Studies on Pyrazines. **14** [1].

The Syntheses of 2,5-Dihydroxypyrazines and Their Derivatives

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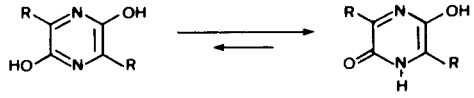
Received October 30, 1985

Reaction of phenylglycinamide (**1c**) with ethyl benzoylformate (**2c**) in the presence of refluxing ethanolic sodium ethoxide gave 2,5-dihydroxy-3,6-diphenylpyrazine (**3i**) in 19% yield. This synthetic method, however, was limited to the preparation of **3i**. On the other hand, α-aminoamides **1** condensed with α-ketoesters **2** to give the intermediates **5**, which were also prepared by condensation of **1** with α-ketalesters **6**, followed by hydrolysis of the ketal moeity. Cyclization of **5** with refluxing methanolic sodium methoxide gave only disubstituted 2,5-dihydroxypyrazines **3**. Acetylation of **5** with refluxing acetic anhydride/acetic acid led to direct formation of 2,5-diacetoxypyrazines **9**. Similarly, compounds **5** could be converted into 2,5-dichloropyrazines **4**.

J. Heterocyclic Chem., **23**, 871 (1986).

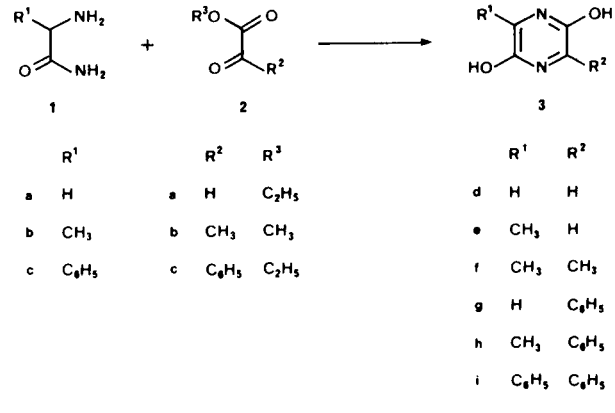
The 2,5-dihydroxypyrazines are a remarkably interesting class of compounds in pyrazine chemistry since the predominant tautomer, 5-hydroxy-2(1*H*)-pyrazinone, was found to undergo a Diels-Alder reaction with electron-deficient and strained olefin affording a bicyclic adduct [2-4]. The first example of the synthesis for 2,5-dihydroxypyrazine was the 3-benzyl-6-methyl substituted compound,



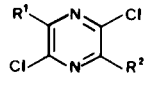
which was unexpectedly formed by isomerization of 3-benzylidene-6-methyl-2,5-piperazinedione [5]. Subsequently, Karmas and Spoerri reported [6] that 2,5-dihydroxy-3,6-dimethyl- and -3,6-diphenylpyrazines were prepared by ether cleavage of the corresponding 2,5-dimethoxypyrazines with methanolic sodium methoxide at 170-180°. The same workers also showed that these 2,5-dihydroxypyrazines exhibited a relatively high degree of stability to base but they were sensitive to acid resulting in hydrolytic fission of the pyrazine ring. Conversely, monoalkyl or monoaryl 2,5-dihydroxypyrazines were found to be very unstable even to base. Thus, the dihydroxypyrazines could not be obtained when the dimethoxypyrazines were treated with methanolic sodium methoxide under the above reaction conditions although the starting material were completely consumed. Indeed, we have not found any instance of a successful synthesis for monosubstituted 2,5-dihydroxypyrazines whereas a few disubstituted compounds have been described in literatures [3,7,8]. As a part of our synthetic approach to the title compounds, we investigated the condensation reactions of α-aminoamides and α-ketoesters. We present here such a construction of 2,5-dihydroxypyrazines and their derivatives, in particular 2,5-diacetoxypyrazines.

