[CONTRIBUTION FROM THE LABORATORY SERVICE, VETERANS ADMINISTRATION HOSPITAL]

Pyrazines. II. The Rearrangement of Pyrazine-N-Oxides[1]

BERNARD KLEIN, JUDITH BERKOWITZ, AND NATALIE E. HETMAN

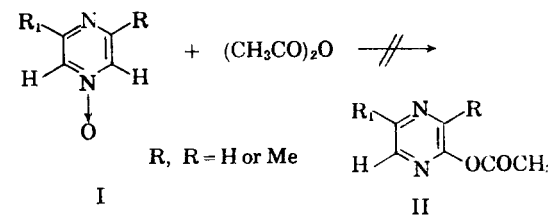
Received April 14, 1960

The action of acetic anhydride on pyrazine-*N*-oxides is reported. Pyrazine-1-oxide, 3-methylpyrazine-1-oxide, and 3,5-dimethylpyrazine-1-oxide do not rearrange to form the corresponding 2-acetoxy compounds. On the other hand, 2,5-dimethylpyrazine-1-oxide, 2,6-dimethylpyrazine-1-oxide, and 2,3,5,6-tetramethylpyrazine-1-oxide rearrange to form the 2-acetoxymethyl derivatives. Presumably, the reaction will occur when an adjacent methyl group is available. Pyrazine-1,4-dioxide does not rearrange with boiling acetic anhydride. 2-Methylpyrazine-1,4-dioxide reacts smoothly to form 3-acetoxymethylpyrazine-1-oxide. 2,5-Dimethylpyrazine-1,4-dioxide gives a reaction product from which 2,5-dimethylpyrazine-1-oxide and 2-acetoxymethyl-5-methylpyrazine-4-oxide are isolated. On prolonged heating a small amount of 2,5-diacetoxymethylpyrazine is produced. 2,6-Dimethylpyrazine-1,4-dioxide gives 2-acetoxymethyl-6-methylpyrazine and 2,6-dimethylpyrazine-4-oxide. The acetoxymethylpyrazines are smoothly converted to the corresponding pyrazylmethanols (hydroxymethylpyrazines). The ultraviolet and infrared absorption spectra are presented. The mechanism of the rearrangement is discussed in terms of a two-step, cyclic intermediate pathway.

The rearrangement of heterocyclic *N*-oxides with acetic anhydride to form acetoxy derivatives is now a well known reaction.[2,3] When this reaction is applied to 2- and 4-alkylpyridine-*N*-oxides, an alternate course is followed, leading to the formation of 2- and 4-acetoxyalkylpyridines.[4-9] Similar reactions have been described in other heterocyclic series as well, *e.g.*, quinoline,[10a-c] benzimidazole,[11] and isoquinoline.[12]

Koelsch and Gumprecht[13] reported the action of acetic anhydride on 3-methylpyrazine-1-oxide, 2,5-dimethylpyrazine-1-oxide, and 2,5-dimethylpyrazine-1,4-dioxide. The present authors have extended the reaction of pyrazine and methyl-substituted pyrazine mono- and di-*N*-oxides with acetic anhydride. This report presents the results of these studies.

Pyrazine mono-N-oxides. It has been found that pyrazine-1-oxide, 3-methylpyrazine-1-oxide, and 3,5-dimethylpyrazine-1-oxide, in contrast to the reaction with pyridine-*N*-oxide,[2] did not react with acetic anhydride to give the corresponding 2-acetoxypyrazines.[14] In each case starting material



I II

was recovered. At the same time a good deal of dark resinous material was formed indicating that some reaction had taken place. It is suspected that this reaction is a counterpart of the reaction in the pyridine series with the formation of free radical intermediates.[15-16]

On the other hand, 2,5-dimethylpyrazine-1-oxide (VI), 2,6-dimethylpyrazine-1-oxide, and 2,3,5,6-tetramethylpyrazine-1-oxide, rearranged to form the corresponding 2-acetoxymethylpyrazine derivatives. Presumably, the reaction will proceed when an adjacent methyl group is available.[4,6]

(1) Presented in part at the 136th meeting, American Chemical Society, Atlantic City, September 1959.

(2) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947); *Chem. Abstr.*, **45**, 9337c (1951).

(3) See E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953) for leading references.

(4) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(5) G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, **1**, 347 (1953), *Chem. Abstr.*, **49**, 10948e (1955).

(6) O. H. Bullitt and J. T. Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

(7) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **77**, 1281 (1955).

(8) G. Kobayashi, S. Furukawa, and T. Kawada, *J. Pharm. Soc. Japan*, **74**, 790 (1954); *Chem. Abstr.*, **49**, 1164c (1955); S. Furukawa, *Pharm. Bull. Japan*, **3**, 413 (1955); *Chem. Abstr.*, **50**, 13926a (1956).

(9) F. Cislak, U. S. Patent 2,748,141, May 29, 1956.

