[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Reactions of Pyridine-Type Bases with Iodine and Certain Quinolines or Isoquinolines Containing a Reactive Methyl Group

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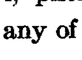
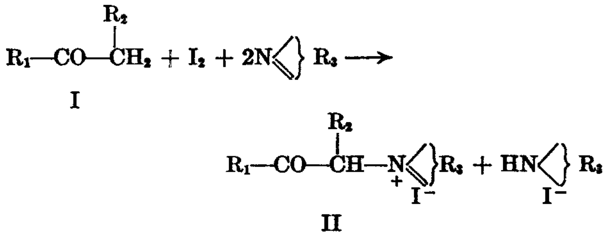
Quinoline-type bases with a methyl group in the 2 or 4 position and isoquinoline-type bases with a methyl group in the 1 position undergo reaction with iodine and pyridine, or certain bases related to pyridine, to give quaternary salts. The preparation and structure of a number of these quaternary salts is described herein.

A number of authors have recorded the preparation of quaternary salts of Type II when compounds containing an active methyl or methylene group, such as I react with iodine and heterocyclic tertiary amines.[2] Quaternary salts were reported wherein R_1 was aryl,[2a] substituted aryl,[2b–e] thienyl,[2c] 2-nitrocyclopropyl,[2f] or a substituted cyclopentanoperhydrophenanthrene derivative,[2a,g] where R_2 was alkyl, phenyl or hydrogen,[2c] and where R_3 N was any of a number of heterocyclic nitrogeneous bases of the pyridine type.[2d] Recently Sapper and Southwick,[3] prepared 1(1,4-diphenyl-2-keto-3-butenyl)pyridinium iodide from benzyl styryl ketone, iodine, and pyridine, thus extending the reaction to an active methylene group adjacent to an α,β unsaturated system. Using the reaction with iodine and pyridine, Reid and Bender[4] prepared pyridinium salts from 2-methylbenzothiazole, 2-methylbenzoxazole, and from 2-methylquinazoline. This reaction has been used for the preparation of pyridinium salts from 2-methyl-γ-chromone,[5a] and from N-methyl-2-picolinium iodide.[5b]



I

II

In the present paper we show that quinoline type bases with a methyl group in the 2, or 4 position and isoquinoline type bases with a methyl group in the 1 position undergo reaction with iodine and pyridine, and certain bases related to pyridine to give quaternary salts.

When quinaldine reacts with iodine and the various pyridine like bases, the quaternary salts are formulated as III. The structures of the products obtained in these reactions were established in detail by means of the following lines of evidence.

1. The presence of an active methylene group in the molecule was established in each case by means of the picryl chloride test of Krohnke.[6]
2. In the case of 1-(2-quinolylmethyl)pyridinium iodide (IIIa), the methylene group was further established by conversion to 2-quinolyl-N-(p-dimethylaminophenyl) nitrone (IV) using the method of Krohnke[7] and subsequently converting IV to the known 2-quinolinecarboxaldehyde-2,4-dinitrophenylhydrazone.[8]
3. The structure of each of the quaternary salts prepared from quinaldine, was established in detail by independent synthesis and conversion to a common derivative. Thus 2-bromomethylquinoline was prepared[9a] and allowed to react with the appropriate heterocyclic tertiary amine to give the corresponding quaternary bromide.[9b,c] These bromides were in turn converted to picrates and compared with the corresponding picrates obtained from the iodides. A summary of the mixed melting point data obtained in this comparison process is presented in Table I.

When lepidine reacts with iodine and the various heterocyclic bases the structures are formulated as V. Evidence for this assignment of structure is

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[1] From the Ph.D. Thesis of S. V. Abramo (1956).

[2] (a) L. C. King, *J. Am. Chem. Soc.*, **66**, 894, 1612 (1944). (b) L. C. King, M. McWhirter, and D. Barton, *J. Am. Chem. Soc.*, **67**, 2089 (1945). (c) L. C. King, M. McWhirter, and R. L. Rowland, *J. Am. Chem. Soc.*, **70**, 289 (1948). (d) L. C. King and M. McWhirter, *J. Am. Chem. Soc.*, **68**, 716 (1946). (e) J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.*, **68**, 868, 1131 (1946). (f) L. I. Smith and V. A. Englehardt, *J. Am. Chem. Soc.*, **71**, 2676 (1949). (g) R. H. Baker and E. N. Squire, *J. Am. Chem. Soc.*, **70**, 1487 (1948).

