Improved Synthesis of Quinaldines by the Skraup Reaction

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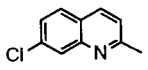
Received July 13, 1992

A series of substituted quinaldines was synthesized with much improved yields from the reaction of crotonaldehyde and the corresponding anilines using either *p*-chloranil or 2,3-dichloro-1,4-naphthoquinone as the oxidant.

J. Heterocyclic Chem., **30**, 17 (1993).

In the process development of a series of drug candidates for asthma, notably the LTD_4 antagonist MK-0679, we were faced with a problem of making a large quantity of 7-chloroquinaldine (**1**).



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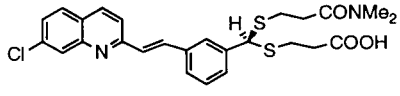
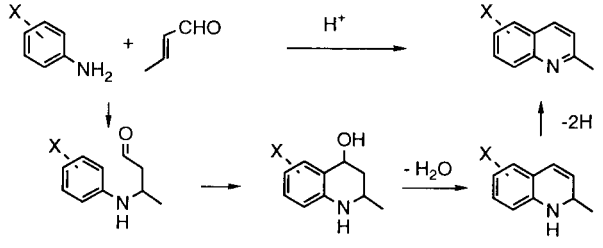


MK-0679

Quinaldines in general and 7-chloroquinaldine in particular have been made by the classical Skraup or Doebner-Miller reaction between anilines and crotonaldehyde or its equivalent (Scheme 1) [1,2]. The reactions are usually carried out in refluxing mineral acid, like sulfuric acid or hydrochloric acid. The yields of these reactions are generally low, and the reason lies in the mechanism. The simplest possible mechanism is shown in Scheme 1 [1]. In this mechanism, the aniline adds to crotonaldehyde in a Michael addition reaction followed by condensation of the aldehyde with the aromatic ring in a Friedel-Crafts reaction. Elimination of water gives the dihydroquinaldine which must be oxidized to form the quinaldine product. While several other mechanisms have been proposed and

Scheme 1



the mechanism is still the subject of controversy, all proposed pathways include an oxidation step [1,4]. When the reaction is carried out without added oxidant, which is usually referred as the Doebner-Miller reaction, the oxidant is apparently the imine formed from the aniline and crotonaldehyde, so part of the starting material is consumed as the oxidant. The yields are usually around or below 50%. When an extra oxidant is added to the reaction, which is usually referred as the Skraup reaction, the yield increases but with few exceptions the yield is still low [1,2]. One additional problem with 7-chloroquinaldine is that when 3-chloroaniline is reacted with crotonaldehyde, both 5- and 7-chloroquinaldines (**1** and **2**) are produced, making isolation of the pure product difficult. Although the zinc chloride complex has been used in the isolation of the 7-chloro isomer [3], it creates a serious environmental concern on an industrial scale.

In this work, we have found that the yield of the quinaldines can be substantially improved using quinones as oxidants. Furthermore, with 3-substituted anilines, the 7- *vs.* 5-substituted quinaldine ratio can be improved by using 2-butanol as solvent. Due to increased yield and isomer ratio, purification of quinaldine product as the simple hydrochloride salt is now possible.

Results and Discussion.

Yield Increase in the Preparation of 7-Chloroquinaldine by Addition of Oxidants.

When 3-chloroaniline was reacted with crotonaldehyde in aqueous ethanol under catalysis of hydrochloric acid, a complex mixture was produced (Eq. 1). Both 7-chloro and 5-chloroquinaldines were formed in the ratio of 5.0 to 1. The assayed yield for the desired 7-chloroquinaldine was 42% and it could be isolated as the complex with zinc

Table I

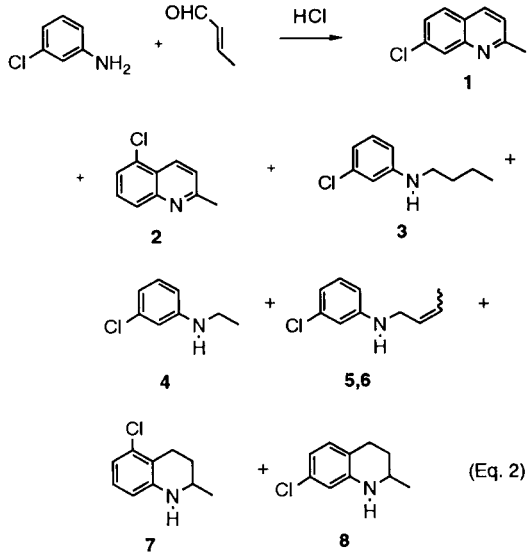
Effects of Added Oxidants on the 7-Chloroquinaldine Yield [a]

