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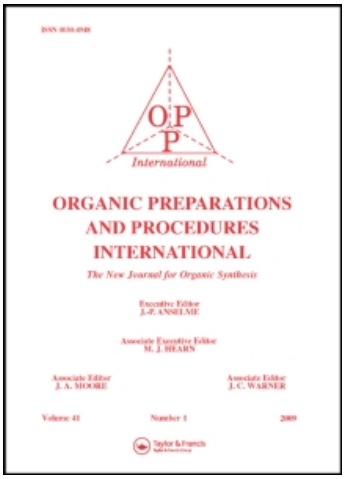


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# THE REACTION OF AMINES WITH METHYLENE CHLORIDE. A BRIEF REVIEW

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ORGANIC PREPARATIONS AND PROCEDURES INT. 16(2), 97-114 (1984)

# THE REACTION OF AMINES WITH METHYLENE CHLORIDE.

## A BRIEF REVIEW

John E. Mills*, Cynthia A. Maryanoff, Robin M. Cosgrove,
Lorraine Scott, David F. McComsey

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# THE REACTION OF AMINES WITH METHYLENE CHLORIDE. A BRIEF REVIEW

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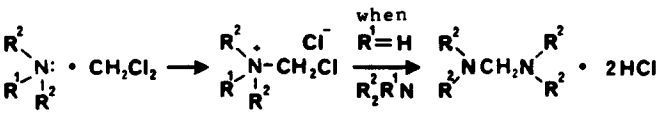
## SCOPE AND HISTORICAL

In recent years, methylene chloride has become a popular solvent for many applications because of its polarity, density, low toxicity and low boiling point. However, the fact that methylene chloride is an alkylating agent is often disregarded. It has been established that amines, in particular certain secondary and tertiary amines, undergo a facile reaction leading to hydrochloride salts, aminals, and/or quaternary salts. In its most general form, the reaction is shown below.




Cognizance of this reaction may prevent irreproducible results through modifications of reaction conditions or isolation procedures. In some cases, the simple expedient of stripping the solvent from an amine immediately after an extraction, rather than allowing the solution to stand overnight, may improve isolated yields significantly. A thorough knowledge of the existing literature should be helpful in determining which modifications, if any, are necessary. To date, no review of the reactions of amines with methylene chloride has been assembled. Because much of the existing literature is inaccessible through traditional search techniques, publication of the present review is timely. The confusion

caused by the inaccessibility is illustrated below. During the 1950's, a number of articles were published on the reaction of chloroform with tertiary amines.[1-7] In those articles it was established that it was not chloroform itself, but rather bromochloromethane and methylene chloride impurities which reacted with the amines to form salts. In 1970, Wright and Wulff[8] published what they felt was the first case of isolation of an alkylated product obtained from the reaction of methylene chloride with a tertiary amine. A probable explanation for the oversight of the papers published in the 1950's is that those papers were indexed under the keyword chloroform in Chemical Abstracts.

A large body of information has been generated on the reaction of methylene chloride with amines. This review cites only those articles providing proof of covalent bond formation between methylene chloride and amines. In addition, selected articles providing quantitative data on the reactivity of methylene chloride are discussed. Unpublished work from our laboratories on the reaction of secondary amines is also included. This review will firmly establish the facility of the reaction of methylene chloride with amines. It will also dispel the misconception that phosgene and hydrogen chloride impurities in methylene chloride are a major concern when one is working with amines.

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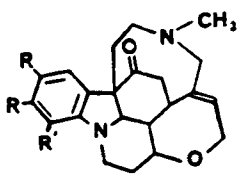
## I. REACTIONS WITH TERTIARY AMINES

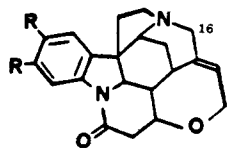
By far, the majority of articles which have been published on the reaction of methylene chloride with amines involve quaternary salt formation. In addition to the formation of the chloromethyl quaternary chloride salt, some investigators have observed the formation of the methyl quaternary salt, and occasionally demethylation. Methyl quaternary salt formation is not necessarily due to transfer of a methyl group from a quaternary to a tertiary nitrogen, as evidenced by formation of a methyl quaternary salt of benactyzine, a compound which does not possess an

N-methyl group. It is possible that this methyl quaternary salt is derived from impurities in the methylene chloride. The identity of the impurities or the mechanism of formation of the methyl quaternary salt from methylene chloride is unknown.

