... *Journal of Forensic Sciences*, JFSCA, Vol. 28, No. 1, Jan. 1983, pp. 18-31.

ABSTRACT: Clandestine, or illegal, laboratories are operated by the criminal element to circumvent legal requirements with the goal of supplying drugs of abuse to the illicit market. Investigation of clandestine drug manufacturing laboratories is a high priority of the U.S. Drug Enforcement Administration (DEA) because elimination of these laboratories will prevent drugs of abuse from reaching the illicit drug traffic. One of the important responsibilities of forensic chemists assisting in investigations of clandestine drug laboratories is to be familiar with the methods of synthesis being used by clandestine laboratory operators. A review of clandestine laboratory seizures during the period of 1978 through 1981 will be provided to familiarize forensic chemists with current information on the types of laboratories being seized in the United States and the methods of synthesis being used.

KEYWORDS: criminalistics, controlled substances, synthesis, methamphetamine, phencyclidine, amphetamine, methaqualone, methylenedioxyamphetamine

United States Federal law provides for legitimate manufacture of controlled drug substances. The Controlled Substances Act (Public Law 91-513), recognizing that many controlled drugs have a useful medical purpose, established a system of annual registration, under which a firm is registered to manufacture or import a limited amount of controlled drugs to ensure an adequate and uninterrupted supply of these substances. Maintenance of effective controls against diversion of particular controlled substances to other than legitimate medical, scientific, or industrial channels is the goal of the Act.

Clandestine, or illegal, laboratories have been established in the United States to supply controlled drugs for the illicit market. Because discovery and closing of these laboratories will eliminate this source of supply, investigation of clandestine drug-manufacturing activities is a high priority of the U.S. Drug Enforcement Administration (DEA).

Close coordination between investigators and forensic chemists is important at various stages of clandestine laboratory investigations because of the highly technical nature of these investigations. Specific stages requiring such coordination are

- Activities before the seizure takes place
- Activities during the seizure
- Laboratory examination of the evidence
- Court testimony during criminal prosecution

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[1]Chief, Forensic Sciences Division, Drug Enforcement Administration, Department of Justice, Washington DC.

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TABLE 1—*Types of*

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Amphetamine
Methaqualone
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Cocaine
Cannabis (hashish oil
Other (includes LSD,
Total

[a]First three quarters

R. S. Frank[1]

The Clandestine Drug Laboratory Situation in the United States

REFERENCE: Frank, R. S., **"The Clandestine Drug Laboratory Situation in the United States,"** *Journal of Forensic Sciences*, JFSCA, Vol. 28, No. 1, Jan. 1983, pp. 18-31.

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Total

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The important activities of the forensic chemist prior to seizure include advising investigators on the type of drug being produced, the quantities involved, and an appropriate time for scheduling seizure and providing technical information necessary for preparation of the search warrant. There are many controlled drugs that can be synthesized in clandestine laboratories and a multitude of different methods of synthesis. Knowledge of those syntheses that are frequently encountered is important for:

- *safety reasons*—Chemists must be able to recognize reactions in progress and how to safely handle them. Also, hazardous situations must be dealt with immediately.
- *evidentiary reasons*—Chemists must be able to demonstrate that a particular drug is being synthesized and to disregard items of little or no evidentiary value.
- *prosecutive reasons*—Chemists must be able to explain fully in court all steps in the synthesis.
- *intelligence reasons*—Chemists must identify important reagents and precursors that will aid in reducing the supply of illicit drugs.

Types of Clandestine Laboratories

During the 45-month period ending in September 1981, the DEA seized a total of 751 clandestine drug laboratories in the United States. After increasing in each of the previous years, the number of seizures declined by close to 20% in the first nine months of 1981 compared to the previous year. Whether this decline was caused by a reduction in the number of illicit laboratories operating, a reduction in enforcement efforts, or other factors is not fully known. The steady decrease in phencyclidine (PCP) laboratory seizures, however, is attributed to regulation by Congress of the manufacture of the precursor piperidine.

Table 1 identifies the type and numbers of clandestine drug laboratories seized during this period. Brief descriptions of the most popular methods of synthesis used in the five most seized laboratories are presented below.

Methamphetamine

Methamphetamine laboratories comprised more than 50% of all laboratories seized by DEA during the 45-month period. Reports by forensic chemists were available on 190 of the laboratories. One of three methods was used in 70% of the laboratories.

The most popular method of synthesis (over 50%) was the reaction of a mixture of phenyl-2-propanone, methylamine, mercuric chloride, and aluminum metal in alcohol (Fig. 1).

TABLE 1—*Types of numbers of laboratories seized by DEA in the 45-month period before September 1980.*

Laboratory Type	Year of Seizure			
	1978	1979	1980	1981[a]
Methamphetamine	63	121	121	73
Phencyclidine	57	46	46	24
Amphetamine	13	20	23	12
Methaqualone	6	7	14	12
Methylenedioxyamphetamine	3	5	7	1
Cocaine	4	4	4	2
Cannabis (hashish oil and so forth)	5	4	2	2
Other (includes LSD, PCE, PHP, DMT, DET)	3	10	18	19
Total	154	217	235	145

[a]First three quarters.