[3] D. I. Sapper and P. L. Southwick, *J. Org. Chem.*, **21**, 105 (1956).

[4] W. Reid and H. Bender, *Chem. Ber.*, **89**, 1893 (1956).

[5] (a) J. Schmutz, R. Hirt, and H. Lauener, *Helv. Chim. Acta*, **35**, 1168 (1952). (b) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).

[6] F. Krohnke and H. Schmeiss, *Ber.* **70**, 1728 (1937), demonstrated that compounds containing a reactive methylene group, react in basic solution with picryl chloride or chloranil to give an intense color. This process serves as a convenient test for the unsubstituted methylene group.

[7] F. Krohnke, *Ber.* **69**, 2006 (1936).

[8] C. E. Kwartler and H. G. Lindwall, *J. Am. Chem. Soc.*, **59**, 524 (1937).

[9] (a) D. Ll. Hammick, *J. Chem. Soc.* **123**, 2882 (1923). (b) B. R. Brown, D. Ll. Hammick, and B. H. Thewlis, *J. Chem. Soc.* 1145 (1951). (c) B. R. Brown and H. E. Wild, *J. Chem. Soc.* 1158 (1956).

TABLE I

MELTING POINT OF PICRATES

	Iodide, °C.	Bromide, °C.	Mixed M.P., °C.
1-(2-Quinolylmethyl)-pyridinium	162–163	163–164	160–163
1-(2-Quinolylmethyl)3-picolinium	147–148	146–147	145–148
2-(2-Quinolylmethyl)iso-quinolinium	197–197.5	196.5–197	196–197
3-Methyl-2-(2-quinolyl-methyl)isoquinolin-ium	147–148	144–146	147–149

based on the mode of formation, analytical data and a positive picryl chloride test in each case indicating the presence of the active methylene group. In addition, 1-(4-quinolylmethyl)pyridinium iodide (Va) was converted to 4-quinolyl-*N*(*p*-dimethylaminophenyl)nitrone (VI).

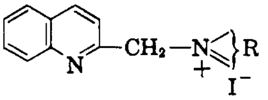
The quaternary salts produced when 2,6-dimethylquinoline reacts with iodine and the various heterocyclic bases are formulated as VII. In these cases the assignment of structure is based on the method of preparation, on physical properties and analysis, and on the presence of an active methylene group as shown by the picryl chloride test.[6] The structures VIII, are assigned to the quaternary salts produced when 1-methylisoquinoline reacts with iodine and the various heterocyclic bases. Again in these cases the assignment of structures is based on the method of preparation, on the physical properties and analytical data, and on the presence of an active methylene group.[6]

In the cases of the quaternary salts IX and X prepared from the methoiodides of quinaldine and lepidine the structures were established by basic hydrolysis. Compound IX was converted to 1-(1-methyl-2-quinolylidenylmethyl)pyridinium iodide (XI) and subsequently to the known *N*-methyl-2-quinolone.[10] Compound X was converted to *N*-methyl-4-quinolone[11] (XII).

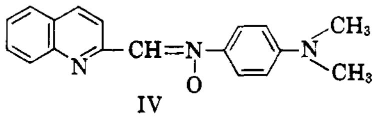
Detailed data for the preparation, analysis, and preparation of derivatives of each of the compounds are presented in the experimental part.

EXPERIMENTAL[12]

Starting materials. The heterocyclic tertiaryamines pyridine, 3-picoline, isoquinoline, 3-methylisoquinoline, quinaldine, and lepidine were commercially available materials. 1-Methylisoquinoline was prepared from isoquinoline by way of a Reissert compound;[13] b.p. 126–128°/16 mm., n_D 1.6125.