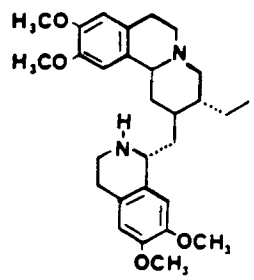
Tertiary amines which have been shown to react with methylene chloride are listed in Tables 1-3. There are additional reports of chloromethyl quaternary salt formation from chloroform. As indicated above, these salts probably arose from impurities (bromochloromethane and methylene chloride) in the chloroform used.



Icajine R = R' = H
Vomicine R = H, R' = OH
Novacine R = $OCH_3$, R' = H



Strychnine R = H
Brucine R = $OCH_3$



Emetine

In addition to the tertiary amines listed in Tables 1-3, Phillipson[9] has reported that emetine, reserpine, and quinine, when allowed to stand in methylene chloride, show the presence of more polar spots detected by TLC. The identities of these spots were not determined. Furthermore, 16-hydroxystrychnine, 16-hydroxybrucine, icajine, vomicine, and novacine were specifically reported not to react with methylene chloride.

The reaction of tertiary amines with alkyl halides to form quaternary salts (Menschutkin reaction) is known to occur through an $S_N2$ mechanism.[10] In general, those amines which contain at least two N-methyl groups or those amines in which the alkyl substituents are conformationally restricted so that the electron lone pair on nitrogen is readily accessible, appear to be most reactive. Swain[11] and Davies[12] have reported that steric interactions have a major effect on the rate of the reaction.



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TABLE 1. Reaction of Natural Products Containing Tertiary Amines with Methylene Chloride

| AMINE | CONDITIONS[a] | PRODUCTS[b] | YIELD[c] | REF. |
|---|---|---|---|---|
| Strychnine | RX, 10 hrs | CMC | 48% | 3 |
| " | RT, 2 hrs | CMC | NG | 9 |
| Brucine | RT, 2 hrs | CMC | NG | 9 |
| Isotetrandrine | NG | CMC | NG | 29 |
| Tetrandrine | NG | CMC | 16% | 28 |
| Tubotaiwine | NG | CMC | NG | 31 |

a) RX-reflux, RT-room temperature, NG-not given; b) CMC-chloromethyl chloride quaternary salt; c) NG-not given.

TABLE 2. Reaction of Drug Entities Containing Tertiary Amines with Methylene Chloride

| AMINE | CONDITIONS[a] | PRODUCTS[b] | YIELD[c] | REF. |
|---|---|---|---|---|
| Imipramine | RT, 90 da | CMC<br>MC<br>DM | 80% | 30,32 |
| Atropine | NG | CMC | NG | 14 |
| Meperidine | NG | CMC | NG | 14 |
| " (Pethidine) | NA | CMC | NA | 33 |
| Dextromethorphan | NA | CMC | NA | 33 |
| Brompheniramine | RX, 24 hrs | CMC | NG | 34 |
| Diphenylpyraline | RX, 24 hrs | CMC | NG | 34 |
| Cyclizine | RX, 24 hrs | CMC | NG | 34 |
| Cyproheptadine | RX, 24 hrs | CMC | NG | 34 |
| 3-Quinuclidinyl diphenylacetate | NG | CMC | NG | 14 |
| N-(2,5-dimethylphenyl)quinuclidinyl-3-carboxamide | NG | CMC | NG | 14 |
| Benactyzine | NG | CMC | NG | 14 |
| " | RT, 4 mos | CMC<br>MC | 3%<br>0.3% | 15 |
| Pereirin | warm | CMC | NG | 35 |
| Amitriptyline | RT, 14 hrs | CMC<br>MC | 1.2%<br>1.2% | 36 |

a) RX-reflux; RT-room temperature, NA-thesis not available, NG-not given; b) CMC-chloromethyl chloride quaternary salt, MC-methyl chloride quaternary salt, DM-demethylated amine; c) NG-not given, NA-thesis not available.



