[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Mannich Reaction on 2,5-Dimethylpyrazine[1]

BY SEYMOUR M. LINDER AND PAUL E. SPOERRI

The Mannich reaction has been applied for the first time to 2,5-dimethylpyrazine. Of the amines tried, positive reactions were obtained only with dimethylamine, piperidine and morpholine. It was found that one, or more usually two, of the hydrogen atoms of each of the methyl groups could be substituted.

In the course of our investigations of the properties of 2,5-dimethylpyrazine it seemed of interest to ascertain whether the methyl groups were sufficiently reactive to undergo the Mannich reaction. This reaction had not previously been applied to the pyrazine system.

When a mixture of dimethylpyrazine, dimethylamine hydrochloride and 37% formaldehyde was refluxed in alcohol, the only observed reaction was the formation of dimethylaminomethanol. Under these conditions, dimethylaminomethanol does not react with 2,5-dimethylpyrazine. At the higher temperature obtained using isoamyl alcohol as the solvent, successful results were obtained with dimethylamine and piperidine.

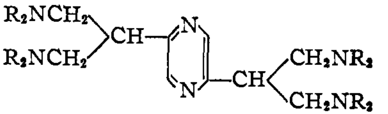
In confirmation with the findings of Bodendorf and Koralewski,[2] the yield was improved by conducting the reaction in such a way that the formation of dimethylaminomethanol was minimized, namely, by adding aqueous formaldehyde slowly to a refluxing mixture of dimethylpyrazine and dimethylamine hydrochloride.

TABLE I

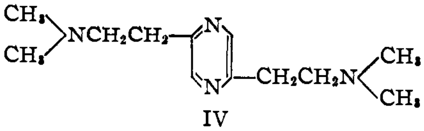
I, 2,5-Bis-[bis-(dimethylaminomethyl)-methyl]-pyrazine; II, 2,5-bis-[bis-(piperidinomethyl)-methyl]-pyrazine; III, 2,5-bis-[bis-(morpholinomethyl)-methyl]-pyrazine; IV, 2,5-bis-(β-dimethylaminoethyl)-pyrazine.

Amine hydrochloride	Solvent	Type of formaldehyde	Product
Dimethylamine	Ethanol	37% aq.	Dimethylaminomethanol
Dimethylamine	Isoamyl alcohol	Para	I
Piperidine	Isoamyl alcohol	Para	II
Diethylamine	Isoamyl alcohol	Para	None
Di-*n*-butylamine	Isoamyl alcohol	Para	None
Morpholine	Isoamyl alcohol	Para	None
Methylbenzylamine	Isoamyl alcohol	Para	None
Dibenzylamine	Isoamyl alcohol	Para	None
Dimethylamine	None	37% aq.	I and IV
Morpholine	None	37% aq.	III
Dimethylamine	10% HCl	37% aq.	None
Dimethylamine	Concd. HCl	37% aq.	None
Dimethylamine	Glacial HOAc[a]	Para	None
Dimethylamine	Ethylene glycol	Para	None

[a] Plus a trace of pyridine.



I, II, III



IV

The 2,5-dimethylpyrazine was prepared by the reduction of oximinoacetone with stannous chloride.[3]

2,5-Bis-[bis-(dimethylaminomethyl)-methyl]-pyrazine (I) and 2,5-Bis-(β-dimethylaminoethyl)-pyrazine (IV). A.—A mixture of 4.3 g. of dimethylpyrazine, 6.5 g. of dimethylamine hydrochloride, 2.4 g. of paraformaldehyde and 25 ml. of isoamyl alcohol was heated to reflux. After 15 minutes, an oil separated which crystallized partially on continued heating. After refluxing for 10 hours, the mixture was cooled and the upper layer decanted and discarded. The residue crystallized when warmed with methanol to give 4.0 g. (40%), m.p. 235–238° dec. After three recrystallizations from 80% methanol, the material melted at 237–238° dec.

Anal. Calcd. for $C_{18}H_{36}N_6\cdot 4HCl\cdot H_2O$ (I): C, 43.20; H, 8.46; Cl, 28.35. Found: C, 42.98; H, 8.42; Cl, 28.31, 28.16.

