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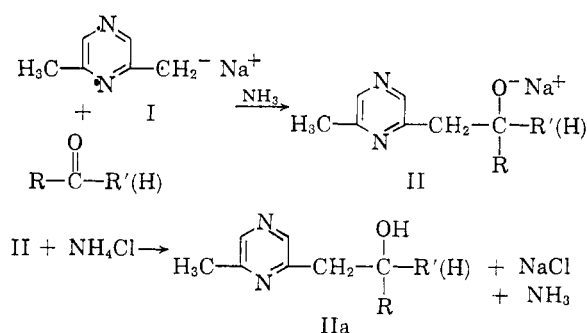
## The Chemistry of Pyrazine and Its Derivatives. VI. The Synthesis of Carbinols Containing the Pyrazine Nucleus<sup>1</sup>

MARWAN R. KAMAL<sup>2</sup> AND ROBERT LEVINE

Received September 29, 1961

2-Methyl-6-pyrazylmethylsodium was made to undergo aldol-type condensation with several aldehydes and ketones to give the corresponding secondary and tertiary carbinols containing the pyrazine nucleus. 1-Pyrazyl-3-dimethylamino-propane was also condensed with three representative ketones using sodium amide in liquid ammonia as the condensing agent to give the corresponding tertiary carbinols. The reaction of the methylpyrazine anion with styrene oxide to give a secondary carbinol and the oxidation of this carbinol to the ketone are also discussed.

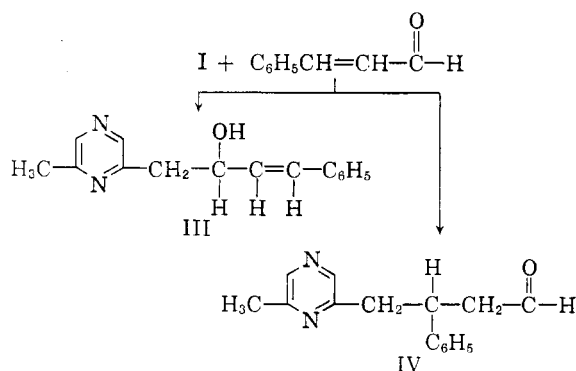
In the last paper of this series<sup>3</sup> we reported the successful acylation and alkylation of 2,6-dimethylpyrazine and other pyrazine derivatives by using sodium amide in liquid ammonia as the condensing agent. In this paper we report the successful reaction of 2-methyl-6-pyrazylmethylsodium with aldehydes and ketones in an aldol-type condensation to give secondary and tertiary carbinols,



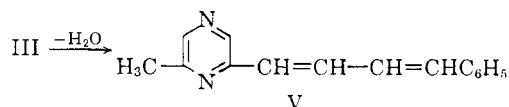
respectively. The results of these condensations are summarized in Table I. The molar ratio of the reactants employed in these condensations was 2:2:1, *i.e.*, two equivalents of sodium amide, two equivalents of 2,6-dimethylpyrazine, and one equivalent of aldehyde or ketone. In the case where cyclopentanone was the ketone used, some cyclopentylidenecyclopentanone (15.0%) was obtained in addition to a 27.3% yield of the expected alcohol, when the molar ratio of the reactants was 2:2:1. When equivalent quantities of the reactants were used, the yield of the alcohol was reduced to 18.8% and no cyclopentylidenecyclopentanone was isolated. The cyclopentylidenecyclopentanone is the result of the self-condensation of cyclopentanone, followed by dehydration. Such self-condensations of

cyclopentanone in the presence of sodium amide have been observed earlier.<sup>4</sup>

In the condensation of 2,6-dimethylpyrazine with cinnamaldehyde, there was the possibility that the product could be the result of 1,2- (III) or 1,4- (IV) addition.