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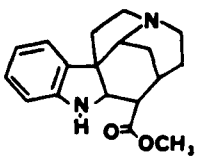
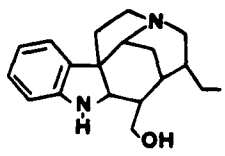
TABLE 3. Reaction of Other Tertiary Amines with Methylene Chloride

| AMINE | CONDITIONS[a] | PRODUCTS[b] | YIELD | REF. |
|---|---|---|---|---|
| Bis-nordihydrotoxiferine | RT, 72 hrs | CMC? | 100% | 37 |
| Trimethyl amine | RT, 1-2 da | CMC | 70% | 38 |
| Triethyl amine | RT, 10 wks | CMC | 23% | 20 |
| " | RT, 3 da | CMC | 1% | 8 |
| N-Methylpiperidine | RT, 6 da | CMC | 12% | 20 |
| N-Methylpyrrolidine | RT, 5 da | CMC | 42% | 20 |
| Pachycarpine | 160°C, 30 hrs | * | 78.2% | 16 |

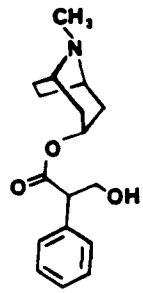
a) RT-room temperature; b) CMC?-possible chloromethyl chloride quaternary salt, CMC-chloromethyl chloride quaternary salt, *-bisquaternary salt.



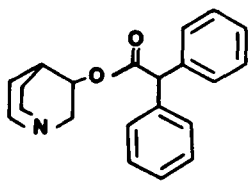
Tubotaiwine



Pereirin

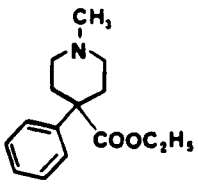


Atropine

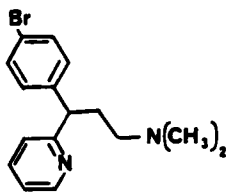


3-Quinuclidinyl

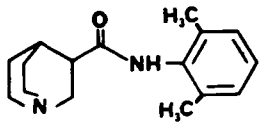
*diphenylacetate*



Meperidine

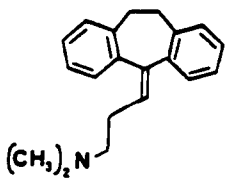


Brompheniramine

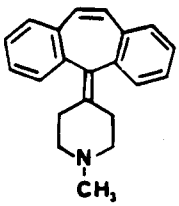


N-(2,5-dimethylphenyl)

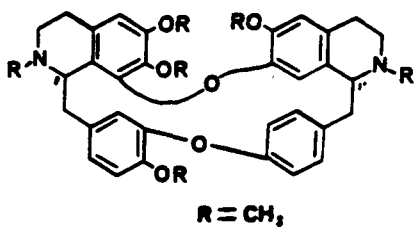
quinuclidinyl-3-carboxamide



Amitriptyline



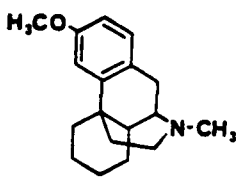
Cyproheptadine



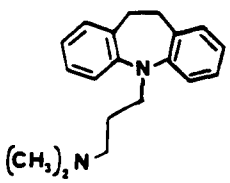
R = CH3

Tetrandrine (1-S, 1′-S)

Isotetrandrine (1-R, 1′-S)



Dextromethorphan



Imipramine



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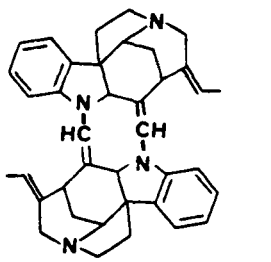
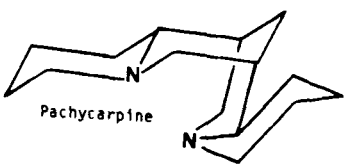
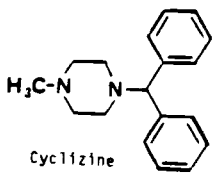
In several of the papers cited in Tables 1-3, the major supporting evidence for quaternary salt formation derives from mass spectra. In at least one case, mass spectral evidence was used to support the claim of bis-quaternization.[13,14] Later work by Nordholm[15] states that formation of bis-quaternized product lacked proof due to the observation of methyl quaternary salt formation in this reaction. The ions found in the mass spectrum of the methyl quaternary salt of benzactyzine were the same ions being used as evidence for bis-quarternization.



