

# THE MANNICH CONDENSATION OF COMPOUNDS CONTAINING ACIDIC IMINO GROUPS<sup>1</sup>

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# ABSTRACT

The synthesis of several new Mannich bases was accomplished by the condensation of secondary amines and formaldehyde with the following compounds: (1) 2-pyrrolidone, (2) 2,4-thiazolidinedione, (3) hydantoin, (4) 5,5-dimethyl-hydantoin, (5) uracil, (6) ethylnitramine, and (7) n-butylnitramine.

## INTRODUCTION

While much work has been done on the Mannich condensation of compounds containing acidic hydrogen on carbon, considerably fewer data are available on the Mannich reaction of substances possessing active hydrogens on nitrogen, as it can be seen from this historical introduction.

Feldman and Wagner (6) prepared piperidinomethyl derivatives of succinimide, phthalimide, and carbazole. In their study of morpholinomethyl derivatives of urea and substituted ureas, Weaver, Simons, and Baldwin (13) condensed morpholinomethanol with phthalimide and succinimide. N-(Morpholinomethyl)- and N-(piperidinomethyl)-phthalimide were also synthesized by Moore and Rapala (12). The condensation of benzothiazole-2-thione and related compounds with formaldehyde and secondary amines was described in the German patent 575,114 in 1933. The purpose of the latter work was to prepare methylenediamine derivatives for use in the rubber industry.

Bachman and Heisey (1) condensed benzimidazole and benzotriazole with formaldehyde and secondary amines. Baker, Ouerry, Kadish, and Williams (2) prepared two Mannich bases of 4-quinazolone in reactions with formaldehyde, piperidine, and morpholine respectively. The Mannich condensation of pyrazole was studied by Huttel and Jochum (9). Butenandt and Hellmann (3) studied the reaction of hydantoin with formaldehyde and piperidine. However, they did not investigate the reaction product further. The most recent work on the synthesis of N-Mannich bases has been published by Hellmann and Löschmann (8). They describe the condensation of isatin, phthalimide, succinimide, and carbazole and give a few references on the previous publications of other authors.

That the alkylnitramines undergo a condensation with piperidinomethanol was observed by Franchimont (7) as early as 1910. However, he did not give any data on analysis and properties of the reaction product.

The objective of this work was to investigate the Mannich condensation of the cyclic imino compounds containing one or two imino groups in addition to the carbonyl groups as the hydrogen activators. We also studied the condensation of alkylnitramines in which the nitro group activates the hydrogen atom of the imino group.

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# DISCUSSION

We consider the replaceability of a hydrogen of the imino group by halogens or by metals, or by both, as the guiding principle enabling us to indicate the compounds possessing the ability to react in the Mannich condensation. On the bases of a similar behavior of ketones and imides in the reactions of halogenation and salt formation via enolization, we can assume that the Mannich condensation in both groups of compounds must follow the same course. Lieberman and Wagner (11) postulated the formation of a carbanion from a C—H acid compound as a necessary step in this reaction. It is reasonable to assume that the N—H acidic substance undergoes an analogous change to give a mesomeric anion in which the negative charge is located in the group N—C=O. The formation of the Mannich base may be visualized as the addition of the intermediate methylene-ammonium cation or the protonated dialkylaminomethanol at the mesomeric anion, as in the example of the reaction of 2-pyrrolidone.



Most of the condensations of imino carbonyl compounds were carried out using free secondary bases, but not their salts because of the sensitivity of the N—CH<sub>2</sub>—N bond towards acids. However, in a few cases the condensation was successful using even secondary amino hydrochlorides. Thus 2-pyrrolidone [2-pyrrolidinone] was successfully condensed with morpholine and piperidine bases, and dimethylamine hydrochloride as well.

2,4-Thiazolidinedione (4, 14) possesses acidic properties and forms alkali and silver salts. It reacted very easily at 0° with morpholine, piperidine, and dimethylamine. Even methylamine reacted with two molecules of the 2,4thiazolinedione to give (VII). Both hydantoin [2,4-imidazolidinedione] and 5,5-dimethylhydantoin [5,5-dimethyl-2,4-imidazolidinedione] demonstrated their ability to react in the Mannich condensation with two molecules of formaldehyde and two molecules of morpholine. No reaction products were obtained in the attempted condensations of both hydantoins with piperidine and dialkylamines respectively.

We found that uracil [2,4-(1H, 3H)-pyrimidinedione] reacted with morpholine and formaldehyde to give 1-(morpholinomethyl)uracil. Despite the close resemblance to uracil, dihydrouracil did not react in the Mannich reaction.

