tions. We also wish to express our thanks to M. Robinson, B. Creapeau and C. Stimmel in the Riker Analytical Department for the optical rotations, infrared spectra and equivalent weight determinations.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A New Synthesis of Indole-3-aldehydes. The Reaction of Hexamethylenetetramine with Some Mannich Bases

BY H. R. SNYDER, SAMBASIVA SWAMINATHAN[1] AND HOMER J. SIMS

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When gramine, the Mannich base from indole, dimethylamine and formaldehyde, is heated in acetic acid or dilute propionic acid with hexamethylenetetramine and the reaction mixture is poured into water, indole-3-aldehyde is formed. The process provides a very convenient synthesis, and it can be applied to Mannich bases related to substituted indoles. Certain phenolic Mannich bases can be converted to aldehydes in the same way, but in poorer yields. Mannich bases derived from ketones evidently do not undergo the reaction.

A large number of amines of the type RCH_2-$NR'R''$ prepared by the Mannich reaction are active alkylating agents, and many of them react with primary or secondary amines by a process of amine exchange[2] in which the residue RCH_2– is transferred to another nitrogen atom. It would seem likely that such reactive Mannich bases, either in acid solution or in the form of their quaternary salts, might react with hexamethylenetetramine to give salts of the type (I) encountered in the Sommelet[3] synthesis.

$$RCH_2{}^+NHR'R''\ {}^-X + C_6H_{12}N_4 \longrightarrow \underset{\text{I}}{RCH_2{}^+NC_6H_{12}N_3\ X^-} + R'R''NH$$

The success of such an interchange then would make possible the conversion of a tertiary amine or a quaternary salt to an aldehyde, since salts of the type I are easily hydrolyzed to yield aldehydes.[3]

The conversion of primary and secondary amines containing a radical of the benzyl type by means of a modified Sommelet reaction has been described.[4,5] The success of this process led to the formulation of a mechanism for the ordinary Sommelet reaction consisting in *the initial formation of a primary amine* which is dehydrogenated and hydrolyzed to an aldehyde.[5] In accordance with this mechanism benzyldimethylamine was found not to give benzaldehyde. Thus it would seem likely that the conversion of gramine to indole-3-aldehyde could occur *only* if amine interchange is the *initial* step.

In a test of the proposed interchange gramine (β-dimethylaminomethylindole, a Mannich base of indole) and hexamethylenetetramine were heated in glacial acetic acid solution for five minutes and the solution was diluted with cold water. From the solid material which separated, 3-indolealdehyde was obtained in 25% yield. A considerable amount of resinous material was formed also. A number of experimental variations were studied, and it was found possible to obtain the pure aldehyde (m.p. 191–193°) in 53% yield by carrying out the reaction over a period of one hour in 66% propionic acid. The use of indole Mannich bases derived from secondary amines other than dimethylamine, such as diethylamine and piperidine, offered no advantage.

Since gramine is easily obtained from indole by means of the Mannich reaction, this sequence provides a very convenient synthesis of indole-3-aldehyde. It is also very attractive for the synthesis of certain substituted indole-3-aldehydes. In the present work 2-carbethoxyindole-3-aldehyde and 2-phenylindole-3-aldehyde were obtained in best yields (60–70% and 70–80%, respectively) when the reactions were carried out in refluxing glacial acetic acid over periods of only three and five minutes, respectively. However 2-methylindole-3-aldehyde could be obtained in only trace amounts under any experimental conditions tried. Evidently the character of a substituent in the α-position has a profound influence on the course of the reaction.

Although the new synthesis was suggested by the analogy to the Sommelet reaction, it is conceivable that under the conditions used the Mannich bases are hydrolyzed to indole, formaldehyde and the secondary amines, and that the aldehyde is formed from indole. The process would then be similar to the Duff[6,7] synthesis, in which a phenolic aldehyde is prepared from a phenol, hexamethylenetetramine and glyceroboric acid. However, when indole was substituted for its Mannich base none of the aldehyde was formed; hence the process cannot be regarded as a variant of the Duff reaction.

Another method of converting an amine to an aldehyde, as a derivative, is that devised by Fisher[8] in which an α-aminoaldehyde or ketone[9,10] is transformed into an osazone by the action of phenylhydrazine. It was of interest to find whether gramine would react in a similar way to give the phenylhydrazone of indole-3-aldehyde. An attempt yielded only resinous materials.