(10) (a) K. Oda, *J. Pharm. Soc. Japan*, **64**, No. 8A, 6 (1944); *Chem. Abstr.*, **45**, 9523i (1951); (b) T. Itai, *J. Pharm. Soc. Japan*, **65**, 70 (1945); *Chem. Abstr.*, **45**, 8525h (1951); (c) I. J. Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953).

(11) F. Montanari and A. Risaliti, *Gazz. chim. ital.*, **83**, 278 (1953), *Chem. Abstr.*, **47**, 12388f (1953).

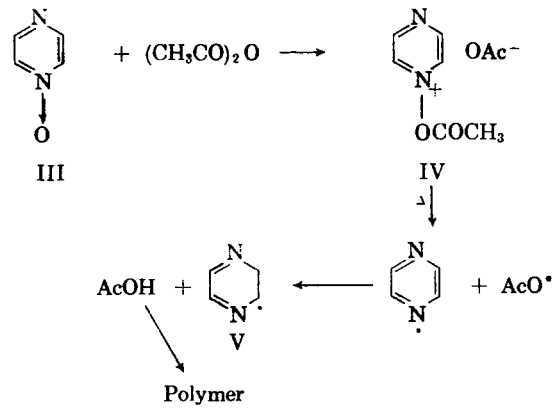
(12) M. M. Robison and B. L. Robison, *J. Org. Chem.*, 21, 1337 (1957); *J. Am. Chem. Soc.*, **80**, 3443 (1958).

(13) C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **3**, 1603 (1958).

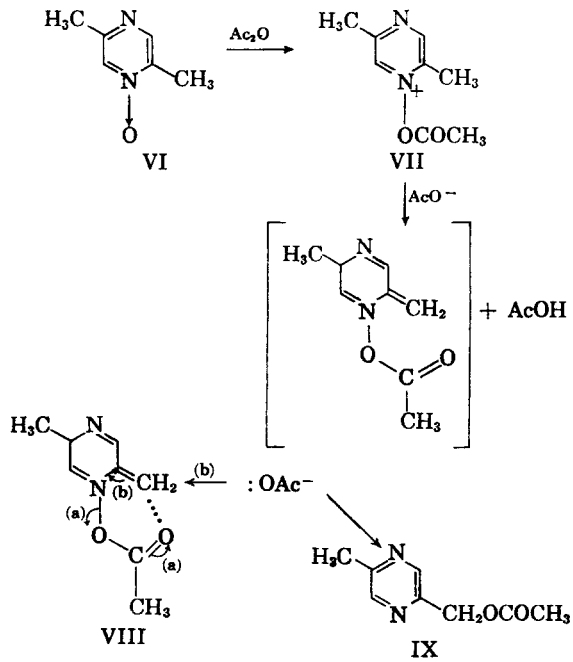
(14) Koelsch and Gumprecht (ref. 13) claimed that 3-methylpyrazine-1-oxide with acetic anhydride gave an acetate, which on saponification produced the 2-hydroxypyrazine. The ultraviolet absorption spectrum of the latter, however, closely resembled that of a pyrazine mono-*N*-oxide, rather than a hydroxypyrazine or pyrazinone (see ref. 17). After our work was completed, an exchange of letters with Dr. Hideyo Shindo, Sankyo Co., Ltd., Tokyo, Japan, brought to our attention the work of Dr. M. Asai [*Yakugaku Zasshi*, **79**, 1273 (1959)] who also found that 3-methylpyrazine-1-oxide did not rearrange on heating with acetic anhydride. He was able to obtain 2-acetoxypyrazine in only 3% yield by prolonged heating of pyrazine-1-oxide in acetic anhydride.

(15) V. Boekelheide and D. L. Harrington, *Chem. & Ind. (London)*, 1423 (1955).

(16) V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **80**, 6590 (1958).



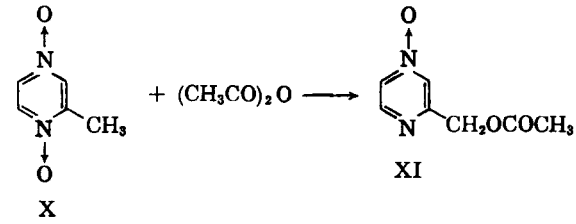
This would lend some additional support to a rearrangement mechanism involving an intramolecular cyclic intermediate.[7,10c,16] Thus, in the case of VI:



The course of the reaction was readily followed by measuring the disappearance of the *N*-oxide absorption peak at about 260 mμ and the appearance of an absorption peak at about 275 mμ, which is characteristic of the parent heterocycle.[17]

Pyrazine di-N-oxides. The action of acetic anhydride on pyrazine and methyl substituted pyrazine di-*N*-oxides was also investigated. As expected, pyrazine-1,4-dioxide was unaffected. 2-Methylpyrazine-1,4-dioxide reacted smoothly to form 2-acetoxymethylpyrazine-4-oxide. The course of this reaction was followed by measuring the decline and eventual disappearance of the absorption maxima at 235 and 295 mμ and the formation of absorption peaks at approximately 220 and 260 mμ, characteristic of pyrazine mono-*N*-oxides.[17]

