Studies on Pyrazines. 4. (1). The Synthesis of 2-Hydroxy-6-phenylpyrazine and its Derivatives

Nobuhiro Sato

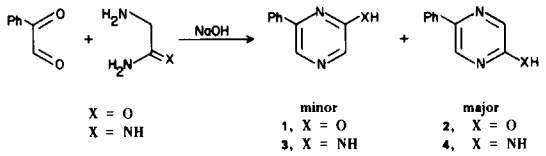
Department of Chemistry, Yokahama City University, Mutsuura-cho, Kanazawa-ku, Yokohama 236, Japan

Received October 26, 1977

This report describes a new method for the preparation of 2-hydroxy-6-phenylpyrazine (**1**). Amino acetal **5** was converted to glycyl amino acetal **7** by two steps in excellent yield. Cyclization of **7** to **1** was accomplished in 33% yield by refluxing in acetic acid followed by oxidation with manganese dioxide. Compound **1** was also prepared by hydrolysis of amino- and methoxypyrazines **3** and **15**, derived from 2-hydroxy-5-phenylpyrazine (**2**) and the 2-amino homologue **4**, respectively, and by decarboxylation of 2-hydroxy-5-phenylpyrazinecarboxylic acid (**19**).

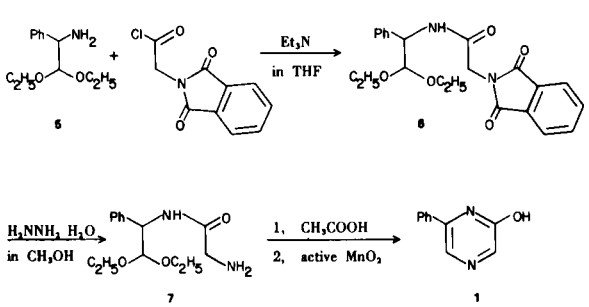
J. Heterocyclic Chem., 15, 665 (1978)

It is well known that hydroxypyrazines are conveniently prepared by condensation of 1,2-dicarbonyl compounds and α-amino acid amides (2,3). In the condensation, when an unsymmetrical dicarbonyl compound is used as a starting material, only one compound is isolated, *e.g.*, on treatment of phenylglyoxal with aminoacetamide 2-hydroxy-5-phenylpyrazine (**2**) is formed but the 6-phenyl homologue **1** was not detected (4,5). However, we have found **1** in the reaction mixture as a minor component (**1**/**2** = *ca.* 1/20) and also have made a similar observation in the reaction of phenylglyoxal with aminoacetamidine (4,6) to form 2-amino-6-phenylpyrazine (**3**) and its 5-phenyl homologue **4**.



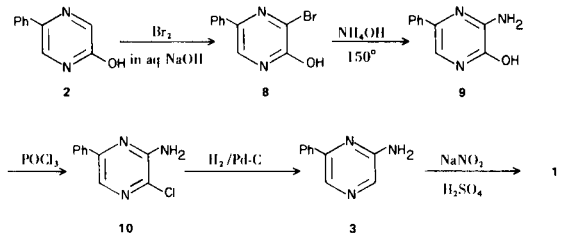
Thus, these condensations are not appropriate for the synthetic preparation of **1** because of low yields and difficult purification (7). In this paper we propose another synthetic method for the title pyrazine **1** (Scheme I). Simultaneously, for the purpose of structural establishment, **1** was prepared by chemical transformation involving the ortho bromination of hydroxy- (8) and aminopyrazines (9-11) **2** and **4**, respectively (Schemes II and III).