The new reaction has been applied to phenolic Mannich bases, such as 1-dimethylaminomethyl-

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(7) J. Duff and V. Furness, *ibid.*, 1512 (1951).

(8) E. Fischer, *Ber.*, **26**, 95 (1893).

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2-naphthol which yielded 32% of 2-hydroxy-1-naphthaldehyde when treated with hexamethylenetetramine in boiling glacial acetic acid. In 66% propionic acid 1-piperidinomethyl-2-naphthol was converted in 20% yield to the aldehyde but no product was obtained from 1-morpholinomethyl-2-naphthol under the same conditions. The mixture of Mannich bases from phenol yielded a small amount of salicylaldehyde when treated with hexamethylenetetramine in glacial acetic acid. The per cent. yield could not be calculated in the absence of information as to the composition of the mixture of Mannich bases used. From 2-methyl-6-dimethylaminomethylphenol in 66% propionic acid there was obtained only a resinous product.

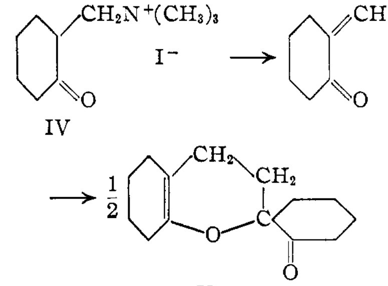
No successful application of the aldehyde preparation to ketonic Mannich bases has been found. When β-dimethylaminopropiophenone or its hydrochloride was refluxed with hexamethylenetetramine in glacial acetic acid or in 66% propionic acid there was no indication of the formation of benzoylacetaldehyde. The products obtained in such trials were oily semi-resinous mixtures, which may have contained the vinyl ketone and its polymers. If benzoylacetaldehyde were formed in these experiments it might have trimerized to tribenzoylbenzene; however, attempts to isolate tribenzoylbenzene were not successful. The Mannich base from dimethylamine, formaldehyde and acetoveratrone was recovered unchanged after boiling one hour with hexamethylenetetramine in 66% propionic acid.

The Mannich base of 2-nitropropane, formaldehyde and dimethylamine was unaffected by boiling with hexamethylenetetramine in 66% propionic acid. This result was expected, since the Mannich base is not an active alkylating agent[11] and cannot undergo loss of secondary amine to form a nitroölefin. The reaction also failed with α-dimethylaminomethylpyrrole, a Mannich base which has been used successfully as an alkylating agent.[12] Much resinous material formed, probably as a result of the instability of the pyrrole nucleus in acid solution.

If the conversion of gramine to indole-3-aldehyde does proceed through the Sommelet intermediate it might be possible to isolate this salt (I, R = 3-indole) by operating under conditions that would not favor its hydrolysis to the aldehyde, especially if the more active alkylating agent, gramine methiodide, were used. Although the supposed intermediate salt has not yet been obtained, it has been found that benzylhexamethylenetetrammonium chloride (III) is formed when a chloroform solution of benzylphenyldimethylammonium chloride (II) and hexamethylenetetramine is heated. This observation lends support to the view that the aldehydes are formed *via* the Sommelet process, and it suggests that quaternary salts such as II, related to benzylamines, can be converted to the corresponding benzaldehydes merely by heating with aqueous hexamethylenetetramine. Indeed, it was found that benzaldehyde is formed in 50% yield when an aqueous solution of the salt II and hexamethylenetetramine is subjected to steam distillation.

$$\underset{\text{II}}{C_6H_5CH_2N^+(C_6H_5)(CH_3)_2Cl^-} + C_6H_{12}N_4 \longrightarrow \underset{\text{III}}{C_6H_5CH_2{}^+NC_6H_{12}N_3Cl^-} + C_6H_5N(CH_3)_2$$

Several of the Mannich bases which had not yielded aldehydes were converted to their methiodides and these were tested in reactions with hexamethylenetetramine. In none of these instances was there any advantage in the use of the quaternary salt. The methiodide of α-dimethylaminomethylcyclohexanone (IV) was converted to the dimer[13,14] (V) of α-methylenecyclohexanone when it was heated with aqueous hexamethylenetetramine. It would appear that the addition of hexamethylenetetramine only aids amine elimination from quaternary salts of ketonic Mannich bases.