III

R = a, pyridine
b, 3-picoline
c, isoquinoline
d, 3-methylisoquinoline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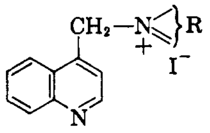
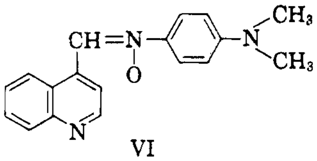
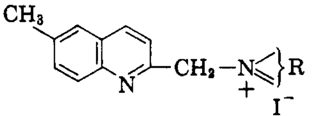
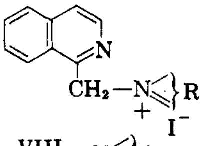

V

R = a, pyridine
b, isoquinoline
c, 3-methylisoquinoline

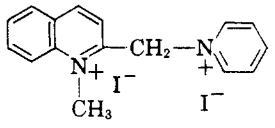

VI

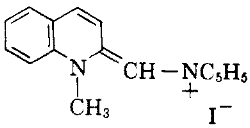

VII

R = a, pyridine
b, isoquinoline
c, 3-methylisoquinoline


VIII

R = a, pyridine
b, 3-picoline


IX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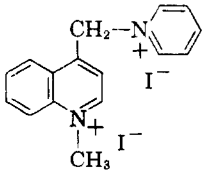
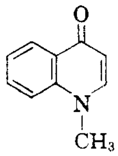

X


XII

Quinaldine methoiodide,[14] and lepidine methoiodide[15] were prepared by reaction of the appropriate base with methyl iodide in acetone solution.

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(10) P. Friedlander and F. Muller, *Ber.*, **20**, 2010 (1887).

(11) H. Meyer, *Monatsh.*, **27**, 255 (1906).

(12) Analysis by H. Beck. Except where otherwise indicated, all melting point and decomposition point data was observed on a Fisher-Johns block.

(13) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

(14) O. Doebner and W. Van Miller, *Ber.* **16**, 2468 (1883).

(15) S. Hoogewerfe and W. Van Dorp, *Rec. trav. chim.*, **2**, 317 (1883).

ω-Bromoquinaldine was prepared by the method of Hammick and co-workers.[9a]

Picryl chloride test for active methylene group. A few mg. of the compound being tested was suspended in 5 cc. of 2*M* sodium hydroxide solution; 3 cc. of a solution of picryl chloride in chloroform (1 g./100 cc.) was added and the mixture was shaken. A deep green or red color was taken as a positive test.[6]

Preparation of quaternary salts and derivatives. The method of preparation and work up of the quaternary iodides was essentially the same in each case. The process is described in detail for 1-(2-quinolylmethyl)pyridinium iodide (IIIa). Significant deviations in preparation work up or purification will be described when appropriate.

1-(2-Quinolylmethyl)pyridinium iodide (IIIa). To a mixture of 29 g. (0.2 mole) quinaldine and 40 g. (0.5 mole) pyridine, 50.8 g. (0.2 mole) of iodine was gradually added with stirring. The mixture was heated at 100° for 2 hr. The reaction mixture was extracted with ether to remove unreacted starting materials, with water to remove pyridinium hydroiodide, and with acetone to remove any quaternary triiodide which may have formed during the reaction. Recrystallization from 80% ethanol gave 70 g. (100%) of light yellow needles melting with decomposition at 228–233°. This compound gave a positive picryl chloride test.

Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76. Found: C, 51.09; H, 3.63.

The compound was recrystallized from 80% ethanol containing a small amount of pyridine;[16] yield 90%, m.p. 238–239°.

Anal. Found: C, 52.04; H, 3.65.

This preparation was attempted in various quantities from 0.05 mole to 0.5 mole. The yields were consistently high.

Bromide. This compound separated as white needles from an acetone solution of pyridine and ω-bromoquinaldine; m.p. 237–239°.[9b]

Perchlorate. From the bromide or the iodide by treatment with 20% perchloric acid. Recrystallized from ethanol; m.p. 189.5–190°, from either source.

Anal. Calcd. for $C_{15}H_{13}O_4N_2Cl$: C, 56.17; H, 4.08. Found: C, 56.42; H, 4.04.

Picrate. From the bromide or from the iodide by addition of saturated picric acid in ethanol to an ethanolic solution of the salt. M.p. 162–163°, from the iodide. M.p. 163–164°, from the bromide (Table I).