Added oxidant	7-Chloroquinaldine yield by gc (%)
None	42
$FeCl_3$	55
$CuCl_2$	49
DDQ	58
o-Chloranil	59-66
p-Chloranil	81 (67) [b]
1,4-Benzoquinone	53

[a] The reactions were done with fast addition of crotonaldehyde (4-5 minutes) and magnetic stirring except with *p*-chloranil. 3-Nitrobenzenesulfonic acid sodium salt, 3-chloronitrobenzene with catalytic amount of ferric chloride and 9,10-anthraquinone all did not have any effect on the yield. [b] Slow addition of crotonaldehyde gave 81% yield and fast addition gave 67% yield, see text.

chloride in 35% yield. Examination of the mother liquor by gc-ms showed at least six major peaks besides the chloroquinaldines. Their mass spectra are consistent with either the reduced imines **3-6**, or/and tetrahydroquinaldines **7,8** which could be derived from the dihydroquinaldine intermediates. Apparently, part of the starting material was consumed as the oxidant.

To increase the yield, some commonly used oxidants in the Skraup reaction were tested. The results are listed in Table I. Some improvements in yield were observed with ferric chloride and copper(II) chloride, but not with the two nitro compounds. There were reports of using 3-nitrobenzenesulfonic acid as the oxidant to make 7-chloroquinaldine from 3-chloroaniline and paraldehyde [2]. An isolated total yield of 60% was reported for the 7- and 5-chloro isomers in 3:1 ratio. The reaction was carried out in concentrated sulfuric acid at a much higher temperature of 130°, as opposed to milder conditions we employed (3 *N* hydrochloric acid, 80-90°). 3-Chloronitrobenzene plus catalytic amount of ferric chloride did not have much effect either, probably because the temperature was not high enough.



Quinones are useful oxidants in dehydrogenation-aromatization reactions but have not been used in the Skraup quinoline synthesis. When we tried DDQ, we were encouraged that the yield of 7-chloroquinaldine increased substantially, from 42% to 58%. The side products were suppressed. Similar results were observed for tetrachloro-1,4-benzoquinone (*p*-chloranil) and tetrachloro-1,2-benzoquinone (*o*-chloranil). With *p*-chloranil, the assayed yield for 7-chloroquinaldine was 81% and with *o*-chloranil, the yield was 66%. Even benzoquinone gave an improved yield for 7-chloroquinaldine. 9,10-Anthraquinone has a much lower reduction potential and it had no effect on the reaction. The best oxidant is *p*-chloranil because it is less expensive and more stable than DDQ or *o*-chloranil in the strongly acidic conditions used in the reaction. It is less soluble in alcohol so its tendency to oxidize the aniline starting material is low. In fact, all of the *p*-chloranil was added to the reaction mixture at the beginning, while DDQ or *o*-chloranil had to be added slowly to the reaction together with crotonaldehyde. Use of quinones as oxidants in the Skraup quinoline synthesis offers several advantages. The yields of quinaldines are high and the reaction conditions are milder than the conditions when nitro compounds are used. Quinones are easier to dispose than ferric chloride or copper(II) chloride.

Another possibility we tested was to add another amine to the reaction mixture so that the corresponding imine with crotonaldehyde could be the oxidant. But addition of one equivalent of butyl amine or cyanoamine did not have any effect on the reaction.

Improved Isomer Ratio for 7- *vs.* 5-Chloroquinaldine.

We found that solvents have substantial effects on the isomer ratio and Table II summarizes the results. As seen in the table, pure alcohol gave a higher ratio than the alcohol-water mixture. Butanol gave a higher ratio than ethanol but mixtures of *t*-butyl alcohol-acetonitrile or *t*-butyl alcohol-dioxane gave lower ratios which were not expected based on the polarity of the solvents. The yield of 7-chloroquinaldine was lower when only 1.0 equivalent of hydrogen chloride was used. So, more than 1.0 equivalent of hydrogen chloride was necessary to get a normal yield although more hydrogen chloride also causes the isomer ratio to drop, as seen in the last two entries in the table. *t*-Butyl alcohol was found to react readily with hydrogen chloride gas at room temperature, so 2-butanol was chosen as the solvent for the reaction.