Scheme I

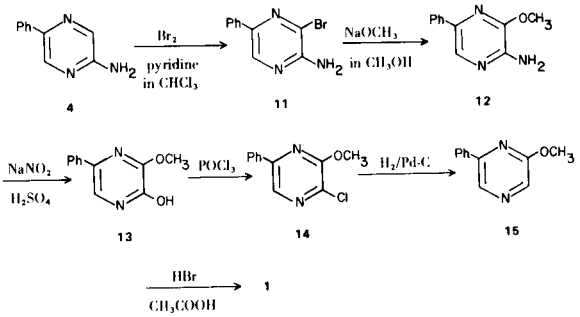


Amino acetal **5** was readily converted to glycyl amino acetal **7** by two steps in excellent yield. Cyclization of **7** to **1**, the key step of this synthetic method, was attempted under various acidities. Glycyl amino acetal **7** was unreactive under mild conditions (*e.g.*, acetic acid-ethanol, 1:3 v/v, reflux 20 hours), and changed to tary material under drastic ones (*e.g.*, trifluoroacetic acid, reflux 5 hours). Consequently, **1** was obtained in 33% yield by refluxing **7** in acetic acid for 5 hours, followed by oxidation with active manganese dioxide.

Scheme II



Scheme III



In Scheme II (12), bromination of **2** with bromine in acetic acid and pyridine, which was previously employed for that of 2-hydroxy-3-phenylpyrazine (8), failed and resulted in formation of tary material and a small amount of 2,3-dihydroxy-5-phenylpyrazine. This bromination was achieved by treating **2** with bromine in aqueous sodium hydroxide. On using one equivalent of bromine in this procedure, a considerable amount of **2** was recovered

unchanged, which complicated the isolation of the brominated product **8**. When **2** was treated, however, with an excess amount of bromine, further bromination occurred at the *para* position of the phenyl group to form 2-hydroxy-3-bromo-5-(4′-bromophenyl)pyrazine (**16**). In contrast, the bromination of aminopyrazine **4** proceeded readily on treatment with bromine in chloroform or acetic acid to form **11** in excellent yield (Scheme III).

Hydroxymethoxypyrazine **13** was also prepared from hydroxybromopyrazine **8** on treatment with sodium methoxide. The methoxylation of the bromo group of **8** and **11** required temperatures up to 130° (13).

On chlorination of the hydroxy group of **9** and **13**, the yields depended upon the original substituents, amino or methoxy groups, as well as upon the reaction conditions. Namely, aminohydroxypyrazine **9** gave **10** in 21% yield on treatment with phosphoryl chloride at reflux for 24 hours, whereas under more drastic conditions (190° for 24 hours) the yield increased to only 34%. In contrast, conversion of methoxyhydroxypyrazine **13** to **14** was achieved in excellent yield under mild conditions such as reflux for 1 hour, while prolonged heating and higher temperatures brought about further displacement of the methoxy group to produce 2,3-dichloro-5-phenylpyrazine.

The methoxy group of **15** was readily hydrolyzed with hydrobromic acid in acetic acid at reflux to produce **1** in excellent yield, but this hydrolysis proceeded incompletely with hydrochloric acid in place of hydrobromic acid. In contrast, an attempt to convert methoxychloropyrazine **14** to 3-chloro-2-hydroxy-6-phenylpyrazine (14) with hydrochloric acid brought about further hydrolysis of the chloro group to form 2,3-dihydroxy-5-phenylpyrazine.

Hydroxyaminopyrazine **9** was also prepared by the Hofmann degradation of 3-hydroxy-6-phenylpyrazinecarboxamide (**17**) which was synthesized by condensation of phenylglyoxal with aminomalonamide (2). In contrast to the previous description (2) and our predescribed observations, this condensation provided a considerable amount of isomeric pyrazine **18** as well as **17**. These isomers could be separated by functional recrystallization from ethanol. Decarboxylation of hydroxypyrazine carboxylic acid **19**, prepared by hydrolysis of **18**, afforded **1** in excellent yield (15).