Treatment of phenylglycinamide (**1c**) and ethyl benzoylformate (**2c**) with refluxing ethanolic sodium ethoxide gave the expected 2,5-dihydroxy-3,6-diphenylpyrazine (**3i**). Another possible isomer, 2,6-dihydroxy-3,5-diphenylpyrazine, which was readily prepared by a two-step sequence of reactions starting from 3,6-diphenyl-1-hydroxy-2(1*H*)-pyrazinone [9], was not detected in the condensation product. The cyclization reaction to **3i** was best effected by using 1.2-2.2 equivalents of sodium methoxide to 19% yield, but reacting with a large excess of the base decreased the yield of **3i** greatly. The structure of **3i** was further confirmed by conversion into 2,5-dichloro-3,6-diphenylpyrazine (**4i**) easily obtained by chlorination of 3,6-diphenyl-2,5-piperazinedione with phosphoryl chloride [10]. Unlike the successful synthesis of **3i**, reaction of α-aminoamide **1c** with ethyl glyoxylate (**2a**) or methyl pyruvate (**2b**) in an analogous fashion failed to produce the 2,5-dihydroxypyrazines **3**,

Scheme 1



	1		2		3	
	R^1		R^2	R^3	R^1	R^2
a	H	a	H	C_2H_5	H	H
b	CH_3	b	CH_3	CH_3	CH_3	H
c	C_6H_5	c	C_6H_5	C_2H_5	CH_3	CH_3
					H	C_6H_5
					CH_3	C_6H_5
					C_6H_5	C_6H_5



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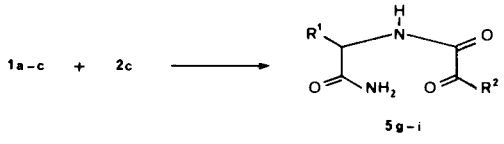
giving only a small amount of the starting α-aminoamides upon work-up. We therefore turned our attention to the isolation of the intermediates **5**, which would be expected to undergo more varied cyclization reactions to 2,5-dihydroxypyrazines **3** or their derivatives.

Ethyl benzoylformate (**2c**) was treated with α-aminoamides **1a-c** in methanol to afford the corresponding intermediate **5** in good yields (see Table 1). However, reaction of α-aminoamides **1** with methyl pyruvate (**2b**) yielded a tarry material instead of giving compounds **5**. The desired intermediates **5e′,f** were obtained though in low yields, by reaction of the corresponding α-aminoamides **1** with pyruvic acid in the presence of dicyclohexylcarbodiimide as the condensing agent. The synthesis of **5d,e,e′,f** was most effectively carried out by condensation of α-aminoamides **1** and α-ketalesters **6**, followed by hydrolysis of the ketal moeity in the resulting product **7**, as outlined in Scheme 3. Trifluoroacetic acid was of choice for hydrolysis of **7** to afford almost quantitatively the corresponding compounds **5**. The results are summarized in Table 2. The parent compound **5d** was alternatively prepared by condensation of dimethyl tartrate with glycinamide (**1a**) and oxidative cleavage of the resulting product **8** with periodic acid in 39% overall yield (see Scheme 4).

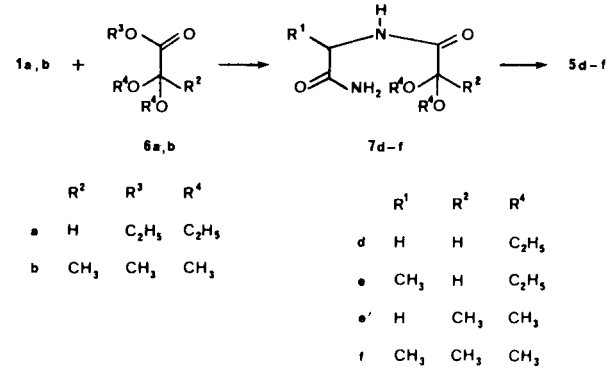
Conversion of **5f,h,i** into the corresponding disubstituted 2,5-dihydroxypyrazines **3** could be accomplished by treatment with refluxing methanolic sodum methoxide (see Table 3). The yields of **3** were optimized by using 2 equivalents of the base, in contrast prolonged heating