In this work, alkylnitramines were prepared by the procedure of Curry and Mason (5). The attempted condensations of alkylnitramines with formaldehyde and secondary amines under reflux gave no desired products. However, the condensation succeeded when the reaction mixture was kept at 0° for 12 hr. It was found that dimethylamine and diethylamine did not undergo the Mannich condensation with *n*-butyl- and ethyl-nitramine. All attempts to form Mannich bases using methylnitramine were unsuccessful.

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For the purpose of identification, the ultraviolet spectra of alkylnitramines and their derivatives were determined in absolute alcohol (DU Beckman spectrophotometer).

Compound	$\lambda_{max}, m\mu$	$\epsilon_{\max}$
Aethylnitramine	230	14010
Ethvlnitramine	227 - 232	28230
-Butylnitramine	231-233	9727
V-(Morpholinomethyl)- ethylnitramine	232	6603
<i>n</i> -butylnitramine	234	2931

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Although the observed values of  $\lambda_{max}$  are in agreement with the reported absorption spectra (10), the values of the molecular extinction coefficients are considerably higher than those given for methyl- and *n*-butyl-nitramine.



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# EXPERIMENTAL

# 1-(Morpholinomethyl)-2-pyrrolidone (I)

In a 50 ml. three-necked flask, a solution containing 2.55 gm. (0.03M) of 2-pyrrolidone in 20 ml. of water and 2.8 gm. (0.03M) of morpholine was placed. The mixture was stirred and 2.7 ml. (0.03M) of 35% formaldehyde was added slowly. The reaction mixture was refluxed at 100° for one hour. Upon cooling, the solution was extracted with chloroform and the extract was concentrated by distillation on a water bath. To this residue, 25 ml. of ethanol was added and the solution was concentrated by further distillation. After 12 hr., solid white crystals of I appeared which, after several crystallizations, melted at 68.5–69.5°. The total yield was 1.5 gm. (27.2%). The yield of I was increased to 2.1 gm. (37.8%) when the reaction time was extended to two hours.

Anal. Calc. for  $C_9H_{16}N_2O_2$ : N, 15.26%. Found: N, 15.12%.

# 1-(Piperidinomethyl)-2-pyrrolidone (II)

The compound II was prepared by refluxing the mixture of 2.55 gm. of 2pyrrolidone, 2.7 ml. of 35% formaldehyde, 2.7 ml. of piperidine, and 20 ml. of water at 100° for one-half hour in the same manner as described for the above experiment. A precipitate was crystallized from ethanol and yielded 1.5 gm. (27.4%) of white crystals which melted at  $47.5-49^\circ$ .

Anal. Calc. for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O: N, 15.37%. Found: N, 15.25%.

# 1-(Dimethylaminomethyl)-2-pyrrolidone (III)

The reaction mixture of equimolar amounts (0.03M) of 2-pyrrolidone, 35% formaldehyde, dimethylamine hydrochloride, and 20 ml. of water was heated at 68° for one-half hour with constant stirring. The solution was cooled, made alkaline with 20% solution of potassium carbonate, and extracted with chloroform. The extract was evaporated and fractionally distilled to yield 1.5 gm. (37.4%) of a liquid product (III), b.p. 64-67° at 1 mm. pressure.

Anal. Calc. for C<sub>7</sub>H<sub>14</sub>N<sub>2</sub>O: N, 19.7%. Found: N, 19.72%.

# 3-(*Piperidinomethyl*)-2,4-thiazolidinedione (IV)

To the solution of 3.5 gm. of 2,4-thiazolidinedione in 15 ml. of ethanol, an equimolar amount of formaldehyde and piperidine was added at 0°. In short time, crystals of IV appeared. After crystallization from absolute ethanol 6.17 gm. (95.9%) of white crystals, m.p. 76–77°, was obtained.

Anal. Calc. for  $C_9H_{14}N_2O_2S$ : C, 50.44; H, 658; N, 13.02%. Found: C, 50.69; H, 6.55; N, 13.04%.

3-(Morpholinomethyl)-2,4-thiazolidinedione (V)

This substance was formed with great ease by the interaction of 2,4-thiazolidinedione, formaldehyde, and morpholine and was obtained as white crystals, m.p. 147°, in 99.9% yield.

Anal. Calc. for C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S: N, 12.95%. Found: 13.05%.