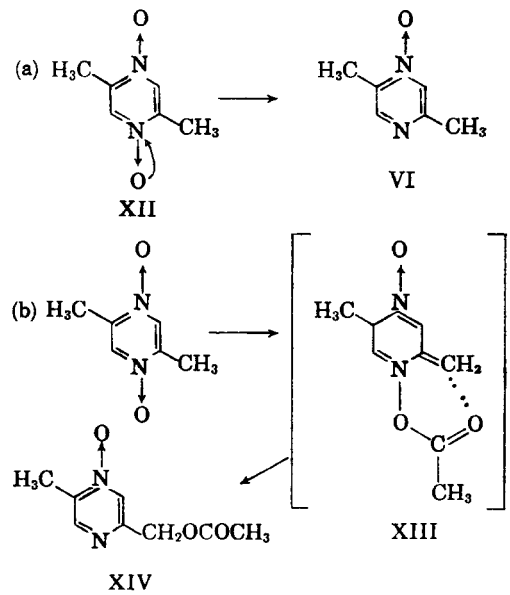
(17) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, **81**, 5160 (1959).



When 2,5-dimethylpyrazine-1,4-dioxide, (XII), was heated in acetic anhydride, two principal products were obtained. They were 2,5-dimethylpyrazine-1-oxide and 2-acetoxymethyl-5-methylpyrazine-4-oxide, m.p. 73–74.5°. Prolonged heating of XII in acetic anhydride produced small amounts of 2,5-diacetoxymethylpyrazine (XV).

Koelsch and Gumprecht[13] in their study of this reaction isolated a mixture of 2-acetoxymethyl-5-methylpyrazine (IX) and 2,5-diacetoxymethylpyrazine (XV). The difference in products can be explained, in part, by procedural differences. In this laboratory the course of the reaction was followed spectrophotometrically, and terminated at the mono-*N*-oxide stage. Koelsch and Gumprecht, following the heating period, permitted the reaction mixture to stand for a prolonged period before workup.[18]

The formation of the four compounds thus produced as a result of the action of acetic anhydride on 2,5-dimethylpyrazine-1,4-dioxide can be explained by: (a) the ability of acetic anhydride to deoxygenate the $-C=\overset{+}{N}-\overset{-}{O}$ system. This has been observed in other heterocyclic series[19–21]

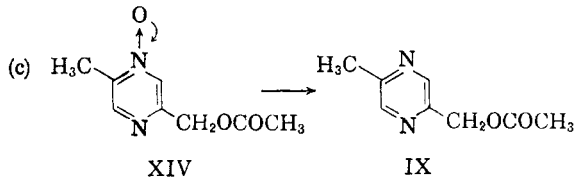


(18) This is not apparent from the published paper but is given in Dr. Gumprecht's thesis [Univ. of Minnesota (1957)].

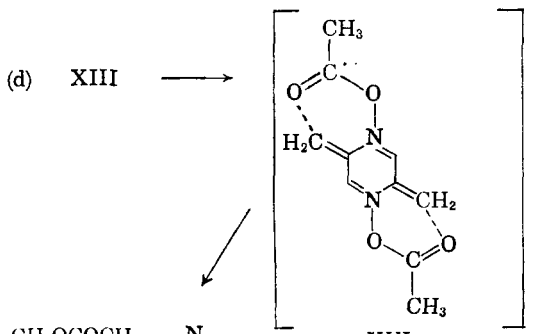
(19) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 479 (1938).

(20) I. Yoshiaka, *J. Pharm. Soc. Japan*, **72**, 1128 (1952); *Pharm. Bull. (Tokyo)*, **2**, 25 (1954); *J. Pharm. Soc. Japan*, **73**, 23 (1953).

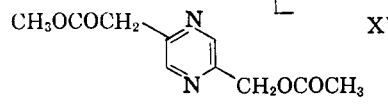
and discussed by Katritzky.[22] In this manner 2,5-dimethylpyrazine-1-oxide (VI) is formed; (b) nucleophilic attack of the acetoxy ion on the alkyl carbon of the coordinated intermediate (XIII) with subsequent rearrangement *via* a cyclic transition[10c,16] to form 2-acetoxymethyl-5-methylpyrazine-4-oxide (XIV); (c) deoxygenation of XIV by acetic anhydride, which would give 2-acetoxymethyl-5-methylpyrazine (IX); (d) nucleophilic attack of an acetoxy anion on both alkyl carbons of a doubly coordinated intermediate (XVI), arising in turn, from XIII and rearrangement at both ends of the cyclic transition to give XV. The possibility that the rearrangement may take a stepwise course: XII → XIV → XV must also be considered.