Scheme 2

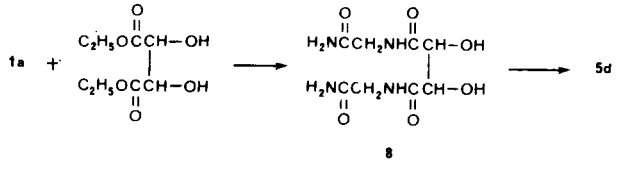


caused decomposition of the desired products **3**. As anticipated, attempts to convert **5d,e,g** to the parent and monosubstituted 2,5-dihydroxypyrazines **3** under the same reaction conditions resulted in a slight formation of unidentified solids, probably decomposition products.

Scheme 3



Scheme 4



We previously reported [11] successful cyclization of *N*-oxamoyl α-aminoketals in acetic acid to 2,3-dihydroxypyrazines. As cited above, however, the acidic reagents are clearly unsuitable for the preparation of acid-sensitive 2,5-dihydroxypyrazines. Despite their instability to acidic

Table 1

Condensation Reactions of α-Aminoamides **1** with Ethyl Benzoylformate (**2c**) to Compounds **5g-i**

α-Aminoamide	Reaction Conditions Temparature/time	Product	Yield, %
1a	rt [a]/ 10 days	**5g**	69
1b	rt [a]/ 24 hours	**5h**	76
1c	40°/3.5 hours	**5i**	86

[a] Room temperature.

Table 2

Preparation of Compounds **5d-f**

α-Aminoamide	α-Ketalester	Condensation Temperature/time	Reaction Product	Yield, %	Hydrolysis of **7** Product	Yield, %
1a	**6a**	rt [a]/3 days	**7d**	61	**5d**	94
1a	**6b**	50°/27 days	**7e′**	49	**5e′**	99
1b	**6a**	50°/15 days	**7e**	64	**5e**	98
1b	**6b**	40°/74 days	**7f**	39	**5f**	96

[a] Room temperature and then 50° for 3 hours.

Table 3

Preparation of 2,5-Dihydroxypyrazines **3**

Starting Material	Reagent	Reaction Time	Product	Yield, %
5f	CH_3ONa/CH_3OH	1 hour	**3f**	27
5h	CH_3ONa/CH_3OH	15 minutes	**3h**	37
5i	CH_3ONa/CH_3OH	3 hours	**3i**	70
5i	CH_3CO_2H	20 hours	**3i**	47

Table 4

Preparation of 2,5-Diacetoxypyrazines **9**

Starting Material	Reaction Time, hour	Product	Yield, %
5d	4	**9d**	28
5e	3	**9e**	9
5f	9	**9f**	24
5g	140 [a]	**9g**	15
5h	120	**9h**	52
5i	5	**9i**	68

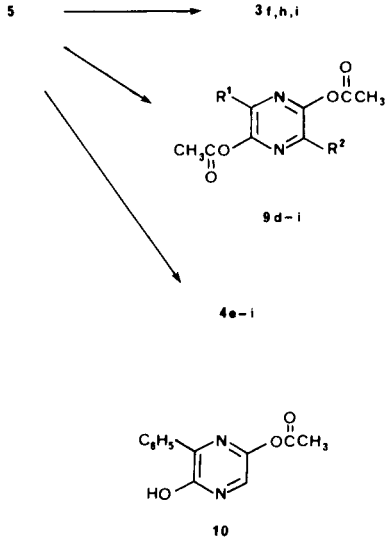
[a] At 80-90°.

