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127. Tetsuzo Kato and Takuitsu Niitsuma: Synthesis of Methylpyridine Derivatives (XXI).*1 Amination of Chloro-2,6-lutidines and Their N-Oxides *via* a Hetaryne Mechanism.

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A number of papers have been published recently, especially by Kauffmann,[1] Levine[2] and Hertog[3] and their groups, dealing with investigations on the "heterocyclic aryne" mechanism for rearrangements occurring during reactions of heterocyclic aromatic compounds with nucleophilic reagents.

Hertog reported that aminations of 3- as well as 4-chloro-, bromo- and iodopyridines with potassium amide in liquid ammonia proceeded *via* 3,4-pyridyne. This was based on the facts that in all reactions, mixtures of 3- and 4-aminopyridine of the same composition (ratio of the amounts of isomers=1:2) were formed. Amination of 2-chloro or 2-iodopyridine produced almost pure 2-aminopyridine in a high yield, and no trace of 3-aminopyridine or other by-products was discovered.

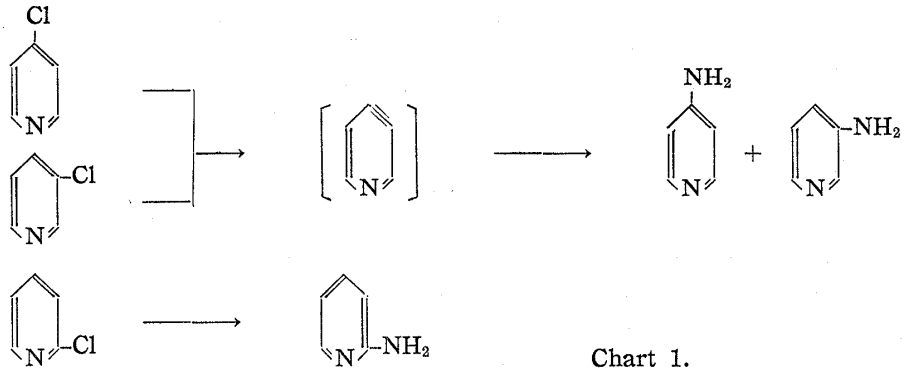

Chart 1.

However, little work seems to have been done on this subject in the field of heterocyclic amine N-oxide chemistry. In a previous paper[4] we reported that the amination of chloropyridine N-oxides gave results entirely the reverse of those in the chloropyridine series reported by Hertog; that is, the reaction of 2-chloropyridine 1-oxide proceeded *via* a 2,3-pyridyne mechanism giving 2- and 3-aminopyridine 1-oxide, but amination of 3- or 4-chloropyridine 1-oxide proceeded presumably *via* an S_N-2 mechanism to give 3- or 4-aminopyridine 1-oxide respectively. A few months later Martens and Hertog[5] also reported the same reaction, giving results quite the same as ours, but they thought the reaction of 3-chloropyridine 1-oxide proceeded *via* a 2,3-pyridyne 1-oxide intermediate, and they did not make a choice between the possible mechanisms for the formation of 4-aminopyridine 1-oxide from 4-chloropyridine 1-oxide.

In this connection we decided to investigate the amination of methylpyridines and their N-oxides, since these might clarify whether the reaction proceeds *via* a pyridyne

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*1 Part XX: T. Kato, H. Yamanaka, T. Adachi: Yakugaku Zasshi, **85**, 611 (1965).
*2 Kita-4, Sendai, Miyagi-ken (加藤鉄三, 新妻卓逸).
1) T. Kauffmann, F. Boettcher: Angew. Chem., **73**, 65 (1961).
2) R. Levine, W. Leake: Science, **121**, 780 (1955).
3) H. den Hertog, *et al.*: Rec. Trav. Chim. Pays-Bas, **80**, 1376 (1961); Tetrahedron Letters, **15**, 643 (1962).
4) T. Kato, T. Niitsuma, N. Kusaka: Yakugaku Zasshi, **84**, 432 (1964).
5) R. Martens, H. Hertog: Rec. Trav. Chim. Pays-Bas, **83**, 621 (1964).