The infrared absorption spectrum of the product showed no carbonyl bonds in the region between 1600–1750  $\text{cm}^{-1}$ , with a strong band at 3300  $\text{cm}^{-1}$  indicating a hydroxyl group was present. When a dehydration<sup>5</sup> of the product was effected a compound was obtained with analysis corresponding to a dehydrated product. This compound also shows the disappearance of the 3300- $\text{cm}^{-1}$  band (conjugated C=C bonds show bands near 1600  $\text{cm}^{-1}$ ).<sup>6</sup>



A reverse aldol-type reaction was observed when 1-(2-methyl-6-pyrazyl)-2-phenylpropanol-2, (IIa, R = CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub>) was treated with zinc chloride and hydrochloric acid in a benzene solution. The products 2,6-dimethylpyrazine and acetophenone were obtained. These are the starting materials in

(1) This work was supported in part by a grant from Wyandotte Chemicals Corp.

(2) This paper is based on part of a thesis presented by M. R. Kamal to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) M. R. Kamal and R. Levine, *J. Org. Chem.*, **27**, 1355 (1962).

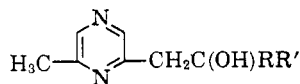
(4) C. R. Hauser, B. I. Ringler, F. W. Swamer, and D. F. Thompson, *J. Am. Chem. Soc.*, **69**, 2649 (1947).

(5) The dehydration procedure will be described in a subsequent publication.

(6) L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, 1954, p. 40.

TABLE I

THE ALDOL-TYPE CONDENSATION OF 2-METHYL-6-PYRAZYL METHYLSODIUM (I) WITH ALDEHYDES AND KETONES, RCOR', TO GIVE ALCOHOLS OF THE TYPE,

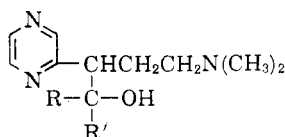


R	RCOR'	R'	Yield, %	B.P. or M.P.	Mm.	$n_D^{25}$	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	H	H	25.6	128-130	0.8	1.5097	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> O	66.63	66.39	8.95	9.15		
C <sub>6</sub> H <sub>5</sub> <sup>a</sup>	H	H	58.0	88-89 <sup>i</sup>			C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> O	72.87	73.36	6.59	6.73		
C <sub>8</sub> H <sub>7</sub> <sup>b,c</sup>	H	H	78.5	105.6-107 <sup>k</sup>			C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O	74.97	74.74	6.71	6.56		
CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	37.7	83-85	1.2	1.5088	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> O	65.03	65.03	8.49	8.81		
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	58.3	102-103	2	1.5075	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> O	66.63	66.93	8.95	9.17		
CH <sub>3</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	38.5	99.5-100	0.9	1.5064	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub> O	68.00	68.36	9.34	9.47		
C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	62.2	111-113	0.8	1.5062	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub> O	68.00	67.98	9.34	9.34		
Cyclopentanone <sup>d,e</sup>			27.3	109-111	1.1	1.5303	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub> O					14.57	14.65
Cyclohexanone <sup>f</sup>			47.0	121-123	0.9	1.5325	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O	69.86	69.75	8.79	8.75		
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> <sup>g</sup>	CH <sub>3</sub>	54.5	131-132	0.7	1.5655	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O	73.65	73.83	7.06	7.06		
C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> <sup>h</sup>	C <sub>2</sub> H <sub>5</sub>	45.8	129-130	0.5	1.5595	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O	74.41	74.44	7.49	7.47		
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> <sup>i</sup>	C <sub>6</sub> H <sub>5</sub>	100	144-145.5 <sup>l</sup>			C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O	78.60	78.78	6.25	6.50		

