreacted starting material. The structure of **7** is established by elemental and spectral analyses. In particular, the nmr spectrum is remarkably informative, *i.e.*, the signal of the methyl group in **7** appears at δ 2.35, which resonates at a lower field than that of aminomethylpyrazines **1,2**, and **3**, or aminobromopyrazines **4** and **6**, all of which have no electron-withdrawing bromine atom at the adjacent carbon of the methyl substituent. Such deviation of the methyl signal was also observed in **5**. This novel formation of **7** is presumably attributed to the suppression of the electrophilic substitution at the 3-position by electron-withdrawing inductive effect of the ammonium group which forms as the reaction proceeds, thus the orientation of this group on bromination is probably opposite to that of free amino group.

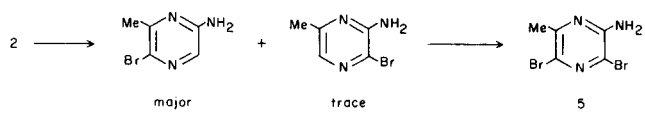
Scheme III



7

Another interest of the bromination is the progress of the reaction on **2** which gives dibromopyrizine **5**. As a result of pursuing the reaction by tlc, the bromination was revealed to proceed almost stepwise. However, monobromopyrazine **8** generates exclusively until at least 0.65 equivalent of bromine is consumed, and the other monobromopyrazine **9** and dibromopyrazine **5** subsequently form.

Scheme IV



major 8 trace 9 5

Table II

Physical Properties of Aminobromopyrazines

Compound	Ir (potassium bromide), cm^{-1}	Nmr (dimethylsulfoxide-d_6), δ		
		CH_3	NH_2	Ring proton
4	3470, 3290, 3160, 1645, 1581, 1510, 1467, 1381 1369, 1318, 1192, 1098, 1049, 894, 791, 758	2.26	6.35	7.86
7	3320, 3160, 1643, 1576, 1516, 1483, 1378, 1314, 1196, 1063, 979, 903, 879, 709	2.35	6.57	7.76
5	3450, 3290, 3150, 1630, 1538, 1446, 1396, 1267, 1109, 1080, 1030, 1020, 977, 749, 710, 666	2.35	6.80	
8	3360, 3320, 3180, 1647, 1570, 1538, 1402, 1373, 1227, 1056, 960, 881, 857, 724, 648	2.34	6.47	7.49
6	3380, 3300, 3200, 1628, 1535, 1443, 1420, 1397, 1248, 1193, 1147, 983, 902, 772, 668	2.27	6.37	7.90

Compound	Mass, m/e (relative intensity)
4	189 (93), M^+ 187 (93), 161 (7), 159 (8), 121 (10), 119 (9), 109 (6), 108 (77), 82 (6), 81 (84), 80 (7), 79 (5), 68 (5), 67 (100), 56 (13), 55 (11), 53 (11), 43 (18), 42 (7), 41 (7), 39 (16)
7	189 (41), M^+ 187 (45), 162 (10), 160 (9), 109 (5), 108 (56), 83 (5), 82 (6), 81 (100), 80 (6), 67 (39), 66 (9), 54 (37), 53 (8), 43 (5), 42 (38), 41 (18), 40 (31), 39 (8)
5	269 (49), 267 (100), M^+ 265 (50), 188 (29), 186 (30), 161 (15), 159 (13), 147 (49), 145 (50), 134 (21), 132 (20), 121 (10), 120 (9), 119 (12), 118 (7), 107 (11), 93 (7), 95 (5), 79 (10), 81 (12), 66 (63), 64 (13), 54 (28), 53 (9), 52 (6), 43 (24), 42 (61), 39 (8)
8	189 (41), M^+ 187 (43), 162 (19), 160 (20), 108 (6), 81 (14), 68 (5), 67 (100), 66 (9), 54 (5), 42 (44), 41 (22), 40 (32), 39 (8)
6	189 (100), M^+ 187 (95), 162 (26), 160 (26), 121 (8), 119 (8), 108 (22), 106 (7), 104 (7), 82 (5), 81 (74), 79 (5), 67 (62), 66 (39), 55 (22), 54 (74), 53 (26), 42 (14)

Table III

Debromination of Aminobromomethylpyrazines (a)