1-(2-Quinolylmethyl)-3-picolinium iodide (IIIb). Prepared from quinaldine, 3-picoline, and iodine. Yield (73%) of reddish crystalline material, m.p. 189–195°. Repeated recrystallization from ethanol solution gave 58% of peach colored crystals; m.p. 201–202° with decomposition.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.05; H, 4.17. Found: C, 53.38; H, 4.17.

Bromide. By reaction of ω-bromoquinaldine with 3-picoline in acetone solution; m.p. 217–219°.

Picrate. From the iodide or from the bromide by addition of saturated picric acid in ethanol. M.p. 147–148° from the iodide. M.p. 146–147°, from the bromide (Table I).

2-(2-Quinolylmethyl)isoquinolinium iodide (IIIc). Prepared from quinaldine, isoquinoline, and iodine. Extraction separately with ether, acetone, water and again with acetone gave a reddish crude material which on crystallization several times from 50% ethanol gave 39% of light yellow crystals; m.p. 201–202°, with decomposition.

Anal. calcd. for $C_{19}H_{15}N_2I$: C, 57.30; H, 3.80. Found: C, 57.03; H, 3.87.

Bromide.[9c] From isoquinoline and ω-bromoquinaldine in acetone. The crystals obtained were converted directly to the picrate.

Picrate. From the bromide or from the iodide by addition of saturated picric acid in ethanol. M.p. 197–197.5° from the iodide. M.p. 196.5–197° from the bromide (Table 1).

3-Methyl-2-(2-quinolylmethyl)isoquinolinium iodide (IIId). Prepared from quinaldine, 3-methylisoquinoline, and iodine. After heating for 12 hr. and extracting separately with ether, water, and acetone; the dark crude product was recrystallized from 80% ethanol. Yield, 81%, of tan crystals melting at 197–201°.

Anal. Calcd. for $C_{20}H_{17}N_2I$: C, 58.26; H, 4.16. Found: C, 55.31, 55.80; H, 3.79, 3.68.

Recrystallization from ethanol containing a small amount of pyridine gave material melting at 204°.[16]

Anal. Found: C, 58.28; H, 3.94.

Bromide. From 3-methylisoquinoline and ω-bromoquinaldine. The product was converted directly to the picrate.

Picrate. From the bromide or iodide by addition of saturated picric acid in ethanol. M.p. 147–148° from the iodide. M.p. 144–146° from the bromide (Table 1).

1-(4-Quinolylmethyl)pyridinium iodide (Va). Prepared from lepidine, pyridine, and iodine. Yield 63% of crude product, m.p. 209–210° with decomposition. Recrystallization from ethanol-water gave 48% of yellow prisms, m.p. 220–223° with decomposition.

Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76. Found: C, 51.74; H, 3.76.

2-(4-Quinolylmethyl)isoquinolinium iodide (Vb). Prepared from lepidine, isoquinoline, and iodine. Yield 59% of yellow needles; m.p. 197–200° with decomposition. Recrystallization from ethanol-water-pyridine[16] gave yellow needles, 41%; m.p. 215.5–217° with decomposition.

Anal. Calcd. for $C_{19}H_{15}N_2I$: C, 57.30; H, 3.80. Found: C, 57.32; H, 3.65.

3-Methyl-2-(4-quinolylmethyl)isoquinolinium iodide (Vc). Prepared from lepidine, 3-methylisoquinoline, and iodine. Yield 80% of substance; m.p. 197–199°. Recrystallization from 80% ethanol gave 44% of yellow staves; m.p. 201–204°.

Anal. Calcd. for $C_{20}H_{17}N_2I$: C, 58.26; H, 4.16. Found: C, 57.96; H, 4.13.

1-[2-(6-Methylquinolyl)methyl]pyridinium iodide (VIIa). Prepared from 2,6-dimethylquinoline, pyridine, and iodine. Yield 87% of red solid softening at 160°, melting at 165–167°. Recrystallization from ethanol-water gave 62.3% of a yellow solid; m.p. 169–170° with decomposition. Recrystallization from ethanol-water-pyridine for an analytical sample gave white plates melting at 172–174°.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.05; H, 4.177. Found: C, 53.70; H, 4.20.