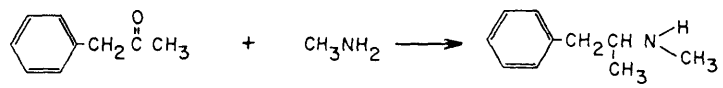

FIG. 1—*Reaction of mixture of phenyl-2-propanone, methylamine, mercuric chloride, and aluminum metal in alcohol to form methamphetamine.*

In the next most popular method (less than 10%), the product of an acetaldehyde/methylamine reaction was refluxed with benzylmagnesium chloride (Fig. 2).

It should be noted that at none of the 16 laboratories using this reflux method was methamphetamine actually synthesized. The reason is that the order in which the precursors are added described in an underground publication entitled *Whole Drug Manufacturer's Catalog Transmittal by Chewbacca Darth* differs from the normal synthesis procedure. The increase in popularity of this method in 1980 is believed to have resulted from regulation of phenyl-2-propanone as a Schedule II controlled substance on 11 Feb. 1980.

The third most popular method of synthesis (also less than 10%) used a Leuckart reaction, refluxing phenyl-2-propanone with either methylamine and formic acid or *N*-methylformamide to form the *N*-formylmethamphetamine intermediate and then refluxing the intermediate with hydrochloric acid to form methamphetamine (Fig. 3).

Six other methods of synthesis have been found with substantially less frequency in laboratories synthesizing methamphetamine. They are:

- Combining phenyl-2-propanone and methylamine and reduce the intermediate 1-phenyl-2-methyliminopropane (eight laboratories) (Fig. 4).
- Hydrogenating ephedrine in acetic acid and perchloric acid with palladium on barium sulfate (six laboratories) (Fig. 5).
- Reacting phenyl-2-propanone and methylamine in the presence of sodium cyanotrihydroborate at slightly acidic pH (three laboratories, with one having also used Method 1) (Fig. 6).

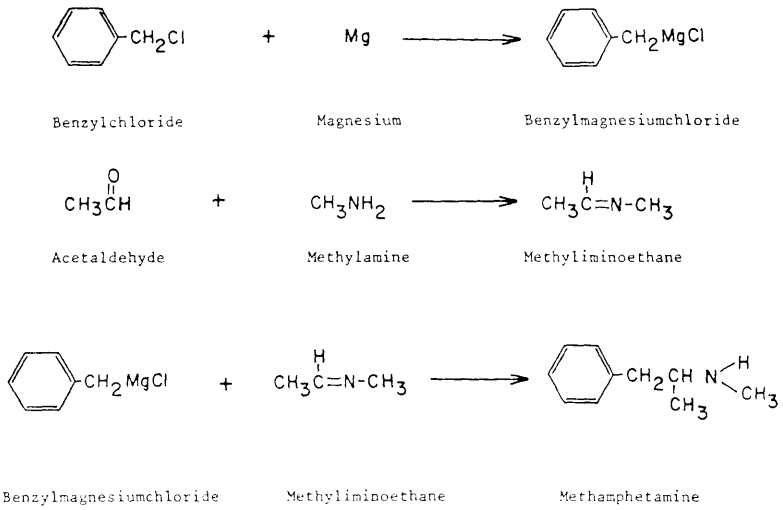

FIG. 2—*The product of an acetaldehyde/methylamine reaction was refluxed with benzylmagnesium chloride to form methamphetamine.*

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Ephedrine

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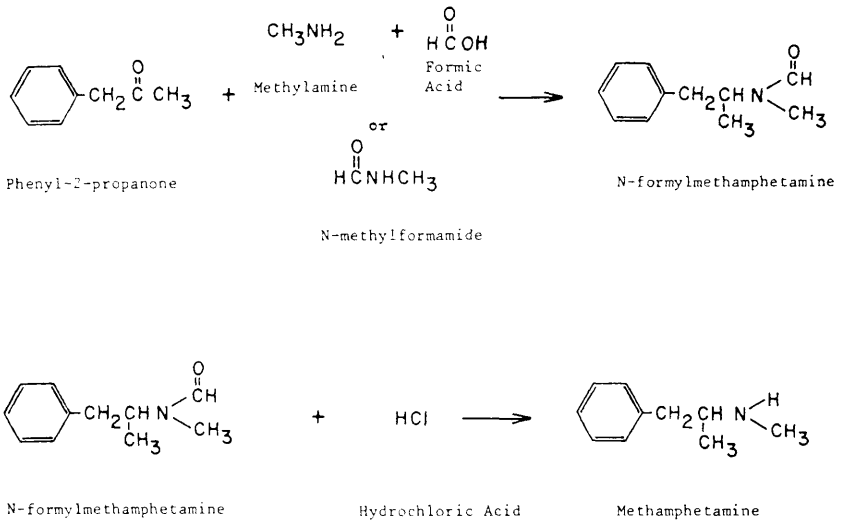


FIG. 3—*Using a Leuckart reaction, P2P is refluxed with either methylamine and formic acid or* N-*methylformamide to form the* N-*formylmethamphetamine intermediate and then refluxed the intermediate with hydrochloric acid to form methamphetamine.*