<sup>a</sup> Compound formed a picrate, m.p. 144.6-145.6° (from ethanol), *Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>8</sub>: C, 51.44; H, 3.86. Found: C, 51.43; H, 4.12. <sup>b</sup> C<sub>8</sub>H<sub>7</sub> = 1-styryl radical. <sup>c</sup> Dehydration of the carbinol gave 1-(2-methyl-6-pyrazyl)-4-phenylbutadiene-1,3, m.p. 100.4-101.2° (from ether-pentane mixture). *Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>: C, 81.01; H, 6.35. Found: C, 81.43; H, 6.45. <sup>d</sup> Cyclopentylidenecyclopentanone (15.0%), b.p. 186-188° at 1.1 mm. was isolated; semicarbazone, m.p. 216-217° (from ethanol) (lit.<sup>16</sup> value for b.p. 119-121° at 13 mm., semicarbazone, m.p. 217°). <sup>e</sup> When equivalent quantities of 2,5-dimethylpyrazine, sodium amide, and cyclopentanone were used, the yield of carbinol dropped to 18.8% and no cyclopentylidenecyclopentanone was obtained. <sup>f</sup> Compound formed picrate, m.p. 103.5-104.5° (from ethanol). *Anal.* Calcd. for C<sub>13</sub>H<sub>21</sub>N<sub>5</sub>O<sub>8</sub>: C, 49.65; H, 4.86. Found: C, 49.78; H, 4.93. <sup>g</sup> Compound formed picrate, m.p. 143.4-144.0° (from ethanol). *Anal.* Calcd. for C<sub>20</sub>H<sub>19</sub>N<sub>5</sub>O<sub>8</sub>: C, 52.51; H, 4.18. Found: C, 52.57; H, 4.42. <sup>h</sup> Compound formed picrate, m.p. 127.4-128° (from ethanol). *Anal.* Calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>5</sub>O<sub>8</sub>: C, 53.50; H, 4.49. Found: C, 53.29; H, 4.59. <sup>i</sup> Compound formed a *nonhygroscopic* hydrochloride when reacted with concd. HCl, m.p. 163.6-164.0°. *Anal.* Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>OCl: C, 69.83; H, 5.86. Found: C, 70.07; H, 5.86. <sup>j</sup> Recrystallized from petroleum ether (b.p. 60-70°). <sup>k</sup> Recrystallized from ethanol. <sup>l</sup> Recrystallized from a methanol-water mixture.

TABLE II

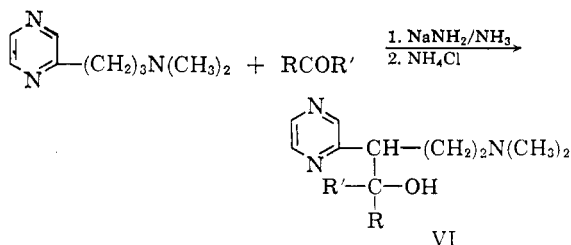
THE ALDOL-TYPE CONDENSATION OF 1-PYRAZYL-3-DIMETHYLAMINOPROPANE WITH KETONES RCOR' TO GIVE CARBINOLS OF TYPE



Ketone R	RCOR'	R'	Yield, %	B.P. or M.P.	Mm.	Formula	Carbon, %		Hydrogen, %	
							Calcd.	Found	Calcd.	Found
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	58.0	68.8-69.6 <sup>b</sup>		C <sub>13</sub> H <sub>23</sub> N <sub>3</sub> O	65.79	65.48	9.77	9.84
2-C <sub>4</sub> H <sub>3</sub> S <sup>a</sup>	CH <sub>3</sub>	CH <sub>3</sub>	65.0	150-153	0.6	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> OS	61.82	62.25	7.26	7.62
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	81.0	130.0-130.6 <sup>c</sup>		C <sub>22</sub> H <sub>26</sub> N <sub>3</sub> O	76.05	76.31	7.25	7.34

<sup>a</sup> 2-C<sub>4</sub>H<sub>3</sub>S = 2-thienyl radical. <sup>b</sup> Recrystallized from pentane. <sup>c</sup> Recrystallized from an ethanol-water mixture.

the preparation of the 1-(2-methyl-6-pyrazyl)-2-phenylpropanol-2. A related reversal was previously<sup>7</sup> observed when 1-pyrazyl-2-phenyl-2-propanol (the product obtained from the reaction of methylpyrazine and acetophenone) was treated with ethanolic potassium hydroxide. Following the same procedure as above for the condensation of 2,6-dimethylpyrazine with aldehydes and ketones, 1-pyrazyl-3-dimethylaminopropane was condensed with three representative ketones to give carbinols of type, VI.