The free base was obtained in crystalline form by dissolving the hydrochloride in the smallest amount of water and adding an excess of 30% sodium hydroxide. After two sublimations, a sample melted at 92–94°.

Anal. Calcd. for $C_{18}H_{36}N_6$ (I): C, 64.23; H, 10.78; N, 24.99. Found: C, 64.26; H, 10.93; N, 24.97, 24.75.

The methanolic mother liquor from which the hydrochloride was originally crystallized was concentrated *in vacuo* and the residue taken up in hot alcohol. On cooling the solution, crystals formed, which melted at 199–203°. The yield was 300 mg. After three recrystallizations from methanol–ether, the material melted at 201–204°.

Anal. Calcd. for $C_{12}H_{24}N_4Cl_2$ (IV): C, 48.80; H, 8.19; Cl, 24.00. Found: C, 48.30; H, 8.41; Cl, 24.17.

The free base is an oil which decomposes on distillation and cannot be characterized as such.

B.—A mixture of 10.8 g. of dimethylpyrazine and 16.3 g. of dimethylamine hydrochloride was heated to refluxing with stirring. The salt melted, forming a two-phase mixture. While the solution was refluxing and stirring, 16.2 g. of 37% formaldehyde was added dropwise over a period of 1.5 hours. After the addition, the refluxing and stirring was continued for two hours. On cooling, crystals separated, which were removed by filtration, washed with alcohol, and dried. The material melted at 235–238° dec. and is the bis-compound (I). The yield was 9.3 g. (37.5%).

The mother liquor was concentrated *in vacuo*, giving an oil, which was dissolved in hot alcohol. On cooling crystals formed which melted at 194–196°. The yield was 6.6 g. (22.4%). This is the mono compound (IV).

C.—A mixture of 10.8 g. of dimethylpyrazine, 16.3 g. of dimethylamine hydrochloride and 16.2 g. of 37% formaldehyde was heated in an oil-bath at 130° under a reflux condenser. After 3.5 hours, 10 g. more of 37% formaldehyde was added. After heating an additional 3 hours, the mixture was cooled. Crystals formed and were removed by filtration and washed with alcohol. The material melted at 235–238° dec. and proved to be the bis-compound (I). The yield was 5 g. (20%).

2,5-Bis-[bis-(trimethylammonium methyl)-methyl)]-pyrazine Tetrabromide.—A solution of 870 mg. of free base (I) in 10 ml. of acetone was mixed with 10 ml. of an acetone-methyl bromide solution containing 0.4 g. of methyl bromide per ml. A reaction took place almost instantly with the formation of a crystalline solid. The solid was removed

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[1] This paper is based upon the thesis by Seymour M. Linder in partial fulfillment of the requirements for the degree of Master of Science in Chemistry. It was presented at the Meeting-in-Miniature of the Metropolitan-Long Island Group of the New York Section of the American Chemical Society in Brooklyn on March 17, 1950.

[2] K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

[3] R. R. Joiner, Thesis, Polytechnic Institute of Brooklyn, 1941.

by filtration, washed with acetone and dried. It decomposed slowly but did not melt below 360°. An analytical sample was prepared by recrystallization from a methanol-water (3:1) mixture and drying at 100°.

Anal. Calcd. for $C_{22}H_{48}N_6Br_4$: C, 36.88; H, 6.75; N, 11.73. Found: C, 36.60; H, 6.84; N, 12.09 (Dumas).

2,5-Bis-[bis-(piperidinomethyl)-methyl]-pyrazine (II).—Piperidine hydrochloride, prepared from 6.8 g. of piperidine, was mixed with 4.3 g. of dimethylpyrazine, 2.4 g. of paraformaldehyde and 40 ml. of isoamyl alcohol and the mixture heated to reflux. Solids started to separate after 15 minutes. After refluxing for 8 hours, the mixture was cooled and the solid removed by filtration, washed with alcohol and dried; m.p. 216–220°; yield 4.1 g. (30%). After two recrystallizations from 70% alcohol, the product melted at 232–233°.

Anal. Calcd. for $C_{30}H_{52}N_6 \cdot 4HCl \cdot 2H_2O$: C, 53.05; H, 8.92; N, 12.38. Found: C, 53.20; H, 8.74; N, 11.90.