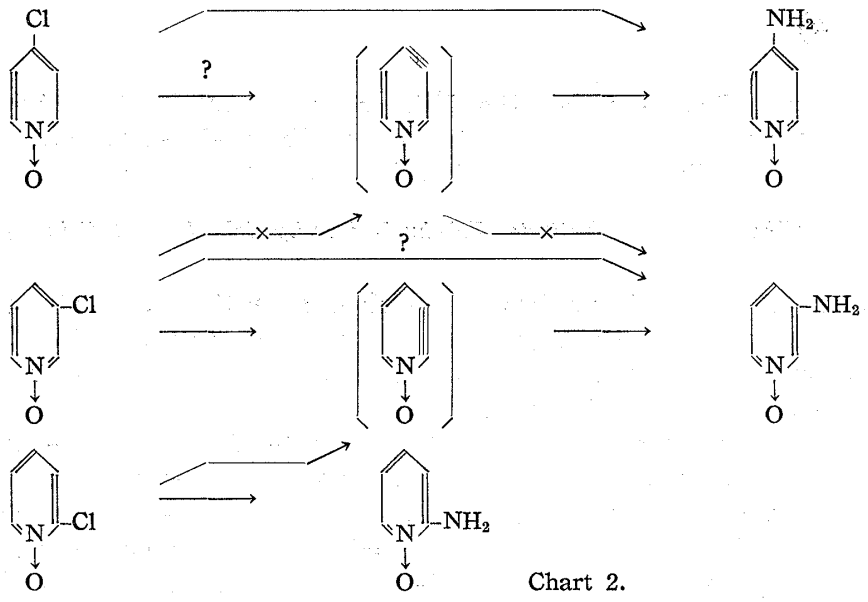

Chart 2.

intermediate or an addition-elimination mechanism such as an S_N-2 reaction. In this paper aminations of 3-chloro-2,6-lutidine, 4-chloro-2,6-lutidine and their N-oxides with potassium amide in liquid ammonia are described.

Aminations were carried out according to the procedure described before.[4] Chlorolutidine was added to a solution of potassium amide (prepared by adding a fourfold amount of potassium to liquid ammonia in the presence of a trace of ferric chloride) and the mixture was stirred for 1.5 hr. at −33°. The reaction products, which were isolated by evaporation of the ammonia and extraction of the residue with ethanol, were identified by mixed melting point test and comparison of the Rf value on thin layer chromatography with those of authentic samples. Quantitative analysis was done by gas chromatography. In the case of N-oxide derivatives, gas chromatography could not be used because volatile aminopyridines could not be obtained in quantitative yields from reduction of the aminolutidine 1-oxides, and in this case, a quantitative

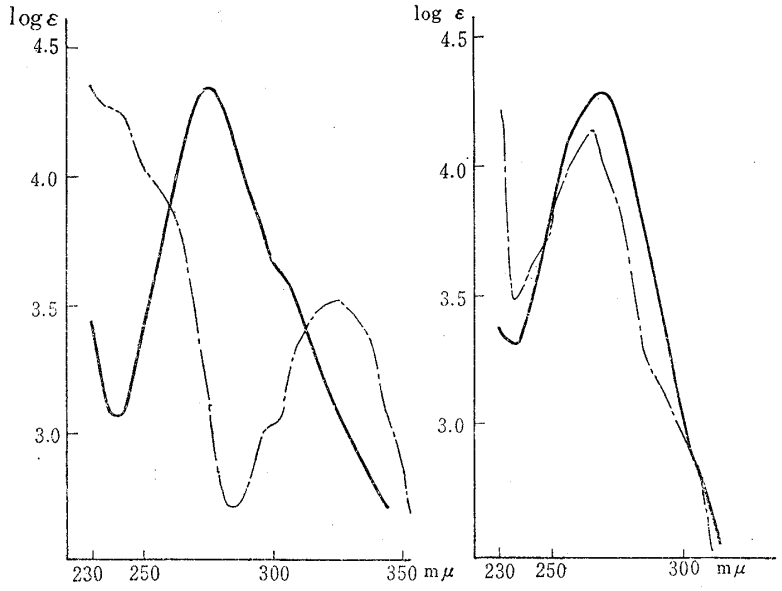

Fig. 1.

——— 4-NH_2-2,6-Lut. N→O
—·—·— 3-NH_2-2,6-Lut. N→O
——— 4-Cl-2,6-Lut. N→O
—·—·— 3-Cl-2,6-Lut. N→O

analysis was made by the photometric procedure. As shown in Fig. 1, 4-amino-2,6-lutidine 1-oxide has a strong absorption maximum at 274 mμ and the 3-amino isomer has one at 323 mμ. Those of the starting chloro derivatives appear at ca. 265 mμ, but in the reaction of the N-oxide series recovery of the starting material was not observed.

