Clandestine Manufacture of Amphetamine from Benzaldehyde: An Investigative Analysis of its Synthesis

This thesis is presented to the Centre for Forensic Science of The University of Western Australia as a part of the requirements for the degree of Master of Forensic Science.

The work recorded in this thesis was carried out during 2000 to 2001 at the Chemistry Centre of WA under the supervision of Dr D. Reynolds and at the University of Western Australia under the supervision of Associate Professor E.L. Ghisalberti.

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I dedicate this thesis to my parents
whose love and belief in my ability
has been steadfast.

Acknowledgments

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I would like to thank everybody in the Forensic Science Unit (WA) and the Chemistry Centre (WA) for generously giving up their time to answer my questions.

Finally, my sincerest gratitude to my family for their continued support throughout my years of study.

Abstract

A number of chemicals from clandestine amphetamine laboratories were seized in Perth, Western Australia. A common element to all of these laboratories was the chemicals and 'homemade' equipment used. Two of the chemicals recovered from the laboratories, ammonium carbonate and zinc, are not normally associated with amphetamine manufacture. Typed and hand written 'recipes' were also found at two of the laboratories. The research described here is concerned with an investigation of the possible synthetic routes employed in the manufacture of amphetamine. The variation in yields with varying reaction conditions has also been examined. The likely role of ammonium carbonate and zinc in the sequence is suggested and the use of alternative, easily obtainable reagents in some reactions has been considered. This information can be used to provide a more accurate estimation of the yield of this reaction for court proceedings, and to determine past and future production, an aspect which is crucial in the sentencing of manufacturers of illicit drugs.

Abbreviations used in the text

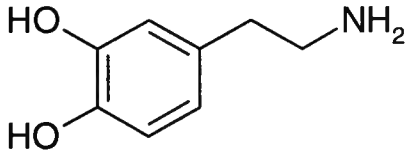
ABCI	Australian Bureau of Criminal Intelligence
ACT	Australian Capital Territory
AFP	Australian Federal Police
Adrenalin	Epinephrine
Amphetamine	*2-Amino-1-phenylpropane*
b.p.	boiling point
CDL	Clandestine drug laboratory
Dopamine	*4-(2-Aminoethyl)-1,2-benzenediol*
Ephedrine	*1-Phenyl-1-hydroxy-2-(aminomethyl)propane*
Eq	equivalents
FT-IR	Fourier Transform Infrared Spectroscopy
GC-MS	Gas Chromatography Mass Spectrometry
HPLC	High Performance Liquid Chromatography
Pseudoephedrine	*1-Phenyl-1-hydroxy-2-(aminomethyl)propane*
MDA	*3,4-Methylenedioxyamphetamine*
MDMA	*3,4-Methylenedioxymethylamphetamine*
Methylamphetamine	*1-Phenyl-2-(aminomethyl)propane*
mol	moles
mmol	milli moles
m.p.	melting point
Noradrenaline	*(R)-4-(2-amino-1-hydroxyethyl)-1,2–Benzenediol*
P2P	*1-Phenyl-2-propanone*
PVC	Polyvinylchloride
TFA	Trifluoroacetic acid

Contents

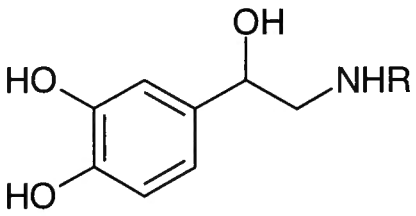
Chapter One

1. Introduction

Amphetamines are potent psychomotor stimulants that directly affect the central nervous system (CNS). Their use causes a release of excitatory neurotransmitters dopamine and noradrenaline from storage vesicles in the CNS. The generic term "amphetamines" is used to describe compounds that incorporate the phenylethylamine pharmacophore, and includes drugs such as pseudoephedrine, phentermine, dextroamphetamine, methylamphetamine, methylenedioxyamphetamine (MDA) and ecstasy (MDMA). Some of these have become popular drugs of abuse and thus, targets for clandestine laboratories for over 50 years.[1] Particular amphetamines can be acquired legally by prescription, however their medical uses are limited and include the treatment of respiratory congestion, childhood hyperactivity, obesity and narcolepsy, a rare disorder in which persons often lapse into deep sleep.

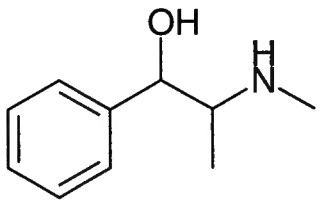


Dopamine

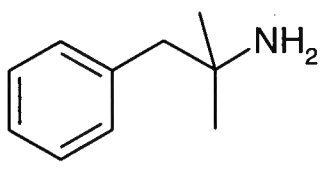


R= H, Noradrenaline

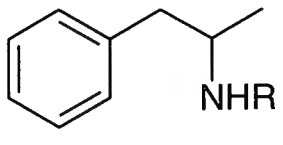
R=CH_3, Adrenaline



Pseudoephedrine

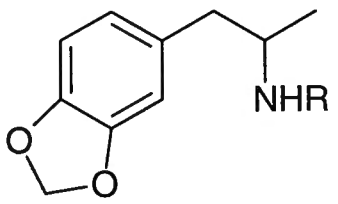


Phentermine



R=H, Amphetamine

R=CH_3, Methylamphetamine



R=H, MDA

R=CH_3, MDMA

1.1. Effects of amphetamine use

Since the mid-1980s, illicit use of amphetamines has remained a significant problem in Australia.[2] Amphetamines are the most commonly used illicit drugs after cannabis, with approximately 9% of the population having used them. They are particularly common among younger groups, as many as 21% of 20 to 29 year olds have become long term users.[2]

Amphetamines can be administered orally, by inhalation or intravenous injection. High doses of amphetamines, especially by injection, can result in a form of schizophrenic paranoid psychosis, delusions and hallucinations.

However psychosis is not the only psychological outcome associated with regular amphetamine use. High proportions of users demonstrate symptoms such as anxiety, panic attacks, paranoia and depression. The emergence of such symptoms is associated with injection of the drugs, greater frequency of use and dependence upon amphetamines.[1] The estimated direct health care cost of drug dependence and harmful use of drugs in Australia in 1992 was $1.0 billion, of which $43 million is the cost arising from the use of illicit drugs.[3]

1.2. Amphetamine seizures

During 1999-2000, Australian Customs seized 21.5 kilograms of amphetamines destined for the Australian market. Although the number of seizures (60) were nine less than those recorded for the previous year[4], the average weight of amphetamine per seizure increased from 145 grams to 358 grams.

Despite further seizures in 2000/01 by the Australian Federal Police (AFP) of amphetamine–type substances totalling 412 kg, of which 152 kg was methylamphetamine (Ice)[5], large quantities of amphetamines continues to be produced domestically. Domestic seizures of amphetamines during 1999-2000 totalled 4861 (where the drug weight was recorded), in which 381.3 kg were recovered, an increase of 124.4 kg on the previous year (1998-1999).[4]

The samples of amphetamine seized in Australia is generally of low quality. Forensic analysis of samples seized in 1999-2000 revealed that the amount of amphetamine varied between 1 to 65 %.[4] These results relate to unrepresentative sample, since samples of drugs seized are analysed for forensic purposes only in contested court cases.

1.3. Clandestine laboratories seizures

A Clandestine Drug Laboratory (CDL), by definition, is an illicit operation consisting of sufficient combination of apparatus and chemicals that either have been or could be used in the manufacture or synthesis of prohibited drugs.[6] Such operations are potentiality hazardous to the operator, neighbours, investigators and to the environment. Police intelligence continues to link organised crime groups - among them outlaw motorcycle gangs (OMCG) - to the manufacture and distribution of amphetamine–type substances.

The Australian Bureau of Criminal Intelligence (ABCI) has reported that the number of importations of amphetamines to Australia has decreased in recent years. This could indicate that domestic production has increased, lessening the demand for costly and high-risk imported substances. Statistics from Australian law enforcement agencies, for the period 1997-2000, show that the number of seizures of clandestine laboratories increased from 95 in 1997-1998 to 150 in 1999-2000. The greatest number of clandestine laboratories were found in Queensland (Table 1).[4] The popularity of these laboratories is due, in part, to the fact that amphetamine is easy to manufacture and the starting materials are relatively inexpensive.

Table 1: Clandestine laboratory seizures, by State and Territory (1999-2000)

State/Territory*							
New South Wales	Victoria	Queensland	South Aust	Western Aust	Northern Territory	ACT	Total
20	**18**	**79**	**14**	**17**	**1**	**1**	**150**

*Note: No clandestine laboratories were found in Tasmania (Source: ABCI).

1.4. Health and Safety

Frequently, it is found that operators in clandestine laboratories have little knowledge or experience in chemistry. Thus, they face risks from corrosive chemicals, toxic chemicals, fires and explosions. However, due in part to this inexperience, the illicit manufacture of amphetamine also poses a risk to the end users, because the final product is often contaminated with starting materials, by-products, and cutting agents or diluents.

There are many controlled drugs that can be synthesised in clandestine laboratories and a multitude of different methods of synthesis. An aim of the present work was to investigate methods, assumed or found to have been used recently at a number of clandestine laboratories. Such information is of forensic importance. Each clandestine laboratory is unique and presents different types of hazards. If the type of chemical reaction used is known, it may be possible to avoid or reduce the risk of exposure to both chemical and physical hazards that may be encountered by investigators. The forensic chemist must be able to recognise reactions in progress and how to safely handle them. A hazardous situation must be dealt with immediately and safely.

1.5. Prosecution

The offence of manufacturing or preparing a prohibited drug is covered in the *Misuse of Drugs Act*, section 6(1)(b), in Western Australia. If the product seized already exists within the original substance (eg ephedrine/pseudoephedrine is extracted from Sudafed with methylated spirits), then the offence is classed as a step taken in the preparation. If a chemical process is used to convert a particular chemical to another substance (eg 1-phenyl-2-propanone to amphetamine), then this is classed as a step in the manufacture of a prohibited drug.[6] Forensic chemists have a role in identifying reagents and precursors found in clandestine laboratories. They must be able to demonstrate that a particular drug was being synthesised, to explain fully in court all steps in the synthesis and to disregard items of little or no evidentiary value.

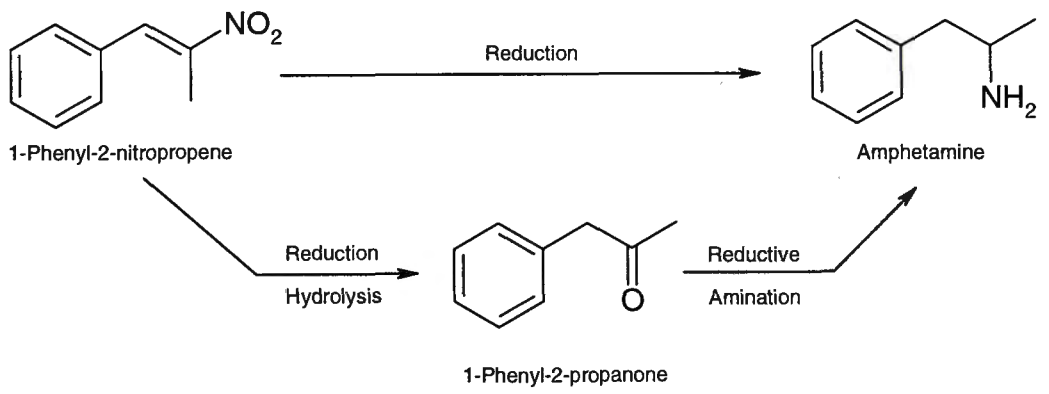
The successful prosecution of clandestine laboratory operators depends on the forensic chemist's thorough knowledge of the manufacturing procedure. Frequently, the synthetic route used can be inferred from evidence of purchase of the chemical precursors. Establishing the link between the purchase of these chemicals and those found on the laboratory premises can be important to the prosecution.

The identification of by-products present in a sample of an illicit drug can be extremely useful in establishing the method of synthesis used. If no finished product is available, then analysing the seized unwashed laboratory equipment, residues and liquids can provide the characteristics of the precursors used, by-products formed and indicate traces of final product. This information often allows verification that a controlled substance was being manufactured, or that an attempt was made for its production. This "chemical fingerprinting" yields valuable information on the reaction sequence used and on the expertise of the operator.

1.6. Manufacturing methods

A variety of synthetic methods for the production of amphetamine-type compounds are available. One of the most common methods employed by clandestine laboratory operators in Western Australia for the manufacture of amphetamine, has been the reductive amination of 1-phenyl-2-propanone (P2P) *via* the Leuckart reaction.

Scheme 1



This approach involves the use of the precursor 1-phenyl-2-nitropropene (β-methyl-β-nitrostyrene). This precursor may be synthesised from benzaldehyde and nitroethane and converted directly to amphetamine under reducing conditions, or used to synthesise P2P (Scheme 1).

1.7. Case Report

Clandestine Drug Laboratory Specialists assisted the Western Australian Police Service in the seizure of a suspected amphetamine laboratory located in Perth. During an examination of documents located at a number of premises, handwritten and typed 'recipes' for the manufacture of amphetamine were found. In conjunction with the precursors and chemicals discovered on the site, and intermediates detected upon analysis, it was possible to determine that a novel method was being used to manufacture amphetamine.

The items seized from one crime scene included round bottom flasks, 20 L stainless steel reaction vessels and homemade condensers (PVC tubing with glass or copper used for internal liner and common garden hose fittings for plumbing). Reagents and solvents included 20 L drums of glacial acetic acid, toluene and formic acid, ammonium carbonate (10 kg) and zinc powder (500 g). Precursors and intermediates consisted of benzaldehyde (16 L), nitroethane (2.5 L), 1-phenyl-2-nitropropene (1.4 kg) and 1.0 L of liquid identified as 1-phenyl-2-propanone. N-formylamphetamine and amphetamine were present in a separatory funnel.

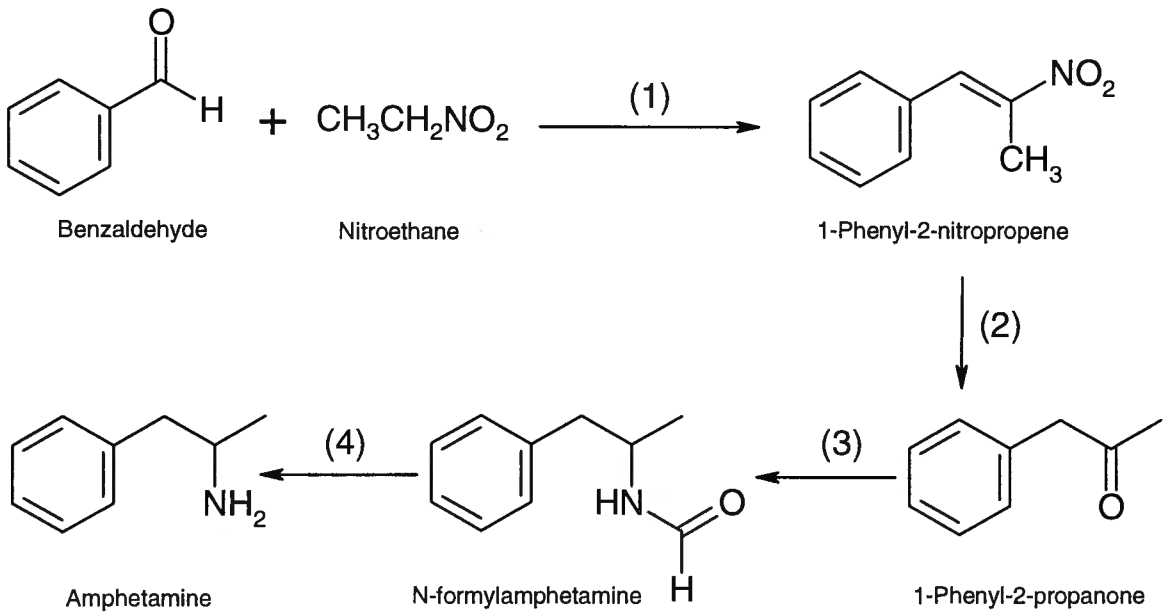
Based on the items seized and 'recipes' for the process, it was calculated that 1.4 kg of 1-phenyl-2-nitropropene would yield 500 g of amphetamine hydrochloride. In addition, 16 g of amphetamine was identified in the separatory funnel and could be recovered by separation and crystallisation as the hydrochloride salt. It was estimated that approximately 6 kg of amphetamine hydrochloride could be produced from 16 L of benzaldehyde available.

1.8. Research Objectives

The research presented in this thesis was undertaken for the purposes of establishing the synthetic processes employed in a number of clandestine laboratories. This information is useful in linking an illicit laboratory to seized material and also in providing information on precursors and expertise involved in the production. It can also allow the overall yield of the process to be estimated. This is important in determining past and future production, an aspect which is crucial for court proceedings and for sentencing purposes.

At a number of clandestine laboratories, some of the chemicals seized were not normally associated with the manufacture of amphetamine. The likely use of these chemicals needed to be established. The manufacturing process selected may reflect the operator's desire to avoid chemicals that are likely to be monitored at chemical supply companies by law enforcement agencies, and to substitute these chemicals with those which attract less attention. The possibility that other reagents could be used in some of these reactions was examined.

Scheme 2



In this thesis, the manufacturing process shown in Scheme 2 is considered in some detail. Each step is considered in individual chapters and the more significant findings are summarised in a separate chapter.