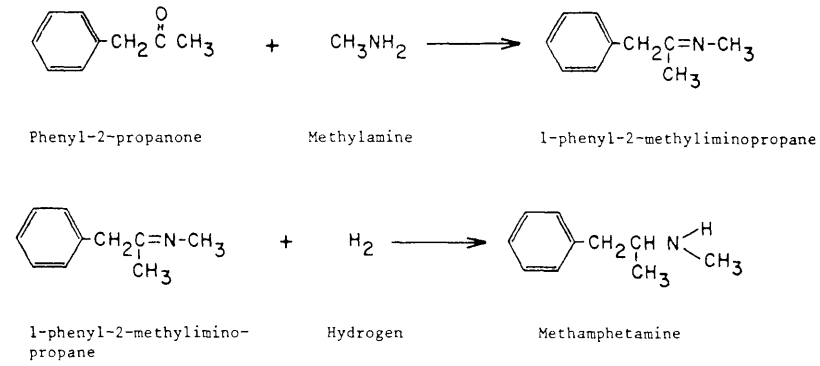


FIG. 4—*Methamphetamine synthesis by combining P2P and methylamine and reducing the intermediate 1-phenyl-2-methyliminopropane.*

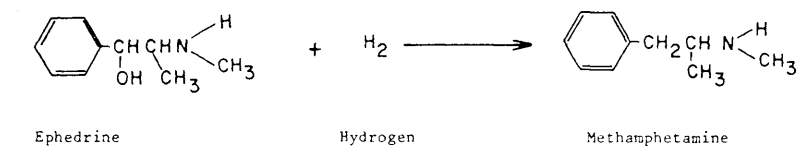


FIG. 5—*Methamphetamine synthesis by hydrogenating ephedrine in acetic acid and perchloric acid with palladium on barium sulfate.*

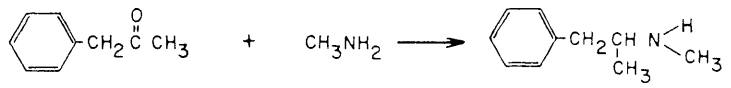


FIG. 6—*Methamphetamine synthesis by reacting P2P and methylamine in the presence of sodium cyanotrihydroborate at slightly acid pH.*

• Extraction of Vicks® Inhaler (two laboratories). It should be noted that the product of this method is the levo isomer only, not the racemic mixture common to all the other syntheses.

• Reaction of ephedrine hydrochloride with phosphorus pentachloride or thionyl chloride to form the 1-phenyl-1-chloro-2-methylaminopropane intermediate, and reduction of the intermediate by one of several methods (two laboratories, one of which also used the other procedure with ephedrine as the starting material) (Fig. 7).

• Reaction of ephedrine and pyridine in the presence of hydrogen iodide and red phosphorus in carbon disulfide to form an intermediate which is reduced to form methamphetamine (one laboratory). This method was observed for the first time in 1981.

Phenyl-2-Propanone

Phenyl-2-propanone (P2P) became a Schedule II controlled substance on 11 Feb. 1980. That change resulted in a significant increase in the number of methamphetamine laboratory operators synthesizing P2P (see Table 2).

The most frequently used method for synthesizing P2P (over 75%) relied on refluxing of phenylacetic acid and acetic anhydride with sodium acetate or pyridine or each. One laboratory was found to be synthesizing its own phenylacetic acid (Fig. 8).

Other methods have been found to be used for synthesizing P2P were:

• Reacting benzyl cyanide, ethyl acetate, and sodium ethoxide to form the intermediate alpha-phenylacetoacetonitrile, which is reacted with sulfuric or phosphoric acid to form P2P (approximately 10%) (Fig. 9).

• Reacting phenylacetic acid and acetic acid in a combustion tube containing a thorium oxide or manganese oxide catalyst (approximately 5%) (Fig. 10).

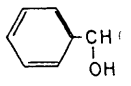
• Reacting benzaldehyde and nitroethane in butylamine to form the 1-phenyl-2-nitropropene intermediate, which is reacted to P2P by refluxing with iron and hydrochloric acid (approximately 4%) (Fig. 11).

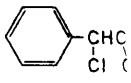
• Reacting magnesium with ethanol in the presence of diethylmalonate to form ethoxymagnesiumdiethylmaleate, adding phenylacetyl chloride, and decomposing the resulting (2-phenylaceto)diethylmalonate with acid to form P2P (the one laboratory using this method was found in 1981) (Fig. 12).

Phencyclidine

During the 45-month period, a total of 173 phencyclidine (PCP) laboratories was seized at a relatively constant rate, until the significant recent reduction. Reports by forensic chemists were available on 73 of the laboratories. Three methods of synthesis were identified.

The first (approximately 47%) involves combining a cyclohexanone/sodium bisulfite aqueous solution with a potassium cyanide/piperidine aqueous solution to form the intermediate 1-piperidino-cyclohexane carbonitrile. The intermediate is then added to a phenylmagnesium bromide Grignard reagent to form PCP (Fig. 13).