From the amination of both 3-chloro-2,6-lutidine and 4-chloro-2,6-lutidine a reaction product was obtained from which 3-amino-2,6-lutidine was isolated as a main product (15%) with a small amount of 4-amino-2,6-lutidine. Amination of 3-chloro- and 4-chloro-2,6-lutidine 1-oxide produced 4-amino-2,6-lutidine 1-oxide as a main product with the 3-amino isomer as a by-product. The results obtained are summarized in Table I.

Table I.

Product (%) / Starting material	3-NH_2 compd.	4-NH_2 compd.	Recovery
3-Cl-Lut.	13	1	1.3
4-Cl-Lut.	15	2	8.7
3-Cl-Lut. N→O	13	50	—
4-Cl-Lut. N→O	6.5	34	—

From the above data there is little doubt that all of these reactions have proceeded *via* a 3,4-pyridyne or 3,4-pyridyne 1-oxide intermediate. In contrast to aminations in the pyridine 1-oxide series, it is of interest to see that both 3- and 4-chlorolutidine 1-oxide are converted into a mixture containing 3- and 4-aminolutidine 1-oxide *via* a 3,4-pyridyne intermediate.

Although we predicted an S_N-2 mechanism for the amination of 3-chloropyridine 1-oxide in a previous paper,[4] Martens and Hertog[5] preferred the route *via* 2,3-pyridyne 1-oxide as shown in Chart 2. Evidence for this intermediate resulted from the course of the amination of 2-chloropyridine 1-oxide, and they explained that 3-aminopyridine 1-oxide is the only addition product formed from 2,3-pyridyne 1-oxide by assuming that the N→O group by its strong −I effect directs the amide ion exclusively to the 3-position. They also proposed that amination of 2-chloropyridine 1-oxide proceeded chiefly by an addition-elimination reaction, such as an S_N-2 mechanism, to give the 2-amino derivative and partly *via* a 2,3-pyridyne intermediate to give the 3-amino derivative. Moreover, because 2-aminopyridine 1-oxide is unstable in liquid ammonia in the presence of potassium amide, yields of both amino derivatives were low.

Although the detailed mechanism for these reactions is obscure, one point worth considering is a comparison of the reactivities of chloropyridines and their N-oxides towards nucleophilic reagents in the S_N-2 reaction. Liveris and Miller[6] reported the rate of reaction of chloropyridines and their N-oxides with sodium methoxide in absolute methanol, and stated that the order of reactivity is 4-chloropyridine 1-oxide>

Table II. Rate Constants at 50° and Some Derived Parameters for the Reaction of Sodium Methoxide in Methanol[6]

	4-Cl·Py·NO	2-Cl·Py·NO	3-Cl·Py·NO	4-Cl·Py	2-Cl·Py	3-Cl·Py
K_2 (L·mole^{-1}·sec^{-1})	1.00×10^{-3}	6.40×10^{-4}	1.16×10^{-6}	8.91×10^{-7}	3.31×10^{-8}	1.09×10^{-11}
ΔE (kcal·mole^{-1})	19.0	20.3	24.6	25.2	28.9	32.8
ΔS (e.u.)	−15.6	−12.4	−11.7	−10.4	−5.33	−9.21

6) M. Liveris, J. Miller: J. Chem. Soc., **1963**, 3486.

2-chloropyridine 1-oxide>3-chloropyridine 1-oxide>4-chloropyridine>2-chloropyridine >3-chloropyridine as shown in Table II.

On the other hand it is well recognized that the methyl group is deactivating in nucleophilic substitution reactions. Kato and Hayashi[7] have investigated the kinetics for the reaction of chloromethylpyridine 1-oxides with sodium methoxide, and derived the following rate constant; 4-chloro-2,6-lutidine 1-oxide (k_2 at 50°, 1.43×10^{-5} L·mole^{-1}·sec^{-1}; ΔE=23.2 kcal. mole^{-1}).

Based upon the facts described above, the formation of a 2,3-pyridyne 1-oxide intermediate from 3-chloropyridine 1-oxides seems to be a reasonable assumption, because the amination of 4-chlorolutidine 1-oxide obviously proceeds *via* a pyridyne mechanism in spite of the fact that it is more reactive in an S_N-2 reaction than 3-chloropyridine 1-oxide. In the same way it seems likely that the amination of 4-chloropyridine 1-oxide proceeds by an addition-elimination reaction such as S_N-2 reaction and that amination of the 2-isomer occurs chiefly by the same mechanism with a small amount of 2,3-pyridyne formation.