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Chapter Two

2. Syntheses of 1-Phenyl-2-nitropropene

Nitroalkenes are readily synthesised in good yields.[1] Using aromatic aldehydes, nitroalkenes can be prepared in a single step as shown in Scheme 1. These nitroalkenes have proven to be useful for the facile production of the homologous ketones.

Scheme 1

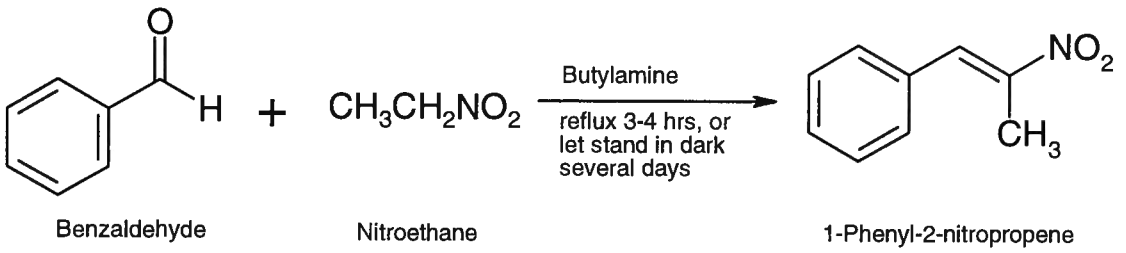
$$ArCHO + RCH_2NO_2 \xrightarrow[\text{amine}]{\text{Primary}} ArCH{=}C(NO_2)R$$

Although this reaction was first carried out using zinc chloride as an acid catalyst, bases such as alcoholic potassium hydroxide or alcoholic methylamine have normally been used.[2] Condensation of benzaldehyde with nitroethane using zinc chloride as a catalyst afforded 1-phenyl-2-nitropropene in 56% yield. A similar yield (52%) was obtained when benzaldehyde and nitroethane, in 1:1.5 molar ratio, were allowed to react in the presence of 5% methanolic methylamine at room temperature for 3-7 days. Heating the solution produced amounts of high melting polymers and reduced the yield. A slightly higher yield (64%) was obtained by heating an ethanolic solution of equimolar amounts of benzaldehyde and nitroethane in the presence of 0.05 mol eq. of butylamine for 8 hr.[1]

Ammonium acetate in acetic acid has also been used to achieve this reaction. Refluxing an acetic acid solution of the reactants and ammonium acetate (0.5 mol eq.) for 2 hr afforded the product in 55% yield. The relatively high solubility of the product in acetic acid might explain the lower yield. The use of butylamine[3] or amylamine[4] as catalysts has been reported (Scheme 2). With 0.1 mol eq. of amylamine, a mixture of benzaldehyde and nitroethane allowed to stand in the dark for 14 days afforded 1-phenyl-2-nitropropene in 75% yield.[4]

A two step approach to the synthesis of the nitroalkene did not improve the yield. In this reaction, the imine was first prepared by heating benzaldehyde with butylamine in benzene. Acetic acid and one equivalent of nitroethane were added to the imine and the mixture was heated under reflux for 1 hr to give the nitroalkene in 61% yield.[5]

Scheme 2



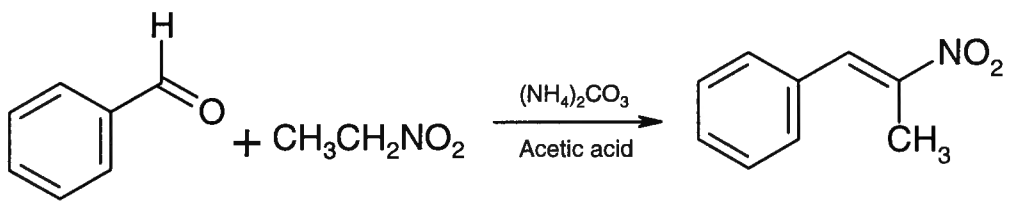
Benzaldehyde Nitroethane 1-Phenyl-2-nitropropene

2.1. Western Australian method

Over the past three years in Western Australia (WA), four clandestine laboratories where amphetamine was being produced were uncovered. Similar chemicals were seized from each of these laboratories: benzaldehyde, nitroethane, ammonium carbonate, formic acid, acetic acid and zinc powder. A minimum amount of glassware was found and the equipment used was often homemade.

The aim of the work described in this section was to establish the method(s) used for the first step in the preparation of amphetamine, to determine the possible yield and plausible variations. It was assumed that benzaldehyde and nitroethane were condensed using ammonium carbonate in acetic acid as the catalyst. Large quantities of ammonium carbonate (10 kg) and acetic acid (20 L) were found at a number of sites.

Scheme 3



Benzaldehyde Nitroethane 1-Phenyl-2-nitropropene

2.2. Results and Discussion

The yields of 1-phenyl-2-nitropropene obtained from the reaction of benzaldehyde and nitroethane with ammonium carbonate as the catalyst were determined for various concentrations of the three components (Table 1). For comparison, the effect of using butylamine as the catalyst was also investigated. A method described in a 'recipe' seized at a clandestine site, but obtained after most of the work described here was completed, was also repeated. In each case, the progress of the reactions was monitored by GC-MS analysis.

Table: 1-Phenyl-2-nitropropene

Benzaldehyde	Nitroethane	Catalyst	Reaction Time (Hours)	Yield (%)
0.1 mol	0.1 mol	0.01 mol eq.$(NH_4)_2CO_3$	2	22.5
0.92 mol	0.92 mol	0.01 mol eq. $(NH_4)_2CO_3$	2	47
75 mmol	50 mmol	0.25 mol eq. $(NH_4)_2CO_3$	6	54
0.15 mol	0.1 mol	0.25 mol eq. Butylamine	3	53
0.03 mol	0.02 mol	0.1 mol eq. Butylamine	4	62
97 mmol	98 mmol	0.25 mol eq. $(NH_4)_2CO_3$	1	39*

* Method followed from an actual recipe seized at a clandestine laboratory site.

In the first reaction, 0.01 mol eq. of ammonium carbonate was added to equimolar (0.1 mol) amounts of benzaldehyde and nitroethane in acetic acid. The mixture was heated under reflux for 2 hr, although GC-MS analysis indicated that the reaction was essentially complete after 1 hr. Recovery of the product afforded 1-phenyl-2-nitropropene in 22.5% yield. The product was characterised by ^{1}H-NMR and FT-IR spectroscopy (Fig. 1 and 5, appendix), and from the melting point. As expected, the double bond has the *E*-configuration. This is deduced from the chemical shift of the vinylic proton at δ 8.1, in agreement with that observed for the *E*-isomer and not for that observed (δ 6.3) for the *Z*-isomer.[6]

This reaction was repeated on a ten-fold scale and the yield of the product recovered increased to 47%. The increase in yield probably reflects the relatively smaller loss of material in a large scale reaction.

A third experiment was carried out using benzaldehyde and nitroethane in a 1.5:1 ratio. The amount of catalyst was increased to 25% and the reaction was allowed to proceed for 6 hours. This afforded 1-phebnyl-2-nitropropene in 54% yield

Reactions using the same ratio of reactants and 0.25 mol eq. and 0.1 mol eq. of butylamine afforded the product in 53% and 62% yields, respectively. The yield in the second of these experiments is in good agreement to that (64%) obtained by Hass *et al.*[2] using 5% butylamine as catalyst.

The final experiment was based on a method described in a 'recipe' seized at a clandestine laboratory site. Benzaldehyde, nitroethane and ammonium carbonate were combined in a molar ratio of 1:1:0.25 in excess acetic acid. The mixture was heated under reflux for 1 hr. Work-up gave the nitroalkene in 39% yield.

There were a number of differences in the clandestine synthesis compared to the laboratory synthesis. In the clandestine synthesis, ammonium carbonate was first added to acetic acid, followed by nitroethane. It was emphasised that benzaldehyde be added last. After heating for 1 hr, the mixture was poured into a bucket containing crushed ice. Once the ice had melted, the water was decanted. The thick yellow oil remaining at the bottom of the bucket was poured into a Buchner funnel where it crystallised on attempted filtration. In the large-scale laboratory synthesis, comparable amounts of nitroalkene (42%) could be recovered from the first crop of crystals. An additional 12% could be obtained by extraction of the mother liquor by extraction with toluene. For clandestine purposes, recovery of this extra material is not worth the extra level of sophistication needed. Thus, an extraction solvent such as toluene, separatory funnels (expensive and cumbersome to use for large-scale preparations), drying agents and methods for removal of the solvent, are not required.

2.3. Conclusion

Benzaldehyde, nitroethane and ammonium carbonate in acetic acid heated under reflux was found to produce 1-phenyl-2-nitropropene in a yield comparable to that obtained using catalysts such as butylamine. Presumably, the catalyst involved is ammonium acetate. The best yield for this reaction was achieved using the three compounds in a 1.5:1.0:0.25 ratio and heating under reflux for 6 hr. The nitroalkene was obtained in 54% yield with respect to nitroethane. GC-MS analysis showed that the maximum yield was achieved after 1 hr.

The clandestine method required benzaldehyde, nitroethane and ammonium carbonate in a molar ratio 1:1:0.25 and heating under reflux for 1 hr. The product, obtained in 39% yield, is relatively pure and can be used in the next step without the need for purification. Higher recovery of the product is sacrificed in order to simplify the procedure. The simple nature of this reaction means that unskilled operators can successfully produce this intermediate for the production of amphetamine. Ammonium carbonate, which is not a chemical closely monitored by law enforcement agencies, and acetic acid offers a suitable and inexpensive substitute for butylamine as a catalyst in the production of 1-phenyl-2-nitropropene.

Initially it was planned to apply some form of simplex optimisation[7,8,9] to the experiments in order to achieve the optimal yield. The object of the experiment is to optimise the relative yield of 1-phenyl-2-nitropropene by simultaneously varying the molar ratio of reactants and the relative reaction time applying statistical analysis to the results.

Unfortunately this rationale could not be explored and a more conventional approach to optimisation, by varying one factor at a time, may have been more appropriate in the course of these experiments. Nonetheless reasonable estimates for the optimum conditions have been established through the experiments described in this thesis.

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Chapter Three

3. Syntheses of 1-Phenyl-2-propanone

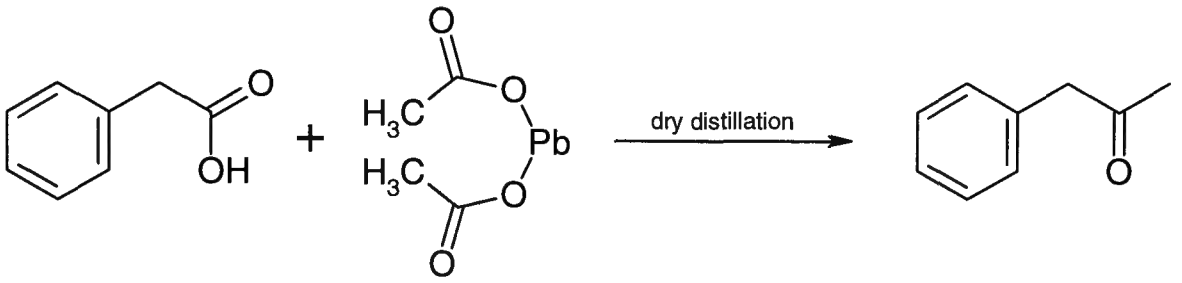
The sale and supply of chemicals known to be used in the illicit manufacture of drugs is restricted. 1-Phenyl-2-propanone (P2P) was included in the Seventh Schedule controlled substance *Poisons Act* of Western Australia in August 1992. As a result of agreements with the chemical supply industry all persons wanting to purchase chemicals that can be used in the synthesis of illicit drugs are required to fill in an End User Declaration (EUD) and must provide proper identification showing current residency, as well as a full explanation for the request. All transactions involving the sale or transfer of these chemicals may be reported to law enforcement agencies. As a result of these tighter controls placed on 1-phenyl-2-propanone, illicit drug chemists are denied ready access to this starting material. It is therefore likely that most clandestine laboratories engaged in reductive amination reactions in Australia now use homemade 1-phenyl-2-propanone.[1]

3.1. Methods of manufacture

Various methods for the synthesis of 1-phenyl-2-propanone have been reported in the literature. The most common of these used in clandestine laboratories are listed below:

- Distillation of a mixture of lead salts of phenylacetic and acetic acids.[2]
- Pyrolysis of phenylacetic acid and acetic acid over thorium oxide.[3]
- Treatment of phenylacetic acid with acetic anhydride, and sodium acetate or pyridine.[4]
- Hydrolysis of α-phenylacetoacetonitrile with sulfuric acid.[5]
- Friedel-Crafts alkylation of benzene with chloroacetone.[6]
- Reduction of 1-phenyl-2-nitropropene in the presence of iron, ferric chloride and hydrochloric acid.[8]

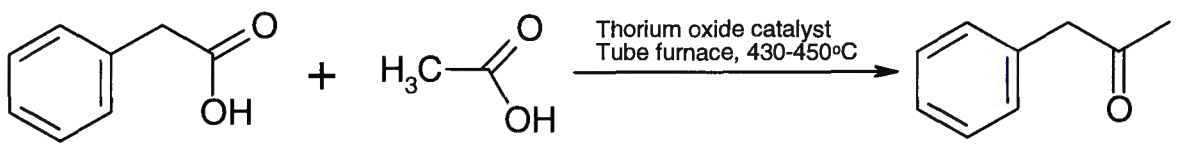
Scheme 1



Phenylacetic acid | Lead (II) Acetate | 1-Phenyl-2-propanone

The dry distillation of equimolar amounts of phenylacetic acid and lead acetate over a direct flame, followed by distillation of the product, provides 1-phenyl-2-propanone in 36% yield (Scheme 1). [2]

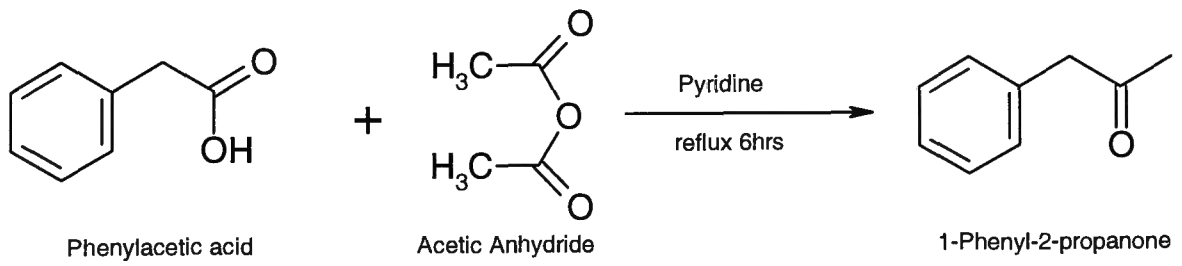
Scheme 2



Phenylacetic acid | Acetic acid | 1-Phenyl-2-propanone

1-Phenyl-2-propanone can also be produced by reacting phenylacetic acid and acetic acid (1:2 molar ratio) in a combustion tube containing a thorium oxide catalyst (Scheme 2). After fractional distillation of the product, a yield of between 55 and 65% can be obtained. [3]

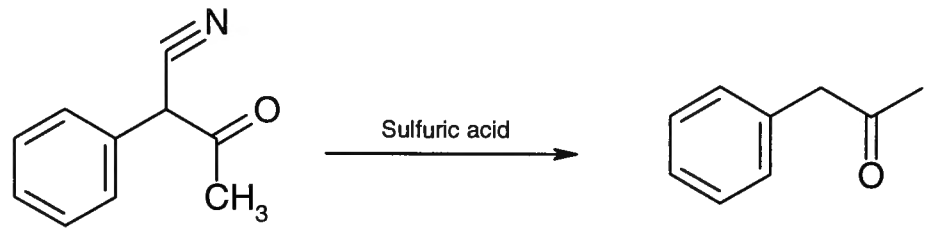
Scheme 3



Phenylacetic acid | Acetic Anhydride | 1-Phenyl-2-propanone

Reaction of phenylacetic acid with excess acetic anhydride and pyridine under reflux for six hours gave, after fractional distillation, 1-phenyl-2-propanone in 56% yield (Scheme 3). [4]

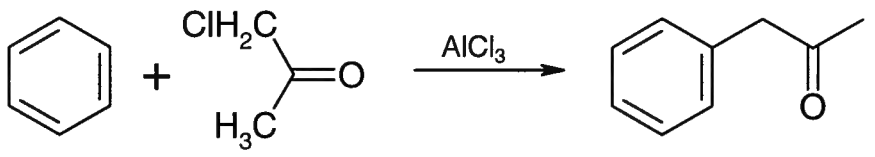
Scheme 4



alpha-Phenylacetoacetonitrile 1-Phenyl-2-propanone

Hydrolysis of α-phenylacetoacetonitrile with aqueous sulfuric acid gave 1-phenyl-2-propanone in 77-86% yield (Scheme 4).[5]

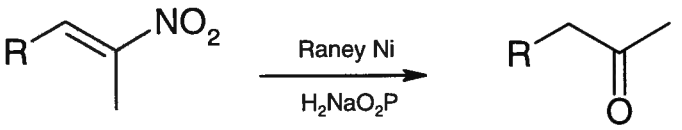
Scheme 5



Benzene Chloroacetone 1-Phenyl-2-propanone

Friedel-Craft alkylation of benzene with chloroacetone also yields 1-phenyl-2-propanone. Chloroacetone in benzene is treated with 2 molar equivalents of aluminium chloride under reflux for five hours. The mixture is extracted with benzene and then distilled. 1-Phenyl-2-propanone is recovered from the distillate *via* the sodium bisulphite addition product, followed by steam distillation. The distillate is extracted with ether, the ether evaporated and vacuum distilled to give a 32% yield of 1-phenyl-2-propanone (Scheme 5).[6]

Scheme 6

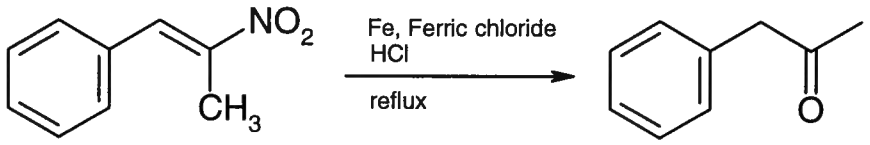


Nitroolefin Ketone

The reduction of nitroolefins with metals, followed by hydrolysis, provides ketones in excellent yield. A general procedure has been described by Monti *et al.*[7] A suspension of Raney nickel and an aqueous solution of sodium hypophosphite is added

(in several portions under stirring) to a solution of the nitroolefin in ethanol-aqueous acetate buffer. After 2 hours at 40-60° C the catalyst was filtered off, water added and the solution extracted with ether. Evaporation of the solvent yields the carbonyl compound, which is purified by distillation. The reduction of 1-phenyl-2-nitropropene gives the ketone in 88% yield (Scheme 6).