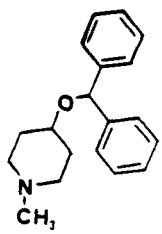
Bis-nordihydrotoxiferine



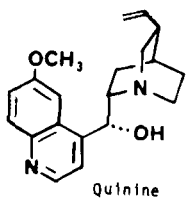
Pachycarpine



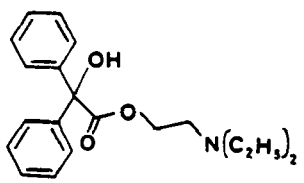
Cyclizine



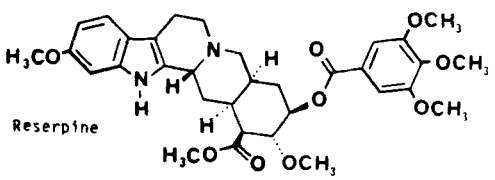
Diphenylpyraline



Quinine



Benactyzine



Reserpine

Only one example of bisquaternary salt formation from methylene chloride which was verified by NMR spectroscopy has appeared in the literature.[16] The steric requirements of pachycarpine are such that this bisquaternary salt is stable despite the close proximity of the two positively charged centers. Studies by Rembaum[17] and Ottenbrite[18] have shown that such bisquaternary salts, if formed, are typically very unstable.



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As analytical techniques have been developed, the ability to observe and identify quaternary salts has improved. In many of the examples given in the Tables above, the salts were first observed by TLC or HPLC. Quaternization is so facile that these salts can be observed after a simple extraction. This fact suggests that caution be exercised when methylene chloride is used with tertiary amines.

## II. REACTIONS WITH SECONDARY AMINES

The products of the reactions of methylene chloride with secondary amines may be broken down into three groups: amine hydrochloride salts, aminals, and other Mannich adducts (formally derived from methylene iminium salt alkylation of an electron-rich carbon atom). Under typical reaction conditions the hydrochloride salts precipitate. These salts are therefore easily isolated and characterized. The symmetrical aminals are frequently oils and remain dissolved in the methylene chloride. Mannich adducts with various nucleophiles can be isolated under special conditions.

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Secondary amines which have been reported to react with methylene chloride to yield aminals and salts are shown in Table 4. Conditions reported for this reaction appear, in many cases, to be unnecessarily harsh. Dimethylamine, for example, reacts slowly even at 0°.

Table 4 also lists a number of secondary amines which have been studied in our laboratories. It should be noted that some N-methylamine derivative (<5%) was formed with each of the amines that reacted to give an aminal. A possible mechanism by which this product forms is not obvious. Hydride transfer to an iminium species would result in N-methylation. Similar hydride transfers have been postulated to account for by-products observed in the Eschweiler-Clarke reaction.[19]

The presence of an iminium species in the reaction of pyrrolidine with methylene chloride was established as follows. When pyrrolidine was

allowed to react with methylene chloride in the presence of N-methylpyrrole, a trace amount of the pyrrole Mannich base, 1-methyl-2-(pyrrolidinomethyl)pyrrole, was identified by gas chromatography (co-injection with authentic material), and GC/mass spectra.

TABLE 4. Reaction of Secondary Amines with Methylene Chloride

| AMINE | CONDITIONS[a] | PRODUCTS | YIELD[b] | REF.[c] |
|---|---|---|---|---|
| Dimethylamine | 60-70°, 3 hrs | Amine HCl<br>Aminal | 50%<br>50% | 39 |
| " | NG | Aminal | NG | 40 |
| " | neat, 0° | Amine HCl | 0.8% | TW |
| Diethylamine | 40°, 9 kbar | Aminal | NG | 21 |
| Piperidine | Reflux, 24 hrs | Amine HCl<br>Aminal | 60%<br>5% | 41 |
| Pyrrolidine | NaOH, RT, 18 hrs | Aminal | 40% | TW |
| " | RT, 18 hrs | Aminal | 82% | TW |
| Morpholine | NaOH, RT, 48 hrs | Aminal | 70% | TW |
| " | NaOH, 45°, 3 hrs | Aminal | 75% | TW |
| " | NaOH, 45°, 67 hrs | Aminal | 93% | TW |
| " | neat, 45°, RT (8, 14 hrs) | Aminal<br>Amine HCl | 12%<br>51% | TW |
| Methylethylenediamine | NaOH, RT, 45° (5.5, 17 hrs) | Aminal | 80% | TW |
| " | neat, RT, 10 ds | Aminal | 79% | TW |
| N-Methylphenethylamine | NaOH, RT, 1 wk | Aminal | 48% | TW |
| Tetrahydroiso-quinoline | NaOH, RT, 1 wk | Aminal | 75% | TW |

a) NG-not given, RT-room temperature; b) NG-not given; c) TW-this work.