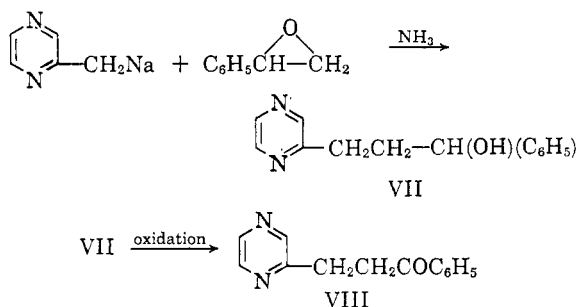
The results of these condensations are summarized in Table II.

Although the acylation of 1-(2-pyridyl)-3-di-

(7) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5666 (1959).

methylaminopropane has been reported,<sup>8</sup> there are apparently no reports in the literature that any aldol-type condensations have been effected with this compound or its pyrazine analog.

Finally, the reaction of pyrazylmethylsodium with styrene oxide in liquid ammonia was effected. Equivalent quantities of sodium amide, methylpyrazine, and styrene oxide were employed. The secondary alcohol, VII, 1-phenyl-3-pyrazylpropanol-1 was obtained in 72.7% yield. This alcohol is formed as a result of opening of the epoxide ring at the primary carbon which is the less hindered. The acidic potassium dichromate oxidation of the alcohol resulted in the formation of the ketone VIII which was further characterized by conversion to its 2,4-dinitrophenylhydrazone. If the epoxide ring opening has occurred at the secondary carbon to yield a primary alcohol, then the acid dichromate oxidation would have led to the formation of an acid. No acid was isolated from the oxidation.



Compounds VII and VIII are homologs of previously synthesized alcohols<sup>9</sup> and ketones which resulted from the condensation of methylpyrazine with benzaldehyde and ethyl benzoate, respectively.

The results obtained in this study for the opening of styrene oxide by the methylpyrazine anion are consistent with the previously reported openings of this epoxide ring with anions.<sup>10-12</sup>

#### EXPERIMENTAL<sup>13</sup>

1. *Synthesis of 1-(2-methyl-6-pyrazyl)-2-phenylpropanol-2.* Using the synthesis of 1-(2-methyl-6-pyrazyl)-2-phenylpropanol-2 as an example for the aldol-type condensations of 2,6-dimethylpyrazine with aldehydes and ketones, the procedure which was employed follows.

To 0.5 mole of sodium amide,<sup>14</sup> prepared from sodium (0.5 g-atom, 11.5 g.) in 500 ml. of anhydrous liquid ammonia,

(8) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 1152 (1960).

(9) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157 (1959).

(10) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

(11) R. M. Adams and C. A. Van der Werf, *J. Am. Chem. Soc.*, **72**, 4368 (1950).

(12) G. Van Zyl, J. F. Zaack, E. S. Huyser, and P. L. Cook, *J. Am. Chem. Soc.*, **76**, 707 (1954).

(13) The methylpyrazine and 2,6-dimethylpyrazine used in this investigation were supplied through the courtesy of Wyandotte Chemicals Corp.

was added 0.5 mole (54.0 g.) of 2,6-dimethylpyrazine dissolved in 50 ml. of anhydrous ether over a 15-min. period. The reaction mixture was stirred for another 30-min. period. Acetophenone (0.25 mole, 30.0 g.), mixed with an equal volume of anhydrous ether, was added over a 20-min. period and the reaction mixture was stirred for an additional hour. Ammonium chloride (30.0 g.) was added to quench the reaction, and the ammonia was replaced with 300 ml. of ether. The mixture was then poured over ice and made strongly acidic. The ether layer was separated and the remaining aqueous phase was extracted with several portions of ether which were combined with the original ether phase. The aqueous phase was made strongly basic with dilute sodium hydroxide solution and then extracted with several portions of chloroform. From the distillation of the ether and the chloroform extract there were obtained 31.2 g. (54.5%) of 1-(2-methyl-6-pyrazyl)-2-phenylpropanol-2, b.p. 131-132° at 0.7 mm.