media, 2,5-dihydroxy-3,6-diphenylpyrazine (**3i**) was exceptoinally easy to prepare by cyclization of **5i** with refluxing acetic acid. On the other hand, an addition of acetic anhydride to the acetic acid solution brought about the cyclization of **5** and successive acetylation of the resulting 2,5-dihydroxypyrazines **3** to give 2,5-diacetoxypyrazines **9**, some of which were independently prepared by acetylation of 2,5-dihydroxypyrazines **3** with the same reagent. On the direct conversion of **5** to **9**, large excess of acetic anhydride and high dilution procedure had an effect on improving the yields of **9**. A lack of the acid anhydride did not sufficiently achieve the acetylation, *e.g.*, reaction of **3g** with 4 equivalents of acetic anhydride in similar fashion preferred the formation of monoacetoxypyrazine **10** (yield 18%) rather than that of diacetoxypyrazine **9g** (yield 2%). Structure of the former product, or the position of acetoxy group, was speculated by ^{1}H-nmr spectrum. Thus, methyl signal of the acetyl group in the monoacetoxypyrazine appears at δ 2.31, which corresponds to estimated chemical shift of methyl protons in 5-acetoxy-2-hydroxy-3-phenylpyrazine **10** (δ 2.3) rather than those in the 6-phenyl analogue (δ 2.2) [12]. On the other hand, reaction of **7** with acetic anhydride in refluxing acetic acid was expected to produce diacetoxypyrazines **9** without isolating the intermediate **5**, but the majority of the starting material was recovered unchanged upon work-up. The ketal moeity of **7** still survived refluxing trifluoroacetic acid and acetic anhydride for 2-3 hours; under the reaction conditions the compound **7** underwent acetylation of the amide group. Several attempts for conversion of diacetoxypyrazines **9** into the parent, 3-methyl-, or 3-phenyl-2,5-dihydroxypyrazine failed, *i.e.*, no reaction at all took place. However, 2,5-diacetoxy-3,6-dimethylpyrazine **9f** was successfully transformed to the dihydroxypyrazine **3f** by treatment with potassium hydrogen carbonate in refluxing methanol in 53% yield.

Direct conversion of **5** into 2,5-dichloropyrazines **4**, most of which were known compounds, was similarly accomplished by reacting with phosphoryl chloride under reflux in 2-32% yields.

Our recent investigations revealed that 2,5-dihydroxy-3-phenylpyrazine **3g** was unstable even to neutral solution resulting in fission of the pyrazine ring. These results will be described in a future publication.

Scheme 5



EXPERIMENTAL

All melting points were determined in capillary tubes and are uncorrected. Elemental analytical data were obtained for all new compounds and are summarized in Table 6. The ^{1}H-nmr spectra were recorded on a JEOL JMN-MH-100 instrument with tetramethylsilane as an internal standard, and those of pyrazine compounds are summarized in Table 5.

2-Aminopropionamide (**1b**).

Ethyl 2-bromopropionate (146 g, 0.81 mole) was added dropwise to concentrated ammonium hydroxide (800 ml) saturated with ammonia gas at 0°. The resulting solution was stirred for 3 hours below 0°, and allowed to stand at 0-2° for 7 days. After standing for additional 7 days at room temperature, the solution was evaporated below 50° (bath temperature), and the residual oil was crystallized from acetone on cooling to give the hydrobromide of the title compound **1b** (131 g, 96%), mp 164-169° (lit [13] mp 156-160°).

A solution of methanol (50 ml) containing sodium methoxide (2.6 g, 0.048 mole) was added dropwise to a solution of the hydrobromide of **1b** (7.7 g, 0.046 mole) in methanol (150 ml) at room temperature. The mixture was stirred for 2 hours and then evaporated below 40° *in vacuo*. The