Yields of some aminals may be improved by addition of aqueous base. Under these conditions, amine hydrochlorides are converted to the free base which can then continue to react with the methylene chloride. It appears that the secondary amines react more rapidly with methylene chloride than their derived aminals. No evidence of a quaternary aminal has been found. The quaternary salt could decompose through the reaction shown below.[20] The net result of such decomposition should be more rapid formation of the aminal.

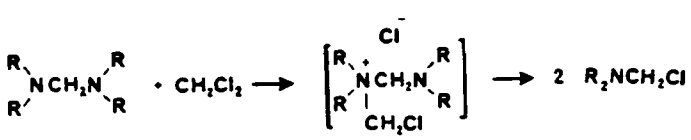



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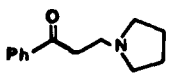
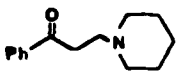
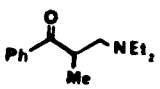
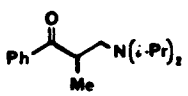
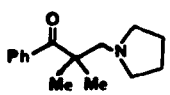
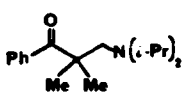
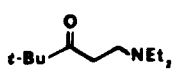
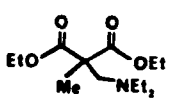
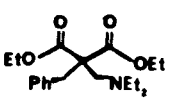
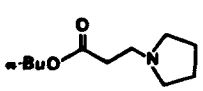
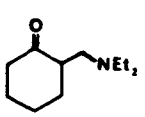
TABLE 5. Reaction of Secondary Amines with Methylene Chloride and Ketones or Esters Under Pressure[21]

| PRODUCT | STARTING MATERIALS CONDITIONS | YIELD |
|---|---|---|
|  | Acetophenone, Pyrrolidine<br>9 kbar, 20°, 72 hrs | 34% |
|  | Acetophenone, Piperidine<br>8 kbar, 40°, 24 hrs | 86% |
|  | Propiophenone, Diethylamine<br>9 kbar, 22°, 43 hrs | 30% |
|  | Propiophenone, Diisopropylamine<br>8 kbar, 40°, 39 hrs | 14% |
|  | Isobutyrophenone, Pyrrolidine<br>9 kbar, 40°, 48 hrs | 56% |
|  | Isobutyrophenone, Diisopropylamine<br>9 kbar, 48°, 72 hrs | 14% |
|  | Pinacolone, Diethylamine<br>6 kbar, 40°, 48 hrs | 30% |
|  | Diethyl methylmalonate, Diethylamine<br>6 kbar, 48°, 61 hrs | 71% |
|  | Diethyl benzylmalonate, Diethylamine<br>9 kbar, 48°, 48 hrs | 12% |
|  | n-Butyl acetate, Pyrrolidine<br>9 kbar, 48°, 72 hrs | 32% |
|  | Cyclohexanone, Diethylamine<br>9 kbar, 22°, 48 hrs | 26% |

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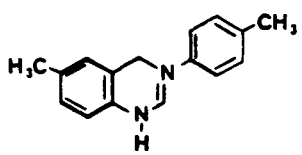
In the aqueous base system, the possibility exists that methylene chloride is reacting with hydroxide to form formaldehyde. The formaldehyde may be responsible, in part, for aminal formation and/or production of the methylated amine (vide infra).

Recently, Matsumoto[21] reported the formation of Mannich bases from the reaction of ketones or esters with methylene chloride and secondary amines at a pressure of 6-9 kbar. Those products are reported in Table 5. None of these Mannich products have been observed in our laboratories at atmospheric pressure even after extended reaction times.

## III. REACTIONS WITH PRIMARY AMINES

Although methylene chloride undoubtedly reacts with primary amines, the rate of this reaction appears to be much slower than the rate with secondary or tertiary amines. Williams[1] studied the rate of formation of ionic halide in the reaction of a number of alkyl amines with chloroform. He concluded that the amines were initially reacting with bromochloromethane and methylene chloride impurities in the chloroform, and that most secondary amines reacted more rapidly than primary amines. Unfortunately, none of the organic products were identified in this reaction.