Scheme 7

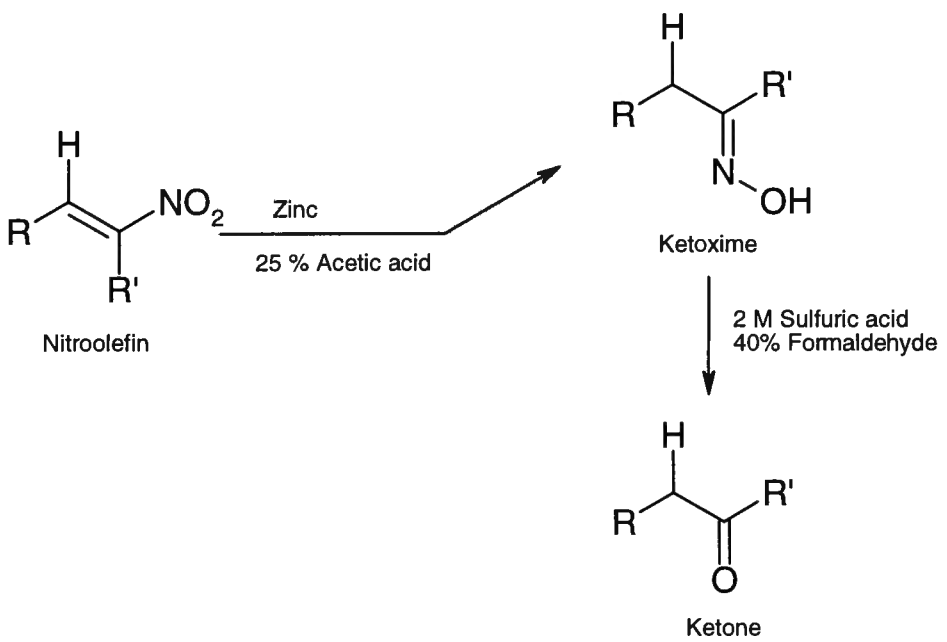


1-Phenyl-2-nitropropene

1-Phenyl-2-propanone

Hass *et al.*[8] reported that when 1-phenyl-2-nitropropene, 40 mesh cast iron turnings, distilled water, ferric chloride and concentrated HCl were heated (85-95° C) for 5 to 6 hours, followed by distillation, gave 1-phenyl-2-propanone in 75% yield (Scheme 7).

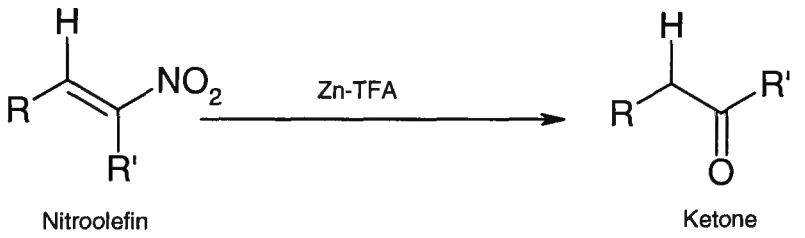
Scheme 8



Nitroolefin

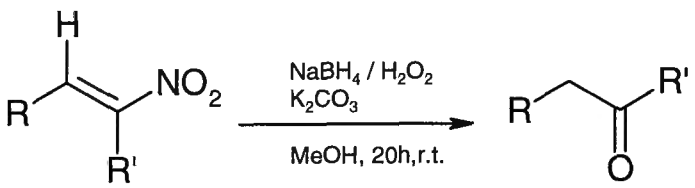
The reduction of nitroolefins to the ketoxime intermediate using zinc powder and acetic acid proceeds smoothly in 50-60% yield.[9] The ketoximes can be hydrolysed to ketones by refluxing with 2 molar sulfuric acid and a hydroxylamine acceptor (40% formaldehyde). Yields of the ketone were reported to be around 80%, with an over-all yield from the nitroolefin of 40-48% (Scheme 8).

Scheme 9



The direct conversion of nitroolefins to the corresponding ketones with zinc/acetic acid has been known for a long time.[10] This reaction requires forcing conditions and long reaction times and its application is limited to compounds that do not contain other labile functional groups. However, this is not a problem for the preparation of 1-phenyl-2-propanone and other simple aryl ketones. It is worthwhile noting a recent modification of this method.[10] The use of stoichiometric amounts of zinc/trifluoroacetic acid (TFA) in organic solvents such as dimethylformamide or methanol greatly reduces the reaction time (from 3-6 hr to 15 min) and the temperature required (ambient temperature) with a modest increase in yield (Scheme 9).

Scheme 10



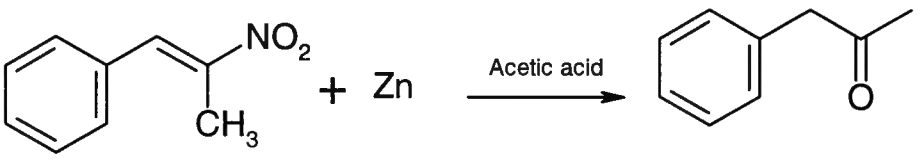
A new practical procedure for the conversion of nitroalkenes into ketones uses $NaBH_4/H_2O_2$ to give good yields (48-80%) of the ketone (Scheme 10).[11]

The methods illustrated above for the manufacture of 1-phenyl-2-propanone are those in which the chemical operations are not complicated. Many other synthetic routes for 1-phenyl-2-propanone, are known[12], but are not important in the present context. The most common synthesis for 1-phenyl-2-propanone in Australia and in the western and northwestern parts of the United States[12] appears to be the reaction of phenylacetic acid and acetic anhydride (Scheme 3).

3.2. Western Australian method

In Western Australia (WA), the method using phenylacetic acid and acetic acid in a tube furnace has been found only once in the past 7 years (Scheme 2). The most frequently encountered method for the synthesis of 1-phenyl-2-propanone in WA is the reduction of 1-phenyl-2-nitropropene with zinc in acetic acid (Scheme 11).

Scheme 11



1-Phenyl-2-nitropropene Zinc metal 1-Phenyl-2-propanone

The chemicals and equipment found at four separate clandestine laboratories were all very similar. The precursor chemicals seized included large amounts of benzaldehyde, nitroethane, ammonium carbonate, zinc powder, acetic acid and formic acid. From the size of reaction vessels and quantities of materials seized, the illicit process was probably being carried out in up to kilogram batches. It was postulated that ammonium carbonate was being used as a base in the condensation reaction of benzaldehyde and nitroethane to produce 1-phenyl-2-nitropropene. Formic acid and ammonium carbonate react to form ammonium formate, a reducing agent associated with the Leuckart reaction. This suggested that reductive amination of 1-phenyl-2-propanone was involved. The presence of zinc powder, seized in 500g quantities, and acetic acid indicated that these were used for the conversion of 1-phenyl-2-nitropropene to 1-phenyl-2-propanone. Typed and hand written recipes found at the scene were not received until the end of the present project. The aim of the following study was to determine the yields under different reaction conditions for this reaction, to determine if other metals could be substituted for zinc and if zinc could be used to replace other metals in similar reactions.

3.3. Results and Discussion

The conversion of 1-phenyl-2-nitropropene to the key amphetamine precursor 1-phenyl-2-propanone was investigated. Yields of 1-phenyl-2-propanone by the variation of concentration of reactants, temperature, time and solvent composition have been determined. The 1-phenyl-2-propanone used in these studies was synthesised from 1-phenyl-2-nitropropene in a one step process (scheme 11) and either isolated as the crude reaction product or purified by vacuum distillation, silica gel chromatography or steam distillation (Table 1).

Table 1: Conversion of 1-phenyl-2-nitropropene to 1-phenyl-2-propanone

Molar ratio of nitrostyrene:zinc	Reaction Time (Hours)	Solvent used in extraction	Yield (%)	Purification method
1:5	1.5	Dichloromethane	19	N.A
1:5	2	Toluene	27	N.A
1:5	1.5	Toluene	32	N.A.
1:5*	5	Toluene	43	Vacuum distilled
1:5*	3	Toluene	26	Silica filtration
1:5	2	None	53	Steam distilled
1:2.5**	1	None	39	Steam distilled

*An extra equivalent of zinc was added in some reactions as, when monitored by GC-MS, starting material remained.

**Method followed from an actual recipe seized at a clandestine site.

N.A. - Not applicable.

3.3.1. Synthesis of 1-phenyl-2-propanone

To 1-phenyl-2-nitropropene in acetic acid, five equivalents of zinc were cautiously added portionwise and the mixture was refluxed for 1.5 hr. Recovery of the product by extraction with dichloromethane was 93%, the yield of P2P from this reaction (determined by GC-FID) was 19%. Increasing the reaction time to 2 and 4 hr. afforded a yield of 8% and 6.5 % respectively (determined by GC-FID). Each reaction was monitored by GC-MS and was essentially complete in thirty minutes. The reduced yields of the ketones is probably due more to the extraction technique, which was

hindered by the formation of emulsions, than to the reaction time. The spectral data, GC-MS and FT-IR (Fig. 6, appendix), were consistent with those of 1-phenyl-2-propanone.

The effect of varying the amount of zinc on the yield of 1-phenyl-2-propanone was studied. A solution of 1-phenyl-2-nitropropene in acetic acid was heated to 100° C with one, two, three and four equivalents of zinc powder. Analysis by GC-MS indicated an increasing proportion of zinc resulted in a greater rate of 1-phenyl-2-propanone production.

3.3.2. Other metals

The reduction of 1-phenyl-2-nitropropene using Raney nickel and sodium hypophosphite (Scheme 6), iron metal and hydrochloric acid (Scheme 7) and zinc metal in acetic acid (Scheme 8) have been documented in the literature.[7.8.9] It was of some interest to determine if metals other than zinc could be used in the reaction under study. If so, it could provide an alert to monitor diversion of these metals from legitimate sources.

Equimolar amounts of tin (granulated), aluminium (powder), iron (filings), and zinc (granulated, activated with copper) and 1-phenyl-nitropropene were combined in glacial acetic acid and were heated to (100-105° C) for 2 hours. The yield of these reactions was not determined, however the rate of formation of the desired product was monitored by GC-MS.

Table 2. Substitution metals

Substitution Metal	Reaction with Nitrostyrene to give 1-Phenyl-2-propanone
Tin (granulated)	Desired product obtained - reaction incomplete
Aluminium (powder)	No Reaction
Iron (filings)	Desired product obtained - reaction incomplete
Zinc (granulated)	Small amount of product

Al , Zn, Fe, Sn, Zn(Pwdr).

Increasing efficiency

1-Phenyl-2-propanone was detected by GC-MS in the reaction using tin, iron or granulated zinc. In the reaction using aluminium metal, only starting material was observed by GC-MS. Tin and iron can be used to substitute for zinc metal, however zinc powder was determined to be the most efficient metal in the reduction of 1-phenyl-2-nitropropene to 1-phenyl-2-propanone. Iron filings, granulated zinc and tin, due to their physical characteristics for example a lack of surface area, did not have the same reactivity as zinc metal in the powdered form. A study of the reactivity of the powdered form of these metals is of some interest, however time constraints precluded an investigation in the present work. However, in respect to the availability of these materials to clandestine laboratories, tin and iron offer two possible substitutes for zinc.

Table 3: Standard Reduction Potentials

Reaction	Potential (volts)
$2H^+ + 2e^- \leftrightarrows H_2$	0.0000
$Al^{+3} + 3e^- \leftrightarrows Al$	-1.706
$Zn^{+2} + 2e^- \leftrightarrows Zn$	-0.7628
$Fe^{+2} + 2e^- \leftrightarrows Fe$	-0.409
$Sn^{+2} + 2e^- \leftrightarrows Sn$	-0.1364

Source: CRC. Handbook of Chemistry and Physics.

$$\xrightarrow[\text{Increasing reduction potential}]{\text{Sn,Fe, Zn, Al}}$$

The standard reduction potentials for these metals indicate aluminium would be the most reactive metal with acetic acid, followed by zinc, iron and tin. However aluminium has a thin film of the protective oxide and would not react under acidic conditions. Under experimental conditions the metals in a granulated form did not have the same reactivity as zinc metal in the powdered form.

3.3.3 Two phase solvent system

1-Phenyl-2-nitropropene can be converted to 1-phenyl-2-propanone with iron and hydrochloric acid in the presence of ferric chloride and a two-phase solvent system (toluene/water) as reported in scheme 9. This method gave a yellow oil (53%), containing 1-phenyl-2-nitropropene (31%), 1-phenyl-2-propanone (11%) and the intermediate 1-phenyl-2-propanone oxime (ketoxime; Scheme 8) (1%). Monitoring by GC-MS indicated that the reaction in a toluene two-phase mixture is slower compared to that using acetic acid.

3.3.4 Reactivity of 1-phenyl-2-propanone

The reactivity of 1-phenyl-2-propanone in the presence of zinc and acetic acid was examined by combining the three reactants and heating to reflux for 1 hr. Analysis by GC-MS showed that no new compounds were formed, indicating that 1-phenyl-2-propanone does not react in the presence of zinc and acetic acid.

3.3.5 Varying the combination of reagents

Adding a solution of 1-phenyl-2-nitropropene in acetic acid to a suspension of zinc powder in acetic acid, refluxing for 12 hours yielded unreacted nitrostyrene. In further experiments a solution of 1-phenyl-2-nitropropene was added down the condenser to a refluxing solution of zinc in acetic acid the reaction was refluxed for 2 hr. Analysis by GC-MS indicated the major component was starting material. When the reaction time was increased to 4 hours the yield of P2P from this reaction was 11% (determined by GC-FID).

3.3.6 Extraction with toluene

Toluene is more readily available than dichloromethane and is a common material found at clandestine laboratories where it is used as an extraction solvent. The reactions described in the previous section were repeated, but the product was recovered by extraction with toluene, yields of 27-32% were obtained (determined by GC-FID).

3.3.7 Synthesis of 1-Phenyl-2-propanone and purification:

Various methods were used to purify samples of the ketone obtained from reactions similar to those described above. Vacuum distillation afforded a yield of 43%, silica gel chromatography 26% and steam distillation 51%. The spectral data, ^{1}H-NMR (Fig. 2 appendix), were consistent with those of 1-phenyl-2-propanone.

3.3.8 Clandestine method (Experiment based on handwritten notes)

The method described in a 'recipe' involved refluxing 1-phenyl-2-nitropropene with 2.5 equivalents of zinc powder in 90% acetic acid for one hour and steam distillation of the product.

In a 20L stainless steel container add 250g of zinc to 2L of acetic acid and 200 mL of distilled water. The zinc is allowed to react and 250g of 1-phenyl-2-nitropropene is added. The mixture is refluxed for one hour. Water is added, approximately 17 to 18 L. The apparatus is then changed to a distillation setup and the mixture is brought to the boil (180 ^{o}C) then turned down (150 ^{o}C). The distillate should appear at a rate of two drips per second, minimum, if not the heat is turned up. Distillation occurs for eight hours to fill a 20L bucket. Washing soda (sodium carbonate) is added. The distillate is split into two 10L lots. The product 1-phenyl-2- propanone (P2P) appears as a yellow liquid at the top and a tap located at the bottom of the 10L bucket is used to drain the water layer.

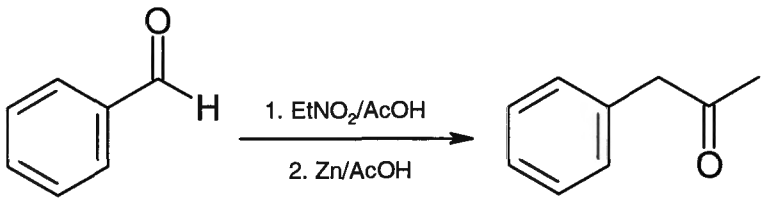
The experimental procedure reported above was replicated on one hundredth of the scale. After steam distillation the distillate was extracted with toluene (because of the small scale of the reaction) to give 1-phenyl-2-propanone in 39% yield. The reaction was monitored by GC-MS and was essentially complete after 1 hour. The differences to the laboratory experiments was the order in which the materials were combined, the concentration of acetic acid (98% to 90%) and the number of zinc equivalents used (5 eq to 2.5 eq).