Table II

Solvent Effects on 7-Chloro *vs.* 5-Chloroquinaldine Ratio in Absence of *p*-Chloranil

Solvent	Equivalents of HCl	7-Cl/5-Cl isomer ratio	Yield of 7-Cl isomer
EtOH-H_2O (7/1)	1.5	5.0	41%
EtOH	1.0	5.9	27%
t-ButOH	1.0	7.4	31%
t-ButOH/CH_3CN (1/1)	1.0	5.7	
t-ButOH/dioxane (2.5/1)	1.0	4.3	
t-ButOH-H_2O (9/1)	1.5	5.3	40%
2-ButOH	1.0	7.5	
2-ButOH	2.0	6.4	40%

Attempted use of phosphoric acid or toluenesulfonic acid as the catalyst in the reaction gave much lower yields and no isomer ratio change was observed.

Yield Increase by Slow Addition of Crotonaldehyde.

Detailed examination of the effects of the rate of addition of the crotonaldehyde and the stirring during the reaction showed that slow addition and efficient stirring were critical for good yields. When crotonaldehyde solution (1.70 g in 5 ml solvent) was added in 4-5 minutes with the reaction mixture stirred by magnetic stirrer, the assayed yield for 7-chloroquinaldine was 67%. When the reaction was mechanically stirred and the addition carefully controlled with a syringe pump to take 8 minutes, the yield increased to 74%. When the crotonaldehyde solution was added in 42 minutes (0.2 ml/minute), the assayed yield was 81% for 7-chloroquinaldine. If the 13% 5-chloro isomer was counted, the total yield of quinaldine was 94%. This slow addition technique with a syringe pump was used for all the subsequent reactions.

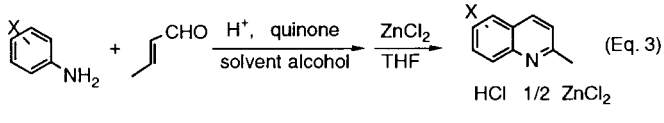
Alternate Isolation Procedure for 7-Chloroquinaldine.

The improved yield of 7-chloroquinaldine and less complex product mixture gave us a better opportunity to eliminate zinc chloride in the isolation step because it is expensive to dispose. We found that the hydrochloride salt of 7-chloroquinaldine has low enough solubility in alcohol so that if the reaction is carried out in anhydrous alcohol, the hydrochloride salt precipitates out at the end of the reaction upon cooling. But THF has to be added to the product mixture to dissolve the reduced *p*-chloranil. Thus, under optimized conditions, 3-chloroaniline was reacted with crotonaldehyde in anhydrous 2-butanol in the presence of 1.0 equivalent of *p*-chloranil and 3 equivalents of hydrogen chloride. 7-Chloroquinaldine was isolated as the hydrochloride salt in 61% yield after recrystallization and the 7- *vs.* 5-chloro isomer ratio was over 99:1.

Preparation of Other Substituted Quinaldines.

We found that these improved reaction conditions can be used for the synthesis of other substituted quinaldines, with modifications in some cases. Typically, a substituted aniline is reacted with a slight excess of crotonaldehyde (1.3 equivalents), an equimolar quantity of *p*-chloranil or 2,3-dichloro-1,4-naphthoquinone, and three equivalents of hydrogen chloride in an alcohol solvent to give the quinaldine, which upon treatment with zinc chloride in THF will precipitate out as a complex (Eq. 2). We still used the zinc chloride complexes for isolation because the solubility of these compounds in aqueous alcohols are low while that of the hydrochloride salts are high. This makes it possible to use aqueous hydrochloric acid directly in the reaction. THF was added at the end of the reaction to dissolve the reduced quinones. The yields of the quinaldine zinc chloride complexes ranged from 59 to 85% and the results are summarized in Table III.