Hunt and Wagner[22] showed that p-toluidine, when heated with methylene chloride in a sealed tube at 100° for 36 hours, gives 3-p-tolyl-6-methyl-3,4-dihydroquinazoline (no yield was provided). The probable mechanism of formation of this product has been provided by Wagner.[23]




## IV. MECHANISTIC STUDIES WITH SECONDARY AMINES

Since reactivity of methylene halides in $S_N2$ reactions is known to be less than that of a number of other alkyl halides,[24] we performed a



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series of experiments to determine the mechanism of the reaction with secondary amines.

Since bromochloromethane is known to be more reactive than methylene chloride,[24] the possibility exists that a trace of $CH_2BrCl$ in the methylene chloride catalyzed the reaction, as shown below. This was ruled out by mass spectral evidence as no bromine-containing impurity in the methylene chloride used in any of our studies was found.

$$CH_2ClBr \cdot R_2NH \longrightarrow R_2\overset{+}{N}(H)CH_2Cl\ Br^- \xrightarrow{CH_2Cl_2} R_2\overset{+}{N}(H)CH_2Cl\ Cl^- \cdot CH_2ClBr$$

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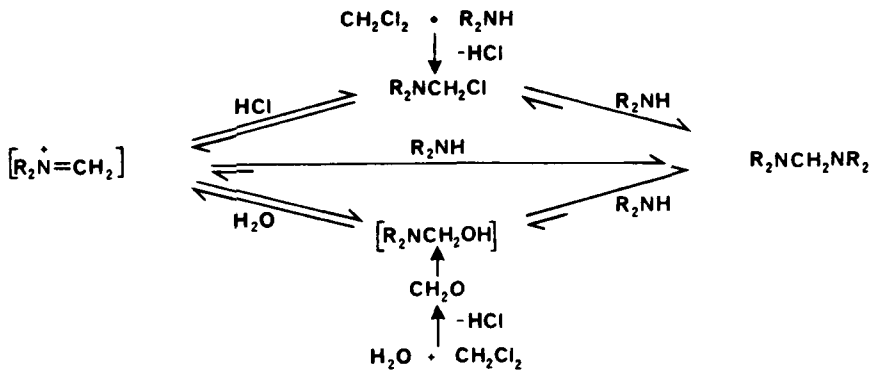
Attempts to trap a chloromethyl carbene with 2,3-dimethyl-2-butene failed to produce any of the expected chlorocyclopropane although aminal was formed under the reaction conditions. This experiment suggests that the carbene pathway is inoperative; however, it is possible that any carbene formed may not have been efficiently trapped by the alkene.

$$R_2NH \cdot CH_2Cl_2 \longrightarrow R_2\overset{+}{N}H_2\ Cl^- + :CHCl \xrightarrow{R_2NH} R_2NCH_2Cl$$

Experiments in which methylene chloride was reacted with pyrrolidine in the presence of $D_2O$/NaOD showed that the aminal formed in this reaction contained less than 3% deuterium. A second set of experiments using $CD_2Cl_2$ with $H_2O$/NaOH and pyrrolidine gave results consistent with the first experiment. Therefore, it has been established that a carbene pathway, if operative at all, is only a minor pathway and that the major mechanistic pathway is direct displacement either by amine, by hydroxide, or a combination of both.




## V. CONCLUSION

As stated above, acceptable yields of aminals may be obtained from secondary amines and methylene chloride by running this condensation in the presence of aqueous base. Furthermore, tertiary amines react with methylene chloride to give crystalline chloromethyl quaternary chlorides. Considering the alternative methods for the preparation of symmetrical aminals,[25] and the variety of derivatives which can be made for the characterization of tertiary amines,[26] the utility of this reaction appears to be very limited. However, if one considers the practical consequences of the reaction of methylene chloride with amines, the importance of this reaction cannot be overstated.

After an extraction with methylene chloride, undesirable results may be obtained if an amine is allowed to remain in solution overnight in the presence of a drying agent. Precipitated amine salts will be removed during filtration of the drying agent, resulting in lower isolated yields. Furthermore, isolated secondary amines, if used in further reactions , may not react as expected due to the presence of and decomposition of aminals.

There are a number of phase-transfer reactions in which methylene chloride is reported to be the solvent of choice.[27] If one of the



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substrates contains an amine, the desirability of this solvent should be questioned.

Due to its cost, availability, low toxicity and unique solvating ability, it is doubtful that methylene chloride will be replaced by other less reactive solvents. Cognizance of the reactivity of this solvent should lead to anticipation of possible difficulties and measures designed to minimize those difficulties.