2-[2-(6-Methylquinolyl)methyl]isoquinolinium iodide (VIIb). Prepared from 2,6-dimethylquinoline, isoquinoline, and iodine. Yield 53%; m.p. 190–193°. Recrystallization five times from ethanol-water using large quantities of Norit A gave 24% of light yellow product; m.p. 205.5–207° with decomposition.

Anal. Calcd. for $C_{20}H_{17}N_2I$: C, 58.26; H, 4.16. Found: C, 58.58; H, 4.15.

3-Methyl-2-[2-(6-methylquinolyl)methyl]isoquinolinium iodide (VIIc). Prepared from 2,6-dimethylquinoline, 3-methylisoquinoline, and iodine. Yield 84% of a light brown solid; m.p. 205–208°. Recrystallization from ethanol-water gave 70% of yellow prisms melting with decomposition at 209–210°.

Anal. Calcd. for $C_{21}H_{19}N_2I$: C, 59.17: H, 4.49. Found: C, 59.39; H, 4.60.

1-(1-Isoquinolylmethyl)pyridinium iodide (VIIIa). Prepared from 1-methylisoquinoline,[13] pyridine, and iodine. Yield 97% of dark crystalline material; m.p. 170–200°. Recrystallization from ethanol-water using decolorizing charcoal gave 75% of white crystals; m.p. 215–218°, with decomposition.

Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76. Found: C, 51.83; H, 3.57.

1-(1-Isoquinolylmethyl)-3-picolinium iodide (VIIIb). Prepared from 1-methylisoquinoline, 3-picoline, and iodine. Crude yield 72%; m.p. 192–195°. On recrystallization from

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(16) This procedure was used whenever a low carbon analysis indicated the molecule retained extra hydriodic acid.

ethanol-water, 64% of white plates; m.p. 206–211°, was obtained.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.06; H, 4.17. Found: C, 52.80; H, 3.99.

1-(2-Quinolylmethyl)pyridinium iodide methoiodide (IX). Prepared from 1-methylquinaldinium iodide,[14] pyridine, and iodine. Crude yield 30% of orange needles; m.p. 178–180°. Recrystallization from 90% ethanol gave yellow needles; m.p. 183–184° with decomposition.

Anal. Calcd. for $C_{16}H_{16}N_2I_2$: C, 39.21; H, 3.29. Found: C, 38.96; H, 3.27.

1-(4-Quinolylmethyl)pyridinium iodide methoiodide (X). Prepared from N-methyllepidinium iodide,[15] pyridine, and iodine. Crystallization from ethanol gave 53% of greenish yellow plates; m.p. 186–188°. Recrystallization for an analytical sample gave yellow plates darkening at 187–191°, decomposing at 191–193°.

Anal. Calcd. for $C_{16}H_{16}I_2N_2$: C, 39.21; H, 3.29. Found: C, 39.30; H, 3.14.

2-Quinolyl-N-(p-dimethylaminophenyl)nitrone (IV). To a mixture of 3.48 g. (0.01 mole) 1-(2-quinolylmethyl)pyridinium iodide (IIIa) in 5 ml. water and 1.65 g. (0.011 mole) of *N*,*N*-dimethyl *p*-nitroso aniline in 50 ml. ethanol cooled to 0.5°, 10 ml. of *M* sodium hydroxide was added. The mixture was stirred for 45 min. Filtration gave 1.6 g. (54%) of reddish crystals; m.p. 154–155°. Recrystallization from benzene-hexane gave red needles; m.p. 161–161.5°.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.4; H, 5.88. Found: C, 74.69; H, 5.74.