The isolation of 1-phenyl-2-propanone using the clandestine method of steam distillation eliminates the need for a number of items; solvents (toluene) used in extraction, drying agents and methods used to evaporate solvents. The use of a bucket with a tap at the bottom serves effectively as a normal separatory funnel.

The experiment when repeated using 5 equivalents of zinc, gave a satisfactory yield of 1-phenyl-2-propanone (53%) that was considerably higher in purity (GC-MS) compared to that isolated by a toluene extraction.

3.3.9 One-pot conversion of benzaldehyde to 1-phenyl-2-propanone

Scheme 12



Benzaldehyde, nitroethane and ammonium carbonate were added in the molar ratio 1.5:1:0.1 to acetic acid and the mixture refluxed for 1 hr. Five equivalents of zinc in acetic acid were added portionwise to the cooled solution and the mixture was refluxed for 1 hr. Work-up, by extraction with dichloromethane, afforded the product in 87% recovery. Vacuum distillation of the crude product afforded 1-phenyl-2-propanone in a 44% yield.

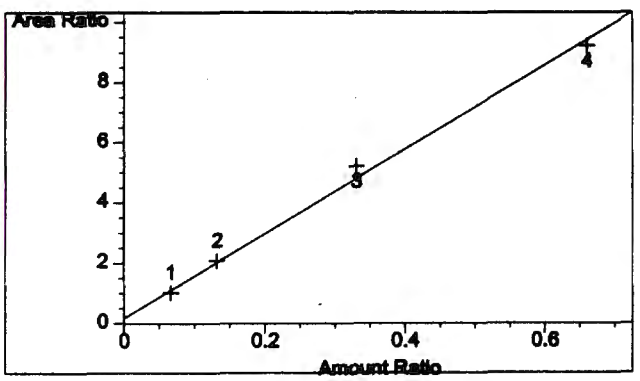
The reaction was monitored by GC-MS and was essentially complete after thirty minutes from the addition of zinc. Following the manufacture of 1-phenyl-2-nitropropene *in situ*, zinc powder and acetic acid can be added to the reaction mixture without prior separation and purification of the nitropropene.

3.4. Determination of P2P in Clandestine reaction mixtures

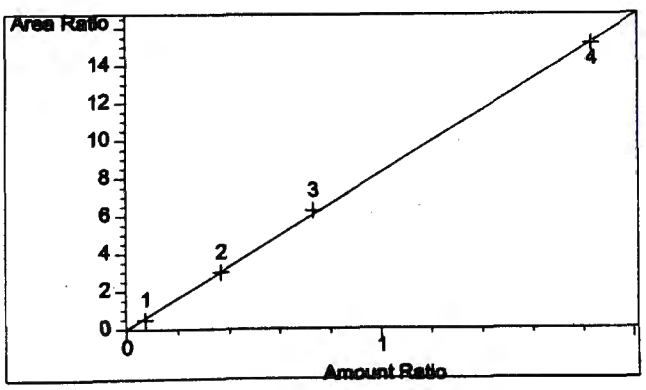
A method was developed for the quantitation of 1-phenyl-2-propanone (P2P) and N-formylamphetamine in clandestine reaction mixtures using gas chromatography flame ionisation. The principal objective of this part of the study was to develop a simple, fast, and efficient method for the quantitation of P2P in reaction mixtures.

A number of compounds were investigated as possible internal standards. Propiophenone, initially chosen because of its similar chemical characteristics (molecular weight and boiling point) to 1-phenyl-2-propanone, had Rt 7.13 which was close to that of P2P (Rt 6.79). Acetophenone, Rt 6.41 and possessing similar chemical properties, was found to be suitable. Ethyl acetate was used as the solvent.

Calibration curves of 1-phenyl-2-propanone and N-formylamphetamine.




```
P2P at exp. RT: 6.922
FID1 A,
Correlation:              0.99777
Residual Std. Dev.:       0.28855
Formula: y = mx + b
        m:       14.01573
        b:        1.80067e-1
        x: Amount Ratio
        y: Area Ratio
```




```
Formylamphetamine at exp. RT: 9.642
FID1 A,
Correlation:              0.99976
Residual Std. Dev.:       0.17287
Formula: y = mx + b
        m:        8.31835
        b:       -8.07315e-3
        x: Amount Ratio
        y: Area Ratio
```

The determination of the concentration of 1-phenyl-2-propanone was done using a four point calibration curve, measuring the ratio of the absolute peak area response of P2P to the absolute peak area of the internal standard acetophenone. The response was found to be linear in the concentration ranges studied with a correlation coefficient of 0.99777 for P2P. A similar technique was used for the determination of N-formylamphetamine in crude reaction mixtures (see Chapter 4). The response was also found to be linear with a correlation coefficient of 0.99976.

3.5. Conclusion

Reduction of 1-phenyl-2-nitropropene using zinc powder in glacial acetic acid was found to afford 1-phenyl-2-propanone in a reasonable yield. The maximum yield for this reaction was achieved using 5 equivalents of zinc powder for each mole of 1-phenyl-2-nitropropene. The procedure was to add zinc powder portionwise to a solution of the nitroalkene in glacial acetic acid followed by heating at reflux for 1-2 hr. However, GC-MS analysis showed that the maximum yield was achieved after thirty minutes. The ketoxime, 1-phenyl-2-propanone oxime, was also detected in the reaction mixture by GC-MS, however this intermediate was eventually converted to the ketone under the reaction conditions.

Substitution of zinc with tin and iron also resulted in the formation of 1-phenyl-2-propanone. Their reactivity was lower than that of zinc because the metals were not in a powdered form. Aluminium powder was unreactive under these conditions. Zinc powder was determined to be the most efficient metal in the reduction of 1-phenyl-2-nitropropene.

1-Phenyl-2-propanone is unreactive in the presence of zinc and acetic acid and therefore, there should be no loss of product thorough side reactions.

The use of zinc in other solvent systems such as toluene/hydrochloric acid was investigated. 1-Phenyl-2-nitropropene in the presence of zinc, toluene and hydrochloric acid and heated at reflux for 1 hour gave an incomplete reaction. Analysis by GC-MS indicated that the intermediate oxime and 1-phenyl-2-propanone were produced.

Variations in the order of addition of reactants produced a lower yield and/or a longer reaction time. Extraction of the product using different techniques was also investigated. Basifying the acidic reaction medium followed by extraction with dichloromethane resulted in the formation of emulsions. Using toluene to extract a diluted reaction mixture was more successful.

Purification of the crude reaction product by steam distillation directly from the reaction mixture, or vacuum distillation following solvent extraction gave satisfactory yields (53% and 43% respectively). Both purification techniques give a product, which is pure when analysed by ^{1}H-NMR and GC-MS. Clandestine operators as indicated by seized 'recipes', prefer steam distillation because of its simplicity.

The clandestine method used a zinc to nitroalkene ratio of 2.5:1 in 90% acetic acid and refluxing for 1 hr. The product recovered by steam distillation was obtained in 39% yield.

It is also possible to manufacture 1-phenyl-2-propanone from benzaldehyde and nitroethane without prior separation and purification of 1-phenyl-2-nitropropene. The addition of zinc powder after the condensation reaction gave a red oil (87%) which, on vacuum distillation, afforded the ketone in 44% yield, with respect to the nitroethane.

The general method described is a departure from the methods of reducing 1-phenyl-2-nitropropene that are commonly found at clandestine laboratories. It requires no knowledge of chemistry, it offers little chance of failure, produces satisfactory yields, does not require expensive chemical apparatus or glassware, and uses currently available (and easily synthesised) precursors. The most significant feature is the use of zinc, which is widely available from a number of commercial sources. It is important for enforcement personnel to be aware of the three major reagents in this method (zinc metal, acetic acid and 1-phenyl-2-nitropropene) for intelligence gathering purposes and for their safety in assessing and seizing such a laboratory.

3.6. References

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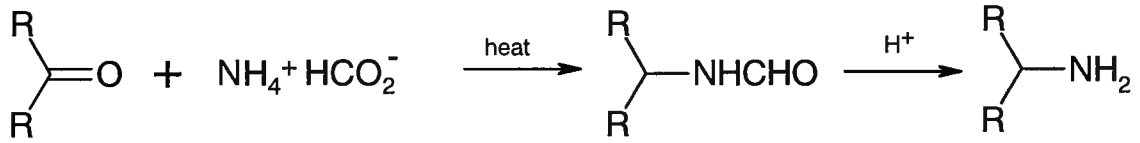
Chapter Four

4. Syntheses of N-formylamphetamine

The reductive amination of carbonyl compounds to the corresponding amines by reaction with excess ammonium formate (Leuckart reaction) is a very useful procedure for the preparation of N-formyl derivatives of amines.[1] The Leuckart method of amphetamine production may be considered as a three-step reaction consisting of:

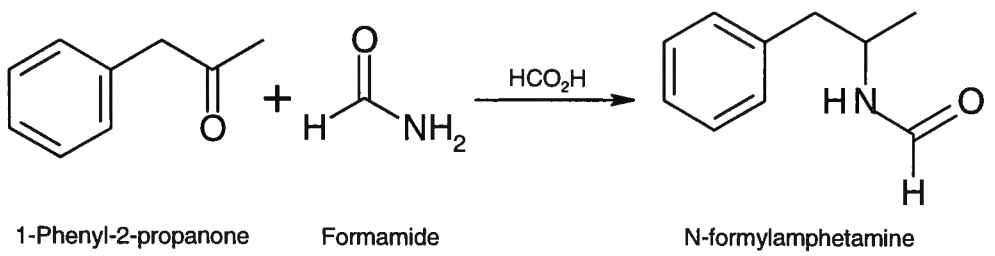
1. A formylation stage: the condensation of 1-phenyl-2-propanone with formamide in the presence of formic acid.
2. A hydrolysis step: hydrolysis of the N-formylamphetamine intermediate with hydrochloric acid.
3. A purification step: extraction of amphetamine and precipitation as the hydrochloride, followed by washing and/or recrystallisation of the product.

Scheme 1. The Leuckart Reaction



The most effective reagent in the Leuckart reaction appears to be ammonium formate or formamide, supplemented by the addition of sufficient 90% formic acid to maintain a slightly acidic medium and serve as an active reducing agent. It has been reported[1] that the ketone and ammonium formate or formamide are usually employed in a molecular ratio of 1:4 or 1:5. Crossley and Moore found that the addition of formic acid to formamide increased the yield in comparison to formamide alone. One to three equivalents of formic acid is generally required. Occasionally, distillation of accumulated water may be necessary to maintain a suitably high reaction temperature.[1]

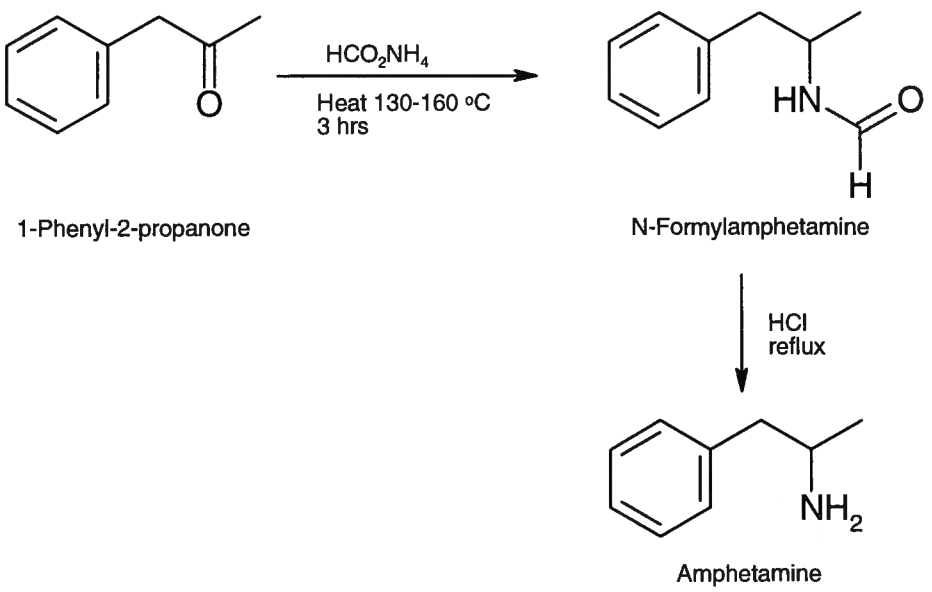
Scheme 2



1-Phenyl-2-propanone Formamide N-formylamphetamine

N-formylamphetamine has been produced when 1-phenyl-2-propanone was allowed to react with formamide and formic acid in a molar ratio of 1:4:0.32 under Dean-Stark conditions. Five equivalents of formic acid were added during the course of the reaction.[2] However no yield for the reaction was given (Scheme 2).

Scheme 3

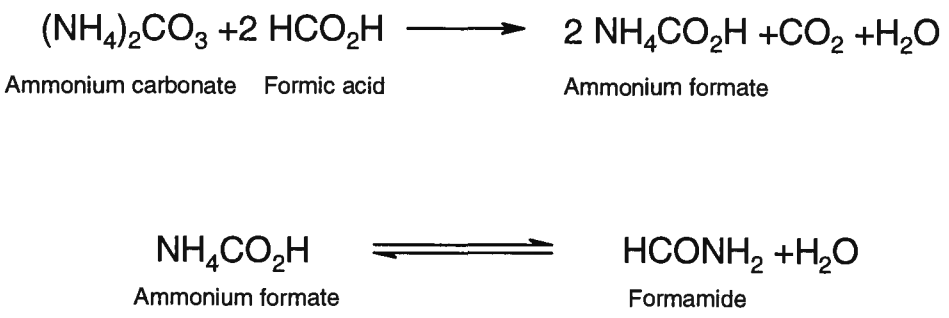


1-Phenyl-2-propanone N-Formylamphetamine

Amphetamine

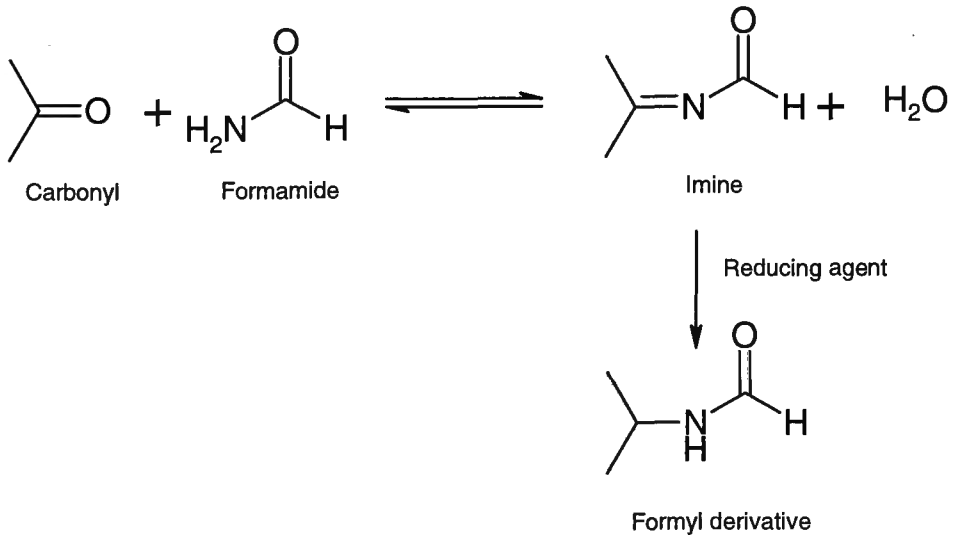
Amphetamine has been synthesised from 1-phenyl-2-propanone *via* N-formylamphetamine using ammonium formate.[3] 1-Phenyl-2-propanone and ammonium formate, in the molar ratio of 1:3 were combined and heated (160-180° C) for 3 hours. The contents of the distillation flask were then cooled and hydrolysed by heating with concentrated hydrochloric acid for 3 hours. The reaction mixture was washed with benzene (to remove unreacted ketone), made alkaline, and steam distilled. The distillate was extracted with benzene and the product distilled to afford 1-phenyl-2-aminopropane (amphetamine) 41% yield (Scheme 3).

Scheme 4



Ammonium formate is well documented as a reducing agent in the literature [4,5,6]. Ammonium carbonate and formic acid generate ammonium formate *in situ*, which in turn can dehydrate to furnish formamide (Scheme 4). This can react with the carbonyl group of 1-phenyl-2-propanone to form the corresponding imine, which can be reduced by formic acid, formamide and/or ammonium formate[1] to form the N-formyl derivative of the corresponding amine (Scheme 5).

Scheme 5

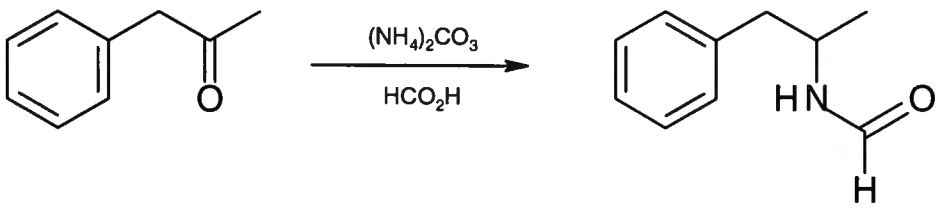


4.1. Western Australian method

Chemicals and 'recipes' seized from several clandestine amphetamine laboratories suggested that N-formylamphetamine was prepared from the reaction of 1-phenyl-2-propanone (P2P), ammonium carbonate and formic acid (Scheme 6). Ammonium carbonate and formic acid form ammonium formate as described in Scheme 5. The use of ammonium carbonate in both the first reaction (see Chapter 2) and third reaction in

the sequence is quite innovative and reduces the total number of chemicals needed for the synthesis of amphetamine from benzaldehyde. Once again clandestine operators were using 'homemade' equipment, condensers and reaction vessels, in this step.