Scheme IV

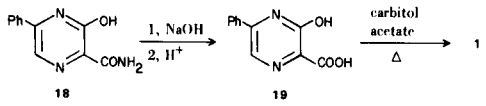
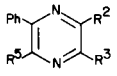


Table I

^{1}H Nmr Spectra of Pyrazine Derivatives



Compound	Solvent (a)	Chemical shift, δ			Coupling constant	
		R^2	R^3	R^5	$J_{2,5}$	$J_{3,5}$ (Hz)
1	A	12.00	8.32	8.04		0.4
2	A	8.13	12.46	8.03	1.5	
8	A		12.84	8.03		
16	A		13.00	8.12		
9	A	6.70	11.80	7.16		
10	B	5.10		8.18		
3	B	4.77	8.31	7.86		0.0
4	A	8.41	5.20	8.03	1.8	
11	A		5.16	8.36		
21	B		5.20			
12	B	4.04	4.89	8.02		
13	A	3.94	12.19	7.57		
14	B	4.09		8.32		
15	B	3.99	8.52	8.09		0.4
17	A	8.39	13.45	8.86		
		8.91				
18	A	13.64	8.46	8.84		
			8.76			
19	A	10.3		8.62		
20	B		8.89	8.49		0.6

(a) A: Dimethylsulfoxide-d_6. B: Deuteriochloroform.

Hydroxypyrazine **1** was converted to 2-chloro-6-phenylpyrazine (**20**) in excellent yield by treating with phosphoryl chloride at temperatures up to 170°.

In the nmr spectra of 2-substituted 6-phenylpyrazines, the ring proton coupling constants are in the range of 0.0-0.6 Hz which agree with the previous descriptions (5,16).

EXPERIMENTAL

Melting points were determined in capillary tubes and are corrected. Boiling points are uncorrected. The infrared spectra were recorded on Hitachi Model EPI-G_3 spectrometer, and the nmr spectra on JEOL JNM-MH-100 instrument with tetramethylsilane as an internal standard. Elemental analytical data are summarized in Table II.

2-Amino-2-phenylacetaldehyde Diethyl Acetal (**5**).

Compound **5** was prepared by reduction of phenylglyoxal diethyl acetal oxime (17) with sodium and ethanol (18), yield 80% from phenylglyoxal diethyl acetal, b.p. 124-125° (10 mm); n_D^{25} 1.4932; ir (neat): 3390, 3310, 1120, 1060 cm^{-1}; nmr (deuteriochloroform): δ 0.91 (3H, t, J = 8.0 Hz), 1.13 (3H, t, J = 8.0 Hz), 1.54 (2H, s), 2.95-3.7 (4H, m), 3.91 (1H, d, 7.0 Hz), 4.28 (1H, d, J = 7.0 Hz), 7.0-7.4 (5H, m).

N-(1'-Phthalimidoacetyl)-2-amino-2-phenylacetaldehyde Diethyl Acetal (**6**).

A solution of phthalimidoacetyl chloride (22.0 g., 0.107 mole) in 50 ml. of dry tetrahydrofuran was added below 5° to a stirred solution of **5** (18.55 g., 0.089 mole) and triethylamine (25 ml.) in 120 ml. of the same solvent. The mixture was stirred for 1 hour at room temperature, and the precipitated product which formed was collected by filtration, washed with cooled water and dried in air to afford 32.35 g. (92%) of **6**, m.p. 190-191°. Recrystallization from ethanol gave colorless prisms, m.p. 192°.

N-Glycyl-2-amino-2-phenylacetaldehyde Diethyl Acetal (**7**).

A mixture of **6** (7.920 g., 0.020 mole) and 80% hydrazine hydrate (1.5 ml.) in 100 ml. of methanol was refluxed for 1 hour and then evaporated to dryness under reduced pressure. Aqueous sodium hydroxide (5%, 200 ml.) was added to the residue, and the mixture was warmed until a solution was obtained. After cooling to room temperature, the solution was extracted with two 50 ml. portions of chloroform. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to afford 5.23 g. (98%) of **7** as an oil, b.p. 180° (0.1 mm); n_D^{25} 1.5152; ir (neat): 3310, 1657, 1518 cm^{-1}; nmr (deuteriochloroform): δ 1.09 (3H, t, J = 7.0 Hz), 1.14 (3H, t, J = 7.0 Hz), 1.51 (2H, s), 3.25 (2H, s), 3.31-3.38 (4H, m), 4.53 (1H, d, J = 3.4 Hz), 5.11 (1H, dd, J = 9.0, 3.4 Hz), 7.12-7.30 (5H, m), 7.31 (1H, s), 8.02 (1H, d, J = 9.0 Hz).