Table 5

^{1}H-NMR Spectral Data of Pyrazine Derivatives

Compound	Solvent [a]	Chemical Shift, δ (ppm)
3f	A	2.17(s, 6H, CH_3), 10.3 (br s, 2H, OH)
3h	A	2.29 (s, 3H, CH_3), 7.35-7.5 (m, 3H, C_6H_5), 8.1-8.25 (m, 2H, C_6H_5), 10.7 (br s, 2H, OH)
3i	A	7.4-7.6 (m, 6H, C_6H_5), 8.15-8.3 (m, 4H, C_6H_5), 11.0 (br s, 2H, OH)
9d	B	2.36 (s, 6H, CH_3CO), 8.27 (s, 2H, pyrazine)
9e	B	2.38 (s, 6H, CH_3CO), 2.46 (s, 3H, CH_3), 8.16 (s, 1H, pyrazine)
9f	B	2.36 (s, 6H, CH_3CO), 2.40 (s, 6H, CH_3)
9g	B	2.25 (s, 3H, CH_3CO), 2.39 (s, 3H, CH_3CO), 7.4-7.55 (m, 3H, C_6H_5), 7.75-7.9 (m, 2H, C_6H_5), 8.24 (s, 1H, pyrazine)
9h	B	2.24 (s, 3H, CH_3CO), 2.39 (s, 3H, CH_3CO), 2.48 (s, 3H, CH_3), 7.4-7.5 (m, 3H, C_6H_5), 7.75-7.9 (m, 2H, C_6H_5)
9i	B	2.29 (s, 6H, CH_3CO), 7.45-7.6 (m, 2H, C_6H_5), 7.85-8.0 (m, 2H, C_6H_5)
4e	B	2.63 (s, 3H, CH_3), 8.26 (s, 1H, pyrazine)
10	A	2.31 (s, 3H, CH_3CO), 7.4-7.5 (m, 3H, C_6H_5), 7.66 (s, 1H, pyrazine), 8.2-8.35 (m, 2H, C_6H_5), 12.5 (br s, 1H, OH)

[a] A: DMSO-d_6; B: deuteriochloroform.

Table 6

Analytical Data [a]

Compound	Mp, °C ([b])	Formula	Analysis, % Calcd./Found C	H	N
5g	122-123 (A)	$C_{10}H_{10}N_2O_3$	58.29 57.92	4.89 4.65	13.58 13.60
5h	164-165 (B)	$C_{11}H_{12}N_2O_3$	59.99 60.21	5.49 5.36	12.72 12.67
5i	202-203 (C)	$C_{16}H_{14}N_2O_3$	68.07 68.38	5.00 4.73	9.92 9.80
7d	100-101 (D)	$C_8H_{16}N_2O_4$	47.05 46.96	7.90 7.71	13.72 13.86
7e	114-116 (D)	$C_9H_{18}N_2O_4$	49.53 49.60	8.28 8.28	12.84 12.81
7e'	142-143 (D)	$C_7H_{14}N_2O_4$	44.20 44.22	7.42 7.59	14.73 14.69
7f	132-133 (D)	$C_8H_{16}N_2O_4$	47.05 47.05	7.90 8.08	13.72 13.70
5e'	115-116 (D)	$C_5H_8N_2O_3$	41.66 41.64	5.59 5.64	19.44 19.25
5f	112-113 (E)	$C_6H_{10}N_2O_3$	45.56 45.54	6.37 6.45	17.71 17.60
8	221-223 (F)	$C_8H_{14}N_4O_8$	36.64 36.28	5.38 5.38	21.37 21.81
3f	>320 (G)	$C_6H_8N_2O_2$	51.42 51.18	5.75 5.69	19.99 19.90
3h	>300 (H)	$C_{11}H_{12}N_2O_2$	65.33 64.93	4.98 4.82	13.86 13.87
3i	301-303(dec.) (B)	$C_{16}H_{12}N_2O_2$	72.71 72.91	4.58 4.45	10.60 10.67
9d	96-97 (B)	$C_8H_8N_2O_4$	48.98 48.89	4.11 4.00	14.28 14.21
9e	173-174 (B)	$C_9H_{10}N_2O_4$	51.42 51.39	4.80 4.78	13.33 13.27
9f	140-141 (B)	$C_{10}H_{12}N_2O_4$	53.75 53.63	5.39 5.39	12.50 12.43
9g	76-78 (B)	$C_{14}H_{12}N_2O_4$	61.76 61.54	4.44 4.48	10.29 10.24
9h	103-105 (B)	$C_{15}H_{14}N_2O_4$	62.93 62.70	4.93 4.92	9.36 9.74
9i	220 (I)	$C_{20}H_{16}N_2O_4$	68.96 68.90	4.63 4.41	8.04 7.95
10	175-178 (B)	$C_{12}H_{10}N_2O_3$	62.60 62.48	4.38 4.41	12.17 12.09
4e	[c]	$C_5H_4N_2Cl_2$	36.84 36.72	2.47 2.54	17.19 17.17