Catalyst	Base	Solvent	4 Yield, % (time) (d)	5 Yield, % (time) (d)	6 Yield, % (time) (d)
5% Pd-C	Et_3N (b)	MeCN	97 (12)	98 (20)	97 (15)
5% Pd-C	Et_3N (b)	AcOET	98 (20)	99 (40)	100 (40)
10% Pd-C	Et_3N (b)	AcOEt	98 (7)	100 (10)	99 (7)
10% Pd-C	KOH (c)	MeOH	97 (3)	93 (8)	95 (4)

(a) Conditions for the hydrogenation were: temperature, 25°; amount of aminobromopyrazine used: 2.7 mmoles; (b) amount of the base and the solvent: triethylamine (5 ml.) in 50 ml. of solvent and (c) potassium hydroxide (7.0 mmoles) in 50 ml. of methanol. (d) Time which was required until uptake of hydrogen ceased: minutes.

Table IV

Physical Properties of Aminomethylpyrazines

Compound	M.p., °C	M.p., °C (literature)	Retention time (c) minutes	Ir (potassium bromide) cm^{-1}
1	120-121 (a)	116-118 (4a) 116 (9) 118 (16)	6.7	3325, 3150, 1661, 1598, 1537, 1483 1387, 1029, 875
2	128-129 (b)	124-125 (4a) 125-126 (16)	7.6	3360, 3320, 3155, 1648, 1587, 1527 1438, 1380, 1261, 1211, 952, 829
3	174 (a)	166-167 (19a) 165-167 (28)	5.3	3395, 3325, 3190, 1643, 1582, 1538 1432, 1382, 1201, 983, 820, 774, 746

(a) Recrystallized from benzene and (b) cyclohexane. (c) The gas chromotogram was recorded on a Hitachi Model 163 instrument equipped 2 m. glass column packed with 2% OV-275 on chromosorb WAW DMCS at 140°.

Compound	Nmr (dimethylsulfoxide-d_6), δ					Mass, m/e (relative intensity)
	CH_3	NH_2	Ring proton		(J, Hz)	
1	2.24	6.03	7.77	7.81	(1.5)	110 (8), M^+ 109 (95), 108 (7), 85 (5), 83 (10), 82 (85), 81 (54), 67 (7), 56 (5), 55 (24), 54 (22), 43 (44), 42 (25), 41 (100), 40 (15), 39 (15)
2	2.23	6.25	7.59	7.73	(0)	110, (8), M^+ 109 (100), 83 (9), 82 (86), 81 (46), 67 (11), 55 (11), 54 (11), 43 (27), 42 (19), 41 (95), 40 (20), 39 (13)
3	2.28	6.08	7.62	7.76	(2.8)	110 (8), M^+ 109 (100), 94 (8), 83 (7), 82 (47), 81 (31), 68 (13), 67 (27), 55 (14), 54 (22), 43 (5), 42 (39), 41 (42), 40 (15)

The structure of **8** is determined by the nmr spectrum on the basis of deviation of the methyl signal to the lower field as predescribed in **7**.

The debromination of aminobromopyrazine to aminopyrazine was almost quantitatively achieved by hydrogenation in the presence of palladium catalyst and base (Table III). The reaction time, however, depended on the catalyst and the solvent. For example, debromination using 10% palladium on carbon in ethyl acetate proceeded three to six times faster than that using 5% catalyst in the same solvent. When 5% palladium catalyst was used, the hydrogenation in acetonitrile was completed enough in half the time required in the case using ethyl acetate. Debromination with 10% palladium catalyst and potassium hydroxide in methanol proceeded the fastest. However, this procedure can not be occasionally applied to dehalogenation of other halopyrazines because the reaction is often very slow or does not proceed at all (24).

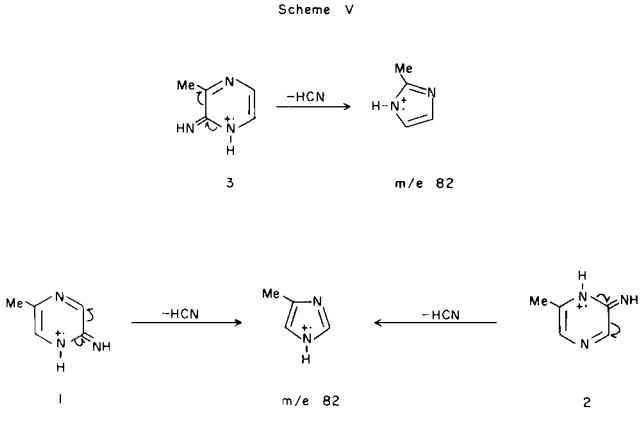
Eventually, aminomethylpyrazines **1**,**2** and **3** were regenerated by the two-stage processes in 73, 91, and 84% overall yields, respectively. These yields were entirely dependent on the yields of bromination.