2-Hydroxy-6-phenylpyrazine (**1**).

A. From Glycyl Amino Acetal **7**.

A mixture of **7** (21.83 g., 0.082 mole) in 400 ml. of acetic acid was refluxed for 6 hours, then condensed to 50 ml. and poured into 500 ml. of water. The solution was extracted with three 200 ml. portions of chloroform, and the combined extracts were washed with water and dried over magnesium sulfate overnight. Active manganese dioxide (20 g.) was added to the mixture, and the resulting mixture was stirred at room temperature overnight and then filtered. An insoluble matter was washed with hot chloroform, and the combined filtrate was evaporated to dryness under reduced pressure. The viscous residue was crystallized with a small amount of methanol, and the precipitate which formed was collected by filtration and dried in air to afford 4.66 g. (33%) of **1**, m.p. 238-240°. Recrystallization from methanol provided colorless tiny needles, m.p. 243-244°; literature (5) m.p. 239-241°; ir (potassium bromide): 1515, 1419, 1321, 1270, 1141, 1050 cm^{-1}.

B. From 2-Amino-6-phenylpyrazine (**3**).

This conversion was accomplished by the procedure of Palamidessi and Bernardi (19) using **3** instead of 2-hydroxy-5-aminopyrazine, yield 85%.

C. From 2-Methoxy-6-phenylpyrazine (**15**).

A mixture of **15** (0.726 g., 3.9 mmoles) in 47% hydrobromic acid (10 ml.) and acetic acid (10 ml.) was refluxed for 2 hours and then evaporated to dryness under reduced pressure. Water was added to the residue, and the precipitated solid which formed was collected by filtration and dried to afford 0.603 g. (90%) of **1**.

D. From 3-Hydroxy-5-phenylpyrazinecarboxylic Acid (**19**).

A mixture of **19** (13.615 g., 0.063 mole) in 60 ml. of carbitol acetate was heated at 200° for 30 minutes and then cooled to room temperature. To the mixture was added 120 ml. of petroleum ether, and the precipitate which formed was collected by filtration to give 10.381 g. (96%) of **1**.

2-Hydroxy-5-phenylpyrazine (**2**).

This compound was prepared by condensation of phenylglyoxal hydrate (38.0 g., 0.25 mole) with α-aminoacetamide hydrochloride (27.6 g., 0.25 mole) according to the procedure of Karmas and Spoerri (3). Three recrystallizations from methanol gave 22.7 g. (53%) of **2** as colorless prisms, m.p. 212°; literature (4) m.p. 207-210°; (5) m.p. 212-214°; ir (potassium bromide): 3200-2600 (broad), 1660, 1497, 1382, 1235, 990 cm^{-1}.

Detection of **1** in the reaction mixture was accomplished as follows. The crude product was chlorinated with phosphoryl chloride at 190° affording a mixture of the chloropyrazines (98%). The glc analysis (5% OV-275 on chromosorb WAW DMSC, 2 m. glass column at 140°) shows the formation of 2-chloro-6-phenylpyrazine (**20**) and its 5-phenyl homologue (4,5) in the relative ratio of about 5:95.

2-Hydroxy-3-bromo-5-phenylpyrazine (**8**).

Bromine (16.0 g., 0.10 mole) was added dropwise below 5° to a stirred solution of **2** (17.20 g., 0.10 mole) in 120 ml. (0.12 mole) of 1 *N* aqueous sodium hydroxide, and the resulting mixture was allowed to stand at room temperature overnight. The precipitated solid was collected by filtration and dried in air to afford 27.5 g. of a mixture of **2** and **8**. Several recrystallizations from ethanol gave 14.85 g. (59%) of **8** as colorless needles, m.p. 223-224°; ir (potassium bromide): 3200-2700 (broad), 1655, 1495, 1237, 1049, 866 cm^{-1}. Similar treatment of **2** with three equivalents of bromine gave **16**, yield 76%; m.p. 227-228°; ir (potassium bromide): 3200-2900 (broad), 1679, 1632, 1606, 823 cm^{-1}.