IV

V

Experimental

Indole-3-aldehyde. (a) In Glacial Acetic Acid.—To a solution of hexamethylenetetramine (4.2 g., 0.03 mole) in 16 ml. of glacial acetic acid was added 5.2 g. (0.03 mole) of gramine (3-dimethylaminomethylindole). When all the amine had dissolved, the solution was heated rapidly and held at the reflux temperature for exactly 5 minutes. After the reflux period the solution was cooled quickly and poured into 100 ml. of water. After 24 hours refrigeration the crude indole-3-aldehyde (2.1 g.) was collected. This product was recrystallized from hot water to give 1.1 g. (25.1%) of pure aldehyde, m.p. 190–193°. There was no depression of melting point with authentic indole-3-aldehyde. The oxime[15] of the aldehyde melted at 196–197°. A mixture of the aldehyde with the oxime began to melt at 165°. Experiments in which the reflux period was varied widely (1 min. to 54 hr.) resulted in lower yields.

(b) In Dilute Organic Acids.—A solution of hexamethylenetetramine (4.20 g., 0.03 mole) and an equimolar portion of a Mannich base related to indole in 15 ml. of dilute acid was added dropwise over a period of 50–60 minutes to a refluxing solution of hexamethylenetetramine (4.20 g., 0.03 mole) in 15 ml. of the same dilute acid. The reaction mix-

TABLE I

CONVERSION OF INDOLE MANNICH BASES TO INDOLE-3-ALDEHYDE BY REACTION WITH HEXAMETHYLENETETRAMINE IN HOT AQUEOUS ORGANIC ACIDS

Mannich base		Acid	Yield (crude)	Yield (pure)		M.p., °C.
				G.	%	
G^a	66%	acetic	2.5–2.75	1.8–2.0	39–47	189–192
G^a	66	propionic	2.4–2.8	2.0–2.3	47–53	191–193
G^a	66	butyric	1.1	0.9	20	189–192
E^b	66	acetic	2.1	1.6	39	191–193
E^b	66	propionic	2.6	1.9	49	189–192

[a] 3-Dimethylaminomethylindole (gramine). [b] 3-Diethylaminomethylindole.

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[11] H. R. Snyder and W. E. Hamlin, THIS JOURNAL, **72**, 5082 (1950).

[12] W. Herz, K. Dittmer and S. J. Cristol, *ibid.*, **69**, 1698 (1947).

[13] C. Mannich and Ph. Hönig, *Arch. Pharm.*, **265**, 598 (1927).

[14] K. Dimroth, K. Resin and H. Zetzsch, *Ber.*, **73B**, 1399 (1940).

[15] N. Putochin, *ibid.*, **59**, 1995 (1926).

ture was cooled, poured into 100 ml. of water and refrigerated for 24 hours. The crude indole-3-aldehyde was collected and recrystallized from hot water. Details of the individual experiments are given in Table I.

The piperidine[16] Mannich base of indole reacted on a smaller scale (0.01 mole) with a longer addition time (75 min.) and yielded 0.6 g. (40%) of relatively pure aldehyde (m.p. 182–189°).

Reaction of Indole with Hexamethylenetetramine.—To a solution of 5.8 g. of indole in 30 ml. of glacial acetic acid heated to boiling was added 7.0 g. of powdered hexamethylenetetramine. The reaction was vigorous and the mixture refluxed spontaneously. After the boiling subsided (not more than 30 seconds), the reaction mixture was poured into 150 ml. of water. An amorphous solid deposited and was separated by filtration. Repeated extraction with hot water of this solid failed to yield any indole-3-aldehyde.

2-Carbethoxyindole-3-aldehyde. (a) In Glacial Acetic Acid.—The Mannich base from 2-carbethoxyindole, used in this experiment, was prepared by Dr. J. P. Pellegrini, Jr., to whom our thanks are due.