Overall, three solvent systems were used: 1-butanol-hydrochloric acid; ethanol-hydrochloric acid; and 2-butanol. For the majority of the cases, 1-butanol-hydrochloric acid was the best choice because it was found that higher reaction temperature gives better yield for the reaction of anilines which are less reactive for this reaction. For example, in the reaction of 4-fluoroaniline to give 6-fluoroquinaldine, the isolated yield was 37% in isopropanol-hydrochloric acid mixture as solvent, 51% in 1-propanol-hydrochloric acid mixture and 59% in *n*-butanol-hydrochloric acid mixture. The reaction temperature was 105° in *n*-butanol-hydrochloric acid, the same as the boiling point of



(Eq. 3)

Table III

Preparations of Substituted Quinaldines (As the $ZnCl_2$ Complexes) [a]

Aniline	Product	Yield %	Solvent [d]	Oxidant [e]	Mp (°C)	Lit Mp (°C) [f]
H	quinaldine	79	1	1	241-244	240-243
2-Me	8-Me	65	3	2	260-263	258-261
3-Me	7-Me [b]	76	2	1	221-224	
4-Me	6-Me	84	1	1	214-218	210-212
2-OMe	8-MeO	56	3	2	221-223	219-220
3-OMe	7-MeO [b]	72	2	2	214-217	
4-OMe	6-MeO [c]	63	3	2	198-201	198-200
2-Cl	8-Cl	83	1	1	256-259	257-260
3-Cl	7-Cl [b]	68	2	1	231-234	234-236
4-Cl	6-Cl	69	1	1	236-240	238-241
3-F	7-F	70	2	1	215-217	
4-F	6-F	59	2	1	237-239	238-241

[a] General formula: quinaldine HCl (1/2$ZnCl_2$). [b] ~2% of 5-isomer after recrystallization from THF-H_2O. [c] Formula: 6-MeO-quinaldine HCl (1/2$ZnCl_2$) 0.5 H_2O. [d] Solvent 1: *n*-butanol-concentrated hydrochloric acid; 2: 2-butanol; 3: ethanol-concentrated hydrochloric acid. [e] Oxidant 1: *p*-chloranil (tetrachloro-1,4-benzoquinone); 2:2,3-dichloro-1,4-naphthoquinone. [f] Ref [3].

Table IV

^{1}H NMR Data of Quinaldine HCl(1/2$ZnCl_2$) Complexes [a]

Quinaldines	CH_3's	Ar-H
H	2.96 (s, 3H)	9.02 (d, J = 8.6, 2H), 7.8-8.4 (m, 5H)
8-Me	3.00 (s, 3H), 2.73 (s, 3H)	8.90 (d, J = 8.0, 2H), 7.6-8.1 (m, 4 H)
7-Me	2.58 (s, 3H), 2.94 (s, 3H)	8.95 (d, J = 8.5, 2H), 7.0-8.2 (m, 4 H)
6-Me	2.50 (s, 3H), 2.93 (s, 3H)	8.86 (d, J = 8.6, 2H), 7.8-8.2 (m, 4 H)
8-MeO	2.25 (s, 3H), 3.41 (s, 3H)	8.17 (d, J = 8.7, 2H), 6.8-7.2 (m, 4 H)
7-MeO	2.90 (s, 3H), 4.00 (s, 3H)	8.90 (d, J = 8.4, 2H), 7.4-7.8 (m, 3 H), 8.1-8.3 (m, 1 H)
6-MeO	2.90 (s, 3H), 3.95 (s, 3H)	8.87 (d, J = 8.6, 2H), 7.6-8.0 (m, 3 H), 8.3-8.5 (m, 1 H)
8-Cl	2.76 (s, 3H)	8.47 (d, J = 8.4, 2H), 7.9-8.1 (m, 2 H), 7.4-7.7 (m, 2 H)
7-Cl	2.91 (s, 3H)	8.92 (d, J = 8.6, 2H), 7.8-8.0 (m, 2 H), 8.2-8.4 (m, 2 H)
6-Cl	2.95 (s, 3H)	8.90 (d, J = 8.7, 2H), 7.8-8.5 (m, 4 H)
7-F	2.92 (s, 3H)	8.96 (d, J = 8.5, 2H), 7.7-8.1 (m, 3 H), 8.3-8.5 (m, 1 H)
6-F	2.95 (s, 3H)	8.96 (d, J = 8.6, 2H), 7.9-8.5 (m, 4 H)

[a] The nmr were taken in DMSO-d_6, chemical shifts are ppm from TMS. The signals for the acidic hydrogens are usually broad and appear at 3-6 ppm.

crotonaldehyde. Anhydrous 2-butanol was used for 3-substituted anilines because it gave the higher 7- *vs.* 5-isomer ratio based on the reaction of 3-chloroaniline. Recrystallization of the crude products was necessary to reduce the 5-isomer to about 2% level. Ethanol-hydrochloric acid was used in cases where the aniline was prone to side reactions and milder conditions were required. The difference caused by the solvents was less profound for reaction of aniline itself.

p-Chloranil was found to be an appropriate oxidant for most reactions. But when the aniline bears strong electron-donating groups, like methoxy group, a milder oxidant, 2,3-dichloro-1,4-naphthoquinone, and lower reaction temperature, by using ethanol as solvent, proved to give higher yields.