2-Hydroxy-3-amino-5-phenylpyrazine (**9**).

A. From 2-Hydroxy-3-bromo-5-phenylpyrazine (**8**).

A mixture of **8** (2.625 g., 0.011 mole) and 150 ml. of aqueous ammonium hydroxide saturated with ammonia gas at 0° in the presence of activated copper powder was heated at 150° in a stainless steel autoclave for 24 hours. Then, an insoluble matter was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residual solid was washed

with a small amount of water and dried to give 1.378 g. (70%) of **9**, m.p. 310° dec.; ir (potassium bromide): 3390, 3190, 1667, 1618, 1529 cm^{-1}.

B. From 3-Hydroxy-6-phenylpyrazinecarboxamide (**17**).

The procedure of McDonald and Ellingson (20) was employed using as starting material **17** instead of 3-hydroxypyrazinecarboxamide, yield 92%.

2-Amino-3-chloro-6-phenylpyrazine (**10**).

A mixture of **9** (7.465 g., 0.04 mole) and phosphoryl chloride (30 ml.) in a sealed tube was heated at 190° for 24 hours and then poured into ice-water. The resulting solution was basified with concentrated aqueous ammonium hydroxide, and the precipitate which formed was collected by filtration, dried and extracted with hot benzene by Soxlet extractor. The benzene solution was evaporated under reduced pressure, and the residue was sublimed at 185° (0.01 mm) to afford 2.871 g. (34%) of **10**, m.p. 190°. Recrystallization from benzene provided colorless needles, m.p. 191-192°; ir (potassium bromide): 3460, 3270, 3140, 1618, 1514, 1445, 1110 cm^{-1}.

2-Amino-6-phenylpyrazine (**3**).

A solution of **10** (1.624 g., 7.9 mmoles) and triethylamine (10 ml.) in 120 ml. of ethyl acetate was hydrogenated in the presence of 10% palladium on carbon (1.6 g.) under atmospheric pressure until the uptake of hydrogen ceased (*ca.* 1.5 hours) and then filtered. The filtrate was evaporated under reduced pressure to give 1.323 g. (98%) of **3**, m.p. 126-127°. Recrystallization from aqueous ethanol (7:3 v/v) afforded colorless plates, m.p. 126-127°; literature (21) m.p. 125-126°; (5) m.p. 126-128°; ir (potassium bromide): 3370, 3270, 3100, 1626, 1527, 1438, 1418 cm^{-1}.

2-Amino-5-phenylpyrazine (**4**).

This compound was prepared by condensation of phenylglyoxal hydrate (14.66 g., 0.0964 mole) with α-aminoacetamidine hydrobromide (21.69 g., 0.0923 mole) according to the procedure of Pitrè and Boveri (6), yield 8.24 g. (52%); m.p. 143°. The analytical sample was obtained by hydrogenation of **11** in the presence of palladium catalyst. Recrystallization from aqueous ethanol (7:3 v/v) gave colorless needles, m.p. 150°; literature (6) m.p. 142°; (4) m.p. 141-143°; ir (potassium bromide): 3340, 3160, 1648, 1589, 1536, 1478, 1446, 1386 cm^{-1}.

2-Amino-3-bromo-5-phenylpyrazine (**11**).

