[CONTRIBUTION FROM THE CHEMICAL & PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE & RUBBER COMPANY]

Vinylpyrazine

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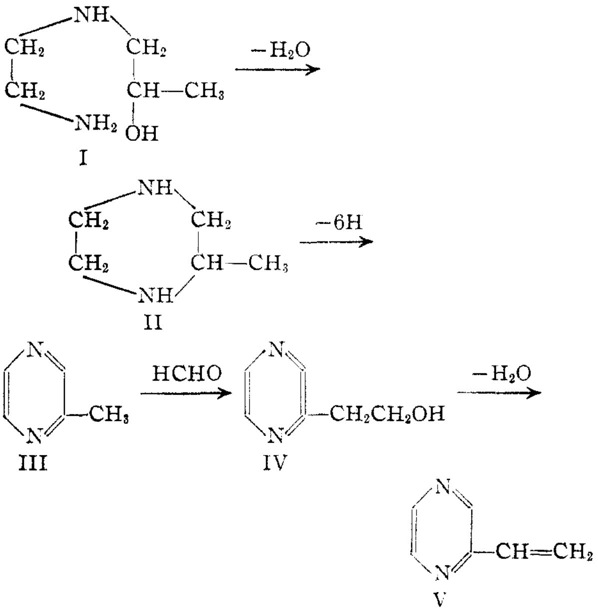
Vinylpyrazine has been synthesized. The intermediates, methylpyrazine and 2-hydroxyethylpyrazine, were prepared from 2-methylpiperazine.

Vinylpyrazine (V) has been prepared in five steps from ethylenediamine. N-(2-Hydroxypropyl)-ethylenediamine[1] from ethylenediamine and propylene oxide was cyclized to 2-methylpiperazine (II) by a method described previously.[2] Catalytic dehydrogenation of 2-methylpiperazine with copper chromite catalyst yielded methylpyrazine (III).

Methylpyrazine was heated in an autoclave with paraformaldehyde to produce 2-hydroxyethylpyrazine (IV) which was converted to vinylpyrazine (V) by dehydration with molten potassium hydroxide. The latter two pyrazine derivatives are new.



Butanol has been reported[3] an effective reaction medium for the preparation of piperazine by cyclodehydration of N-(2-hydroxyethyl)-ethylenediamine; and this was confirmed in the present work. However, when methylpiperazine was prepared from N-(2-hydroxypropyl)-ethylenediamine (I) dissolved in butanol, 1(or 4)-butyl-2-methylpiperazine was obtained in good yield along with 2-methylpiperazine. The reaction therefore provides a new method for synthesizing piperazines alkylated on but one of the nitrogen atoms.

Methylpyrazine (III) was obtained by dehydrogenation of 2-methylpiperazine in vapor phase over copper chromite catalyst. Reaction conditions were similar to those reported by Dixon[4] for the conversion of piperazine to pyrazine. With Raney nickel as catalyst a low yield of methylpyrazine was obtained. Pyrazine can be prepared by oxidation of piperazine with nitrobenzene[3]; however, reaction of 2-methylpiperazine with nitrobenzene gave no methylpyrazine.

Reaction conditions for hydroxymethylation of methylpyrazine were similar to those which have been used for the reaction of formaldehyde with methyl pyridines. Paraformaldehyde and a several-fold excess of methylpyrazine were heated at 165° in an autoclave for about 4 hours. In order to obtain an appreciable yield of 2-hydroxyethylpyrazine (IV) it was necessary to remove all traces of 2-methylpiperazine present as impurity in the methylpyrazine as it was prepared. This conveniently was done by recycling the methylpyrazine. Thus, a quantity of methylpyrazine which gave an 8% yield of IV in an initial reaction with paraformaldehyde gave yields of 33 and 35% in subsequent runs.

In a parallel run with 2-picoline in place of methylpyrazine, yield of 2-(2-hydroxyethyl)-pyridine was 64%. The methyl group of III is both alpha and beta to heterocyclic nitrogen. Beta nitrogen does not activate the hydrogen of a side-chain methyl; 3-picoline does not condense with formaldehyde. It appeared that the beta nitrogen of methylpyrazine reduced the activating effect of the alpha nitrogen on the methyl group, since the maximum yield of 2-hydroxyethylpyrazine was only 38%.

Vinylpyrazine resembled 2-vinylpyridine in properties. It was a colorless liquid which soon discolored in air, becoming yellow, and finally dark brown. Heated with *t*-butyl hydroperoxide, it gave a hard, brown, water-soluble polymer.

Experimental

2-Methylpiperazine.—N-(2-Hydroxypropyl)-ethylenediamine from propylene oxide and ethylenediamine[1] was converted to 2-methylpiperazine by cyclodehydration[2] over Raney nickel catalyst. Reaction at atmospheric pressure in diethylene glycol diethyl ether as diluent gave a yield of 50%, while yields by the autoclave method (dioxane as diluent) were 71–83%.