With the results verified, the application to separate a mixture of aminomethylpyrazines and the scope of this procedure were investigated. For effective separation of the mixture, **2** must be converted into dibromopyrazine **5** because the intermediates **8** and **9** can never be separated from other monobromopyrazines **4** and **6**, respectively. However, when an excess amount of bromine was used, the yields of **4** and **6** were remarkably reduced because of

decomposition with this reagent. Therefore, the precise amount of bromine should be used, which can be determined from the gas chromatography measures the ratio of each aminopyrazine. In this manner, the mixture of aminomethylpyrazines was brominated in 70-80% yields. This result is considerably more satisfactory when compared to the yield (30-50%) by fractional recrystallization. The mixture of aminobromopyrazines could be easily separated by chromatography on silica gel.

Finally, we have found an interesting observation on the fragmentation in the mass spectra of aminopyrazines. The peak at mass 82 results from loss of hydrogen cyanide from the molecular ion. A metastable peak at mass 61.7 (calculated 61.7) provides an evidence to support this fragmentation. The ion at mass 82 in the spectrum of **3** is probably 2-methylimidazole cation (25). On the other hand,

Scheme V



the molecular ion of **1** and **2** probably leads a formation of 4-methylimidazole cation. This speculation is supported by a close resemblence of relative intensities of each ion in the spectra of **1** and **2**.

EXPERIMENTAL

All melting points were determined in capillary tubes and are corrected. Boiling points are uncorrected. Satisfactory analytical data (±0.3% for C, H, N, Br) were obtained for all new compounds listed in Table I. Infrared spectra were recorded on a Hitachi Model EPI-G_3 spectrometer, the nmr spectra on a JEOL Model JNM-MN-100 instrument with tetramethylsilane as an internal standard, and the mass spectra on a Hitachi Model M-70 instrument at 20 eV.

2-Amino-5-methylpyrazine (**1**).

This compound was prepared by condensation of 40% aqueous methylglyoxal (9.02 g., 0.05 mole) with α-aminoacetamidine dihydrobromide (11.75 g., 0.05 mole) according to the procedure of Pitrè and Boveri (9), yield 3.28 g. (60%), m.p. 108-112°. This product is shown by gas chromatography to be a mixture of **1** and **2** in relative ratio about 13:1. Several recrystallizations gave gas-chromatographically pure aminopyrazine **1** as colorless needles. This compound **1** was also prepared as a major product (**1**:**2** = *ca.* 5:1) by condensation of aminomalonamidine with methylglyoxal according to the procedure of Vogl and Taylor (8), followed by hydrolysis and decarboxylation, m.p. 112-116°.

2-Amino-3-methylpyrazine (**3**).

This compound was prepared from 2-methylpyrazine (19.0 g., 0.02 mole) according to the procedure of Hirschberg and Spoerri (19a), yield 7.0 g. (44%), m.p. 80-130°. Since this product was contaminated with a small amount of **2**, pure aminopyrazine **3** was obtained by several recrystallizations.

5-Methylpyrazine-2,3-dicarboxamide.

This material was prepared by esterification of 5-methylpyrazine-2,3-dicarboxylic acid (26) with methanolic hydrogen chloride followed by ammonolysis with methanolic ammonia.

Dimethyl 5-methylpyrazine-2,3-dicarboxylate.

This compound had b.p. 137-138° (4 mm Hg); literature (27) m.p. 32-34°; ir (neat): 2950, 1735, 1310, 1282 cm^{-1}.

5-Methylpyrazine-2,3-dicarboxamide.

This compound had m.p. 216-218°, literature (27) m.p. 215-217°, ir (potassium bromide): 3350, 3140, 1703, 1663 cm^{-1}.

2-Amino-6-methylpyrazine (**2**).