A solution of bromine (3.13 g., 0.02 mole) in 10 ml. of chloroform was added dropwise below -10° to a stirred solution of crude **4**, which was contaminated with a small amount of **3**, (3.328 g., 0.019 mole) and pyridine (1.55 g., 0.02 mole) in 300 ml. of chloroform. The resulting solution was stirred at 20° for 15 hours and then washed with three 200-ml. portions of water. The chloroform solution was dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was dissolved in benzene, and the solution was passed through a column of silica gel (80 g.). The chromatogram was developed first with petroleum ether-benzene (1:1) to afford 0.258 g. (4%) of 2-amino-3,5-dibromo-6-phenylpyrazine (**21**), m.p. 127-128° from cyclohexane; ir (potassium bromide): 3450, 3300, 3200, 1617, 1530, 1510, 1420, 1390, 1180, 1170 cm^{-1}. Further elution, with benzene, gave 4.283 g. (88%) of **11**, which was recrystallized from cyclohexane to provide colorless needles, m.p. 153-154°; ir (potassium bromide): 3450, 3275, 3160, 1612, 1513, 1456, 1440 cm^{-1}.

2-Amino-3-methoxy-5-phenylpyrazine (**12**).

A solution of **11** (3.761 g., 0.015 mole) and 60 ml. of methanol containing 0.48 g. of sodium in a stainless steel autoclave was heated at 134° for 8 hours, and the resulting solution was evaporated to dryness under reduced pressure. The residue was washed with water, dried, sublimed at 130° (0.01 mm) and recrystallized from *n*-hexane to give 2.560 g. (85%) of **12** as colorless needles, m.p. 138-139°; ir (potassium bromide): 3470, 3310, 3170, 1642, 1481, 1216 cm^{-1}.

2-Hydroxy-3-methoxy-5-phenylpyrazine (**13**).

A. From 2-Amino-3-methoxy-5-phenylpyrazine (**12**).

This procedure is essentially the same as the synthesis of **1** from **3**. Recrystallization from methanol gave pale yellow plates, yield 65%, m.p. 249-250°; ir (potassium bromide): 3210, 1706, 1640, 1611, 1555, 1441, 1293, 1148 cm^{-1}.

B. From 2-Hydroxy-3-bromo-5-phenylpyrazine (**8**).

This conversion was achieved by the procedure for synthesis of **12**, yield 92%.

2-Chloro-3-methoxy-5-phenylpyrazine (**14**).

A mixture of **13** (1.042 g., 5.2 mmoles) in 5 ml. of phosphoryl chloride was stirred and refluxed for 1 hour and then cooled to room temperature. The solution was poured into ice-water and extracted with three 20-ml. portions of ether. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to give 0.991 g. (80%) of **14**, m.p. 84-86°. Recrystallization from *n*-hexane afforded colorless needles, m.p. 86-87°; ir (potassium bromide): 1530, 1446, 1423, 1366, 1111 cm^{-1}.

2-Methoxy-6-phenylpyrazine (**15**).

A. From 2-Chloro-3-methoxy-5-phenylpyrazine (**14**).

This conversion was achieved by the procedure for synthesis of **3**, yield 96%, b.p. 113-114° (1 mm), m.p. 46-48°; ir (potassium bromide): 1540, 1445, 1427, 1396, 1282 cm^{-1}.

B. From 2-Chloro-6-phenylpyrazine (**20**).

A mixture of **20** (2.012 g., 0.0106 mole) and 20 ml. of methanol containing 0.36 g. of sodium was refluxed for 5 hours and then evaporated to dryness under reduced pressure. Water (40 ml.) was added to the residue, and the resulting solution was extracted with three 30 ml. portions of ether. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to give 1.877 g. (96%) of **14**.

3-Hydroxy-5 and 6-phenylpyrazinecarboxamide (**18**) and (**17**).