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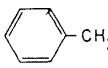

FIG. 9—*Reacting
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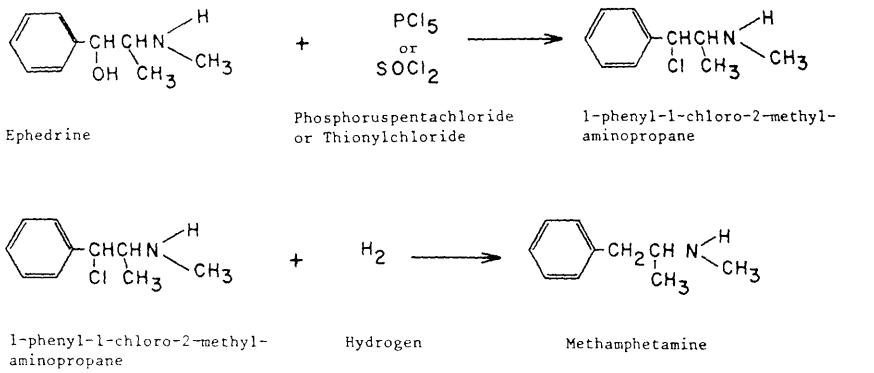

FIG. 7—*Methamphetamine synthesis by reaction of ephedrine hydrochloride with phosphorus pentachloride or thionyl chloride to form the 1-phenyl-1-chloro-2-methylaminopropane intermediate, and reduction of the intermediate by one of several methods.*

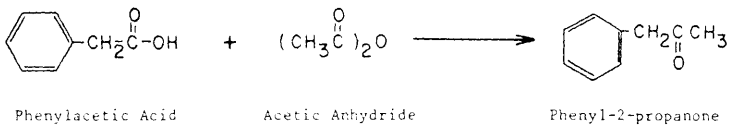

FIG. 8—*Synthesizing P2P by refluxing phenylacetic acid and acetic anhydride with sodium acetate or pyridine or each.*

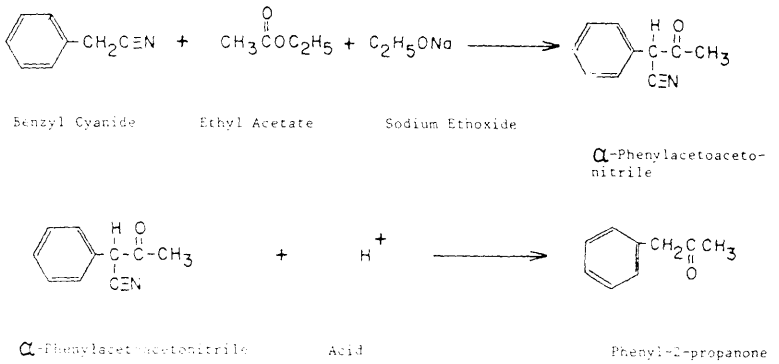

FIG. 9—*Reacting benzyl cyanide, ethyl acetate, and sodium ethoxide to form the intermediate alpha-phenylacetoacetonitrile, which is reacted with sulfuric or phosphoric acid to form P2P.*

TABLE 2—*Increase in synthesis of phenyl-2-propanone.*

Year	No. of Methamphetamine Labs Synthesizing P2P
1978	2
1979	9
1980	26
1981	38[a]

[a]Of the 38 laboratories, 25 synthesized methamphetamine, six (all in 1981) synthesized amphetamine, and six (all in 1981) synthesized P2P only.

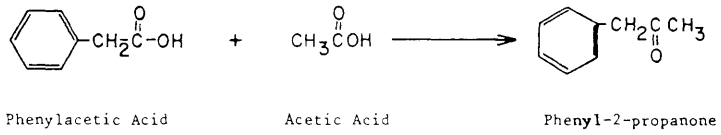

FIG. 10—*Synthesizing P2P by reacting phenylacetic acid and acetic acid in a combustion tube containing a thorium oxide or manganese oxide catalyst.*

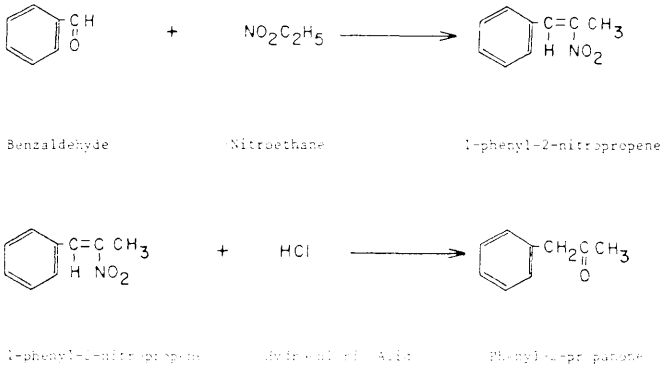

FIG. 11—*Reacting benzaldehyde and nitroethane in butylamine to form the 1-phenyl-2-nitropropene intermediate, which is reacted to P2P by refluxing with iron and hydrochloric acid.*

The second (approximately 37%) involves formation of the 1-piperidinocyclohexane carbonitrile intermediate by reacting piperidine hydrochloride, cyclohexanone, and potassium or sodium cyanide. The intermediate is then added to the Grignard reagent as above (Fig. 14).