XIV IX



XVI



XV

Support for a two-stage reaction may be derived from an experiment during which XII was heated with one equivalent of acetic anhydride in glacial acetic acid. No reaction occurred over one hour, as the ultraviolet absorption spectrum remained unchanged. Upon addition of another equivalent of acetic anhydride, the reaction proceeded in the described manner. A second equivalent of reagent is evidently required to cause the intermediate to react. In this laboratory conversion of XIV to XV took place only after six hours, as demonstrated by the disappearance of the absorption maximum at 260 mμ and formation of a peak at 272 mμ. Additional time is probably necessary to form the intermediate XVI and cause its conversion to XV.

In every instance, considerable amounts of polymeric material formed. This would indicate again the formation or the existence of free radical intermediates, either accompanying or operating parallel with the ionic ones.[16]

In an attempt to establish the structure of XIV, both XIV and IX were treated with 30% hydrogen peroxide in glacial acetic acid hoping to form the known 2-acetoxymethyl-5-methylpyrazine-1,4-dioxide.[13] In each case 2-hydroxymethyl-5-methylpyrazine-1,4-dioxide was obtained. Further treatment with acetic anhydride in pyridine afforded 2-acetoxymethyl-5-methylpyrazine-1,4-dioxide.

This reaction is not a limited one, for 2-acetoxymethyl-3,5,6-trimethylpyrazine similarly treated gave a mixture of a mono- and di-*N*-oxide of 2-hydroxymethyl-3,5,6-trimethylpyrazine. Neither Koelsch and Gumprecht,[13] nor Boekelheide and Linn[4] observed this type of oxidative deacetylation in their studies. This reaction will be studied further.

Treatment of 2,6-dimethylpyrazine-1,4-dioxide with boiling acetic anhydride yielded a mixture of 2-acetoxymethyl-6-methylpyrazine and 3,5-dimethylpyrazine-1-oxide. These were identified by comparison with authentic material. Here, too, the products obtained can be accounted for by the mechanisms discussed above; that is, a coordinated intermediate undergoing attack by acetoxy ion. 3,5-Dimethylpyrazine-1-oxide, as demonstrated earlier, does not undergo further reaction with acetic anhydride and is therefore found in the reaction mixture.

Saponification of the 2-acetoxymethylpyrazine derivatives with alkali takes place readily to give the corresponding 2-hydroxymethyl derivatives (pyrazylmethanols). 2-Hydroxymethyl-5-methylpyrazine was similarly prepared and characterized by Koelsch and Gumprecht.[13] Thus a convenient, fairly general method is now available for the introduction of a functional group into the pyrazine side chain.

The physical properties and other data relating to the compounds reported in this study are given in Tables I and II.

EXPERIMENTAL[23,24]

Materials. The preparation of the pyrazine mono- and di-*N*-oxides used in this study was reported in the first paper of this series.[17,25]

(21) D. L. Vivian, *J. Org. Chem.*, 21, 1034 (1956).

(22) A. R. Katritzky, *Quart. Revs.* (*London*), 10, 395 (1956).

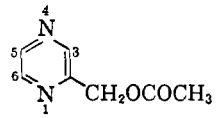
(23) All melting points were taken on a heated block and are uncorrected. Boiling points are also uncorrected.

(24) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, 77, N. Y.

(25) The melting points of some of the compounds reported in the first paper were taken on a heated block with a faulty thermometer and are incorrect. These have been redetermined: pyrazine-1-oxide, m.p. 113–114°; 3-methylpyrazine-1-oxide, m.p. 89–90°; 3,5-dimethylpyrazine-1-oxide, m.p. 130–132°; 2,3,5,6-tetramethylpyrazine-1-oxide, m.p. 100–101.5°. The melting points of the first two compounds are in closer agreement with those reported by Koelsch and Gumprecht.[13]

TABLE I

2-ACETOXYMETHYLPYRAZINES

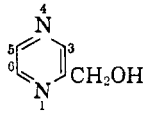


Compound	Yield, %	M.P., B.P.	mm.	t n_D	Empirical Formula	C, %	H, %	N, %
5-Methyl[a]	33	123–125	10	1.5113[17]	$C_8H_{10}N_2O_2$			
6-Methyl	60	127–130	14	1.5025[23]	$C_8H_{10}N_2O_2$	[b]		
3,5,6-Trimethyl	57	145–147	17	1.5053[24]	$C_{10}H_{14}N_2O_2$	[c]		
4-Oxide	36	104–105			$C_8H_8N_2O_3$	Calcd.: 50.00	4.79	16.66
						Found: 50.25	4.79	16.81
5-Methyl-4-oxide	30	73–74.5			$C_8H_{10}N_2O_3$	Calcd.: 52.70	5.53	15.38
						Found: 52.86	5.54	15.30
5-Methyl-1,4-dioxide	33	239–240[d]			$C_8H_{10}N_2O_4$	Calcd.: 48.48	5.09	14.14
						Found: 48.45	5.12	13.95
5-Acetoxymethyl	6	68–70[e]			$C_{10}H_{12}N_2O_4$	Calcd.: 53.56	5.40	
						Found: 53.44	5.34	