A solution of phenylglyoxal hydrate (76 g., 0.50 mole) in 200 ml. of methanol was slowly added below -35° to a stirred suspension of aminomalonamide (58.5 g., 0.50 mole) in 200 ml. of methanol and 100 ml. of water. To the mixture was added dropwise below -35°, 100 ml. (0.6 mole) of 6 *N* aqueous sodium hydroxide. The resulting mixture was gradually warmed to 0° over a period of 2 hours and maintained at 0° overnight. The precipitate which formed was collected by filtration, triturated with water, and the suspension was acidified with 6 *N* hydrochloric acid at *p*H 3. The precipitate was collected by filtration and recrystallized from ethanol to give 29.8 g. (28%) of **18**, m.p. 261°. Further recrystallization from ethanol afforded pale yellow tiny needles, m.p. 262°; ir (potassium bromide): 3430, 3250, 3200, 1664, 1587, 1395, 1313, 1200 cm^{-1}. The mother liquor was also acidified with 6 *N* hydrochloric acid, and the precipitate which formed was washed with methanol and recrystallized from methanol to give 10.9 g. (10%) of **17**, m.p. 255°. Further recrystallization from methanol afforded pale yellow needles,

Table II

Elemental Analysis

Compound	Formula	C		H		N		Halogen		
		Calcd.	Found	Calcd.	Found	Calcd.	Found		Calcd.	Found
5	$C_{12}H_{19}NO_2$	68.86	68.94	9.15	9.13	6.69	6.67			
6	$C_{22}H_{24}N_2O_5$	66.65	66.82	6.10	6.02	7.07	7.05			
7	$C_{14}H_{22}N_2O_3$	63.13	62.87	8.33	8.26	10.52	10.46			
1	$C_{10}H_8N_2O$	69.75	69.89	4.68	4.74	16.27	16.44			
2	$C_{10}H_8N_2O$	69.75	69.97	4.68	4.58	16.27	16.14			
8	$C_{10}H_7BrN_2O$	47.84	47.74	2.81	2.69	11.16	11.12	Br:	31.83	31.57
9	$C_{10}H_9N_3O$	64.16	63.98	4.85	4.62	22.45	22.33			
10	$C_{10}H_8ClN_3$	58.41	58.63	3.92	3.97	20.34	20.31	Cl:	17.24	17.10
3	$C_{10}H_9N_3$	70.15	69.87	5.30	5.36	24.55	24.75			
4	$C_{10}H_9N_3$	70.15	70.32	5.30	5.34	24.55	24.35			
11	$C_{10}H_8BrN_3$	48.02	48.11	3.22	3.17	16.80	16.82	Br:	31.95	31.87
21	$C_{10}H_7Br_2N_3$	36.51	36.61	2.14	2.27	12.77	13.01	Br:	48.58	48.38
12	$C_{11}H_{11}N_3O$	65.67	65.74	5.51	5.51	20.88	20.70			
13	$C_{11}H_{10}N_2O_2$	65.33	65.34	4.98	5.03	13.86	14.15			
14	$C_{11}H_9ClN_2O$	59.88	59.99	4.11	4.15	12.69	12.89	Cl:	16.07	16.10
15	$C_{11}H_{10}N_2O$	70.95	70.74	5.41	5.42	15.05	15.07			
16	$C_{10}H_6Br_2N_2O$	36.40	36.50	1.83	1.80	8.49	8.66	Br:	48.43	48.63
17	$C_{11}H_9N_3O_3$	61.39	61.56	4.22	4.13	19.53	19.42			
18	$C_{11}H_9N_3O_3$	61.39	61.27	4.22	4.04	19.53	19.43			
19	$C_{11}H_8N_2O_3$	61.11	61.09	3.73	3.88	12.96	13.10			
20	$C_{10}H_7ClN_2$	63.01	62.97	3.70	3.67	14.69	14.74	Cl:	18.60	18.73

m.p. 257°; ir (potassium bromide): 3430, 3270, 3205, 1668, 1588, 1449, 1389, 1182 cm^{-1}.

3-Hydroxy-5-phenylpyrazinecarboxylic Acid (**19**).

A mixture of **18** (10.75 g., 0.050 mole) in 200 ml. of 10% aqueous sodium hydroxide was refluxed for 20 hours. After cooling to room temperature, an insoluble matter was removed by filtration, and the filtrate was acidified with 6 *N* hydrochloric acid and allowed to stand at 0° overnight. The precipitate which formed was collected by filtration and dried at 110° to give 11.5 g. of solid. Recrystallization from 2 l. of ethanol afforded 9.48 g. (88%) of **19** as yellow needles, m.p. 219-220°; literature (21) m.p. 208-209°; ir (potassium bromide): 3070-2800 (broad), 1747, 1618, 1420, 1301, 1233, 1145 cm^{-1}.