A third method, found less frequently (approximately 16%), involves reacting piperidine and cyclohexanone in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene with the azeotropic distillation of water to form 1-(1-cyclohexenyl)-piperidine intermediate. The Grignard reagent is then added to form PCP (Fig. 15).

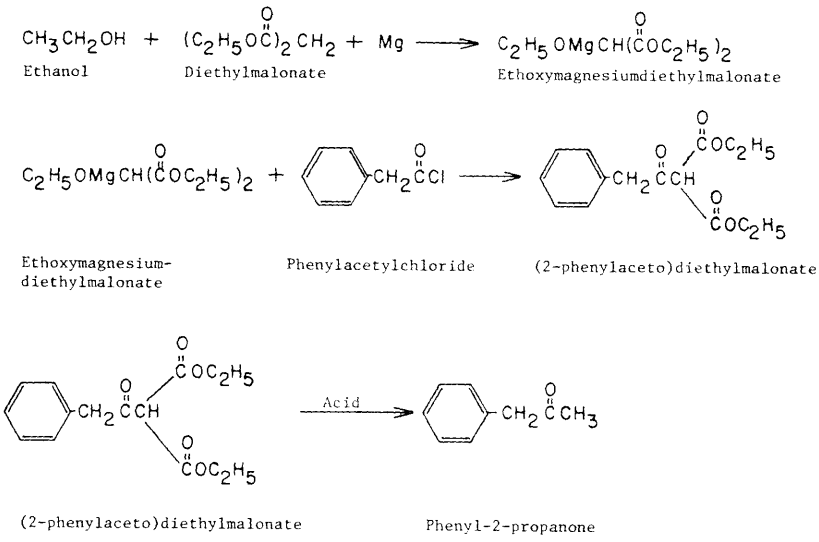

FIG. 12—*Reacting magnesium with ethanol in the presence of diethylmalonate to form ethoxymagnesiumdiethylmaleate, adding phenylacetyl chloride, and decomposing the resulting (2-phenylaceto)diethylmalonate with acid to form P2P.*

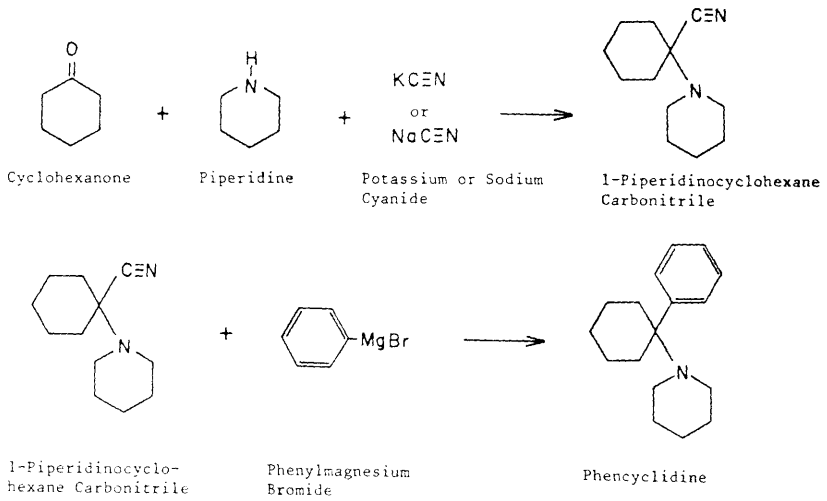

FIG. 13—*Combining a cyclohexanone/sodium bisulfite aqueous solution with a potassium cyanide/piperideine aqueous solution to form PCP.*

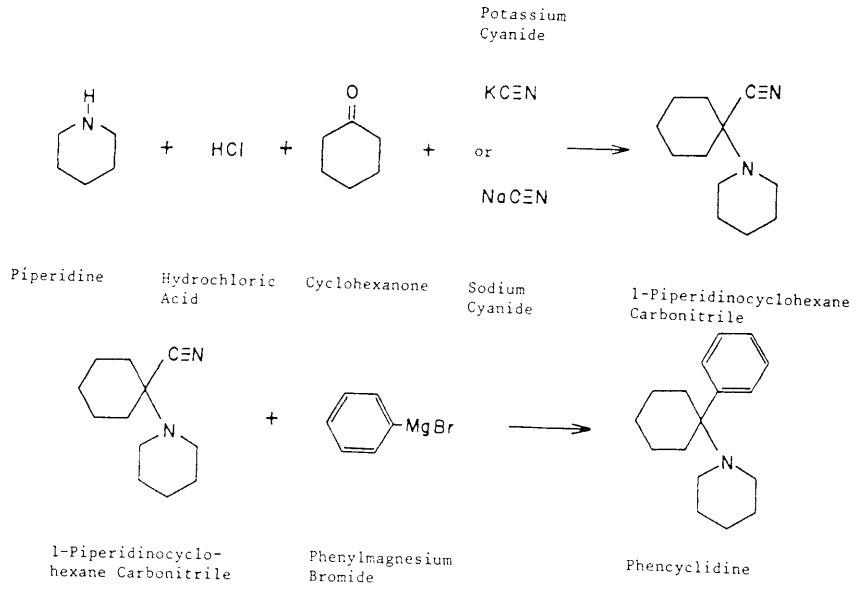

FIG. 14—*Reacting piperidine hydrochloride, cyclohexanone, and potassium or sodium cyanide to form PCP.*