[a] Reference 13 gives the b.p. as 70–71° (0.4 mm.); $n_D^{25°}$ 1.5057. [b] Analyzed as the *picrate*, m.p. 201–202°. Calcd: for $C_{14}H_{13}N_5O_9$: C, 42.53; H, 3.31. Found: C, 42.6, H, 3.6. [c] Analyzed as the *picrate*, m.p. 96–97°. Calcd.: for $C_{16}H_{17}N_5O_9$: C, 45.39; H, 4.05; N, 16.55. Found: C, 45.61; H, 4.08; N, 16.81. [d] Reference 13 gives the m.p. as 241–242°. [e] Reference 13 gives the m.p. as 80–81°.

TABLE II

2-PYRAZINEMETHANOLS



Compound	Yield, %	M.P.	Empirical Formula	C, %	H, %	N, %
5-Methyl	85	36–39[a]	$C_6H_8N_2O$			
6-Methyl	46	43–45	$C_6H_8N_2O$	Calcd.: 58.05	6.49	22.57
				Found: 58.17	6.51	22.57
3,5,6-Trimethyl	60	65–66	$C_8H_{12}N_2O$	Calcd.: 63.13	7.95	18.41
				Found: 63.13	7.93	18.54
5-Methyl-1,4-dioxide		226–228[b]	$C_6H_8N_2O_3$	Calcd.: 46.20	5.10	17.95
				Found: 45.40	5.20	17.82
3,5,6-Trimethyl-*N*-oxide[c]	78[d]	83–85.5	$C_8H_{12}N_2O_2$	Calcd.: 57.12	7.19	16.66
				Found: 57.30	7.31	16.64
3,5,6-Trimethyl-1,4-dioxide	[d]	152.5–154.5	$C_8H_{12}N_2O_3$	Calcd.: 52.16	6.57	15.21
				Found: 52.41	6.71	15.11

[a] B.p. 137–138° (21 mm.); ref. 13 gives m.p. 36–39°. [b] Ref. 13 gives the m.p. 226–228°. [c] The position of the *N*-oxide is as yet undetermined, pending further investigation. [d] Combined yield, see Experimental.

Reaction of pyrazine-1-oxide with acetic anhydride. Solutions of 1.9 g. (0.02 mole) pyrazine-1-oxide in 5 ml. acetic anhydride were refluxed for varying periods up to 6 hr. The pale yellow solution turned dark at the end of 1 hr. but the ultraviolet absorption spectrum of samples taken at 15 min. (first 2 hr.), and then at half-hour intervals remained unchanged. From the reaction mixture, 0.6 to 1.1 g. material, m.p. 110–111°, was recovered. This material exhibited both the infrared and ultraviolet absorption spectrum of pyrazine-1-oxide.[17] The sublimed material did not depress the melting point of authentic material.

Similar experiments with *3-methylpyrazine-1-oxide, 3,5-dimethylpyrazine-1-oxide,* or *pyrazine-1,4-dioxide* and acetic anhydride, in each case, failed to demonstrate any reaction as evidenced by unchanged ultraviolet absorption spectrum,[17] and recovery of starting material.

2-Acetoxymethyl-5-methylpyrazine (IX). A solution of 24.0 g. (0.2 mole) 2,5-dimethylpyrazine-1-oxide in 60 ml. acetic anhydride was heated under reflux. During the course of the reaction, the absorption peak at 260 mμ gradually declined while an absorption peak at 274 mμ developed. At the end of 3 hr., the 260 mμ peak disappeared. The solvent was removed under reduced pressure and the oily black residue was distilled collecting 12.0 g. product, b.p. 127–130° (12 mm.). This was redistilled to give 11.0 g. material, b.p. 123–125° (10 mm.), $n_D^{17°}$ 1.5113; λ_{max}^{liquid} 5.80 μ(—C=O); 8.15 μ[—C—O— stretch, (acetate)].

2-Hydroxymethyl-5-methylpyrazine. A solution of 10.0 g. (0.06 mole) IX in 48 ml. 10% sodium hydroxide was allowed to stand 72 hr. at room temperature. The yellow solution was saturated with salt and continuously extracted with ether for 24 hr. The dried extract was concentrated and chilled to give 6.3 g. product, m.p. 25–28°. This was distilled collecting the portion b.p. 137–138° (21 mm.). This was recrystallized from ether–petroleum ether (b.p. 30–60°), m.p. 36–39°; $\lambda_{max}^{CHCl_3}$ 2.95 μ (OH); 9.70 μ (C—OH).