A further significant difference between 3,4-pyridyne and 2,6-dimethyl-3,4-pyridyne is that the former yielded 4-aminopyridine as a main product with 3-aminopyridine as a by-product (ratio of isomers=2:1), whereas the latter gave 3-aminolutidine as a main product with a small amount of the 4-isomer. This can be understood by considering that the +I effect of the methyl group directs the amide ion chiefly to the 3-position.

In the case of 2,6-dimethyl-3,4-pyridyne 1-oxide, the subsequent stage is entirely the reverse of that in the case of 2,6-dimethyl-3,4-pyridyne as shown in Table I. This also can be understood by assuming that the +I effect of the methyl group is weakened by the strong −I effect of the N→O group, and the subsequent stage is similar to that in the case of 3,4-pyridyne.

Moreover, mole ratio of the yields of the resulting amino isomers is slightly different between the reaction of 4-chloro-2,6-lutidine 1-oxide and that of the 3-chloro isomer; that is, in the case of the reaction of 4-chlorolutidine 1-oxide, mole ratio of the yield of 4-aminolutidine 1-oxide (4-amino : 3-amino=5.2:1) is somewhat higher than that in the case of the 3-chloro isomer (4-amino : 3-amino=3.8:1). This could be explained

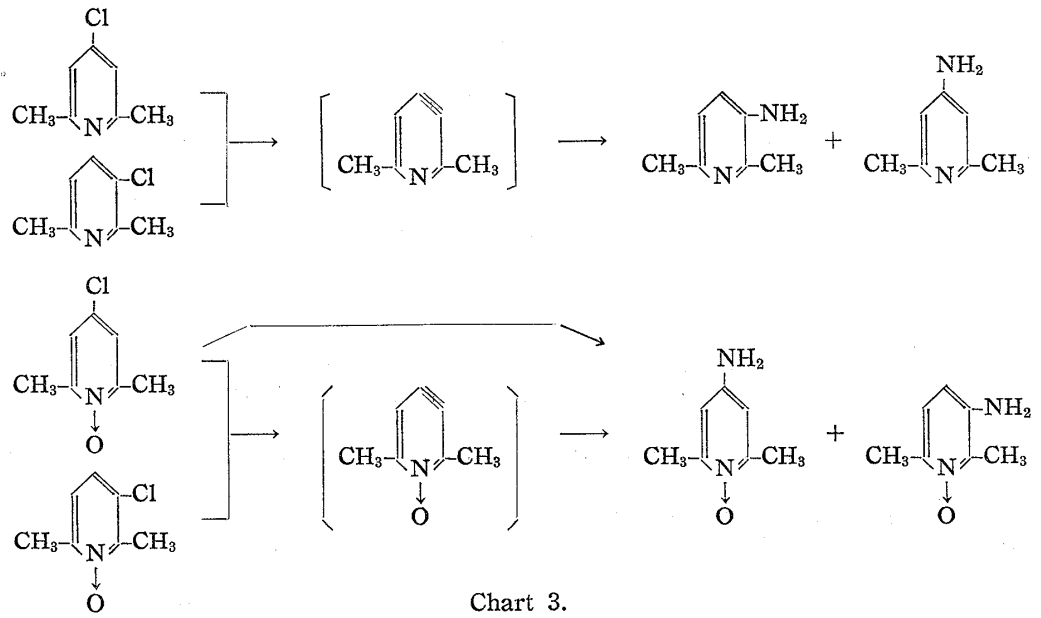

Chart 3.

7) unpublished work.

taking into account the comparison of the reactivity of 4-chlorolutidine 1-oxide and that of the 3-chloro isomer in an S_N-2 mechanism. As described above in the case of the 3-chloro compound it is improbable that its amination proceeds *via* an S_N-2 mechanism because of its low activity in this mechanism. In the case of the 4-chloro isomer, however, its activity in an S_N-2 reaction is fairly strong,[7] therefore 4-chlorolutidine 1-oxide is not only reacting mainly *via* a pyridyne mechanism, but also partly by an addition-elimination mechanism as a side-reaction.

Experimental

Synthesis of Starting Substances and Authentic Samples for Analysis : 3-Chloro-2,6-lutidine——To an ice-cold stirred solution of 10 g. of 3-amino-2,6-lutidine in 190 ml. of 25% HCl was added 8.6 g. of $NaNO_2$, and then 20 g. of Cu powder was added. After being stirred for 45 min. in an ice bath, the cold mixture was made alkaline with NaOH, and submitted to steam distillation to give 5 g. (43%) of 3-chloro-2,6-lutidine, b.p_{30} 75°, picrate m.p. 148° (lit.[8] m.p. 151°).