2-Quinoline carboxaldehyde-2,4-dinitrophenylhydrazone. A solution of 0.4 g. (0.0014 mole) of 2-quinolyl-*N*-(*p*-dimethylaminophenyl)nitrone (IV) was shaken with 50 cc. of 3*N* HCl. Addition of 2,4-dinitrophenylhydrazine precipitated the 2-quinoline carboxaldehyde derivative as yellow plates; m.p. 245–248°. Recrystallization from ethanol-water gave yellow needles which softened at 245° and melted at 252–254°. Reported m.p. 251–253°.[8]

4-Quinolyl-N-(p-dimethylaminophenyl)nitrone (VI). The procedure was essentially the same as for the preparation of 2-quinolyl-*N*-(*p*-dimethylaminophenyl)nitrone (IV). From 3.4 g. (0.01 mole) 1-(4-quinolylmethyl)pyridinium iodide 1.95 g. (65%) reddish crystals was obtained. Crystallization from benzene-hexane gave 1.42 g. (49%) of red needles; m.p. 179–181°.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.40; H, 5.88. Found: C, 74.67; H, 5.63.

1-(1-Methyl-2-quinolylidenylmethyl)pyridinium iodide (XI). To 1 g. (0.0025 mole) of 1-(2-quinolylmethyl)pyridinium iodide methoiodide (IX) dissolved in 5 ml. of water, *M* sodium hydroxide was added dropwise until no further precipitate was observed. The red precipitate was collected by filtration. Yield 0.6 g. (82%) of red powder; m.p. 184–190°.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.05; H, 4.17. Found: C, 52.90; H, 4.14.

N-Methyl-2-quinolone. To 2.5 g. (0.005 mole) 1-(2-quinolylmethyl)pyridinium iodide methoiodide (IX) dissolved in 20 cc. water, 10 ml. of 2*N* potassium hydroxide was added. After the hydrolysis was complete the product was extracted with chloroform. Yield 0.55 g. (68%) of tan material melting at 72–73°. Reported for *N*-methyl-2-quinolone, 73°.[10]

N-Methyl-4-quinolone (XII). A solution of 0.5 g. (0.001 mole) 1-(4-quinolylmethyl)pyridinium iodide methoiodide (X) dissolved in 30 cc. water was treated with 4 ml. of 10*N* sodium hydroxide and the mixture heated on the steam bath for 20 min. Extraction with chloroform followed by evaporation of solvent gave 0.17 g. (100%) of white crystals; m.p. 149°.[10]

Acknowledgment. We wish to thank the American Cyanamid Co. for a research fellowship.

EVANSTON, ILL.

[CONTRIBUTION FROM THE ILLINOIS STATE GEOLOGICAL SURVEY]

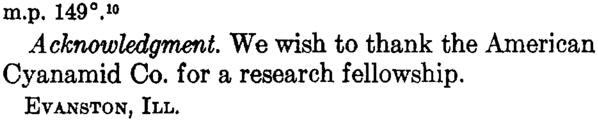
A Combined Deamination and Nitro Reduction Method for Nitroanilines[1]

G. C. FINGER AND R. H. WHITE

Received June 5, 1958

The hypophosphorous acid–cuprous oxide deamination method on nitroanilines has been modified so that the nitro compounds which are formed are reduced in turn by cuprous oxide to the corresponding amines. Over-all yields of 55–65% are reported for three halogenated nitroanilines.

It was reported previously from this laboratory that in the hypophosphorous acid–cuprous oxide deamination of 2-nitro-3,4,6-trifluoroaniline[2] to 2,3,5-trifluoronitrobenzene, a small amount of 2,3,5-trifluoroaniline was isolated as a by-product. Later other halogenated nitroanilines were observed to give similar results. This indicated that part of the desired nitro compound was reduced to the corresponding amine. At the same time it became apparent that the yield of amine varied considerably between similar experiments. The secondary reaction was investigated. As a result of this study, the deamination process has been modified so that complete reduction of the nitro compound also takes place, and the corresponding amine is isolated as the final product.



As the deamination mixture contains two reducing agents, hypophosphorous acid and cuprous oxide,[3] there is the question whether one agent or the combination of both is chiefly responsible for the

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[1] Published by permission of the Chief of the Illinois State Geological Survey.

[2] G. C. Finger, F. H. Reed, and R. E. Oesterling, *J. Am. Chem. Soc.*, **73**, 152 (1951).

[3] Reduction of nitro compounds by copper sponge with sodium hypophosphite has been reported by A. Maihle and M. Murat, *Bull. soc. chim. France*, **7**, 952 (1910).