2-Acetoxymethyl-6-methylpyrazine. A solution of 9.0 g. (0.072 mole) 2,6-dimethylpyrazine-1-oxide (m.p. 50°) in 45

ml. acetic anhydride was heated under reflux for 1.5 hr. at which time the absorption peak at 260 mμ disappeared. The solvent was removed *in vacuo*, the residue was taken up in hot absolute ethanol, decolorized with charcoal, and concentrated *in vacuo*. The residual oil was distilled collecting a total of 7.0 g. of product in two fractions, b.p. 127–130° (14 mm.), $n_D^{22°}$ 1.5017–1.5068. A portion was redistilled, b.p. 98–99° (0.1 mm.), $n_D^{23°}$ 1.5025; $\lambda_{max}^{CHCl_3}$ 5.65 μ; 5.72 μ (—C=O).

2-Hydroxymethyl-6-methylpyrazine. A solution of 7.3 g. (0.04 mole) 2-acetoxymethyl-6-methylpyrazine in 35 ml. 10% sodium hydroxide was allowed to stand 96 hr. The dark red solution was saturated with salt and extracted with ether. The dried extract was concentrated and the residual oil, weighing 2.3 g., solidified on standing in a desiccator under vacuum. Upon recrystallization from ether–petroleum ether (b.p. 30–60°) the colorless crystals melted at 35°. For analysis the material was sublimed *in vacuo* 100–110°, (10 mm.), m.p. 45°. $\lambda_{max}^{CHCl_3}$ 3.0 μ (OH); 9.55 μ (C—OH).

2-Acetoxymethyl-3,5,6-trimethylpyrazine. A solution of 15.2 g. (0.1 mole) 2,3,5,6-tetramethylpyrazine-1-oxide in 51 ml. acetic anhydride was refluxed for 2 hr., although the absorption maximum had shifted from 259 mμ to 285 mμ in 0.5 hr. The solution was concentrated under reduced pressure. Colorless needles, 0.7 g. which appeared in the residue on cooling, were collected and washed with ether. This material melted 320–322°, left an ash on ignition, and was transparent in the ultraviolet. It was not investigated further.

The mother liquor and ether washings were combined, reconcentrated *in vacuo* and distilled giving (a) 1.2 g. of liquid, b.p. 50–75° (14 mm.), m.p. 74°, identified as tetramethylpyrazine; (b) 10.8 g. of product, b.p. 132–135° (9 mm.). This was redistilled, b.p. 145–147° (17 mm.), $n_D^{24.8°}$ 1.5053. $\lambda_{max}^{CHCl_3}$ 5.75 μ (—C=O).

2-Hydroxymethyl-3,5,6-trimethylpyrazine. A mixture of 5.0 g. (0.025 mole) 2-acetoxymethyl-3,5,6-trimethylpyrazine and 25 ml. 10% sodium hydroxide was allowed to stand 2 days during which time the immiscible layers slowly disappeared and the solution turned yellow. The solution was saturated with salt, and continuously extracted with ether for 24 hr The dried extract was concentrated leaving 2.2 g. light yellow solid, m.p. 60°. Two recrystallizations from ether–petroleum ether (b.p. 30–60°) raised the m.p. to 63–65°. For analysis, a portion was sublimed *in vacuo*, m.p. 65°. $\lambda_{max}^{CHCl_3}$ 2.92 μ (OH); 9.45 μ (—C—OH).

3-Acetoxymethylpyrazine-1-oxide. (XI). A solution of 6.3 g. (0.005 mole) 2-methylpyrazine-1,4-dioxide in 30 ml. acetic anhydride was refluxed for 2.5 hr. During this time the absorption maxima at 235 mμ and 295 mμ decreased and disappeared, while new maxima arose at about 220 mμ and 260 mμ, indicating the formation of a mono-*N*-oxide.[17]

The excess solvent was removed under reduced pressure and the black residue was extracted with three 50-ml. portions of boiling ethanol. The combined extracts were decolorized with charcoal and reduced to dryness, leaving 3.0 g. of a greasy, yellow solid. This was recrystallized several times from absolute alcohol (charcoal) to give colorless platelets, m.p. 104–105°, $\lambda_{max}^{CHCl_3}$ 5.75 μ (—C=O); 7.52 μ (N → O)[17]; 11.50 μ (N → O).

2-Acetoxymethyl-5-methylpyrazine-4-oxide (XIV).[26] A solution of 28.0 g. (0.2 mole) XII in 102 ml. acetic anhydride was heated under reflux until the absorption maxima at 230 mμ and 295 mμ of samples taken at 15-min. intervals disappeared and the extinction of a newly formed peak at 260 mμ reached a maximum. In several runs this required about 2 hr. The solvent was removed under reduced pressure and the residual black oil was distilled collecting 7.45 g. amber liquid, b.p. 120–134° at 0.5–1.5 mm., $n_D^{23.5°}$ 1.5279, which crystallized completely on cooling. This was identified as 2,5-dimethylpyrazine-1-oxide, by comparison of its infrared absorption spectrum with that of the pure compound,[17] mixed melting point, and mixed melting point of the picrates, m.p. 148–149°.[27]

Anal. Calcd. for $C_{12}H_{11}N_5O_8$: C, 40.7; H, 3.1. Found: C, 40.55; H, 3.29.