To a solution of 2.0 g. of the dimethylaminomethyl Mannich base (m.p. 82–84°) from 2-carbethoxyindole in 5 ml. of glacial acetic acid, heated to boiling, was added 1.2 g. of powdered hexamethylenetetramine. The reaction mixture was refluxed for 1 minute and poured into 60 ml. of water. The crude aldehyde (m.p. 178–182°, wt. 1.3 g.) crystallized when the resulting solution was cooled. It was filtered and recrystallized from ethanol after treatment with Norit. The recrystallized substance melted at 189°. The alcoholic filtrate when diluted with water deposited more substance melting at 184–185°; total yield of aldehyde, 1.2–1.3 g. (68–72%).

The anil of 2-carboxyindole-3-aldehyde prepared according to the method of Boyd and Robson,[17] by hydrolysis and treatment with aniline, melted at 245–246°.

(b) In Dilute Propionic Acid.—A solution of 4.0 g. of 2-carbethoxygramine and 2.4 g. of hexamethylenetetramine in 15 ml. of 66% propionic acid was added to a boiling solution of 2.4 g. of hexamethylenetetramine in 15 ml. of the same solvent over a period of one hour and then refluxed for an additional 1.5 hours. The solution, after dilution with 200 ml. of water and refrigeration for 24 hours, yielded 1.5 g. (42%) of aldehyde (m.p. 178–185°).

2-Phenylindole-3-aldehyde.—The glacial acetic acid procedure, with a 5-minute reflux period, applied to 3-dimethylaminomethyl-2-phenylindole resulted in a 70–80% yield of 2-phenylindole-3-aldehyde, m.p. 250–255° (dec.). The aldoxime melted at 182–184°.

2-Methylindole-3-aldehyde.—Only an oil was obtained when 3-dimethylaminomethyl-2-methylindole[18] was treated with hexamethylenetetramine in boiling glacial acetic acid. When the Mannich base was refluxed with 66% propionic acid for 5 minutes and the reaction mixture diluted, a small amount of very impure precipitate formed. From this a trace of the phenylhydrazone of 2-methyl-indole-3-aldehyde was obtained; m.p. 197–199°.

3-Dimethylaminomethyl-2-phenylindole.—To a cold (0–5°) solution of 5 ml. of glacial acetic acid, 30% aqueous dimethylamine (0.82 g., 0.005 mole) and 40% formalin (0.38 g., 0.005 mole) was slowly added dry, powdered 2-phenylindole (0.96 g., 0.005 mole). The reaction mixture was cooled in an ice-bath and was stirred frequently. After the addition was complete (*ca.* 4.5 hours), the reaction mixture was allowed to stand at room temperature for 10 hours and was then poured into 75 ml. of water. After 2 hours refrigeration, the pink, acid insoluble precipitate (0.15 g.) was filtered. The filtrate was clarified by treatment with charcoal and Filter-cel. The addition of excess ammonia resulted in the separation of 0.82 g. (65%) of a white precipitate melting at 122–125°. After recrystallization from 50% ethanol the compound melted at 124–126°.

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.26; N, 11.19. Found: C, 81.65; H, 7.20; N, 10.92.

Treatment of Benzyldimethylamine with Hexamethylenetetramine.—A solution of 10 g. of benzyldimethylamine and 11 g. of powdered hexamethylenetetramine in 40 ml. of glacial acetic acid was refluxed for 5 minutes. The reaction mixture was cooled and poured into 400 ml. of water. The characteristic odor of benzaldehyde was not detected. The aqueous solution was made alkaline and extracted with ether. The ether extract after drying and removal of ether yielded a basic oil which when distilled proved to be unchanged benzyldimethylamine (8.9 g.). There was no indication of the formation of benzaldehyde even when the quantity of hexamethylenetetramine was doubled and the period of reflux increased to $^1/_2$ hour.

Treatment of α-Dimethylaminomethylpyrrole with Hexamethylenetetramine.—A solution of 3.19 g. of the Mannich base and 3.5 g. of powdered hexamethylenetetramine in 14 ml. of glacial acetic acid was refluxed for 2 minutes and after cooling, was poured into 125 ml. of water. The resulting solution was extracted with 100 ml. of ether and the ether extract washed successively with water, sodium bicarbonate solution and water. When the ether was removed, the ether extract did not yield any product.

A similar experiment using dilute propionic acid also failed to yield any crystalline product.