[a] Data for **5d** and **5e** could not be obtained due to their strong hygroscopicity. [b] Recrystallized from (A) water, (B) ethanol, (C) isopropanol, (D) ethyl acetate, (E) benzene, (F) water-ethanol, (G) DMF, (H) methanol, (I) THF. [c] Distilled at room temperature (2 mm Hg). Analysis: Cl (Calcd./Found) 43.50/43.49.

residue was extracted with chloroform (100 ml + 2 × 50 ml) to give the aminoamide **1b** (4.0 g, 100%). This compound was pure enough to be used directly in succeeding condensation reactions.

2-Aminoacetamide (**1a**) was obtained from ethyl chloroacetate in a similar manner.

Procedure for Preparing Compounds **7d-f**.

A mixture of α-aminoamide **1** (0.08 mole) and α-ketalester **6** (0.08 mole) in dry ethanol or methanol (2-15 ml) was stirred under the reaction conditions indicated in Table 2. The resulting solution was evaporated to dryness *in vacuo*, and the residue was washed with small amount of ethanol to give the condensation product **7**. In the case of **7e,e'**,**f**, the residual oil was crystallized from ether on cooling, and the precipitates which formed were purified by silica-gel chromatography eluted with ethyl acetate. The results are summarized in Table 2.

Procedure for Hydrolysis of Compounds **7d-f** to **5d-f**.

A mixture of compound **7** (0.01 mole) in trifluoroacetic acid (20 ml) was stirred at room temperature for 2-3 days, and then the solvent was evaporated *in vacuo*. To the residue was added benzene, the solution was again evaporated *in vacuo*. This azeotropic distillation was repeated until complete removal of trifluoroacetic acid. The compound **5** was obtained by triturating the residue with ether. The results are summarized in Table 2.

Procedure for Condensation of α-Aminoamides **1a-c** with Ethyl Benzoylformate (**2c**) to Compounds **5g-i**.

A mixture of α-aminoamide **1** (0.050 mole) and ethyl benzoylformate (**2c**) (8.91 g, 0.050 mole) in dry methanol (50 ml) was stirred under the reaction conditions shown in Table 1. The precipitates which formed were

collected by filtration, washed with small amount of ethanol and dried to give compound **5**. The results are summarized in Table 1.

Condensation of 2-Aminoacetamide (**1a**) with Dimethyl Tartrate to Compound **8**.

A mixture of aminoamide **1a** (4.3 g, 0.058 mole) and dimethyl tartrate (5.1 g, 0.029 mole) in methanol (20 ml) was stirred at room temperature for 4 days. The precipitates which formed were collected by filtration, and the mother liquor was evaporated *in vacuo*. The residue was worked up with methanol to give the second crop. The combined products were washed with small amount of methanol and dried to afford **8** (7.10 g, 95%).

Oxidative Cleavage of Compound **8** to **5d**.

Periodic acid dihydrate (1.5 g, 6.6 mmoles) was added in small portions over a period of 30 minutes to a stirred solution of **8** (1.73 g, 6.6 mmoles) in water (50 ml) at 0-5° under nitrogen, and the mixture was stirred for additional 4 hours in ice-salt bath. The solution was worked up with 4.5 ml of Amberlite IRA-410 (OH form), and resin was removed by filtration. The aqueous solution was evaporated *in vacuo*, and the residual oil was solidified from ether on cooling to give a strongly hygroscopic material **5d** (0.71 g, 41%).