2-Chloro-6-phenylpyrazine (**20**).

A mixture of **1** (1.720 g., 1.0 mmole) and phosphoryl chloride (10 ml.) in a sealed tube was heated at 170° for 12 hours and then poured into ice-water. The resulting solution was neutralized with concentrated aqueous ammonium hydroxide and extracted with three 20 ml. portions of ether. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to give 1.868 g. (98%) of **20**, m.p. 34-35°. Distillation and recrystallization from *n*-hexane afforded colorless needles, b.p. 111-112° (1 mm); m.p. 34-35°; literature (5) b.p. 99-100° (0.3 mm), m.p. 30-31°; ir (potassium bromide): 1512, 1421, 1385, 1151 cm^{-1}.

Acknowledgement.

The author wishes to thank Dr. J. Adachi and Dr. T. Nakagawa for their helpful suggestions.

REFERENCES AND NOTES

(1) Part 3: N. Sato and J. Adachi, *J. Org. Chem.*, **43**, 341 (1978).

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

(3) G. Karmas and P. E. Spoerri, *ibid.*, **74**, 1580 (1952).

(4) S. Sugiura, S. Inoue, Y. Kishi and T. Goto, *Yakugaku Zasshi*, **89**, 1646 (1969); *Chem. Abstr.*, **72**, 90404 (1970).

(5) P. J. Lont and H. C. van der Plas, *Rec. Trav. Chim.*, **92**, 449 (1973); *Chem. Abstr.*, **78**, 147909 (1973).

(6) D. Pitrè and S. Boveri, *Chem. Ber.*, **100**, 560 (1967).

(7) Aminopyrazines **3** and **4** could not be directly separated from the reaction mixture. On treatment of the mixture with bromine, **3** was converted to 2-amino-3,5-dibromo-6-phenylpyrazine (**21**), while **4** was converted to **11**. These brominated products were separable by column chromatography. Therefore, the pure aminopyrazines **3** and **4** were obtained by hydrogenation of **21** and **11**, respectively (see Experimental).

(8) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **78**, 4071 (1956).

(9) R. C. Ellingson and R. L. Henry, *ibid.*, **70**, 1257 (1948).

(10) B. Carmerino and G. Palamidessi, *Gazz. Chim. Ital.*, **90**, 1807 (1960).

(11) G. Palamidessi and L. Bernardi, *ibid.*, **91**, 1438 (1961).

(12) 2-Hydroxy-5-bromo-3-phenylpyrazine is expected as a useful starting material for synthesis of **1**, but this compound is not appropriate for our purpose because the para bromo group is extremely inert to nucleophilic displacement by base: Reference 8.

(13) Similar observation has emerged: G. Palamidessi, *Farmaco, Ed. Sci.*, **18**, 557 (1963); *Chem. Abstr.*, **59**, 13975 (1963).

(14) It is known that 2-hydroxy-3-bromopyrazines are readily

hydrolyzed with hydrobromic acid to form 2,3-dihydroxypyrazines: Reference 8.

(15) Decarboxylation of **19** to **1** has been reported: Reference 5.

(16) R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, **72**, 1646 (1968).

(17) T. P. Karpentsky and E. H. White, *J. Org. Chem.*, **37**, 339 (1972).

(18) W. H. Carothers and W. L. McEwen, *Org. Synth., Coll. Vol.* **2**, 319 (1943).

(19) G. Palamidessi and L. Bernardi, *J. Org. Chem.*, **29**, 2491 (1964).

(20) F. G. McDonald and R. C. Ellingson, *J. Am. Chem. Soc.*, **69**, 1034 (1947).

(21) F. E. King and P. C. Spensley, *J. Chem. Soc.*, 2144 (1952).