Treatment of β-Dimethylaminopropiophenone Hydrochloride with Hexamethylenetetramine. (a) In Glacial Acetic Acid.—A solution of β-dimethylaminopropiophenone (8.9 g., 0.05 mole) and hexamethylenetetramine (7.0 g., 0.05 mole) in 15 ml. of glacial acetic acid was brought to boiling quickly and refluxed for five minutes. The light-orange reaction mixture was poured into 100 ml. of water and refrigerated 24 hours. The small amount of resinous solid which separated was not the expected aldehyde nor its trimerization product.

(b) In Dilute Propionic Acid.—The above experiment was repeated except that 66% propionic acid was used in place of glacial acetic acid and the mixture was refluxed 3 hours. A yellow oil was obtained which had no aldehyde properties.

(c) In Water.—A solution of 3.5 g. of β-dimethylaminopropiophenone hydrochloride and 2.4 g. of hexamethylenetetramine in 10 ml. of water was refluxed for 5 minutes. As soon as heating was started, an oil began to separate. When the reaction mixture was cooled, this oil became viscous. It could not be induced to solidify or crystallize from any solvent. In two blank experiments conducted with the same amounts of reagents but without hexamethylenetetramine no oil was obtained.

(d) In Chloroform.—A solution of 3.5 g. of β-dimethylaminopropiophenone hydrochloride and 2.4 g. of hexamethylenetetramine in 35 ml. of chloroform was refluxed for 17 hours. An amine was evolved throughout the period of reflux after which the reaction mixture was filtered hot. The filtrate when cooled deposited 1.5 g. of a colorless crystalline substance. Concentration of the filtrate to 18 ml. yielded a second crop weighing 1.1 g. The filtrate from the second crop, on complete removal of the solvent gave a viscous oil like that obtained in (c) above. It could not be induced to solidify or crystallize from any solvent.

The two crops of crystals were combined and dissolved in alcohol. When acetone was added to the clear alcoholic solution, colorless needles melting at 194–196° were obtained. The sample for analysis was obtained by repetition of this treatment; m.p. 196–197°.

Anal. Calcd. for $C_6H_{12}N_4 \cdot HCl$: C, 40.8; H, 7.37. Found: C, 40.99; H, 7.46.

According to the literature, hexamethylenetetramine hydrochloride melts at 189°.[19]

Reaction of 2-Dimethylaminomethylcyclohexanone Methiodide with Hexamethylenetetramine.—Hexamethylenetetramine (2.8 g., 0.02 mole) and 2-dimethylaminomethylcyclohexanone methiodide (2.97 g., 0.01 mole) were dissolved in 10 ml. of water and heated to incipient boiling for 15 minutes, during which time a yellow oil separated. The reaction mixture was extracted with ether and the ether solution dried over anhydrous sodium sulfate. The ether was evaporated leaving a yellow oil which formed a semicarbazone (0.8 g.) melting at 189–191°. After recrystallization from 70% ethanol the m.p. was 195–197°.

The analysis suggests that the compound is the semicarbazone of "methylenecyclohexanone dimer."[13,14]

Anal. Calcd. for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 65.63; H, 8.45; N, 15.40.

β-Hydroxy-α-naphthaldehyde. (a) In Glacial Acetic Acid.—A solution of 5 g. of α-dimethylaminomethyl-β-hy-

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(17) W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 555 (1935).

(18) H. Rydon, *J. Chem. Soc.*, 705 (1948).

(19) R. Locquin, *Bull. soc. chim.*, [3] **23**, 663 (1899).

droxynaphthalene in 15 ml. of glacial acetic acid was heated to boiling and 3.5 g. of powdered hexamethylenetetramine was added. The reaction mixture was refluxed for 2 minutes and then poured into 150 ml. of water. A resinous solid separated. The aqueous solution was decanted from the resinous solid which was again washed with water. The washings were combined with the decanted solution.

The aqueous solution deposited a substance in the form of needles melting at 60–70°. After two crystallizations from alcohol it melted at 81–82°; wt. 0.72 g. There was no depression of melting point with authentic β-hydroxy-α-naphthaldehyde. The oxime[20] of the aldehyde melted at 157°.