The residue, 11.0 g., solidified on cooling. This was extracted with boiling benzene and the yellow extract, after decolorization with charcoal, was concentrated to a yellow, low-melting solid that liquefied at room temperature. This was distilled, collecting 5.5 g., b.p. 155–160° (0.5 mm.) which solidified in the receiver, m.p. 50–52°. Several recrystallizations from ether (charcoal) raised the m.p. to 73–74.5°; $\lambda_{max}^{CHCl_3}$ 5.77 μ (—C=O); 7.65 μ (N → O); 11.80 μ (N → O).

2-Hydroxymethyl-5-methylpyrazine-1,4-dioxide. (A) *From 2-acetoxymethyl-5-methylpyrazine* (IX). A solution of 4.0 g. (0.025 mole) (IX) in 8 ml. glacial acetic acid was heated with 11.5 ml. 30% hydrogen peroxide for 24 hr. on a steam bath. The solution was concentrated *in vacuo* until colorless crystals began to form. This was diluted with water and taken to dryness, *in vacuo*. The colorless residue, m.p. 195°, weighed 4.0 g. Two recrystallizations from 95% ethanol and one from absolute alcohol gave 2.0 g. material, m.p. 229–230°.

(B) *From 2-acetoxymethyl-5-methylpyrazine-4-oxide* (XIV). A solution of 3.7 g. (0.02 mole) (XIV) in 9.2 ml. glacial acetic acid, heated 18 hr. on a steam bath with 6.0 ml. 30% hydrogen peroxide and worked up as in (A) gave 1.3 g. material, m.p. 229–230°. Koelsch and Gumprecht (ref. 13) give the m.p. of this compound as 226–228°; λ_{max}^{KBr} 3.05 μ (OH); 3.25 μ (associated OH); 7.75 μ, 7.85 μ, 7.95 μ, 11.35 μ (N → O).

2-Acetoxymethyl-5-methylpyrazine-1,4-dioxide. A mixture of 0.4 g. 2-hydroxymethyl-5-methylpyrazine-1,4-dioxide, 5 ml. acetic anhydride, and 10 ml. pyridine was allowed to stand at room temperature for 18 hr. It was heated for 10 min. on a steam cone and poured into 100 ml. cold water. The solution was acidified to *p*H 2.5 and extracted with chloroform. The dried extract was evaporated to dryness and the yellow residual solid, 0.20 g., melted at 235°. Several recrystallizations from absolute ethanol gave colorless crystals, m.p. 239–240°. Koelsch and Gumprecht (ref. 13) give the m.p. of this compound as 242–243°; $\lambda_{max}^{CHCl_3}$ 5.65 μ (—C=O); 7.90 μ, 11.83 μ (N → O).

2,5-Diacetoxymethylpyrazine (XV). A solution of 4.2 g. (0.03 mole) XII in 15 ml. acetic anhydride was heated under reflux until a sample withdrawn for analysis showed only a single absorption peak at about 270 mμ. This took about 6 hr. Following removal of solvent under reduced pressure, the black tarry residue was extracted with ether. The combined extracts were decolorized and evaporated to dryness, leaving 0.7 g. yellow needles, m.p. 65–67°. For analysis, a small amount was sublimed *in vacuo*, giving colorless needles, m.p. 68–70°; $\lambda_{max}^{CHCl_3}$ 5.75 μ (—C=O). Koelsch and Gumprecht (ref. 13) give the m.p. of this compound as 80–81°.

2-Hydroxymethyl-3,5,6-trimethylpyrazine-N-oxide. To a solution of 3.4 g. 2-acetoxymethyl-3,5,6-trimethylpyrazine in 5.1 ml. acetic acid, 4.5 ml. 35% hydrogen peroxide was added in two portions, half at the beginning of the reaction, and the remainder midway during the 7-hr. heating period (70°). Half the solvent was removed under reduced pressure, the solution was diluted with an equal volume of cold water, brought to *p*H 8 with cold 10% sodium hydroxide, and extracted with chloroform. The combined extracts were dried and evaporated to dryness leaving 2.5 g. of product, the bulk of which melted 63–66°, but which also contained higher melting material. Extraction of the solid with boiling

(26) The preparation of a 2-acetoxymethyl-5-methylpyrazine-*N*-oxide, m.p. 96–97°, by peroxidation of IX, and treatment of the dioxide with acetic anhydride is reported by Koelsch and Gumprecht.[13] It is believed their compound is the 1-oxide.