Methylene chloride is frequently used in the isolation of natural products. Care must be taken to establish if the isolated compounds are natural products or artifacts of the isolation procedure. As shown above, artifacts which may be produced during extraction and isolation include chloromethyl quaternary salts, methyl quaternary salts, methyl amines, aminals, and demethylated amines.

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Papers by Kupchan[27] and Cavé[28] can be used as examples of the possible problems associated with this solvent in natural product isolation. Kupchan isolated tetrandrine and related alkaloids from Cyclea petata Diels, while Cavé isolated isotetrandrine from Limaciopsis loangensis Engl. Both groups isolated chloromethyl quaternary chlorides of the major alkaloid which were attributed to artifacts produced by the solvent. Both groups also isolated N-desmethyl "natural products". In addition, Kupchan reported the isolation of an N-methyl quaternary salt of tetrandrine in amounts nearly equal to the N-desmethyl tetrandrine. Comparison of the amount of the N-desmethyl amine to the amount of N-chloromethyl quaternary salt isolated gives a ratio of approximately 0.02 in both cases. It is surprising that this ratio would be nearly the same since the compounds were isolated from two different plant species and are epimeric. In addition, the fact that in Kupchan's case, an N-methyl quaternary salt and an N-desmethyl compound were isolated in nearly equal quantities suggests the possibility that disproportionation

of the chlormethyl quaternary salt with free amine could be leading to the formation of these products. Only recently has the formation of methyl quaternary salts from tertiary amines and methylene chloride been definitely established.[15,30]

It has been reported that methylene chloride is one of the best solvents for the Menschutkin reaction.[10] The combination of reactivity and unique solvent properties of methylene chloride demands that care be exercised in the use of this solvent with amines. When the contact time of an amine with this solvent may be long, it is well worth the effort to determine if a different solvent is more suitable. In the absence of a better solvent, experiments must be designed to determine the extent of the reaction with the particular amine. Appropriate measures can then be taken to minimize the formation of by-products.

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## EXPERIMENTAL SECTION

$^1H$ NMR and $^{13}C$ NMR spectra were obtained on a JEOL JNM-FX60Q (60 MHz) instrument using $CDCL_3$ as solvent. $Me_4Si$ was the internal reference for $^1H$ spectra. GLC analyses were performed on a Perkin-Elmer Sigma 2B instrument equipped with flame ionization detector and a Perkim-Elmer Sigma 15 data station. All GLC analyses were performed using 6 ft, 3% OV-17 on 100-120 mesh Chromosorb WHP glass columns programmed 40°-280° at 30°/min., 10 min. at final temperature. GC-MS were obtained on a VG-7035 mass spectrometer equipped with an SE-54 capillary column (25 m) operating in the CI mode with methane as the reagent gas (1 torr; source temperature 150°; 500 μA emission current). Except for the amine hydrochloride salt reported in Table 4, all yields are GC % volatiles or yields determined from $^1H$ NMR spectra of crude reaction products. The identities of all aminals were verified by a combination of GC-MS data, $^1H$ or $^{13}C$ NMR data, and comparison of GC retention times to authentic material prepared through the condensation of the secondary amine with formaldehyde.[25] Methylene chloride (Fischer certified) used in these studies was subjected to mass spectral analysis; it contained no bromine containing impurities. $CD_2Cl_2$ used in the mechanistic work was supplied by MSD isotopes (min. purity 99.8 atom % D). Thirty percent NaOD in $D_2O$ was supplied by Aldrich Chemical Company (99+ atom % D).

GENERAL PROCEDURES.- Methylene chloride (30 mL), amine (50 mmole), and 30% aqueous sodium hydroxide (5 mL) were stirred at the tabulated times and temperatures and analyzed for aminal as stated above. All samples analyzed by GLC showed traces of the corresponding N-methylamine derivative.

Condensations conducted neat were set up and analyzed as above, but with no added sodium hydroxide.

Deuterium labeling experiments were performed using $CD_2Cl_2$ (0.5 mL), pyrrolidine (1.4 mmole), and 15% sodium hydroxide (2 mL), or $CH_2Cl_2$ (1 mL), pyrrolidine(1.4 mmole), and 30% sodium deuteroxide (0.1 mL). These experiments were stirred in sealed ampules at room temperature for periods of up to one (1) week. Analysis was conducted by high resolution GC/MS.

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