Procedure of Cyclization of Compounds **5f,h,i** to 2,5-Dihydroxypyrazines **3f,h,i**.

A mixture of **5** (10 mmoles) in dry methanol containing sodium methoxide (1.08 g, 20 mmoles) was stirred under reflux for the time indicated in Table 3. The solution was evaporated *in vacuo*, and water (10 ml) was added to the residue. The aqueous solution was neutralized at *p*H 6-7 with acetic acid or diluted hydrochloric acid, and the precipitates which formed were collected by filtration, washed with water and dried to give 2,5-dihydroxypyrazine **3**.

Compound **3i** was also obtained by treatment of **5i** with acetic acid. Thus, a mixture of **5i** (0.56 g, 2.0 mmoles) in acetic acid (10 ml) was refluxed with stirring for 20 hours. After cooling to room temperature, the precipitates which formed were collected by filtration, washed successively with acetic acid and water, and dried to give **3i** (0.25 g, 47%).

Direct Preparation of 2,5-Dihydroxypyrazine **3i** from **1c** and **2c**.

A mixture of sodium ethoxide (0.82 g, 12 mmoles) in dry ethanol (10 ml) was added to a mixture of **1c** (1.5 g, 10 mmoles) and ethyl benzoylformate (**2c**) (1.80 g, 10 mmoles) in the same solvent (20 ml), and the resulting mixture was stirred under reflux for 5 hours. After cooling to room temperature, the mixture was acidified at *p*H 3 with 1*N* hydrochloric acid. The precipitates which formed were worked up in the predescribed manner to give **3i** (0.50 g, 19%).

Procedure for Preparing 2,5-Diacetoxypyrazines **9d-i**.

A mixture of **5** (20 mmoles) and acetic anhydride (56 ml, 0.59 mole) in acetic acid (194 ml) was stirred under reflux for the time shown in Table 4. The solution was evaporated *in vacuo*, and acetic acid was completely removed by azeotropic distillation with methanol and toluene. The residue was extracted with hot hexane or benzene, and the extract was evaporated *in vacuo* to afford diacetoxypyrazine **9**. In the cases of **9e** and **9g**, the residual oil was crystallized from small amount of ethanol followed by refrigeration.

Compound **9i** was also prepared by acetylation of 2,5-dihydroxypyrazine **3i**. A mixture of **3i** (0.35 g, 1.3 mmoles) in acetic anhydride (1.0 ml) and acetic acid (5 ml) was refluxed for 4 hours and then evaporated to dryness *in vacuo*. The residue was washed with ether to give **9i** (0.30 g, 65%). This compound was identical in every respect with compound prepared from **5i** as described above.

Hydrolysis of 2,5-Diacetoxypyrazine **9f** to 2,5-Dihydroxypyrazine **3f**.

A mixture of **9f** (60 mg, 0.27 mmole) and potassium hydrogen carbonate (80 mg, 0.8 mmole) in methanol (10 ml) was stirred and refluxed for 50 minutes. After cooling to room temperature, the solution was neutralized with acetic acid to afford **3f** (20 mg, 53%). This compound was identical in all respects with 2,5-dihydroxypyrazine prepared from **5f**.

Preparation of 2,5-Dichloro-3-methylpyrazine (**4f**).

A mixture of **5e'** (1.20 g, 8.6 mmoles) in phosphoryl chloride (22 ml) was stirred and heated at 60-70° for 3 hours and then 90-100° for 1 hour. The mixture was poured into ice-water and extracted with several portions of ether. The extracts were washed with water, dried over magnesium sulfate, and evaporated. The residual oil was purified by silica-gel chromatography eluted with benzene. Evaporation of the eluent gave 2,5-dichloropyrazine **4f** (0.08 g, 6%).

Similar treatment of **5e-i** with phosphoryl chloride gave the corresponding 2,5-dichloropyrazines **4e-i**, which were identical in all respects with authentic samples as prepared by known procedures [10,14].

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