Scheme 6



1-Phenyl-2-propanone N-Formylamphetamine

4.2. Results and Discussion

A number of reactions using commercial grade and impure 1-phenyl-2-propanone (P2P) were attempted. All reactions were carried out at a temperature of 160° C, using a ratio of 5 moles of Leuckart reagent to 1 mole of the ketone.[1]

4.2.1. Commercial grade 1-phenyl-2-propanone

The initial experiments were carried out using commercial grade 1-phenyl-2-propanone. The time required for the reaction, typical yields using formamide as the Leuckart reagent, the effect of using excess formic acid and whether it was necessary to remove water generated in the reaction were examined.

4.2.2. Reaction with formamide

1-Phenyl-2-propanone and five equivalents of formamide were heated under reflux and the reaction was monitored by GC-MS. After 7.5 hr, the major component was 1-phenyl-2-propanone and N-formylamphetamine was the minor component. After 12 hours, the reaction was essentially complete and work-up afforded the product in 59% yield.

Table 1: Leuckart reactions using commercial P2P

Leuckart reagent	Time of Reaction (Hours)	Yield (%)
Formamide (5 eq)	12	59
Formamide (5 eq) Formic acid (1 eq)	4	71 to 99
Ammonium carbonate (5 eq) Formic acid (5 eq)	8	50
Ammonium carbonate (5 eq) Formic acid (excess) Distillation of Water	11	50
Ammonium carbonate (5 eq) Formic acid (excess)	24	78

4.2.3. Reaction with formamide and formic acid

1-Phenyl-2-propanone, five equivalents of formamide and one equivalent of formic acid were refluxed at 160° C for four hours. GC-MS monitoring of the reaction indicated that the reaction was complete after 1.5 hr. Work-up afforded the crude product (89%). The oil was washed with hexane to yield a light brown oil (71%) which appeared essentially pure when analysed by GC-MS FT-IR and ^{1}H-NMR spectroscopy (Fig. 3 and 7, appendix).

The proton NMR spectrum showed that the compound existed as a mixture of the *Z*- and *E*- rotamers in 78 and 22% respectively. Separate signals were observed for the secondary methyl group at δ 1.12 (d, J = 7 Hz) (*Z*) and δ 1.23 (d, J = 7 Hz) (*E*), the methine proton group at δ 4.28 (dq, J = 7 Hz) and δ 3.61 (dq, J = 7 Hz) (*E*), and the formyl proton at δ 7.95 (br s) (*Z*) and δ 7.64 (d, J = 11 Hz) (*E*) which showed coupling to the –N-H at δ 6.68 [7].

4.2.4. Reaction with ammonium formate

Using five molar equivalents of ammonium carbonate and formic acid and heating under reflux for 8 hr gave a 50% yield of N-formylamphetamine.

4.2.5. Reaction with ammonium formate in excess formic acid

The reaction was repeated using excess formic acid and heating for eight hours. The water was removed by distillation, then the reaction mixture was heated for an additional 3 hr to give N-formylamphetamine in a 50% yield. A similar experiment in which water was not removed afforded N-formylamphetamine in 78% yield. Some 1-phenyl-2-propanone was observed to co-distill with the water in the first reaction, which may explain the reduced yield. In the second reaction condensation of water was observed in the condenser, effectively removing water from the reaction mixture, driving the formation of formamide.

4.2.6. Procedure used in clandestine laboratory

Two recipes seized from two separate clandestine laboratories indicated that the operators were making ammonium formate *in situ*. The water generated from this reaction was distilled and the co-distilled 1-phenyl-2-propanone was returned to the reaction vessel.

This process was repeated in the laboratory. After 8 hours of refluxing, water was removed by distillation. The reaction was further refluxed for 3 hours to give a 50% yield of N-formylamphetamine. When this reaction was repeated using ammonium carbonate and an excess of formic acid without the distillation of water, the reaction was complete after 24 hours. Although the time required was considerably greater, the yield increased to 78%.

A well-known underground publication[8] describes a variation of the Leuckart reaction. N-formylamphetamine can be prepared by the reaction of P2P with formamide, it is suggested that the two compounds should be combined in a molecular ratio of 1:2 and left to stand at room temperature for approximately one week. A catalytic amount of formic acid is then added and the mixture heated to 160-165° C for one hour. Ammonium formate is also mentioned as a suitable reagent.

4.2.7. Impure 1-phenyl-2-propanone

The homemade equipment typically found at these clandestine laboratories is not ideal for a vacuum distillation of 1-phenyl-2-propanone, although steam distillation has been described in certain seized 'recipes'. This tends to suggest that impure P2P may be used directly in this step.

The experiments in this section were carried out using impure 1-phenyl-2-propanone synthesised from 1-phenyl-2-nitropropene and five equivalents of zinc in acetic acid. The yields of N-formylamphetamine (determined by GC-FID) are based on the starting material consisting of 32% 1-phenyl-2-propanone (determined by GC-FID).

Table 2: Leuckart reactions using impure P2P

Leuckart reagent	**Time of Reaction (Hours)**	**Yield (%) based on 32% P2P**
Formamide (5 eq)	11	39
Formamide (5 eq) Formic acid (1 eq)	3	19
Ammonium carbonate (5 eq) Formic acid (5 eq)	14	86
Ammonium carbonate (5 eq) Excess formic acid	24	78

4.2.8. Reaction with formamide

1-Phenyl-2-propanone and five equivalents of formamide were heated under reflux for 11 hours to give a 39% yield of N-formylamphetamine

4.2.9. Reaction with formamide and formic acid

This reaction was repeated using the same reagents and one molar equivalent of formic acid. The reactants were heated at reflux for three hours to give a 19% yield of N-formylamphetamine. GC-MS monitoring of the reaction indicated that the reaction was complete in 1 hr.

4.2.10. Reaction with ammonium formate

1-Phenyl-2-propanone and five equivalents of both formic acid and ammonium carbonate were heated under reflux for 14 hours to give a yield of 86%.

4.2.11. Reaction with ammonium formate/excess formic acid

This reaction was repeated using an excess of formic acid. The reactants were heated to reflux for 4 days (6 hours a day) to give a yield of 78%.

The results indicate crude P2P can be converted to N-formylamphetamine with ammonium formate in excellent yield.

Table 3: Summary of main reactions

Leuckart reagent	**1-Phenyl-2-propanone (Yield %)**	
	Commercial	**Impure**
Formamide (5 eq)	59	39
Formamide (5 eq) + Formic acid (1 eq)	89-99	19
Ammonium carbonate (5 eq) Formic acid (5 eq)	50	86
Ammonium carbonate (5 eq) Excess formic acid	78	78

The yield of product from the experiments using impure P2P and ammonium formate as the Leuckart reagent was very high (86%), compared to 50% using commercial P2P. Reaction of commercial and impure P2P with ammonium formate in excess formic acid gave similar yields (78%), based on the purity of P2P. All reactions were conducted on a small scale which could explain the variation in yield, also the products may contain traces of acid (acetic) from the previous steps or high molecular weight compounds from side reaction resulting from impure starting material.

4.3. Conclusion

The reaction of 1-phenyl-2-propanone, ammonium carbonate and formic acid was found to produce N-formylamphetamine. Commercial P2P was used initially to find the optimal reaction conditions. The ketone and ammonium formate or formamide were employed in a molecular ratio of 1:5. Reactions using formamide as the Leuckart reagent also included 1 equivalent of formic acid. A large excess of formic acid was added when ammonium carbonate was used.

The reaction of commercial 1-phenyl-2-propanone with formamide supplemented with one equivalent of formic acid increased the yield from 59% to 71%, in a shorter reaction time (12 hr to 4 hr). Using ammonium formate with an excess of formic acid also improved the yield (50 % to 78%), however this lengthened the reaction time by 12 hr. Removal of water by distillation did not improve the yield (50%), but it reduced the reaction time by half (24 hr to 11 hr).

It was unclear whether illicit operators were purifying the 'homemade' P2P. Therefore the yields for the reaction of impure P2P with formamide and ammonium formate were determined. The reaction with formamide gave a satisfactory yield (39%). The addition of formic acid did not improve the yield (19%). The reaction of ammonium formate gave a high yield (86%), adding an excess of formic acid did not improve the yield (78%) and lengthened the reaction time by 10 hours. This result suggests only a catalytic amount of formic acid is required, and an excess of formic acid may interfere with the reaction.

Purification of P2P by distillation would not appear to be essential. Even using impure P2P and ammonium formate the conversions were very high. Operators may not be worried about the yield of these reactions because of the large scaling options present in the initial reactions.

These results indicate that ammonium carbonate has a wide applicability being used as a nitrogen source in the Leuckart reaction and previously as a catalyst to produce 1-phenyl-2-nitropropene. Substitution of ammonium formate for formamide as the Leuckart reagent was found to give N-formylamphetamine in good yields (50 to 78%).

4.4. References

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8. Uncle Fester Secrets of Methamphetamine Manufacture, 4th Ed, Loompanics Unlimited (Washington).

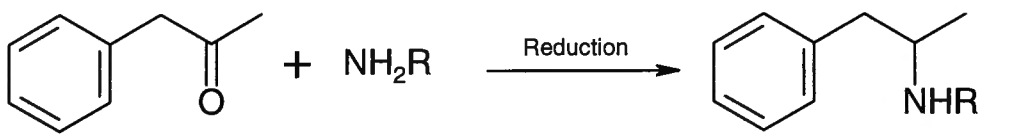
Chapter Five

5. Syntheses of Amphetamine

A number of different chemical methods for the manufacture of amphetamine have been published.[1] Some are relatively straight forward and require only crude makeshift processes, others use sophisticated technology and a number of advanced chemical procedures. The manufacturing process selected is determined by a number of factors, including the availability of chemical precursors and the expertise of the operator.

1-Phenyl-2-propanone is a precursor in the manufacture of amphetamine and methylamphetamine. Most clandestine laboratories in Australia manufacture methylamphetamine by the reduction of ephedrine/pseudoephedrine using a number of different synthetic routes. However the clandestine amphetamine laboratories seized appear to favour the reductive amination of 1-phenyl-2-propanone, often by the Leuckart route.

Scheme 1: Reductive animation of 1-Phenyl-2-propanone



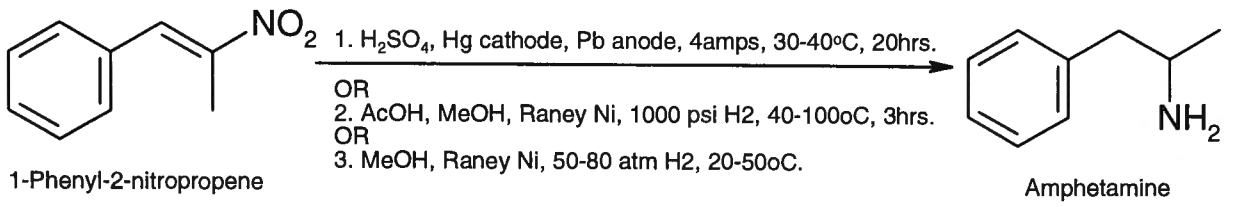
1-Phenyl-2-propanone

R=H, Amphetamine
R=CH_3, Methylaminetamine

The manufacturing techniques commonly encountered in clandestine amphetamine laboratories are listed below.

- Reduction of 1-phenyl-2-nitropropene to amphetamine.[2,3,4]
- Reductive amination of 1-phenyl-2-propanone using a Leuckart reagent.[5]
- Reductive amination of 1-phenyl-2-propanone using Al, NH_4OH and Hg amalgam.[6]
- Reduction of 1-phenyl-2-propanone oxime using a Na amalgam.[7]

Scheme 2

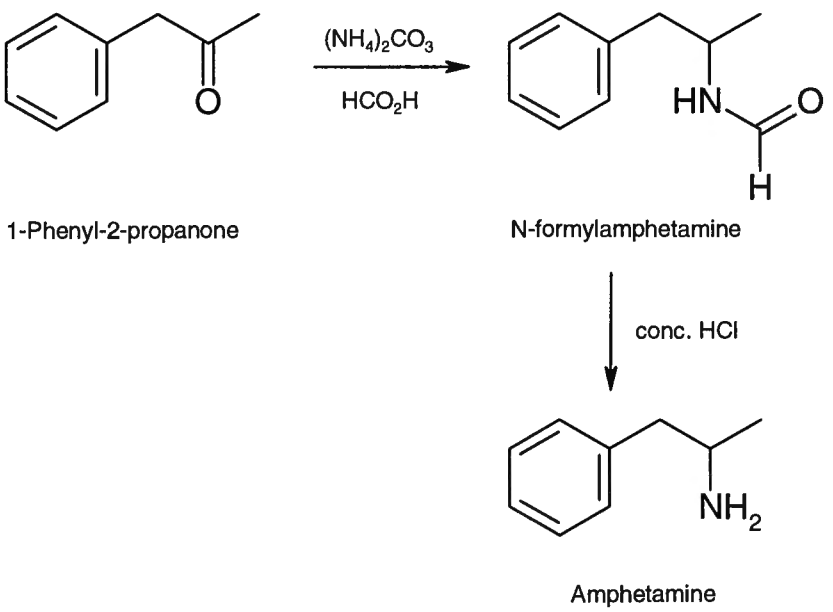


1-Phenyl-2-nitropropene

Amphetamine

Condensation of benzaldehyde with nitroethane yields 1-phenyl-2-nitropropene as described in Chapter 2. The precursor 1-phenyl-2-nitropropene may be converted directly to amphetamine under reducing conditions (Scheme 2).[1] Electrolytic reduction, using sulphuric acid and a mercury cathode and lead anode, has been reported to give a 20% yield of amphetamine.[2] Catalytic reduction of nitrostyrene using a Raney Ni catalyst in an acidic solvent (reaction 2)[3] and in methanol (reaction 3)[4] under elevated pressure gave amphetamine in yields of 60 and 61% respectively.

Scheme 3



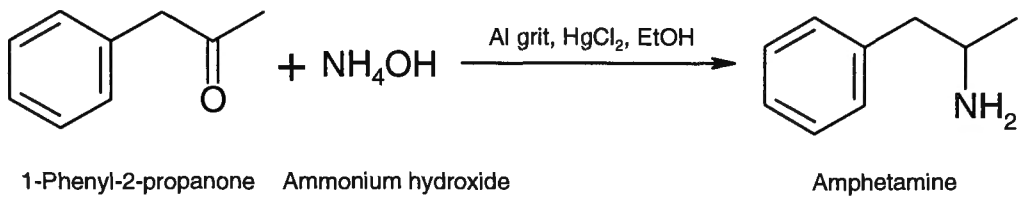
1-Phenyl-2-propanone

N-formylamphetamine

Amphetamine

A variety of methods for the preparation 1-phenyl-2-propanone have been documented in the literature. These methods, and the preparation of 1-phenyl-2-propanone from 1-phenyl-2-nitropropene using Zn-AcOH are described in Chapter 3. 1-Phenyl-2-propanone can be converted to N-formylamphetamine using the Leuckart reagent ammonium formate[5] as described in Chapter 4. N-formylamphetamine is readily hydrolysed with concentrated hydrochloric acid to give amphetamine (Scheme 3).

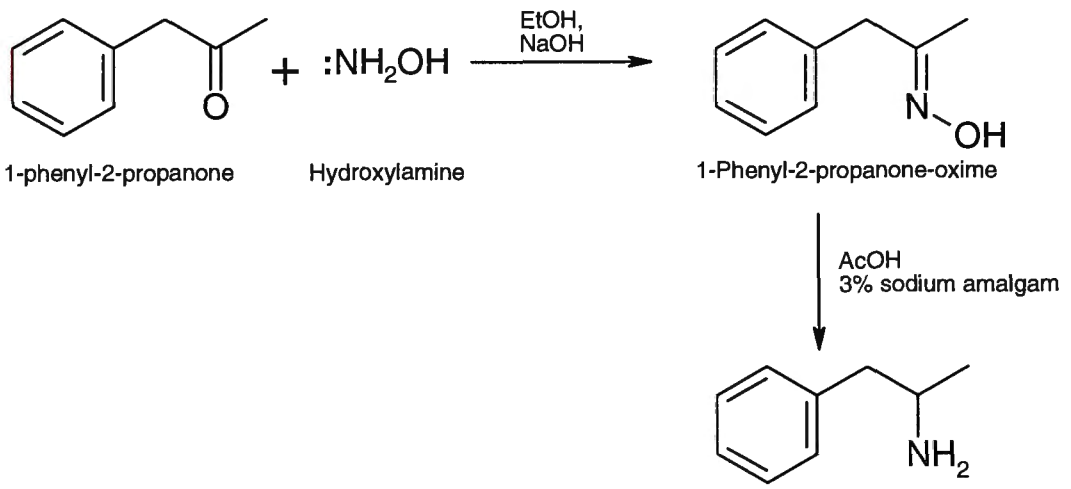
Scheme 4



1-Phenyl-2-propanone Ammonium hydroxide Amphetamine

Amphetamine can be obtained in a 30% yield in a one step synthesis by heating to reflux a mixture of 1-phenyl-2-propanone, ethanol, ammonium hydroxide, aluminium grit and a catalytic amount of mercuric chloride (Scheme 4).[6]

Scheme 5



1-phenyl-2-propanone Hydroxylamine 1-Phenyl-2-propanone-oxime

Amphetamine has also been prepared by the reduction of the intermediate 1-phenyl-2-propanone oxime by means of a sodium amalgam in dilute acetic acid (Scheme 5), however yields were not reported for this method.[7] The oxime is generated upon reaction of 1-phenyl-2-propanone with hydroxylamine.