4-Chloro-2,6-lutidine[9,10]——Following the procedure described before,[10] 2,6-lutidine 1-oxide (15 g.) was reacted with $POCl_3$ (45 g.) to give 7 g. (41%) of 4-chloro-2,6-lutidine, b.p_{20} 69～70°, picrate m.p. 166～167° (lit.[10] m.p. 166～167°).

3-Chloro-2,6-lutidine 1-Oxide——By the usual method, 3-chloro-2,6-lutidine (10 g.) was oxidized with 16 ml. of 35% H_2O_2 in AcOH (75 ml.) to give 10 g. (90%) of N-oxide derivative, m.p. 38～40°, white needles from petr. ether. *Anal.* Calcd. for C_7H_8ONCl : C, 53.36; H, 5.12; N, 8.89. Found : C, 52.79; H, 5.24; N, 8.62.

4-Chloro-2,6-lutidine 1-Oxide[11]——Similar treatment of 4-chloro-2,6-lutidine (5.5 g.) as described above afforded 4-chloro-2,6-lutidine 1-oxide, white needles of m.p. 102～103° from petr. ether, picrate m.p. 147～148° (lit.[11] m.p. 144.5～146°). Yield, 3.3 g. (54%).

3-Amino-2,6-lutidine[12]——A solution of 17 g. of 3-nitro-2,6-lutidine in 70 ml. of MeOH was hydrogenated over 2.5 g. of 38% Pd-Norit catalyst. After 2 hr., 7.75 l. (0.98 molar equivalent at 15°) of hydrogen had been absorbed. The reaction mixture was filtered from catalyst and taken to dryness. Recrystallization of the residue from benzene afforded 12.2 g. (90%) of 3-amino-2,6-lutidine, colorless prisms, m.p. 123° (lit.[12] m.p. 124°). Picrate, m.p. 180～181° (lit. m.p. 181°).

4-Amino-2,6-lutidine[13]——Upon catalytic reduction with PtO_2 (0.4 g.) in 30 ml. of AcOH, 4-amino-2,6-lutidine 1-oxide (3 g.) was reduced to 4-amino-2,6-lutidine, colorless prisms from acetone, m.p. 191～192° (lit.[13] m.p. 191～192°). Yield, 1.8 g. (68%).

3-Amino-2,6-lutidine 1-Oxide——A suspension of 1.5 g. of 3-nitro-2,6-lutidine 1-oxide[14] in 10 ml. of H_2O was hydrogenated over 0.5 g. of 50% Pd-Norit catalyst to give 1.2 g. (98%) of 3-amino-2,6-lutidine 1-oxide, white needles from acetone, m.p. 155～158°. *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28. Found : C, 60.41; H, 7.34; N, 19.95.

4-Amino-2,6-lutidine 1-Oxide[15]——According to the same procedure described above, 4-nitro-2,6-lutidine 1-oxide (3.8 g.) was hydrogenated over Pd-Norit in H_2O to give 3 g. (96%) of 4-amino-2,6-lutidine 1-oxide, white needles from EtOH-acetone, m.p. 264～266° (decomp.) (lit.[15] m.p. 264～266°). Picrate, m.p. 216° (decomp.), (lit.[15] m.p. 214° (decomp.)).

General Procedure——A fourfold amount of potassium metal was added to about 300 ml. of liq. NH_3 in a three-necked round bottom flask equipped with a mechanical stirrer and an acetone-solid CO_2 condenser. A trace of ferric chloride was added and the metal amide was allowed to form. Chlorolutidine or its N-oxide was then added and the mixture was stirred for 1.5 hr. An excess of NH_4Cl was added and the ammonia was allowed to evaporate. The residue was extracted with 99% EtOH. The EtOH fraction was submitted to some of the following procedure; a) recrystallization, b) gas chromatography or c) analysis by UV absorption spectroscopy.

a) Recrystallization——The EtOH fraction was concentrated and a part of the residue was submitted to thin layer chromatography. Al_2O_3 was applied on a glass plate without binder; the Rf values were determined by spraying the developed chromatograms with a $KMnO_4$-H_2SO_4 solution. Rf values and