(27) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε
2-Acetoxymethylpyrazine				
5-Methyl	271[b]			
	274	3.99		
6-Methyl	273	3.99		
3,5,6-Trimethyl	279	4.36		
4-Oxide	219	4.23	260	4.18
5-Methyl-4-oxide	215	4.03	264	4.00
5-Methyl-1,4-dioxide	232	4.11	300	4.04
5-Acetoxymethyl	269	3.84		
2-Hydroxymethylpyrazine				
5-Methyl	274	3.87		
6-Methyl	274	3.83		
3,5,6-Trimethyl	280	3.90		
5-Methyl-1,4-dioxide	232	4.10	300	4.00
3,5,6-Trimethyl-*N*-oxide	216	4.31	259	3.03
			296	3.77
3,5,6-Trimethyl-1,4-dioxide	238	4.52	299	4.34

[a] All spectra taken in distilled water. [b] 95% ethanol.

petroleum ether (b.p. 30–60°) gave 0.9 g. colorless needles, which after several recrystallizations from petroleum ether (b.p. 30–60°) melted 83–85.5°; λ_{max}^{KBr} 2.95 μ (OH); 7.57 μ, 11.65 μ, 11.90 μ (N → O).

The residue from the petroleum ether extractions was recrystallized several times from methanol, to give 0.09 g. colorless crystals, m.p. 152.5–154.5°. This gave the ultraviolet absorption spectrum of a dioxide and is 2-hydroxymethyl-3,5,6-trimethylpyrazine-1,4-dioxide; λ_{max}^{KBr} 3.05 μ (OH); 7.62, 11.72 μ (N → O).

Absorption spectra. The ultraviolet absorption spectra of compounds reported in this paper were obtained with a Beckman DU spectrophotometer, with 1.0-cm. cuvets. These are given in Table III.

Infrared absorption spectra were obtained with a Perkin-Elmer Model 21 recording spectrophotometer either as potassium bromide disks or in chloroform solution.[28]

(28) The authors are indebted to Dr. Oscar Auerbach and the Research Committee, Veterans Administration Hospital, East Orange, N. J., for continued loan of this instrument.

BRONX 68, N. Y.

[CONTRIBUTION FROM THE DEVELOPMENT DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY, DIVISION OF UNION CARBIDE CORPORATION]

A Novel Synthesis of Homopiperazine and Its Monomethyl Derivatives

F. POPPELSDORF AND R. C. MYERLY

Received May 11, 1960

Homopiperazine has been synthesized in a yield of about 32% by a new method involving the catalytic reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine. 1-, 2-, 5-, and 6-methylhomopiperazine, the four possible monomethylhomopiperazines, were prepared analogously. *N*-(2′-Aminoethyl)-1,3-propanediamine and its monomethyl derivatives were formed as co-products in 28 to 50% yields.

The intermediate cyano compounds were made by the interaction of the appropriate diamines and unsaturated nitriles.

Several derivatives of homopiperazine (1,4-diazacycloheptane) (I) have already been shown to have marked and desirable physiological activity.[1,2,3] Progress in finding new active compounds based on homopiperazine has, however, undoubtedly been hampered because of the relative inaccessibility of the base and its simple derivatives. Until very recently, the only methods published[4,5] for the preparation of homopiperazine involved the alkylation of the disodium salt of a *N,N′*-diarylsulfonylethylenediamine with a 1,3-dihalogenopropane followed by acid hydrolysis of the *N,N′*-diarylsulfonylhomopiperazine formed to homopiperazine. These syntheses are tedious and expensive and are, therefore, ill-suited for commercial production. A publication[6] which appeared last year after the work reported in this paper had been completed described the preparation of the cyclic amine (I) by the cyclodehydration of *N*-(2′-hydroxyethyl)-1,3-propanediamine by catalytic means or by pyrolysis of its hydrohalides. Over-all yields based on ethanolamine, the starting material, varied from 7.7 to 10.5% and from 7.4 to 19.2%, respectively.

Of the possible monomethylhomopiperazines, only the 1- and 2-methyl compounds have been reported in the literature. 1-Methylhomopiperazine has been made (a) by the ring enlargement of 1-methyl-4-piperidone by a Schmidt-type rearrangement followed by lithium aluminum hydride reduction of the resulting homopiperazinone,[1,7,8] and (b) in poor yield by the catalytic cyclodehydration

(1) A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *J. Am. Chem. Soc.*, **76**, 5805 (1954).

(2) J. W. Reinertson and P. E. Thompson, *Antibiotics and Chemotherapy*, **5**, 566 (1955).

(3) P. Brookes, R. J. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).

(4) L. Bleier, *Ber.*, **32**, 1825 (1899).

(5) C. C. Howard and W. Marckwald, *Ber.*, **32**, 2038 (1899).

(6) Takeo Ishiguro and Masaaki Matsumura, *Yakugaku Zasshi*, **78**, 153 (1959); *Chem. Abstr.*, **53**, 13163 (1959).

(7) J. G. Scruggs, Ph.D. dissertation, University of Michigan, 1956.

(8) P. S. Wadia and N. Anand, *J. Sci. Ind. Research (India)*, **17B**, 31 (1958); *Chem. Abstr.*, **52**, 15549 (1958).