2,5-Bis-[bis-(morpholinomethyl)-methyl]-pyrazine (III).—A mixture of 10.8 g. of dimethylpyrazine, 24.5 g. of morpholine hydrochloride and 2 ml. of water was heated to refluxing with stirring. A two-phase liquid–liquid mixture was formed. Then 16.2 g. of a 37% solution of formaldehyde was added dropwise over a period of two hours. The mixture was refluxed and stirred for an additional 15 minutes, then cooled. The crystals which formed were removed by filtration, washed with alcohol and dried at 100°.

On recrystallization from methanol-water (4:1), 3.5 g. of material melting at 220–221° with decomposition was obtained. Further recrystallization from this solvent gave a product melting at 224–226°.

Anal. Calcd. for $C_{26}H_{48}N_6O_4Cl_4 \cdot H_2O$: C, 46.71; H, 7.54; Cl, 21.21. Found: C, 46.74; H, 7.47; Cl, 21.52.

Further small amounts of bis compound but no mono compound were isolated from the mother liquors.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

Monomeric Products from the Condensation of Phenol with Formaldehyde and Primary Amines

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3,4-Dihydro-3-substituted-1,3,2H-benzoxazines and N-substituted 2-aminomethylphenols were reprepared from phenol, formaldehyde and representative primary amines. Evidence was presented for the structures assigned.

Phenols having unsubstituted ortho or para positions have been shown to form Mannich bases by condensation with formaldehyde and either primary[2-4] or secondary[5-8] amines. Reaction of phenol with formaldehyde and dimethylamine has been reported to give 2-[7,8] 2,6-bis-[7] and 2,4,6-tris-(dimethylaminomethyl)-phenol.[6] 2,4,6-Tris-(morpholinomethyl)-phenol also has been prepared.[6] In the limited work with primary amines only resinous material was obtained from the condensation of equimolar quantities of 2-aminoethanol, formaldehyde and phenol, although several *o*- and *p*-substituted phenols gave crystalline products under similar conditions.[2] Use of two molar proportions of formaldehyde was reported to result in an even more rapid polymerization. More recently it has been shown that substituted phenols will react with formaldehyde and primary amines to form 3,4-dihydro-1,3,2H-benzoxazines[9] and N,N-bis-(hydroxybenzyl)-amines[10] directly in certain instances as well as the previously reported *o*- and *p*-alkylaminomethylphenols.[2,3]

The fact that phenol has three and primary amines two formaldehyde reactive positions makes possible a great complexity of products, including polymers, from such systems. For example, the reaction of phenol with formaldehyde and methylamine has been proposed as a source of basic resins.[11] In the present study, condensation of phenol with formaldehyde and cyclohexylamine in a molar ratio of 1:2:1, respectively, in refluxing dioxane led to a 60% yield of 3,4-dihydro-3-cyclohexyl-1,3-2H-benzoxazine (I). While analogous liquid benzoxazines from substituted phenols[9] can be obtained readily by simple distillation after removal of reaction solvents, such a procedure results in extensive polymer formation with such products from phenol. However extraction of an ether solution of the crude product with aqueous alkali made possible the subsequent smooth distillation of I with essentially no resin being formed. Similar results were obtained with benzylamine, methylamine and 2-aminoethanol.

The benzoxazines from phenol are highly sensitive to mineral acids. Efforts to prepare a hydrochloride of I by procedures used successfully with analogous products from substituted phenols led to 2-cyclohexylaminomethylphenol (II) with the liberation of formaldehyde. II was also prepared directly from equimolar quantities of phenol, formaldehyde and cyclohexylamine, but in low yield (28%). None of the other possible Mannich bases was isolated. It has been shown, however, that in such condensations N-methylolamines can react selectively at either the ortho or para position of a phenol if both positions are free.[12,13] In contrast to the direct synthesis, the hydrolysis of I to II was essentially quantitative so that the over-all yield of II by this method was 60%. 2-Alkylaminomethylphenols were also prepared from the benzoxazines derived from methylamine, benzylamine and 2-aminoethanol. II was readily reconverted to I in 86% yield by reaction with

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(3) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *ibid.*, **70**, 1363 (1948).

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(8) A. Madinaveitia, *Anales soc. espan. fis. quin.*, **19**, 259 (1921); *C. A.*, **16**, 1230 (1922).

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