5.1. Results and Discussion

The N-formylamphetamine used in this step of the Leuckart reaction was prepared from 1-phenyl-2-propanone, ammonium carbonate and formic acid (Scheme 3). N-formylamphetamine and hydrochloric acid were heated to reflux for 2 hours to form the free base. Following extraction into toluene, HCl gas was used to form the hydrochloride salt (0.6 g). Washing this product with acetone gave amphetamine in a 37% yield. The spectral data, ^{1}H-NMR, FT-IR (Fig. 4 and 8, appendix), and melting point were consistent with those of 2-amino-1-phenylpropane (amphetamine).

5.2. Conclusion

The final step in the Leuckart reaction of the hydrolysis of N-formylamphetamine was found to give the product 2-amino-1-phenylpropane hydrochloride (amphetamine) in a 37% yield.

5.3. References

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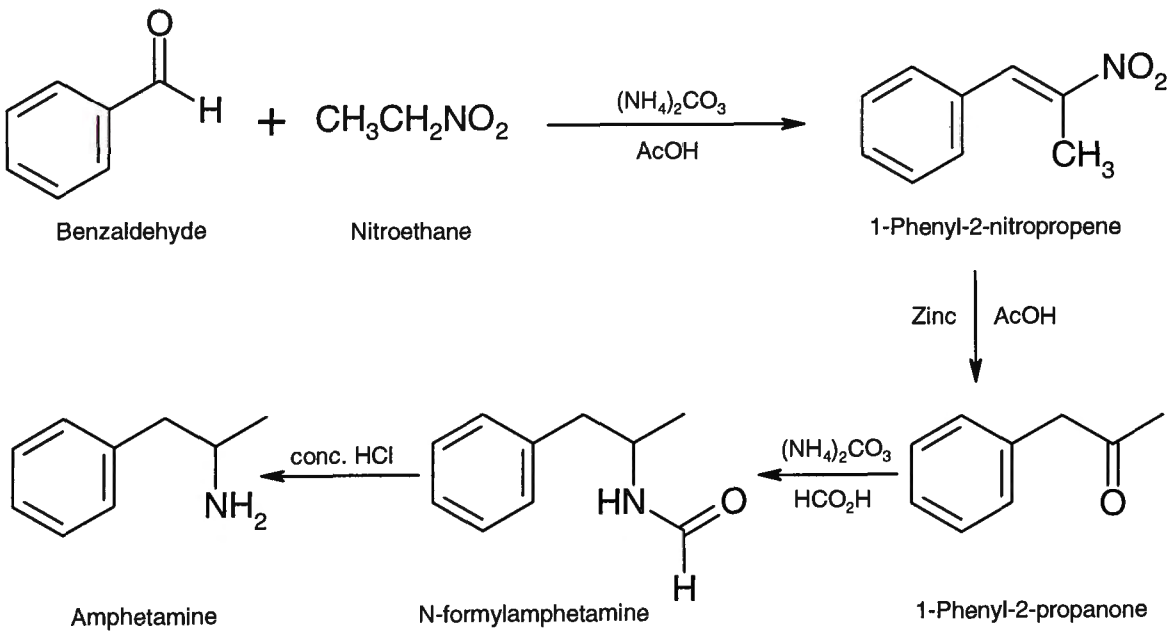
Chapter Six

6. Summary - Synthesis of amphetamine from benzaldehyde

The study presented shows a novel application of the conversion of benzaldehyde to amphetamine using ammonium carbonate and zinc (Scheme 1). The chemicals and apparatus seized from several clandestine laboratories indicated the illicit process was being carried out at up to a kilogram in scale batches, using 'homemade' equipment. The aim of this project was to identify the synthetic process that was used in the preparation of amphetamine from benzaldehyde and to determine the possible yield.

Scheme 1



The scheme above shows the synthetic route that was being employed to manufacture amphetamine. In the initial step benzaldehyde and nitroethane were condensed using ammonium carbonate in acetic acid as the catalyst. The best yield for this reaction was achieved using benzaldehyde, nitroethane and ammonium carbonate in the molar ratio 1.5:1:0.25 and heating under reflux for 6 hr. This reaction gave 1-phenyl-2-nitropropene in a yield of 54% with respect to the nitroethane.

The second reaction used zinc powder in acetic acid to reduce 1-phenyl-2-nitropropene to the ketone (1-phenyl-2-propanone). The nitrostyrene and zinc powder are combined in a molecular ratio of 1:5 and heated under reflux for 2 hr. Following this reaction, steam distillation gave 1-phenyl-2-propanone in a 53% yield.

Tin and iron were found to be useful metals in the substitution of zinc. However zinc powder was determined to be the most efficient metal in the reduction of 1-phenyl-2-nitropropene to 1-phenyl-2-propanone. Further investigation of the substitution of these metals for zinc would be of interest.

1-Phenyl-2-propanone can also be synthesised in a one-pot reaction following the manufacture of 1-phenyl-2-nitropropene *in situ*. Zinc powder and acetic acid can be added to the reaction mixture without prior separation and purification of the nitropropene. 1-Phenyl-2-propanone was obtained following distillation of the crude product in a 44% yield.

Ammonium carbonate is also used as a source of nitrogen, in the reductive amination of 1-phenyl-2-propanone to give N-formylamphetamine. The use of ammonium carbonate in both the first reaction (preparation of 1-phenyl-2-nitropropene) and third reaction, reduces the total number of chemicals needed for the synthesis of amphetamine from benzaldehyde. When ammonium carbonate is combined with formic acid, ammonium formate is generated, a common Leuckart reagent used for the conversion of ketones to their formyl derivatives.

Reacting commercial 1-phenyl-2-propanone with stoichiometric amounts of ammonium carbonate and formic acid gave N-formylamphetamine in a yield of 50%. The use of excess formic acid increased the yield (78%), however lengthened the reaction time by 10 hours. Using impure P2P and ammonium formate as the Leuckart reagent the yield was determined to be between 78-86% by GC-FID analysis, depending whether an excess of formic acid was used. This reaction requires long heating, however may be interrupted and resumed as desired.

The hydrolysis of N-formylamphetamine using hydrochloric acid produced 2-amino-1-phenylpropane (amphetamine) hydrochloride in a 37% yield.

Table 1: Yields of the reactions in the conversion of benzaldehyde to amphetamine.

Precursor	Product	Yield
Benzaldehyde	1-Phenyl-2-nitropropene	54%
1-Phenyl-2-nitropropene	1-Phenyl-2-propanone	53%
1-Phenyl-2-propanone	N-formylamphetamine	78%
N-formylamphetamine	Amphetamine hydrochloride	37%
Benzaldehyde	Amphetamine hydrochloride	8%

The yields for the four steps in the conversion of benzaldehyde to amphetamine are listed in Table 1. The yields of specific interest were those for the manufacture of 1-phenyl-2-nitropropene, 1-phenyl-2-propanone and the overall yield of the conversion of benzaldehyde to amphetamine (8%.). The yields for these reactions were unknown and needed to be determined. The identification and quantitation can be important since higher penalties apply for larger amounts of a specific drug. The yield of a specific reaction can also be used to determine the amount of drug for past and future productions in a seized clandestine laboratory.

This manufacturing technique for amphetamine is relatively simple and requires the operator to have no prior knowledge of chemistry, offers a good chance of success, produces acceptable yields and can be accomplished with inexpensive chemical apparatus. Zinc and ammonium carbonate have been determined as reactants in the manufacture of amphetamine and should be included in any listing of chemicals and ancillary materials known to be used in the illicit manufacture of drugs.

Chapter Seven

Experimental

7. General

Melting points were determined on a Riechert hot stage apparatus and are uncorrected.

Infrared spectra were recorded in the range 4000 to 400 cm^{-1} as KBr discs for solids and single bounce attenuated total reflectance (ATR) for oils, using a Bio-Rad FT-IR, Model FTS 3000 MX.

Nuclear magnetic resonance (NMR) spectra were acquired using a Varian Gemini 200 spectrometer operating at 200 MHz. All NMR spectra were recorded at ambient temperature in deuterochloroform ($CDCl_3$) solution. Chemical shift values are expressed in ppm relative to deuterochloroform (δ 7.26). Signals are described in terms of chemical shift, multiplicity, coupling constants, intensity and assignment. The following abbreviations have been used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad).

Mass spectra were recorded on a Hewlett-Packard 5890 spectrometer mass selective detector. The ionization voltage was 70 eV and the source temperature was 300 °C. The samples were introduced into the mass spectrometer via a gas chromatograph operated in the split mode (20:1) and equipped with a Hewlett-Packard 12.5-m x 0.20-mm i.d. fused-silica column with a 0.33-um film thickness of cross linked methylsiloxane (HP-1). The injector port temperature was 260 °C. The column temperature was held at 70 °C for 2 minutes and programmed to 310 °C at a rate of 20 °C/minute with a hold time of 6 minutes. Samples for GC-MS were prepared by removing an aliquot diluting with water, basified with sodium carbonate if necessary and extracting with dichloromethane. In the description of mass spectra, only molecular ion peaks (M^+), and peaks registering above 10% relative abundance peaks, or the eight most intense peaks were reported in terms of *m/z* and relative abundance. Ions are listed in decreasing order of intensity.

Gas Chromatography Flame Ionization Detection Methodology Quantitative analyses were performed on a Hewlett Packard 5890 gas chromatograph equipped with a Hewlett Packard HP-1 capillary column, cross linked methyl silicone (20m x 0.2 mm x 0.33 μm film thickness), equipped with a flame ionization detector operated with a 75:1 split ratio. The injection port temperature was 250 °C, the column temperature was held at 50 °C for 1 minute and programmed to 300 °C at a rate of 20 °C/minute, detector set at 250 °C. Helium was used as the carrier gas, nitrogen was used as the make up gas. A solution of the internal standard was prepared by accurately weighing approximately 1mg acetophenone and dissolving in 10mL of ethyl acetate. The standard solution of, 1-phenyl-2-propanone was prepared by dissolving a known amount in dichloromethane to give a final concentration of 0.66 mg/mL. For the determination of P2P in crude reactions, samples were prepared by accurately weighing approximately 5 mg into appropriate volumetric flasks to produce a final concentration of 0.5 mg/mL. 50 μL of the internal standard was added to 1 mL of the diluted sample and 5 μL injected into the column to give a response approximately equal to that of the standard P2P response. A similar procedure was used in the quantitation of N-formylamphetamine.

Column chromatography was performed using Merck silica gel 60 with constant proportions of ethyl acetate in hexane as the eluting solvent. Analytical thin layer chromatography (T.L.C.) was carried out using Merck (A.T. 5554) silica gel 60 F_{254} precoated on aluminium sheets. Compounds were routinely detected under short wavelength (254 nm) ultraviolet light.

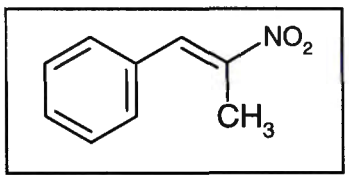
High Performance Liquid Chromatography data was obtained using a Hewlett Packard instrument (Series 1100) using a LiChroCART 125-2 Merck Superspher RP Select B (4 μm) column. Mobile phase consisted of acetonitrile: water: diethylamine (400:600:5, v/v/v) pH 8.0. Column pressure and temperature were 61 Bar and 45° C respectively, flow rate 0.155 mL/ minute, signal was detected using a photo diode array detector at wavelength 214 nm (DAD). Quantitative results were based on peak area using external standards.

7.1. Materials

All chemicals were of reagent grade and solvents were of analytical grade. The internal standard for the GC-FID quantitation, acetophenone, was obtained from Sigma Aldrich.

7.2. Preparation of Compounds

7.2.1. Syntheses of 1-Phenyl-2-nitropropene



Ammonium carbonate as Base

(a) To benzaldehyde (10.6 g, 0.1 mol) and nitroethane (7.5 g, 0.1 mol) in acetic acid (10 mL), ammonium carbonate (0.96 g, 0.01 mol) was added with effervescence and the yellow solution was heated to reflux for 2 hr. The reaction was monitored by GC-MS after 1 and 2 hr. The reaction mixture was cooled in an ice water bath, and the crystalline product (2.85g, 17.5%) was removed by filtration and washed with small amounts of acetic acid. An additional amount was obtained from the mother liquor. The crystalline material was recrystallised from methanol, to give *1-phenyl-2-nitropropene* (3.66 g, 22.5%), m.p. 63-64° C (lit.[1] m.p. 64-65° C).

This reaction was repeated on the ten fold scale to give *1-phenyl-2-nitropropene* in 47% yield.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.45 (s, 3H, CH_3); 7.45 (s, 5H, ArH); 8.1 (s, 1H, vinyl H).

Gas chromatograph retention time: 6.90 minutes.

Mass Spectrum (EI) *m/z*: 163 (13%, M^+), 115 (100 %), 91 (40%), 105 (32%), 51 (21 %), 63(17%), 65(16%), 66 (15 %).

Infrared spectrum ν_{max} / cm^{-1}: Aromatic C-H 3000, C=C 1652, conj NO_2 1517.

(b) To benzaldehyde (7.96 g, 75 mmol) and nitroethane (3.75 g, 50 mmol) in acetic acid (10 mL), ammonium carbonate (1.2 g, 12.5 mmol) was added with effervescence and the yellow solution was heated under reflux for 6 hr. Cooling the reaction mixture gave the first crop of crystals (3.46 g, 42%). The mother liquor was poured into water (200 mL) and the mixture was extracted with toluene (3 x 30 mL). The product recovered was subjected to rapid silica filtration (eluent: 10% ethyl acetate/hexane) to yield an additional 0.97 g (total 4.43 g, 54%).

Butylamine as Base

(a) To benzaldehyde (15.9 g, 0.15 mol) and nitroethane (7.5 g, 0.1 mol) in acetic acid (10 mL), butylamine (1.85 g, 0.025 mol) was added. The yellow solution was heated to reflux for 3 hr. The reaction mixture was cooled, poured into water (200 mL) and extracted with toluene (3 x 50 mL). The organic portion was dried over anhydrous sodium sulfate and the solvent evaporated. The product was recrystallised from methanol (7.05 g, 43%). An additional 1.66 g of product was recovered from the mother liquor (total 8.66 g, 53%).

(b) To benzaldehyde (3.18 g, 0.03 mol) and nitroethane (1.5 g, 0.02 mol) in acetic acid (5 mL), butylamine (0.15 g, 2 mmol) was added. The reaction mixture was heated to reflux for 4 hr. The reaction was cooled to room temperature and a small amount of water (5 mL) was added dropwise. The precipitate was filtered and rinsed with ice-cold acetic acid to afford the first crop (1.22 g). The mother liquor was treated as described above to yield a brown crystalline material. Recrystallisation from methanol yielded an additional 0.82 g. (total 2.04 g, 62%).

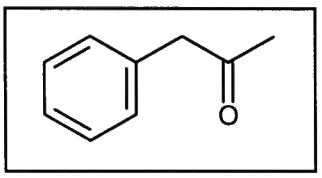
Ammonium carbonate as Base

Experiment based on handwritten notes seized from a clandestine site

To a solution of ammonium carbonate (2.5 g, 26 mmol) in glacial acetic acid (25 mL), nitroethane was added (7.28 g, 97 mmol) with swirling. Benzaldehyde (10.4 g, 98 mmol) was added and the reaction mixture was heated under reflux for 1 hr. The reaction mixture was poured onto crushed ice. When the ice had melted, the water was decanted and the yellow solution was poured into a Buchner funnel where the product crystallised (6.21 g, 39%).

7.2.2. Syntheses of 1-Phenyl-2-propanone

The proportion of 1-phenyl-2-propanone from each reaction were determined by GC-FID.



To 1-phenyl-2-nitropropene (1.6 g, 0.01 mol) in acetic acid (10 mL), zinc powder (3.3 g, 0.05 mol) was added portionwise. The reaction mixture evolved gas and heat turning a red colour. After heating under reflux for 1.5 hr. the mixture was poured into water (200 mL). The solution was basified with sodium carbonate and was extracted with dichloromethane (3 x 30 mL). The product recovered was a red oil (1.24 g), containing 1-phenyl-2-propanone (0.26 g; yield 19%).

Gas chromatograph retention time: 4.27 minutes.

Mass Spectrum (EI) *m/z*: 134 (11%, M^+), 43(100 %), 91 (46%), 65 (19 %), 92 (15%), 63 (10%).

Infrared spectrum ν_{max} / cm^{-1} Aromatic C-H 3032, C=O 1713.

Variation in amount of zinc

To four separate test tubes, each containing 1-phenyl-2-nitropropene (0.8 g, 5 mmol) in acetic acid (10 mL), zinc powder in 1,2,3 and 4 equivalents was added. These were heated to 105° C over a 2 hr. period and samples were monitored by GC-MS at 1 hr. (55 °C), 2 hr. (105 °C).