1(or 4)-Butyl-2-methylpiperazine.—Eight hundred grams (6.78 moles) of N-(2-hydroxypropyl)-ethylenediamine dissolved in 900 g. of *n*-butanol was stirred with 30 g. of Raney nickel catalyst in an autoclave at 200° for 8.5 hours. In addition to 237 g. (35% yield) of 2-methylpiperazine, the reaction mixture when distilled yielded 340 g. (32% yield) of N-(1 or 4)-*n*-butyl-2-methylpiperazine, a colorless non-viscous liquid of b.p. 81–83° (10 mm.) and n^{20}_{D} 1.4607.

Methylpyrazine. A. Nitrobenzene Experiment.—A mixture of 333 g. of 2-methylpiperazine and 409 g. of nitrobenzene was refluxed under a column 25 hours while water and aniline slowly distilled and carbon dioxide was evolved. No methylpyrazine was isolated. A tarry residue remained in the still-pot.

B. Raney Nickel Experiments.—No hydrogen was evolved when 2-methylpiperazine was refluxed with Raney nickel catalyst. However, when 100 ml. of diphenyl ether was added to a mixture of 37 g. of 2-methylpiperazine and 10 g. of Raney nickel catalyst, smooth evolution of gas took

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[1] L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 342 (1943).

[2] L. J. Kitchen and C. B. Pollard, THIS JOURNAL, **69**, 854 (1947).

[3] C. E. Goulding, M.S. Thesis, University of Florida, 1944, p. 24.

[4] J. K. Dixon, U. S. Patent 2,400,398, May 14, 1946.

place at 230°. After an hour of reflux the solution was filtered and yielded a 4-g. fraction (11% conversion) of crude methylpyrazine, b.p. 132–142°, n^{20}_{D} 1.4953, colorless liquid with a disagreeable picoline-like odor.

In an autoclave experiment 100 g. of 2-methylpiperazine dissolved in 350 g. of benzene was agitated with 10 g. of Raney nickel catalyst at 250° for 7 hours. By fractional distillation was obtained 8 g. (approx. 8% yield) of crude methylpyrazine, b.p. 132–140°, n^{20}_{D} 1.4874, with characteristic odor. Also obtained, in addition to benzene and about 20 g. of 2-methylpiperazine, were a low-boiling fraction, b.p.r. 33–79°, n^{20}_{D} 1.4645, with a strong odor of amines; a trace of material with pyrazine-like odor distilling in the pyrazine range; and 28 g. of material of b.p. above 160° and having a disagreeable odor.

C. **Copper Chromite Dehydrogenation.**—Copper chromite catalyst was prepared by the directions of Adkins.[5] Eight-mesh activated alumina was mixed with a paste of the catalyst and water, and the mixture was dried. A glass tube, 19 mm. i.d., was filled to a height of 20 cm. with chunks of the catalyst, which was supported with a plug of copper turnings. The tube, at the bottom, fitted a 2-necked 200-ml. round-bottomed flask and at the top, a condenser. Tube and flask, contacted with thermocouples, were insulated with asbestos, wound with nichrome electric heaters, and further insulated with asbestos.

While the flask was kept in the temperature range 390–500° and the column about 475°, 2-methylpiperazine dissolved in benzene (usually a 45% solution) was added dropwise (two drops per second) from a dropping funnel to the flask. Vapor emerging from the top of the tube was condensed to a light brown liquid which had a greenish fluorescence. Reaction products were fractionated with a 19 mm. i.d. column packed to a height of 18 in. with nickel helices. Yield of methylpyrazine was 37–46%, while 9–25% of the 2-methylpiperazine had not reacted.

In a typical run 200 g. of 2-methylpiperazine dissolved in 300 ml. of benzene was added to the vaporizing flask during 3 hours. The distillate contained about 70 g. of methylpyrazine, a yield of 39%, and 50 g. (25% recovery) of 2-methylpiperazine. There remained 22 g. of undistilled material.

The methylpyrazine, b.p. 135° (735 mm.), had n^{20}_{D} 1.5020–1.5048. A redistilled sample of n^{20}_{D} 1.5044 had m.p. −30 to −29.5° and d^{20}_{4} 1.021 (lit.,[6] d^{20}_{4} 1.0289). Purified methylpyrazine which was recovered from hydroxymethylation experiments had n^{20}_{D} 1.5048 (lit.,[6] $n^{18.7}_{\mathrm{D}}$ 1.5067).

D. **Dehydrogenation and Debutanation of N-Butyl-2-methylpiperazine.**—Eighty-six grams of 1(or 4)-*n*-butyl-2-methylpiperazine mixed with 100 ml. of benzene was passed through the column of copper chromite catalyst at a temperature of 500–530° in the manner described above for 2-methylpiperazine. The yield of methylpyrazine was 31% (16 g.).