Dicarboxamide prepared above (10.0 g., 0.056 mole) was added in small portions at temperatures below −5° to a solution of sodium hypobromite prepared from bromine (9.36 g., 0.059 mole) and 160 ml. of 2.1 *N* aqueous sodium hydroxide, and the mixture was stirred at −5°C for 30 minutes. Then the temperature was gradually raised and maintained at 70-73° for 1 hour. The resulting solution was cooled to room temperature and acidified with concentrated hydrochloric acid at *p*H 2.5. The mixture was allowed to stand at 0° overnight, and the pastelike product was collected by centrifugal filtration and dried to give 4.2 g. (44%) of 3-amino-5-methylpyrazinecarboxylic acid. The filtrate was again acidified at *p*H 2.5 and allowed to stand at 0° for 7 days to provide an additional crop, 2.2 g. (combined yield 75%) of a mixture of 3-amino-5-methyl- and 3-amino-6-methylpyrazinecarboxylic acids.

A mixture of finely powdered 3-amino-5-methylpyrazinecarboxylic acid (8.6 g., 0.056 mole) in 100 ml. of dry tetralin was stirred and refluxed at 202° for 1 hour, and then cooled to room temperature. The precipitate which formed was collected by filtration and washed with a small amount of petroleum ether. The filtrate was extracted with five 50 ml. portions of 10% hydrochloric acid. The combined extracts were basified with 20% aqueous sodium hydroxide, and the resulting solution was extracted with six 50 ml. portions of ether. Without washing with water, the ethereal

Table V

Elemental Analysis

Compound	Formula	C		H		N		Br	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4	$C_5H_6BrN_3$	31.93	31.76	3.22	3.15	22.35	22.38	42.50	42.34
7	$C_5H_6BrN_3$	31.93	31.64	3.22	3.16	22.35	22.34	42.50	42.25
5	$C_5H_5Br_2N_3$	22.50	22.52	1.89	1.85	15.74	15.81	59.87	60.13
8	$C_5H_6BrN_3$	31.93	31.79	3.22	3.11	22.35	22.38	42.50	42.43
6	$C_5H_6BrN_3$	31.93	31.81	3.22	3.13	22.35	22.43	42.50	42.20

solution was dried over potassium hydroxide pellets and evaporated to give an additional crop. The combined products were sublimed at 100° (0.05 mm Hg) to provide aminopyrazine **2**, yield 3.9 g. (64%).

Bromination of Aminopyrazine.

A solution of bromine (0.84 g., 5.3 mmoles) in 5 ml. of chloroform was added dropwise to a stirred solution of aminomethylpyrazine **1** or **3** (0.546 g., 5.0 mmoles) and pyridine (0.42 g., 5.3 mmoles) in 55 ml. of chloroform at room temperature in the dark. Then the mixture was stirred for 30 minutes and washed with two 5 ml. portions of water. The chloroform solution was dried over mangesium sulfate and evaporated to give aminobromopyrazine **4** or **6**, which was purified by sublimation (100°/0.05 mm Hg.). The purity of these products was sufficient for the successive debromination. Analytical samples were further purified by recrystallization. Bromination of **2** was similarly accomplished by using 2.1 equivalent amount of bromine and pyridine. These results and physical properties of aminobromopyrazines are summarized in Table I and II, respectively.

In the bromination of a mixture of aminomethylpyrazines, 1.1-1.5 equivalent amount of bromine and pyridine was used according to the ratio of the aminopyrazines. The separation of the mixture of the brominated compounds was achieved by chromatography on silica gel (20 g./1.0 g.). The first elution with petroleum ether-benzene (1:1) gave dibromopyrazine **5**, and the second one with benzene provided monobromopyrazine **4**. Further elution with benzene-chloroform or chloroform gave **6**. Each of the brominated compounds was purified by sublimation.

Debromination of Bromopyrazines **4**,**5**, and **6**.

A solution of aminobromopyrazine (2.7 mmoles) in a mixture of base and solvent shown in Table III was hydrogenated in the presence of palladium catalyst (0.5 g./1.0 g.) under atmospheric pressure until the uptake of hydrogen ceased. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. When acetonitrile or methanol was used as the solvent, the residue was extracted with several portions of ethyl acetate and the extract was evaporated to dryness. The crude product was purified by sublimation and recrystallization. These results are summarized in Table III.

Acknowledgment.

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