The resinous solid was refluxed with 95% ethanol and the mixture filtered hot. The insoluble yellow solid melted at 220°. The filtrate, when cooled, gave more of the same substance (m.p. 215°), a second crop of which was obtained by concentrating the filtrate. The filtrate from the second crop when evaporated to dryness left a crude solid which was extracted with 5% potassium hydroxide solution. The alkaline extract when acidified with hydrochloric acid deposited 0.9 g. of crude aldehyde. One crystallization from ethanol yielded 0.65 g. of aldehyde melting at 80–81°. The total yield of the aldehyde amounted to 1.37 g. (32%).

The different crops of the high melting yellow substance were combined and crystallized twice from acetone; m.p. 226–227°.

Anal. Found: C, 79.58; H, 5.81.

The substance was light yellow in color and was insoluble in water and 5% potassium hydroxide solution. It did not contain nitrogen.

(b) **In Dilute Propionic Acid.**—A solution of 3.65 g. of α-morpholinomethyl-β-hydroxynaphthalene and 2.5 g. of hexamethylenetetramine in 15 ml. of 66% propionic acid was added to a refluxing solution of 2.5 g. of hexamethylenetetramine in 15 ml. of 66% propionic acid, over a period of 25–30 minutes. Some material deposited on the side of the flask before the end of the reaction time. When the solution was cooled, diluted with 200 ml. of water and refrigerated for 24 hours only a high melting (above 200°) yellow substance deposited.

This experiment was repeated using 1.35 g. of the hexahydrate of ferric chloride in the solution containing the Mannich base. Upon dilution the reaction mixture yielded a black resin. This was extracted with 200 ml. of ether, in three portions, and the ether was evaporated. The residue from the ether extract did not yield any crystalline material.

The piperidine Mannich base was more stable under these conditions. The product obtained from it was reprecipitated from a 5% sodium hydroxide solution and then was recrystallized twice from ethanol. The resulting 2-hydroxy-1-naphthaldehyde (20%) melted at 78–80°.

Reaction of DMP-10 with Hexamethylenetetramine.—(DMP-10 is the Rohm and Haas Company designation for a mixture of *o*- and *p*-dimethylaminomethylphenols.) A solution of 15 g. of DMP-10 and 14 g. of hexamethylenetetramine in 65 ml. of glacial acetic acid was refluxed for 3 minutes and then poured into 300 ml. of water. The resulting solution was steam distilled and 250 ml. of distillate was collected, neutralized with sodium bicarbonate, and extracted with ether. The ether extract was washed with water to remove traces of formaldehyde and then dried over anhydrous magnesium sulfate. When the ether was removed, there remained a liquid weighing 0.9 g. with the characteristic odor of salicylaldehyde.

The dinitrophenylhydrazone melted at 253–254° after one crystallization from a mixture of ethyl alcohol and ethyl acetate. The solution which was steam distilled did not contain any *p*-hydroxybenzaldehyde.

Reaction of Benzyldimethylphenylammonium Chloride with Hexamethylenetetramine in Water Solution.—A solution of the quaternary ammonium chloride (24.7 g., 0.1 mole) and hexamethylenetetramine (28 g., 0.2 mole) in 100 ml. of water was steam distilled. An oily substance separated from the reaction mixture faster than it could be removed by the distillation. After approximately 600 ml. of distillate had been collected, it was extracted with three 100-ml. portions of ether. The amine was extracted from the ether with 5% hydrochloric acid and the ether layer was washed and dried over anhydrous sodium sulfate. After the ether had been evaporated the remaining crude benzaldehyde was distilled to yield 5.0 g. (47%) of product boiling at 177–179°.

Reaction of Benzyldimethylphenylammonium Chloride with Hexamethylenetetramine in Chloroform.—Benzyldimethylphenylammonium chloride (4.95 g., 0.02 mole) and hexamethylenetetramine (2.8 g., 0.02 mole) were dissolved in 40 ml. of chloroform and the mixture was refluxed for 3 hours. Fine needles appeared in the solution after approximately an hour and soon afterward they accumulated rapidly. After standing 12 hours, the solution was filtered and the white crystals were washed with cold chloroform. The product weighed 2.7 g. (51%) and melted at 185–192° (dec.). The chloride ion content was determined by titration with silver nitrate.

Anal. Calcd. for $C_{13}H_{19}N_4Cl$: Cl, 13.24. Found: Cl, 13.53.

URBANA, ILLINOIS

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[20] M. R. Fosse, *Bull. soc. chim.*, [3] **25**, 371 (1901).