In summary, *p*-chloranil and 2,3-dichloro-1,4-naphthoquinone are useful oxidants in the Skraup quinaldine synthesis. The yields of the reactions are high compared to other oxidants and the products are conveniently isolated either as the hydrochloride salt or the zinc chloride complex.

EXPERIMENTAL

General.

All solvents and chemicals were used as received. The ^{1}H and ^{13}C nmr spectra were recorded on a 250 MHz Bruker nmr Spectrometer. Melting points were recorded on a Thomas Hoover Melting Point Apparatus. Hewlett Packard 5890 Gas Chromatograph with a Hewlett Packard 3396A Integator was used for gc analyses. The column was 30 meter DB-1 column, 0.25 mm O.D., 1 μm film. For all the products, satisfactory ^{1}H nmr consistent with assigned structures were recorded and listed in Table IV. Capillary gc analyses of the basified solution of the zinc chloride complexes or the hydrochloride salts showed only one peak unless noted. The reaction yield of 7-chloroquinaldine was determined on gc with tetradecane as the internal standard. For known compounds, melting points and literature values are listed in Table III. For the new compounds, *i.e.*, 7-methyl, 7-fluoro, 7-methoxyquinaldine zinc chloride complexes and 7-chloroquinaldine hydrochloride salt, elemental analyses that are within 0.4% of the calculated values are reported and listed below. The ^{13}C nmr spectra for these new compounds are also listed below.

Synthesis of Quinaldines.

Method 1.

This method was used to prepare quinaldine, 6-methylquinaldine, 6-fluoroquinaldine, 8-chloroquinaldine and 6-chloroquinaldine. To 20 mmoles of the substituted aniline in a three-necked, roung bottom flask, 5 ml of concentrated hydrochloric acid (12 *N*) was added. Then 4.94 g (20 mmoles) of *p*-chloranil (tetrachloro-1,4-benzoquinone) was added to the flask, along with 5 ml of *n*-butanol to wash the solid down into the flask. This mixture was mechanically stirred and heated to reflux. Then a solution of 1.70 g of crotonaldehyde (24 mmoles) in 2 ml of *n*-butanol was added to the refluxing solution at a rate of 0.1 ml/minute using a syringe pump. After addition was complete, the mixture was allowed to reflux another 20 minutes and a solution of 2.73 g (20 mmoles) zinc chloride dissolved in 40 ml of THF was added in several portions. The mixture was allowed then to reflux for another 10-20 minutes, and was then allowed to cool slowly to 0° and stand at 0° for 1 hour. The solid was then collected by filtration, washed with THF, 2-propanol and ether. It was dried at 50°.

Method 2.

This method was used to prepare 7-chloroquinaldine, 7-methylquinaldine and 7-fluoroquinaldine. It was also used to prepare 7-methoxyquinaldine, but the oxidant 2,3-dichloro-1,4-naphthoquinone was used as oxidant instead of *p*-chloranil. This method was essentially the same as method 1 except that the solvent was 2-butanol only. Thus a stock solution of hydrogen chloride in 2-butanol was prepared by passing hydrogen chloride gas into 2-butanol and then it was titrated with standard 0.1 *N* sodium hydroxide solution. The concentration was 4 *N* to 5 *N*. In the reaction, the same amount of starting materials were mixed with the 40 mmoles of hydrogen chloride solution in 2-butanol. Additional

2-butanol was added to make the total 2-butanol solution 25 ml. Then 24 mmoles of crotonaldehyde in 5 ml of 2-butanol was added in the same way. The quinaldines were isolated as the zinc chloride complexes as before. The crude zinc chloride complex was dissolved in a minimum amount of refluxing methanol and excess amount of THF (15 ml/g of product) was added to precipitate the product. The mixture was then cooled to 0° and held at 0° for one hour. The solid was collected by filtration and washed with THF and ether. It was dried at 50°/10 mm Hg. Capillary gc analysis of the four products made in this way showed about 2% of the 5-substituted quinaldine present in the final product.