2-Hydroxyethylpyrazine.—The best yield was 38%. 373 g. of purified methylpyrazine and 25 g. of paraformaldehyde (molar ratio, 4.5 to 1) were heated 4.5 hours in a stainless steel autoclave. The yield of 2-hydroxyethylpyrazine was 37 g. (38%); the distillation residue was 10 g.

The yield was low when the methylpyrazine contained traces of 2-methylpiperazine as impurity, which was removed by the paraformaldehyde during reaction. In three runs, each run carried out with the methylpyrazine recovered from the previous run, the yields of 2-hydroxyethylpyrazine were 8%, 33% and 35%.

The yield was improved when methylpyrazine was present in excess. In a series of runs with methylpyrazine and paraform in 1:1 molar ratio, the maximum yield was 5%, compared with a maximum yield of 38% with methylpyrazine present in several-fold excess.

2-Hydroxyethylpyrazine, purified by redistillation, had b.p. 128.5–129° (10 mm.); n^{20}_{D} 1.5378; d^{20}_{4} 1.163; somewhat viscous liquid with a pink tinge and a slight odor.

Anal. Calcd. for $C_6H_8N_2O$: N, 22.57. Found: N, 22.46.

The α-naphthylurethan had m.p. 88.4–89.2° (from H_2O–MeOH). The phenylurethan was low-melting and hygroscopic and was not obtained pure.

2-(2-Hydroxyethyl)-pyridine.—The autoclave was charged with 427 g. (4.5 moles) of 2-picoline and 23 g. (0.73 mole) of paraformaldehyde, a molar ratio of six to one; and it was agitated 4 hours at 165°. From the reaction mixture was obtained 60 g. of 2-(2-hydroxyethyl)-pyridine, a yield of 64% compared with yields of 33–38% in similar experiments which were carried out with methylpyrazine. Less than 5 g. of residue remained in the still-pot when the product had distilled. 2-(2-Hydroxyethyl)-pyridine distilled as a somewhat viscous, almost colorless liquid with a slight odor; b.p. 110–114° (10 mm.); n^{20}_{D} 1.5374.

The phenylurethan of 2-(2-hydroxyethyl)-pyridine, prepared in heptane and recrystallized from acetone–heptane, had m.p. 123–125°. When the phenylurethan was distilled at atmospheric pressure, the distillate was unchanged phenylurethan, with some decomposed material remaining in the still-pot. When it was distilled with an equal weight of sodium hydroxide, the distillate was a mixture of aniline and 2-vinylpyridine.

Vinylpyrazine.—Vinylpyrazine was prepared by dehydration of 2-(2-hydroxyethyl)-pyrazine with potassium hydroxide at 170° in an apparatus similar to one described by Frank, *et al.*[7] A nickel cup two inches in diameter and six inches deep was charged with 106 g. of potassium hydroxide pellets. The apparatus was evacuated to a pressure of 20 mm., and 63 g. of 2-hydroxyethylpyrazine containing 0.5 g. of phenyl-β-naphthylamine was added during 2 hours. The distillate of 54 g. of crude vinylpyrazine, on redistillation through a column, gave 43 g. (80% yield) of vinylpyrazine, b.p. 60–62°, mainly 61° (20 mm.); n^{20}_{D} 1.5565; d^{20} 1.046. A colorless liquid, it soon turned yellow and was red after standing overnight. On continued standing it turned brown.

Anal. Calcd. for $C_6H_6N_2$: N, 26.49. Found: N, 25.49.

The picrate of vinylpyrazine, prepared in alcohol and recrystallized from alcohol, had m.p. 99.2–100.2°.

Vinylpyrazine monomethiodide was prepared by refluxing excess methyl iodide with vinylpyrazine for 2 hours; letting the mixture stand overnight; evaporating excess methyl iodide; leaching the residue with hot acetone; and crystallizing the product from chilled acetone solution. A mustard-yellow powder, it had m.p. 126°.

Anal. Calcd. for $C_7H_9N_2I$: I, 51.15. Found: I, 51.25.

Polyvinylpyrazine.—Vinylpyrazine containing one-tenth its volume of *t*-butyl hydroperoxide was heated in a test-tube for 5 minutes. On cooling the dark brown product was a hard water-soluble polymer. When heated with benzoyl peroxide vinylpyrazine turned dark brown but did not give a solid polymer.

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[5] H. Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 13.

[6] J. W. Brühl, *Z. physik. Chem.*, **22**, 388 (1897).

[7] R. L. Frank, C. E. Adams, R. E. Allen, R. Gander and P. V. Smith, THIS JOURNAL, **68**, 1366 (1946).