2. *Reaction of 1-(2-methyl-6-pyrazyl)-2-phenylpropanol-2 with zinc chloride and hydrochloric acid.* The carbinol (0.054 mole, 12.4 g.) dissolved in 100 ml. of benzene, 10 g. of zinc chloride, and 10 ml. of concd. hydrochloric acid were refluxed for 3 hr. The reaction mixture was cooled and worked up in the usual manner to give: 2.7 g. (46.5%) of 2,6-dimethylpyrazine, b.p. 78-90° at 35 mm. (The picrate prepared from this compound melts at 174-175° alone and when mixed with an authentic sample); 3.5 g. (54.2%) of acetophenone, b.p. 105-106° at 35 mm. (the 2,4-dinitrophenylhydrazone prepared from this compound melts at 246-248° alone and when mixed with an authentic sample); 1 g. of the starting carbinol, b.p. 131-134° at 8 mm.; and 3.9 g. of a tarry residue.

3. *Condensation of 1-pyrazyl-3-dimethylaminopropane with benzophenone.* To 0.15 mole of sodium amide<sup>14</sup> in 150 ml. of anhydrous liquid ammonia was added 24.8 g. (0.15 mole) of 1-pyrazyl-3-dimethylaminopropane over a 15-min. period. The red-colored solution was stirred for another 0.5 hr. after which 13.7 g. (0.075 mole) of benzophenone dissolved in 50 ml. of anhydrous ether was added over a 20-min. period. The reaction mixture was stirred for another hour and then quenched with 10 g. of ammonium chloride. The ammonia was replaced with ether and then the mixture was carefully poured onto ice. A white solid precipitated, m.p. 128° (crude), and 130-130.6° from ethanol-water mixture. The solid weighed 20.4 g., which represents an 81% yield of 1,1-diphenyl-2-pyrazyl-4-dimethylaminobutanol-1.

4. *Reaction of methylpyrazine, sodium amide, and styrene oxide.* To 0.5 mole of sodium amide<sup>14</sup> in 500 ml. of anhydrous liquid ammonia was added 47.0 g. (0.5 mole) of methylpyrazine over a 15-min. period. The deep red-colored reaction mixture was stirred for another 30 min. Styrene oxide (0.5 mole, 60.0 g.), dissolved in 60 ml. of anhydrous ether, was added over a 20-min. period, and the reaction mixture was again stirred for an additional 90 min. after which it was quenched with 30 g. of ammonium chloride and then worked up in the usual manner to give 77.3 g. (72.7%) of 1-phenyl-3-pyrazylpropanol-1, b.p. 159-161° at 0.9 mm.,  $n_D^{25}$  1.5780.

*Anal.* Calcd. for  $C_{11}H_{14}N_2O$ : C, 72.90; H, 6.59. Found: C, 73.37; H, 6.54.

5. *Oxidation of 1-phenyl-3-pyrazylpropanol-1.* Upon the oxidation of 21.7 g. (0.103 mole) of the carbinol with 20.0 g. of potassium dichromate, following the procedure described in *Organic Syntheses*<sup>15</sup> for the oxidation of menthol, there was obtained 12.5 g. (58.8%) of phenyl 2-pyrazylethylketone, b.p. 145-148° at 0.6 mm.,  $n_D^{25}$  1.5820.

(14) S. R. Harris, and R. Levine, *J. Am. Chem. Soc.*, **70**, 3360 (1948).

(15) L. T. Anderson, *Org. Syntheses*, Coll. Vol. 1, 333 (1932).

(16) M. Gadchot and F. Tabonry, *Bull. soc. chim. France*, [4], **13**, 14 (1913).

Anal. Calcd. for  $C_{12}H_{12}N_2O$ : C, 73.56; H, 5.70. Found: C, 74.09; H, 6.08.

This ketone formed a 2,4-dinitrophenylhydrazone, m.p. 153–154.4° (from ethanol).

Anal. Calcd. for  $C_{12}H_{12}N_2O_4$ : C, 58.15; H, 4.11. Found: C, 58.15; H, 4.23.

PITTSBURGH 13, PA.