8) Beilsteins Handbuch d. Org. Chem., Hauptwerk, **20**, 245.
9) A. Michaelis, R. Hanish : Ber., **35**, 3156 (1902).
10) T. Kato : Yakugaku Zasshi, **75**, 1236 (1955).
11) R. Evans : J. Org. Chem., **27**, 1665 (1962).
12) E. Prazèk : Ber., **72**, 577 (1939).
13) W. Marckwald : Ber., **27**, 1325 (1894).
14) E. Ochiai, M. Ishikawa, K. Arima : Yakugaku Zasshi, **63**, 83 (1943).
15) T. Kato, F. Hamaguchi : This Bulletin, **4**, 174 (1956).

solvents used were the following; 3-amino-2,6-lutidine, 0.33 ($CHCl_3$-benzene=1:1); 4-amino-2,6-lutidine, 0.22 ($CHCl_3$-EtOH=25:2); 3-amino-2,6-lutidine 1-oxide, 0.84 ($CHCl_3$-EtOH=10:1); 4-amino-2,6-lutidine 1-oxide, 0.51 ($CHCl_3$-EtOH=10:1).

After having been identified by thin layer chromatography, the corresponding amino derivatives were separated from the residue by recrystallization.

b) Gas Liquid Chromatography——After evaporation of the solvent, the EtOH fraction was analyzed by gas liquid chromatography. The analysis was carried out in a Hitachi gas cromatgraph KGL-2 provided with a 2 m. copper column (filled with 25% PEG 6000, 0.3% NaOH, 50~100 mesh celite) which was kept at 180°, helium being used as carrier gas (flow rate; 150 ml./min.). The relative retention times (min.) were as follows; 3-amino-2,6-lutidine (13.0), 4-amino-2,6-lutidine (29.2), 3-aminopyridine (19.0). An analysis of the chlorolutidines was carried out similarly, but the column temperature was 104° and the flow rate was 60 ml./min. Relative retention times were as follws; 4-chloro-2,6-lutidine (30.2), 3-chloro-2,6-lutidine (32.6), 2-picoline (11.1).

c) Photometric Procedure——In the case of N-oxide derivatives, a quantitative analysis was made by UV absorption spectroscopy. After confirming that a quantitative analysis of these aminolutidine 1-oxides was possible by checking the applicability of the Lambert-Beer rule, the analysis was carried out on a Hitachi EPU-2A Model. The absorption spectra of these compounds are shown in Fig. 1.

Reaction of 3-Chloro-2,6-lutidine——According to the general procedure described above, 3 g. of 3-chloro-2,6-lutidine was allowed to react with KNH_2 prepared from 3.3 g. of K in 300 ml. of liq. NH_3. Analyses by methods (a) and (b) showed that 3-aminolutidine was the main product (13%) with 4-aminolutidine (1%) and unchanged 3-chlorolutidine (1.3%).

Reaction of 4-Chloro-2,6-lutidine——By the same method described above, reaction of 4-chloro-2,6-lutidine afforded 3-amino-2,6-lutidine (15%), 4-amino-2,6-lutidine (2%) and the starting 4-chloro compound (8.7%).

Reaction of 3-Chloro-2,6-lutidine 1-Oxide——3-Chloro-2,6-lutidine 1-oxide (1.4 g.) was allowed to react with KNH_2 prepared from 1.5 g. of K in liq. NH_3. Analyses by methods (a) and (c) showed that 4-amino-2,6-lutidine 1-oxide was the main product (50%) with 3-amino isomer as a by-product (13%). Recovery of the starting material was not observed.

Reaction of 4-Chloro-2,6-lutidine 1-Oxide——By the same procedure described above, reaction of 4-chloro-2,6-lutidine 1-oxide gave 4-aminolutidine 1-oxide (34%) and the 3-amino isomer (6.5%).

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Summary

Reactions of chloro-2,6-lutidines and their N-oxides with liquid ammonia in the presence of potassium amide proceed *via* a hetaryne mechanism to give 3- and 4-amino compounds. Amination of 3- as well as 4-chloro-2,6-lutidine affords 3-amino-2,6-lutidine as the main product (13~15%) with a small amount of the 4-amino isomer. In the case of amination of their N-oxides, mole ratio of the resulting amino isomers is reverse to that in the case of chlorolutidines. 3-Chloro-2,6-lutidine 1-oxide forms 4-amino-2,6-lutidine 1-oxide as the main product (50%) with the 3-amino isomer as a by-product (13%), and reaction of 4-chloro-2,6-lutidine 1-oxide gives 4-amino compound (34%) and the 3-amino isomer (6.5%).

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