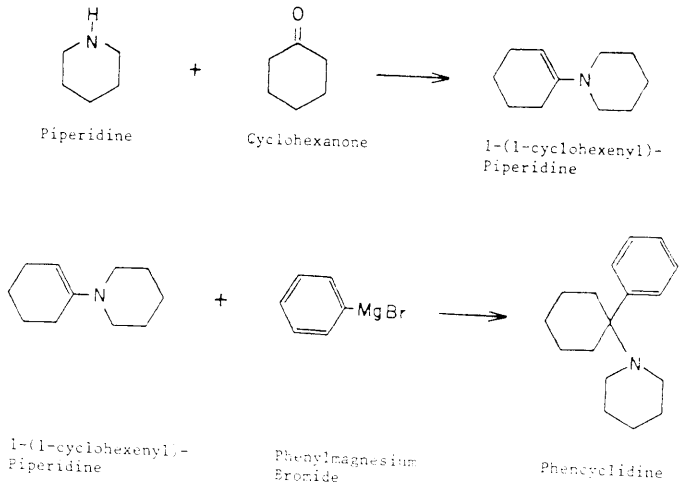

FIG. 15—*Piperidine and cyclohexanone is reacted in the presence of a catalytic amount of* p-*toluene-sulfonic acid in benzene with the azeotropic distillation of water to form 1-(1-cyclohexenyl)-piperidine intermediate. The Grignard reagent is added to form PCP.*

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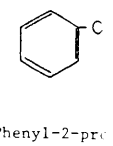
Laboratories



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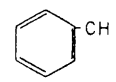

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FIG. 16—*Amph*
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Two additional items regarding PCP laboratories are worthy of note:

1. Although Grignard reagents are commercially available, before 1981 all but one laboratory was found to be synthesizing its own reagent from bromobenzene and magnesium turnings. In 1981, approximately one third of the laboratories utilized commercially available Grignard.
2. Three laboratories were found to be synthesizing piperidine from pyridine. Recently, the DEA established procedures for reporting the purchase of piperidine. This may cause an increase in the use of this synthesis.

Amphetamine

A total of 68 amphetamine laboratories was seized by the DEA during the 45-month period, with the rate showing a steady increase similar to methamphetamine. Reports by forensic chemists were available on 37 laboratories.

Over 70% of the laboratories used the Leuckart reaction, refluxing P2P with ammonium formate or formamide, then adding hydrochloric acid and refluxing again. In 1981, almost 90% of the laboratories used this method (Fig. 16).

Three other methods of synthesis were encountered with significantly less frequency (each approximately 10%):

- Preparation of the 1-phenyl-2-nitropropene intermediate by reacting benzaldehyde and nitroethane in butylamine solution, followed by reduction of the intermediate to amphetamine (Fig. 17).
- Refluxing P2P with hydroxylamine hydrochloride and sodium acetate to form the oxime derivative, then reducing the oxime derivative to amphetamine with lithium aluminum hydride (Fig. 18).
- Reacting a mixture of P2P, ethanol, ammonia, aluminum, and mercuric chloride to form amphetamine (Fig. 19).

Laboratories using the last method were discovered only in 1980.

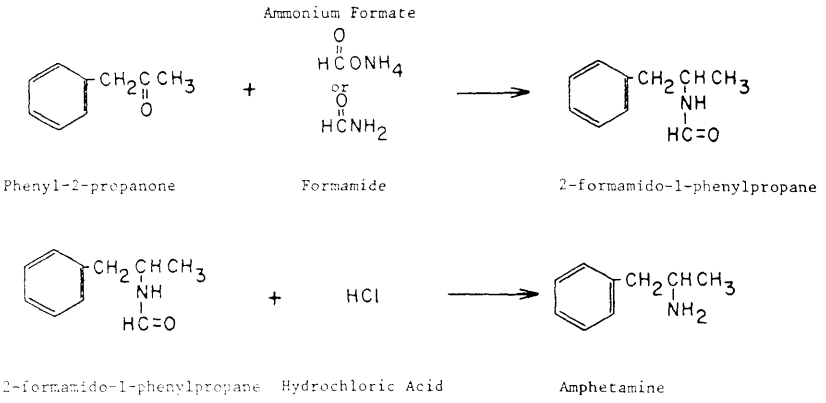

FIG. 16—*Amphetamine made by refluxing P2P with ammonium formate or formamide, then adding hydrochloric acid and refluxing again.*