[CONTRIBUTION NO. 1115 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

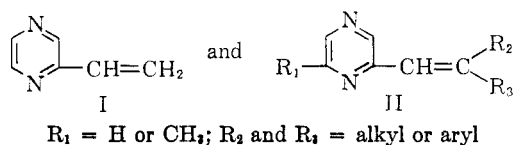
## The Chemistry of Pyrazine and Its Derivatives. VII. The Synthesis of Vinylpyrazine and Substituted Vinylpyrazines<sup>1</sup>

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Vinylpyrazine has been synthesized by a Hofmann exhaustive methylation reaction on the Mannich product obtained from the reaction of methylpyrazine with formaldehyde and dimethylamine hydrochloride. Substituted vinylpyrazines were also synthesized by the iodine-catalyzed dehydration of pyrazylmethylcarbinols.

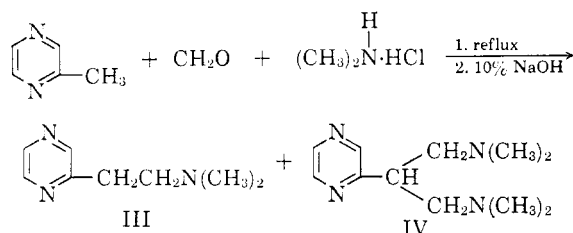
As a part of the investigation in these laboratories on the chemistry of pyrazine derivatives, it was desirable to synthesize vinylpyrazine, I, and substituted vinylpyrazines, II. Such compounds will have an ethylenic double bond which is



conjugated with the pyrazine ring and thus may undergo nucleophilic addition reaction—*i.e.*, Michael condensations. There are many examples in the literature<sup>3</sup> which show the reactivity of 2- and 4-vinylpyridine in such condensations.

Although the synthesis of vinylpyrazine has been reported previously by Kitchen and Hanson,<sup>4</sup> a different synthesis was undertaken in the present study, which appears to be simpler and gives higher yields of vinylpyrazine. Kitchen and Hanson condensed formaldehyde with methylpyrazine in an autoclave (mole ratio, 1:4.5) and obtained a maximum yield of 38% of pyrazylethanol. This carbinol was dehydrated with molten potassium hydroxide to give an 80% yield of vinylpyrazine (30.4% based on methylpyrazine).

In the present synthesis, a Hofmann exhaustive methylation procedure is employed. The Mannich product, III, was obtained from the reaction of methylpyrazine (0.6 mole), formaldehyde (1.05 moles), and dimethylamine hydrochloride (0.63 mole). In addition some bis-Mannich product, IV, was obtained. The free amines were obtained by



the reaction of the hydrochlorides with 10% aqueous sodium hydroxide.

When a larger excess of formaldehyde (1.2 moles) was employed, the yield of the bis product rose from 20.0% to 24.7%. The formation of bis-Mannich products from the reaction of 2,5-dimethylpyrazine, formaldehyde, and secondary amine hydrochloride has been previously observed by Linder and Spoerri.<sup>5</sup> Wiley<sup>6</sup> attempted the condensation of methylpyrazine, formaldehyde, and diethylamine hydrochloride, but he was unable to isolate the free Mannich base.

The compound, III, was quaternized by reaction with methyl iodide to give  $\beta$ -pyrazylethyltrimethylammonium iodide, V. The quaternary compound, V, was then converted to vinylpyrazine by two methods. The first involves the exchange of the iodide ion by a hydroxide ion by the reaction of V with silver hydroxide (from silver oxide and water), to give the quaternary ammonium hydroxide compound, VI. When VI was refluxed in aqueous sodium hydroxide solution, vinylpyrazine was obtained (63.3% yield). The second method involves the direct conversion of the quaternary compound, V, to vinylpyrazine (60.5%) by treatment with aqueous sodium hydroxide.

The trimethylamine formed in these degradations was identified as its picrate by bubbling the gases formed during the reflux into a saturated alcoholic solution of picric acid.

(1) This work was supported in part by a grant from Wyandotte Chemical Corp.

(2) This paper is based on part of a thesis presented by M. R. Kamal to the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) E. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(4) L. J. Kitchen and E. S. Hanson, *J. Am. Chem. Soc.*, **73**, 1838 (1951).

(5) S. Linder and P. Spoerri, *J. Am. Chem. Soc.*, **74**, 1517 (1952).

(6) P. F. Wiley, *J. Am. Chem. Soc.*, **76**, 4924 (1954).