# 3-(Dimethylaminomethyl)-2,4-thiazolidinedione (VI)

The condensation product VI was obtained by a similar procedure in a yield

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of 71.5%. It gave white crystals which after crystallization from absolute alcohol melted at  $82^{\circ}$ .

Anal. Calc. for  $C_6H_{10}N_2O_2S$ : C, 41.36; H, 5.79; N, 16.08%. Found: C, 41.60; H, 5.92; N, 16.05%.

# N-Methyl-N,N-bis(2,4-thiazolidinedionomethyl)amine (VII)

A mixture of 3.5 gm. of 2,4-thiazolidinedione dissolved in 15 ml. of ethanol and 2.7 ml. of 35% formaldehyde was cooled to 0° and 4.85 ml. of 25% methylamine solution was added dropwise. The reaction product was crystallized from absolute ethanol to yield 4.34 gm. (50%) of soft white crystals, m.p. 144–145°.

Anal. Calc. for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>: N, 14.52%. Found: N, 14.59%.

The above experiment was repeated using a 2:2:1 mole ratio of 2,4-thiazolidinedione, formaldehyde, and methylamine respectively. The yield was increased to 7.1 gm. (83%).

# 1,3-Di(morpholinomethyl)hydantoin (VIII)

To the heated solution of 3 gm. (0.03M) of hydantoin in 20 ml. of water, 5.6 ml. of morpholine was added and 5.4 ml. of 35% formaldehyde was introduced dropwise. The mixture was stirred and heated at 85° for 15 min. The reaction product was extracted from the cold solution with chloroform. After recrystallization from ethanol VIII yielded 2 gm. (22%) of white crystals, m.p. 144–145.5°.

Anal. Calc. for C<sub>13</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>: N, 18.84%. Found: 18.76%.

# Acid Hydrolysis of VIII

Dry hydrogen chloride gas was bubbled through the solution of 0.3 gm. of VIII in 25 ml. of absolute ethanol. A white precipitate of hydantoin, m.p. 218°, separated (lit. m.p. 220°).

# 1,3-Di(morpholinomethyl)-5,5-dimethylhydantoin (IX)

The condensation of 5,5-dimethylhydantoin with morpholine and formaldehyde in molar ratio 1:2:2 respectively, was carried out at 90° for 30 min. The product was recrystallized from ethanol to yield 3.9 gm. (39.8%) of white crystals, m.p.  $134-134.5^{\circ}$ .

Anal. Calc. for C<sub>15</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>: N, 17.1%. Found: N, 17.02%.

# 1-(Morpholinomethyl)uracil (X)

Uracil (3.4 gm.) dissolved in 40 ml. of water and morpholine (2.8 ml.) were cooled to 0° and 2.7 ml. of 35% formaldehyde was slowly added. A precipitate was formed which after crystallization from alcohol yielded 2.16 gm. (56%) of white crystals, m.p. 208–209°.

Anal. Calc. for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: N, 19.89. Found: N, 19.92%.

# N-(Morpholinomethyl)ethylnitramine (XI)

The reaction mixture of ethylnitramine, morpholine, and formaldehyde in molar ratio 1:1:1 respectively, was allowed to stand for 12 hr. at 4°. The product XI was crystallized from petroleum ether (b.p. 65–110°). The yield

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of white plates, m.p. 86-87°, of XI was 92%.

Anal. Calc. for C<sub>7</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>: C, 44.43; H, 7.99; N, 22.2%. Found: C, 44.61; H, 8.0; N, 21.97%.

# N-(Piperidinomethyl)-n-butylnitramine (XII)

A solution of 7.1 gm. of *n*-butylnitramine in 20 ml. of alcohol was cooled to 0° and 5.4 ml. of 35% formaldehyde was added dropwise. To this mixture, 5.4 ml. of piperidine was slowly introduced and the flask was kept at  $0^{\circ}$  for 12 hr. The alcohol was evaporated and the residue fractionally distilled. The total yield of XII was 4.6 gm. (35.7%; b.p. 97-100°) at 1 mm.

Anal. Calc. for C<sub>10</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C, 55.78; H, 9.83; N, 19.52%. Found: C, 55.34; H, 10.08; N, 18.79%.

# N-(Morpholinomethyl)-n-butylnitramine (XIII)

The substance XIII was prepared by the method described as above, with the exception that the reaction product was crystalline and it separated from the solution. It was crystallized from petroleum ether (b.p. 30-60°) and obtained as white crystals, m.p.  $53-53.5^{\circ}$ , in 97.6% yield.

Anal. Calc. for C<sub>9</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>: N, 19.34%. Found: N, 19.62%.

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