7-Dimethylquinaldine Hydrochloride·0.5 Zinc Chloride Complex.

This compound had ^{13}C nmr: δ ppm 157.2, 145.3, 144.9, 137.5, 130.9, 128.5, 124.8, 122.7, 118.5, 21.8, 20.3.

Anal. Calcd. for $C_{11}H_{12}NCl_2Zn_{0.5}$: C, 50.46; H, 4.62; N, 5.35; Cl, 27.08. Found: C, 50.17; H, 4.68; N, 5.08; Cl, 27.10.

7-Fluoroquinaldine Hydrochloride·0.5 Zinc Chloride Complex.

This compound had ^{13}C nmr: δ ppm 163.9 (d, J = 255 Hz), 158.8, 145.1, 138.4 (d, J = 13.6 Hz), 132.5 (d, J = 10.7 Hz), 123.2, 123.8, 119.0 (d, J = 25.1 Hz), 104.7 (d, J = 25.2 Hz), 20.7.

Anal. Calcd. for $C_{10}H_9NCl_2FZn_{0.5}$: C, 45.19; H, 3.41; N, 5.27; Cl, 26.68; F, 7.17. Found: C, 45.32; H, 3.28; N, 5.23; Cl, 26.77; F, 6.89.

7-Methoxyquinaldine Hydrochloride·0.5 Zinc Chloride Complex.

This compound had ^{13}C nmr: δ ppm 163.3, 156.6, 144.8, 139.8, 130.5, 122.0, 121.0, 120.8, 99.0, 56.2, 20.2.

Anal. Calcd. for $C_{11}H_{12}NCl_2OZn_{0.5}$: C, 47.56; H, 4.35; N, 5.04; Cl, 23.52. Found: C, 37.56; H, 4.30; N, 5.01; Cl, 25.17.

7-Chloroquinaldine was also isolated as the hydrochloric acid salt. Thus, in one run, 60 g (470 mmoles) of 3-chloroaniline, 40 g (570 mmoles) of crotonaldehyde and 115.6 g (470 mmoles) of *p*-chloranil were allowed to react in a total of 600 ml of 2-butanol, under the catalysis of 740 mmoles of hydrogen chloride dissolved in 2-butanol, in the same way as described in method 2. Crotonaldehyde dissolved in 120 ml of 2-butanol was added during 50 minutes. After the reaction was completed, 360 ml of 2-butanol was removed by distillation under reduced pressure (10 mm Hg). Then 720 ml of toluene was added and 720 ml of solvent was distilled under the same conditions. Then 720 ml of THF was added and the mixture was refluxed for 30 minutes. Alternatively, 2-butanol could be completely removed under high vacuum and THF added directly. The mixture was then cooled to 0° for one hour and filtered. The solid was washed with 8 x 100 ml THF. The wet solid cake was recrystallized from 160 ml of methanol and 720 ml of THF as described in method 2. The final product was 61.2 g (yield 61%) of yellowish white solid, mp 244-246° (lit [2b] 248-249°); ^1H nmr (methanol-d_4): δ ppm 9.06 (d, J = 8.8 Hz, 1H), 8.2-8.4 (m, 2H), 7.9-8.1 (m, 2H), 3.06 (s, 3H); ^{13}C nmr (methanol-d_4): δ ppm 160.7, 147.6, 142.0, 139.5, 132.1, 131.6, 127.3, 125.2, 120.3, 21.1.

Anal. Calcd. for $C_{10}H_9NCl_2$: C, 56.10; H, 4.24; N, 6.54. Found: C, 56.06; H, 4.01; N, 6.40.

Method 3.

This method was used to prepare 8-methylquinaldine, 8-methoxyquinaldine, and 6-methoxyquinaldine. This method is the same as method 2 except that absolute ethanol was the solvent and 60 mmoles hydrogen chloride in ethanol was used as the catalyst. In addition, 2,3-dichloro-1,4-naphthoquinone instead of *p*-chloranil was used as the oxidant.

Acknowledgements.

We thank Mr. M. Reeder in our Department for running the gc-ms samples.

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