Other metals

To four separate test tubes, each containing 1-phenyl-2-nitropropene (0.8 g, 5 mmol) in acetic acid (10 mL), one equivalent of each metal was added. Sn (0.59 g, 5 mmol), Al (0.14 g, 5 mmol), Fe (0.28 g, 5 mmol), and Zn (0.33 g, 5 mmol) were added individually to the different test tubes which were heated to 100-105° C for 2 hr. Samples were monitored by GC-MS at 1 and 2 hr.

Two phase solvent system

To 1-phenyl-2-nitropropene (1.0 g, 6.1 mmol), zinc powder (0.8 g, 12 mmol) in toluene (10 mL), hydrochloric acid (10 mL, 2 M) was added dropwise. The reaction mixture was heated to reflux in an oil bath for 3 hr. The reaction mixture was poured into water (100 mL) and the product was recovered with toluene to yield a yellow oil (0.71 g, 53%). Analysis by GC-FID indicated that the product contained 1-phenyl-2-nitropropene (31%), 1-phenyl-2-propanone (11%) and 1-phenyl-2-propanone oxime (1%).

Reactivity of 1-phenyl-2-propanone

To 1-phenyl-2-propanone (1.34 g, 0 01 mol) in acetic acid (10 mL), zinc powder (3.3 g, 0.05 mol) was added. The resulting solution was refluxed for 1 hr. Samples for GC/MS were taken at 1 hr. Analysis by GC-MS showed only starting material.

Varying the combination of reactants

Zinc powder in acetic acid

To zinc powder (3.3 g, 0.05 mol) in acetic acid (5 mL), a solution of 1-phenyl-2-nitropropene (1.6 g, 0.01 mol) in acetic acid (5 mL) was added in portions. The resulting solution was refluxed for 12 hr. The reaction mixture was poured into water (200 mL) and extracted with toluene (2 x 30 mL). The product recovered was a red oil (1.36g). Analysis by GC-FID indicated that the product contained 1-phenyl-2-nitropropene (61%) and 1-phenyl-2-propanone (6%).

Refluxing solution of zinc powder in acetic acid

To zinc powder (3.3 g, 0.05 mol) in boiling acetic acid (10 mL), a solution of 1-phenyl-2-nitropropene (1.6 g, 0.01 mol) in acetic acid was added down the condenser. The reaction mixture was heated to reflux for 2 hr. and the reaction was monitored by GC-MS every 15 min. Recovery of the product with toluene gave a yellow solid (1.3g,). Analysis by GC-FID indicated that the product contained both 1-phenyl-2-nitropropene (84%) and 1-phenyl-2-propanone (23%).

Increasing the reaction time to 4 hours gave *1-phenyl-2-propanone* (0.14g, 11%).

Extraction with toluene

To 1-phenyl-2-nitropropene (1.6 g, 0.01mol) in acetic acid (10 mL) zinc powder (3.3 g, 0.05 mol) was added in portions. The reaction mixture was heated to reflux for 2 hr. Recovery of the product with toluene afforded a red oil (1.36 g), containing 1-phenyl-2-propanone (0.37g; yield 27%).

This reaction was repeated on a five fold scale to give a crude product (6.11g) containing 1-phenyl-2-propanone (2.2g; yield 32%).

Synthesis of 1-Phenyl-2-propanone

(a) Purification by vacuum distillation

To 1-phenyl-2-nitropropene (8.15 g, 0.05 mol) in acetic acid (50 mL), zinc powder (16.34 g, 0.25 mol) was added in portions. Heat was evolved from the reaction mixture, which turned red from an initial yellow colour. After heating under reflux for 3 hr., an additional 1 equivalent (3.25g) of zinc powder was added and heating was continued for 2 hr. Recovery of the product with toluene afforded a dark red oil (7.04g). Vacuum distillation of this oil yielded *1-phenyl-2-propanone* (2.91 g, 43%); b.p^{14} 100-101 °C (lit.[2] b.p^{14} 100-101 °C).

(b) Purification by silica filtration

To 1-phenyl-2-nitropropene (1.6 g, 0.01 mol) in acetic acid (10 mL), zinc powder (3.3g, 0.05mol) was added in portions and the mixture was heated under reflux. At 2 hours, an additional equivalent (0.66 g) of zinc powder was added to the mixture and heating was continued for 1 hr. The reaction was monitored by GC-MS at 0, 1, 2, 3 hr. Recovery of the product with toluene afforded a red oil (1.05 g) which was purified by column chromatography on silica gel (eluent: 10% ethylacetate/hexane), to give *1-phenyl-2-propanone* as a yellow oil (0.35 g, 26%).

(c) Purification by steam distillation

To 1-phenyl-2-nitropropene (32.64 g, 0.2 mol) in acetic acid (200 mL), zinc powder (65.37 g, 1 mol) was added in portions. The yellow solution turned a deep red with evolution of heat. The mixture was heated under reflux for 2 hr. and monitored by GC-MS at 1 and 2 hr. Water (100 mL) was added to the reaction flask and the mixture was steam distilled to yield *1-phenyl-2-propanone* as a yellow oil (14.32 g, 53%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.15 (s, 3H, CH_3); 3.7 (s, 2H, CH_2); 7.3 (m, 5H, ArH).
Gas chromatograph retention time: 4.28 minutes.
Mass Spectrum (EI) *m/z*: 134 (11%, M^+), 43(100 %), 91 (46%), 65 (19 %), 92 (15%), 63 (10%).
Infrared spectrum ν_{max} / cm^{-1} Aromatic C-H 3030, C=O 1709.

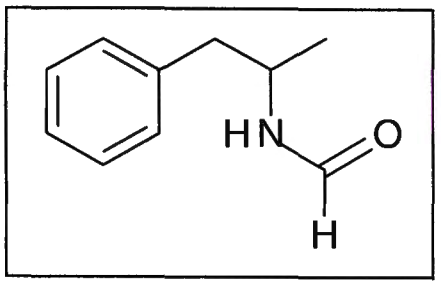
Clandestine method (experiment based on handwritten notes)

To a solution of acetic acid (20 mL) and water (2 mL), zinc powder (2.5 g, 38.3 mmol) was added. The zinc was allowed to react and 1-phenyl-2-nitropropene (2.5 g, 15.3 mmol) was added. The mixture was then heated to reflux for 1 hr. The reaction was cooled, water (170 mL) was added and mixture was steam distilled. The distillate was basified with sodium carbonate, extracted with toluene (2 x 20 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to yield *1-phenyl-2-propanone* as an orange oil (0.8 g, 39%).

One-pot conversion of benzaldehyde to 1-phenyl-2-propanone

To benzaldehyde (8.52 g, 0.08 mmol) and nitroethane (4.05 g, 0.054 mol) in acetic acid (20 mL), ammonium carbonate (0.48 g, 5 mmol) was added with effervescence. The yellow solution was heated to reflux for 1 hr. The reaction mixture was cooled in a water bath while zinc powder (16.3 g, 0.25 mol) was added slowly (vigorous reaction). The reaction mixture was refluxed for 1 hr, cooled and poured into water (200 mL). The mixture was basified with sodium carbonate and extracted with dichloromethane (2 x 75 mL). The product recovered was a red oil (6.32 g), which was distilled to afford *1-phenyl-2-propanone* (3.17 g, 44%).

7.2.3. Syntheses of N-Formylamphetamine



7.2.3.1 Leuckart reactions using commercial 1-phenyl-2-propanone

Formamide

A solution of 1-phenyl-2-propanone (1.34 g, 0.01 mol) and formamide (2.25 g, 0.05 mol) was heated to 160° C under reflux conditions for 7.5 hr. The reaction mixture was poured into water (100 mL) and extracted with toluene (3 x 30 mL). The organic material recovered was an orange oil (1.65 g), that, by GC-MS, appeared to be starting material.

Increasing the reaction time to 12 hours afforded an orange oil (1.24g). This product was washed with hexane to give *N-formylamphetamine* (0.96 g, 59%).

Formamide and formic acid

1-Phenyl-2-propanone (1.34 g, 0.01 mol), formamide (2.25 g, 0.05 mol) and formic acid (0.46 g, 0.01 mol) were combined and heated to 160° C for 2 hr (reaction over heated to 200° C). The reaction was monitored by GC-MS every 30 minutes. The reaction mixture was cooled, poured into water (100 mL) and extracted with dichloromethane (3 x 25 mL). The yellow oil (1.20 g) recovered was subjected to column chromatography on silica gel. Elution with methanol (200 mL) and concentrated ammonia (1% v/v) afforded an orange oil (0.74 g). This product was washed with hexane to give *N-formylamphetamine* (0.59 g, 36%).

This experiment was repeated refluxing for 4 hours to give *N-formylamphetamine* (1.62 g, 99%).

This reaction was repeated refluxing for 2.5 hours to give a dark brown oil (1.44g). The reaction was monitored by GC-MS and appeared essentially complete after 1 hr. The oil was washed with hexane (3 x 25 mL) the solvent evaporated to yield a light brown oil (1.16g, 71%) which appeared to be N-formylamphetamine when analysed by GC-MS and ^{1}H-NMR.

Gas chromatograph retention time: 7.08 minutes.

Mass Spectrum (EI) *m/z*: 163 (1%, M^+), 44 (100%), 72 (96%), 118 (84%), 91 (35%), 65(19%), 117(15 %).

Infrared spectrum ν_{max} / cm^{-1} Aromatic C-H 3000, N-H 3265, C=O 1651.

Ammonium formate

To 1-phenyl-2-propanone (1.34 g, 0.01 mol) in formic acid (2.3 g, 0.05 mol), ammonium carbonate (4.8 g, 0.05 mol) was added portionwise. The reaction was heated to reflux for 8 hr. The reaction mixture was cooled, poured into water (100 mL) and extracted with toluene, then dried over anhydrous sodium sulfate and the solvent evaporated to give *N-formylamphetamine* (0.81 g, 50%).

Ammonium formate and excess formic acid (distillation of water)

To 1-phenyl-2-propanone (1.34 g, 0.01 mol) in formic acid (8.54 g, 0.19 mol) ammonium carbonate (4.8 g 0.05 mol) was added portion wise, reagents dissolved upon heating. Heating was continued for 8 hr at 160° C. The apparatus was changed to a distillation setup. Water was distilled at 105° C and the reaction was further refluxed for 3 hr. The reaction was quenched with water (200 mL), basified with sodium carbonate and extracted with toluene (3 x 30 mL). Removal of the solvent gave *N-formylamphetamine* (0.81 g, 50%).

Ammonium formate and excess formic acid

To 1-phenyl-2-propanone (1.34 g, 1.34 mL, 0.01 mol) in excess formic acid (8.54 g, 0.19 mol), ammonium carbonate (4.8 g, 0.05 mol) was added portionwise. The reaction mixture was heated under reflux for 24 hr, and was monitored by GC-MS at 5 and 24 hr. Recovery of the product gave *N-formylamphetamine* (1.27 g, 78%).

7.2.3.2 Leuckart reactions using impure/crude 1-phenyl-2-propanone

Yields of N-formylamphetamine are based on the content (32%) of 1-phenyl-2-propanone in the starting material.

Formamide

1-Phenyl-2-propanone (1.34 g, 0.01 mol), formamide (2.25 g, 0.05 mol) were heated under reflux for 11 hr. The mixture was cooled, poured into water and extracted with toluene (3 x 30 mL), dried over anhydrous sodium sulfate and the solvent evaporated. The crude product recovered (0.51 g), contained *N-formylamphetamine* (0.240 g; yield 39%).

Formamide and formic acid

1-Phenyl-2-propanone (1.34 g, 0.01 mol), formamide (2.25 g, 0.05 mol) and formic acid (0.46 g, 0.38 mL, 0.01 mol) were heated under reflux for 3 hr. The reaction was monitored by GC-MS every hour. The mixture was cooled, poured into water (100 mL), basified with sodium carbonate, extracted with toluene (3 x 30 mL), dried over anhydrous sodium sulfate and the solvent evaporated. The crude product recovered (0.78g), contained *N-formylamphetamine* (0.101 g; yield 19%).

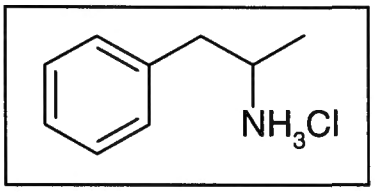
Ammonium formate

To 1-phenyl-2-propanone (1.34 g, 0.01 mol), in formic acid (2.3 g, 0.05 mol) ammonium carbonate (4.8 g. 0.05 mol) was added portionwise. The reaction was heated under reflux for 14 hr. The crude product recovered (1.57 g), contained *N-formylamphetamine* (0.45 g; yield 86%).

Ammonium formate in excess formic acid

To 1-phenyl-2-propanone (1.34 g, 0.01mol) in excess formic acid (8.54 g, 0.19 mol) ammonium carbonate (4.8 g, 0.05 mol) was added portionwise. The reaction was heated under reflux at a temperature of 160° C for four days at 6 hours a day. The crude product recovered (1.35 g), contained *N-formylamphetamine* was (0.405 g; yield 78%).

7.2.4 Synthesis of Amphetamine hydrochloride



N-Formylamphetamine (1.31g, 8.03 mmol) and concentrated 10M HCl (10mL) were combined and heated to 130° C for 2 hr. The reaction was cooled, poured into water (200mL). This solution was basified with sodium carbonate and extracted into toluene (3 x 50mL), then dried over anhydrous sodium sulfate. HCl gas was generated (NaCl and concentrated sulfuric acid) was bubbled through the solution until a precipitate was observed, the solvent was evaporated to afford 2-amino-1-phenylpropane hydrochloride as a brown solid (0.6 g) which was recrystallised from acetone to give a white solid m.p. 145-147° C (lit.[3] 146-147° C). HPLC analysis indicated the purity of the hydrochloride salt to be 82%, the yield of this reaction was (0.49 g, 37%).

^{1}H NMR (200 MHz) δ: 1.4 (d, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.55 (m, 1H, CH), 7.3 (m, 5H, ArH).

Gas chromatograph retention time: 4.30 minutes.

Mass Spectrum (EI) *m/z*: 135 (0.005%, M^+), 44 (100%), 91 (36%), 65 (27%), 42 (18%), 51 (11%).

Infrared spectrum ν_{max} / cm^{-1} Aromatic C-H 3000, N-H 3450.

7.3. References

1. Gairaud, C.B. and Lappin, G.R., "The Synthesis of ω-Nitrostyrenes", *Journal of Organic Chemistry*, 1953, 18, 1-3.

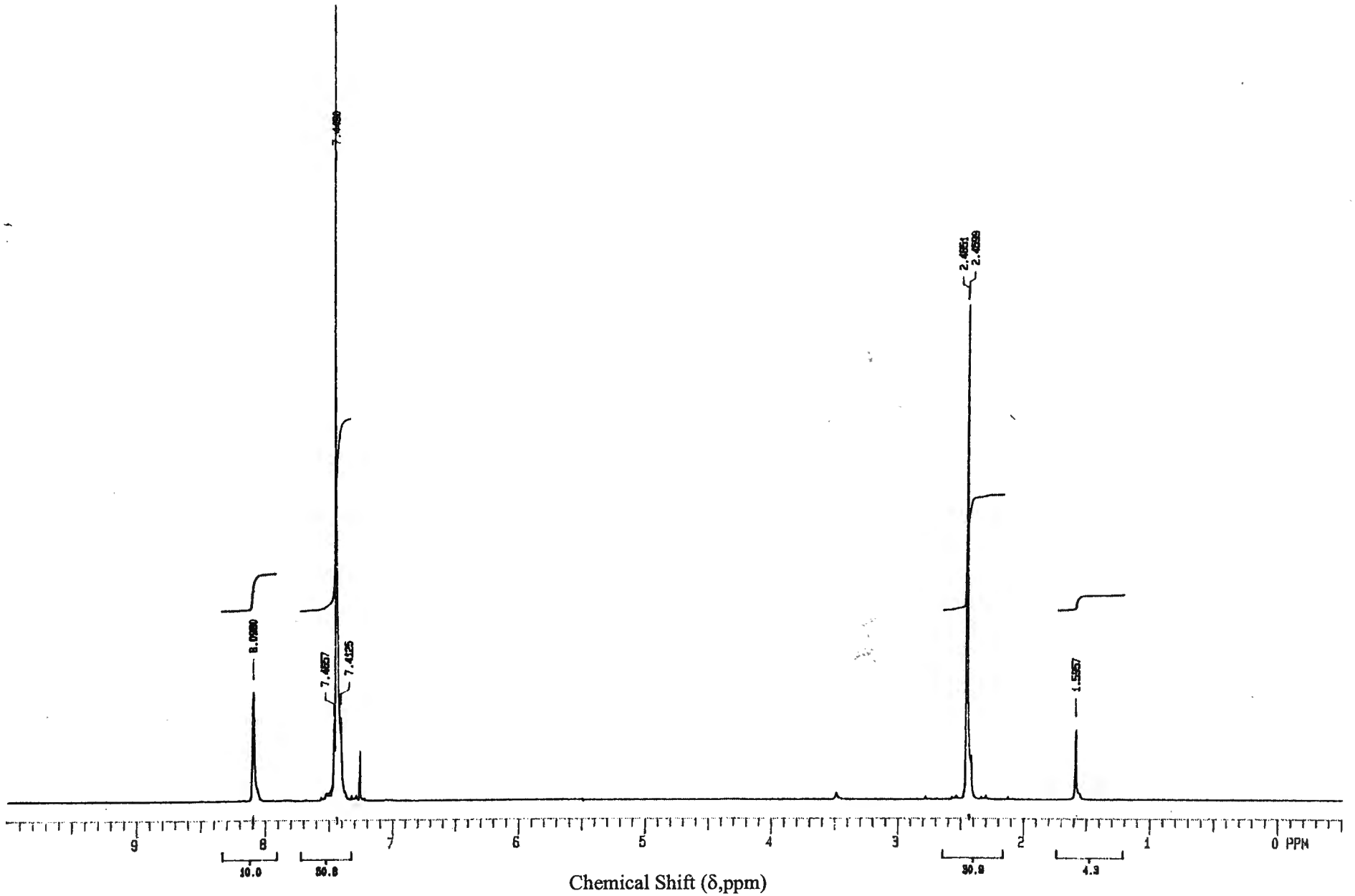
2. The Merck Index Twelfth Edition, 1996, An Encyclopedia of Chemicals, Drugs and Biologicals, Merck Research Laboratories division of Merck & Co., Inc., Whitehouse Station, NJ.