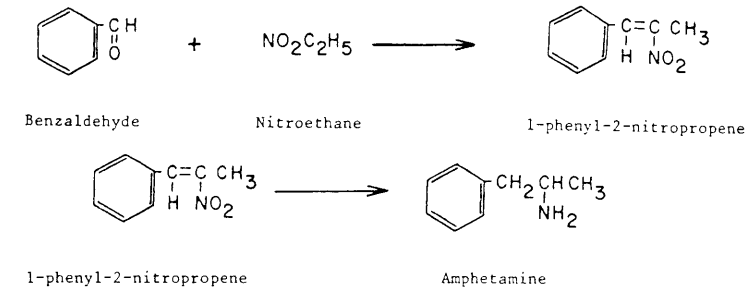

FIG. 17—*Preparation of the 1-phenyl-2-nitropropene intermediate by reacting benzaldehyde and nitroethane in butylamine solution, followed by reduction of the intermediate to amphetamine.*

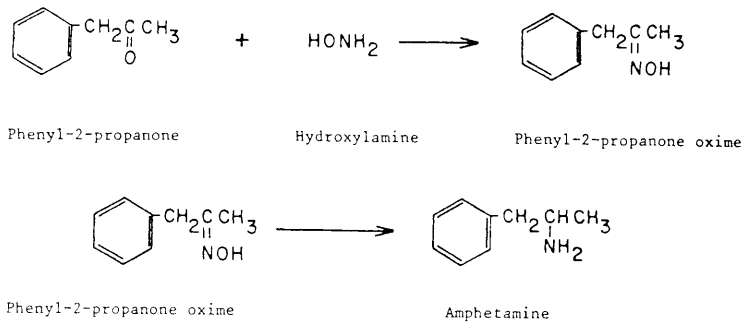

FIG. 18—*Refluxing P2P with hydroxylamine hydrochloride and sodium acetate to form the oxime derivative, then reducing the oxime derivative to amphetamine with lithium aluminum hydride.*

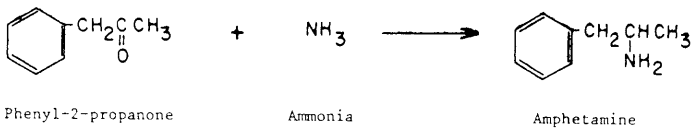

FIG. 19—*Reacting a mixture of P2P, ethanol, ammonia, aluminum, and mercuric chloride to form amphetamine.*

Methaqualone

A total of 39 methaqualone laboratories was seized during the 45-month period, with the rate doubling between 1979 and 1980. Reports by forensic chemists were available on 27 of the laboratories.

The most frequently used method (over 90%), and the only method determined to be used in 1981, involved preparation of *N*-acetylanthranilic acid by reacting anthranilic acid with acetic anhydride. The *N*-acetylanthranilic acid is then refluxed with *o*-toluidine in toluene

with phosphorus trichloride to obtain methaqualone. Phosphorus oxychloride and polyphosphoric acid were used as alternate catalysts, and, in 1981, one laboratory was found using potassium bisulfate as the catalyst. Potassium bisulfate is safer to use but lengthens the reaction time. Another laboratory in 1981 used acetic acid instead of acetic anhydride. Commercially available *N*-acetylanthranilic acid was used in three clandestine laboratories (Fig. 20).

A less frequently used method was forming *o*-toluidine hydrochloride, mixing it in a solid form with *N*-acetylanthranilic acid, and heating the two solids to form methaqualone (Fig. 21). One laboratory operator used a microwave oven to provide the heat.

Methylenedioxyamphetamine

A total of 16 3,4-methylenedioxyamphetamine (MDA) laboratories was seized during the 45-month period. Reports by forensic chemists were available on all 16 laboratories.

The most frequently used method (over 65%) involved reacting isosafrole with a mixture of hydrogen peroxide and formic acid to form the 1-(3,4-methylenedioxyphenyl)-2-propanone intermediate. The intermediate was then reacted with formamide or ammonium formate and then hydrochloric acid to form MDA (Fig. 22).

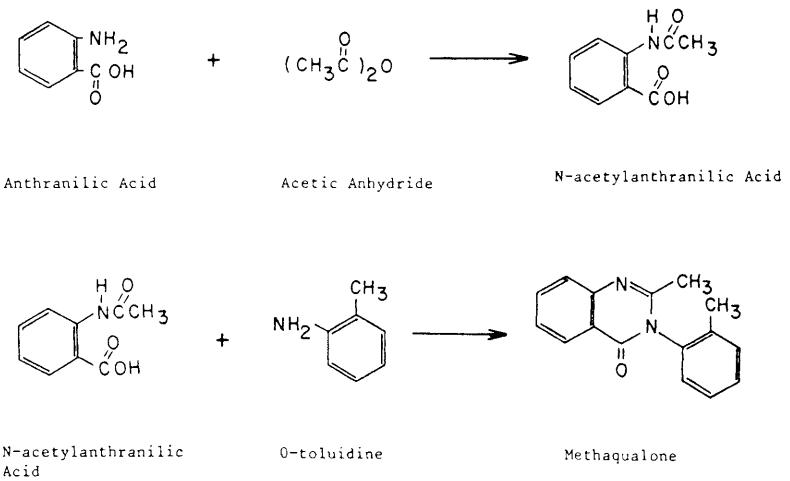

FIG. 20—*Preparation of* N-*acetylanthranilic acid to obtain methaqualone.*

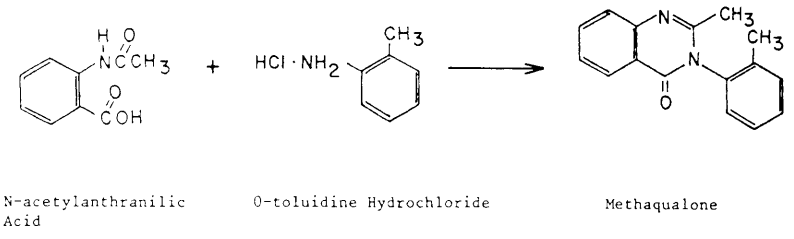

FIG. 21—*Methaqualone was formed by mixing o-toluidine hydrochloride in a solid form with* N-*acetylanthranilic acid and heating the two solids.*

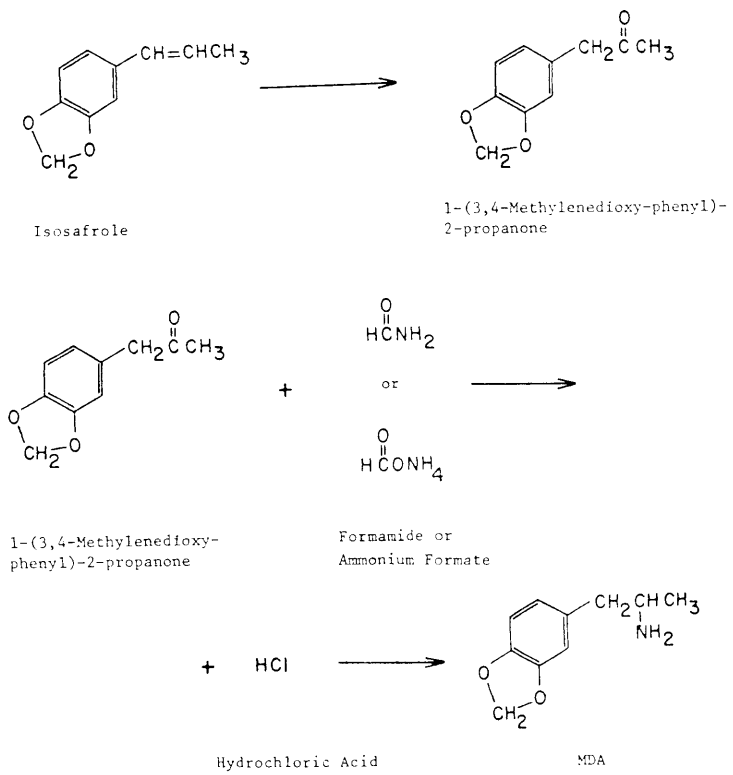

FIG. 22—*MDA formation with isosafrole and a mixture of hydrogen peroxide and formic acid.*

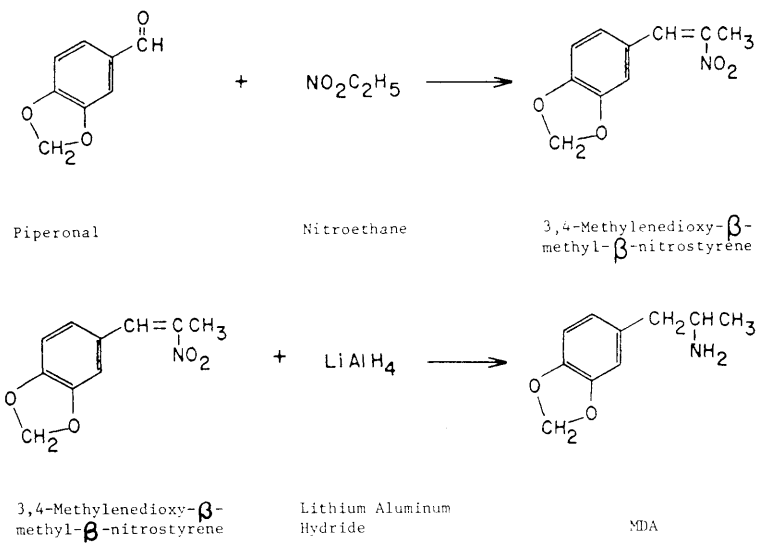

FIG. 23—*MDA formation with a mixture of piperonal, nitroethane, ammonium acetate, and acetic acid.*

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A second method involves refluxing a mixture of piperonal, nitroethane, ammonium acetate, and acetic acid to form 3,4-methylenedioxy-beta-methyl-beta-nitrostyrene intermediate. The intermediate was then refluxed with lithium aluminum hydride to yield MDA (Fig. 23).

Summary

The drugs of choice produced in the United States by clandestine laboratory operators are methamphetamine, phencyclidine, amphetamine, methaqualone, and 3,4-methylenedioxyamphetamine. Although a number of synthesis methods are available in the chemical literature, only the methods reviewed above have been found to be actually used in clandestine laboratories in the United States.

Acknowledgments

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