3. Heilbron and Bunbury, 1953, Dictionary of Organic Compounds, Volume 4, Eyre and Spottiswoode, London.

Appendix

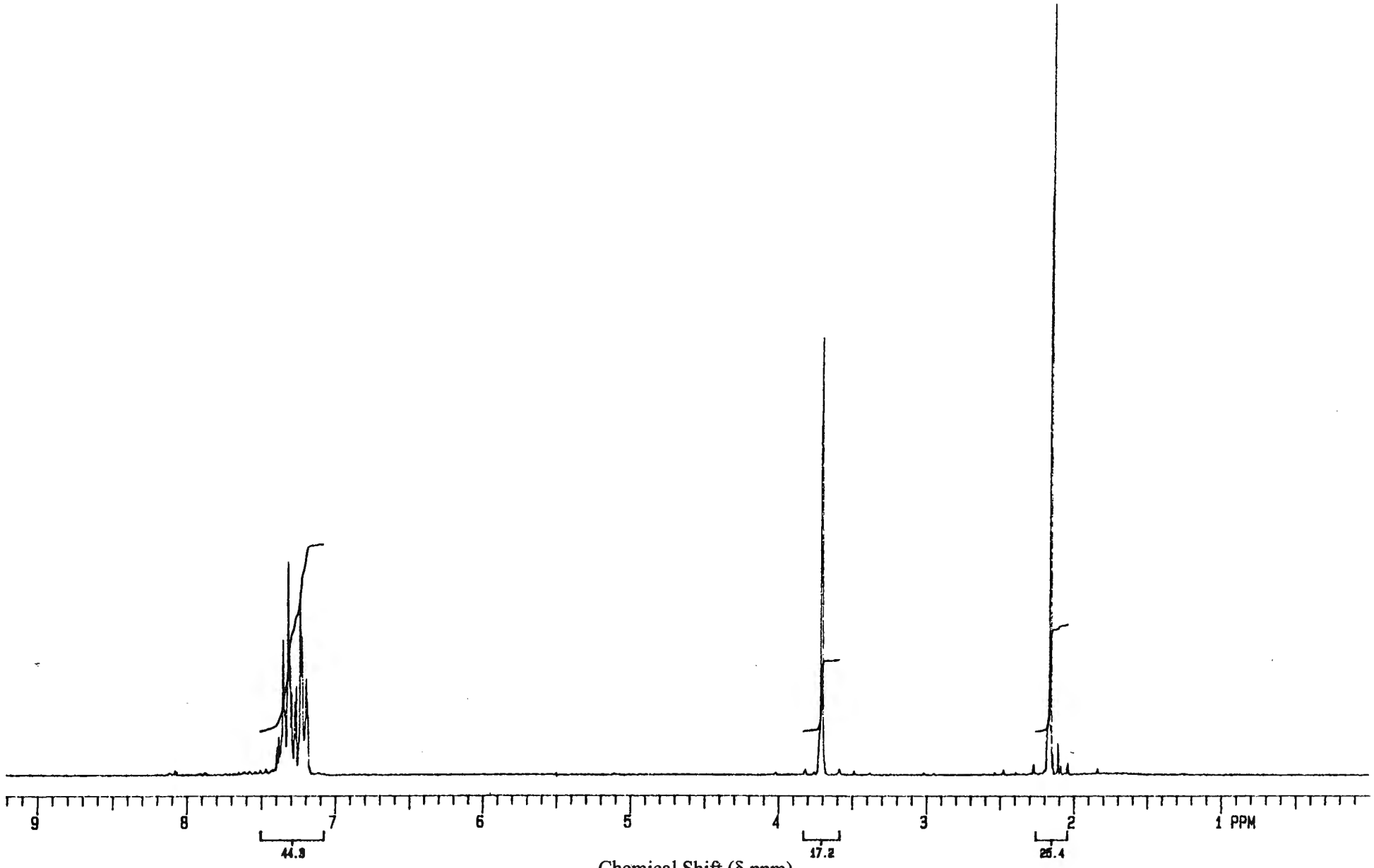
^{1}H-NMR spectra

FT-IR spectra



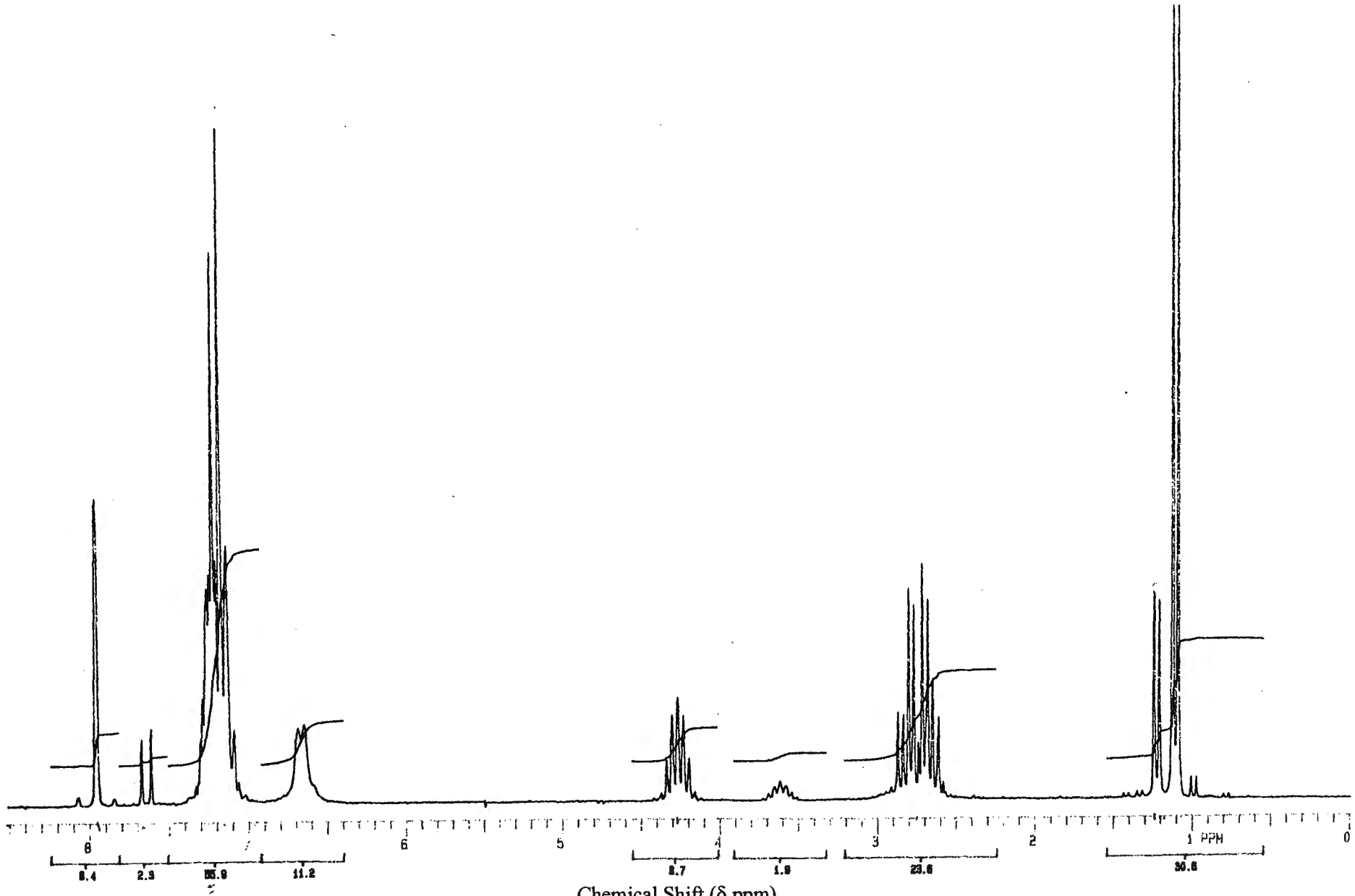
Chemical Shift (δ,ppm)

Fig. 1. ^{1}H-NMR spectrum of 1-phenyl-2-nitropropene. 200 MHz ($CDCl_3$).



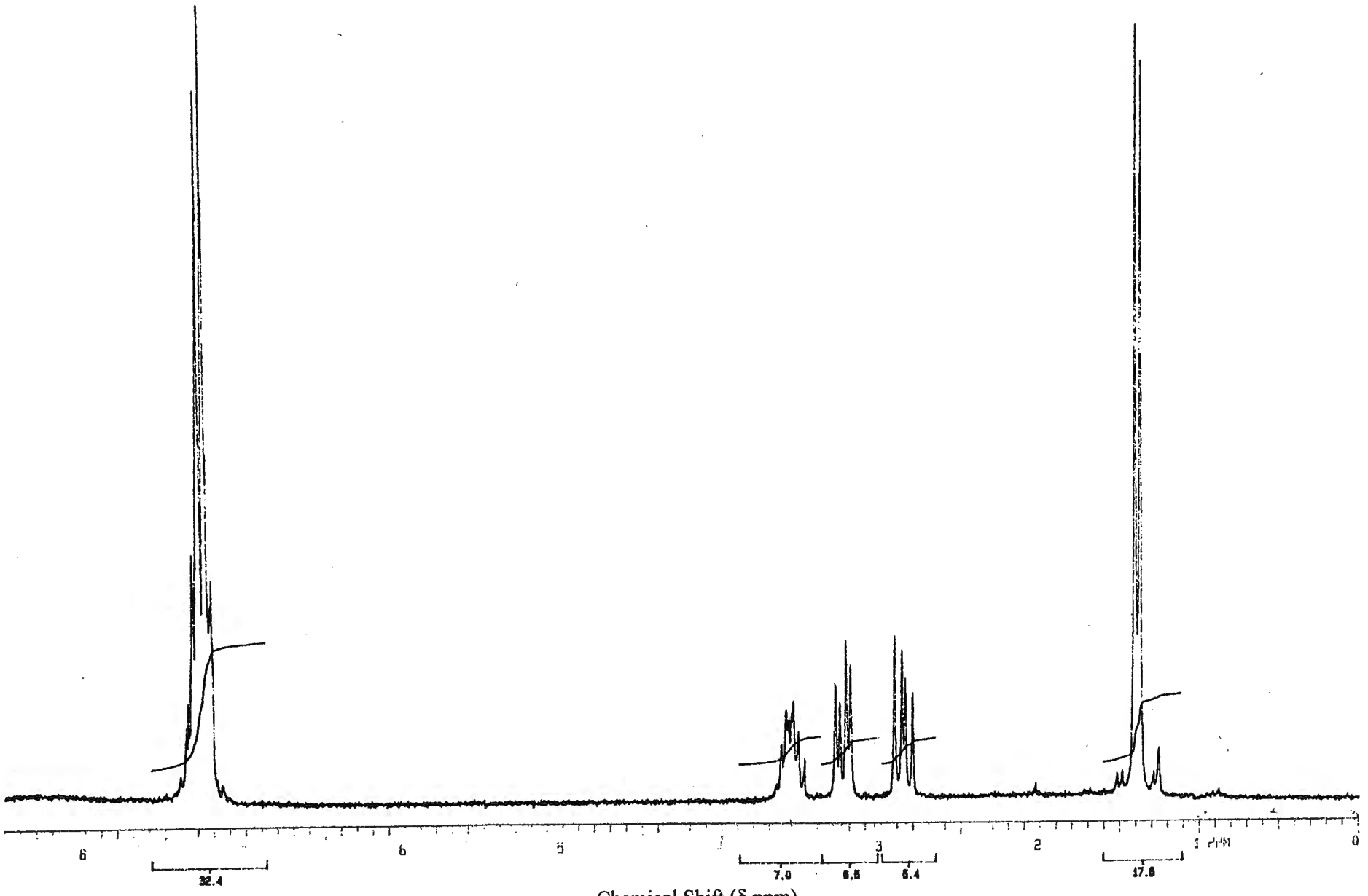
Chemical Shift (δ,ppm)

Fig. 2. ^{1}H-NMR spectrum of 1-phenyl-2-propanone. 200 MHz ($CDCl_3$).



Chemical Shift (δ,ppm)

Fig. 3. ^{1}H-NMR spectrum of N-formylamphetamine. 200 MHz ($CDCl_3$).



Chemical Shift (δ,ppm)

Fig. 4. ^{1}H-NMR spectrum of amphetamine hydrochloride. 200 MHz ($CDCl_3$).

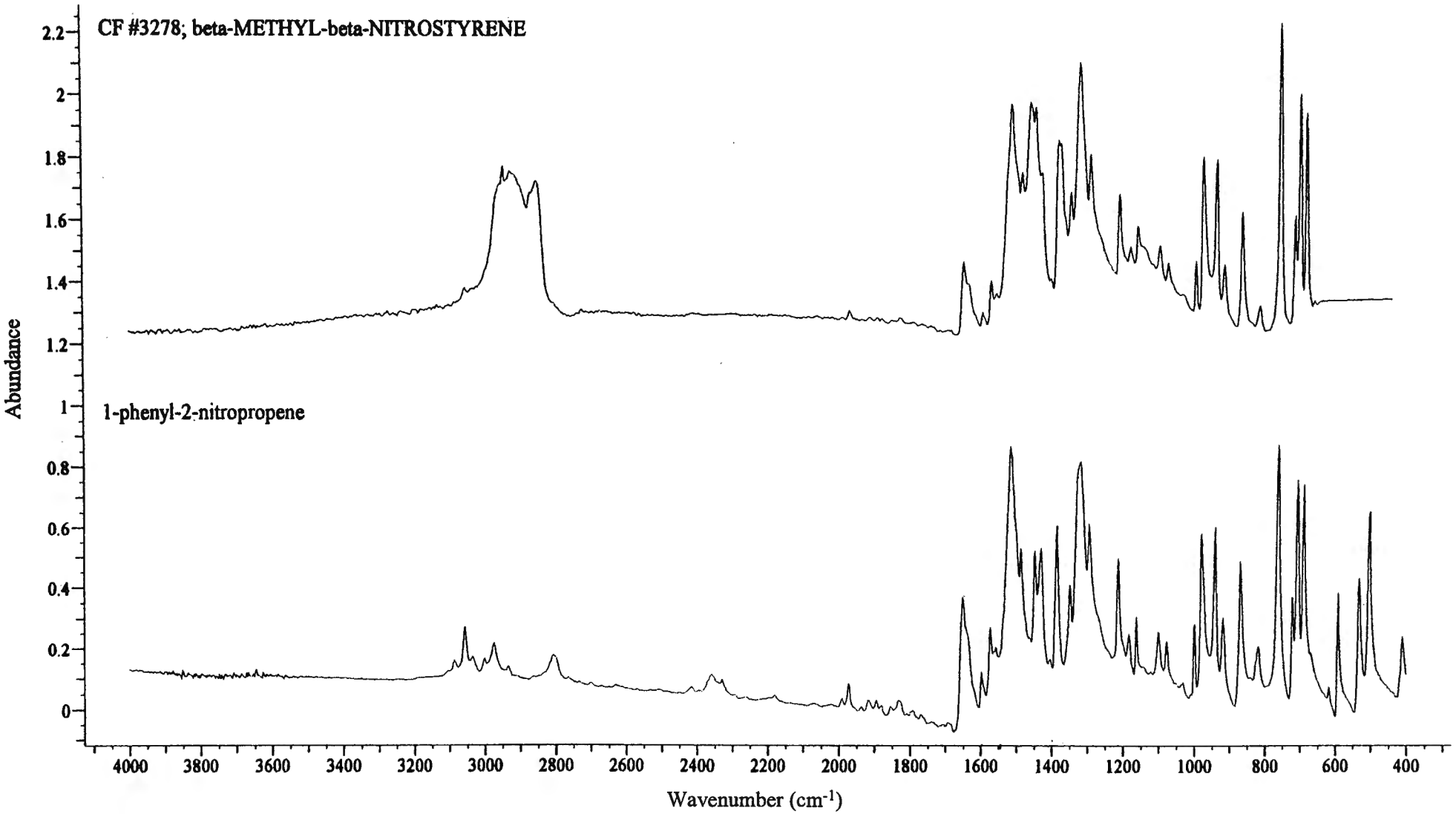


Fig. 5. FT-IR spectra. Comparison of 1-phenyl-2-nitropropene vs known library spectrum.

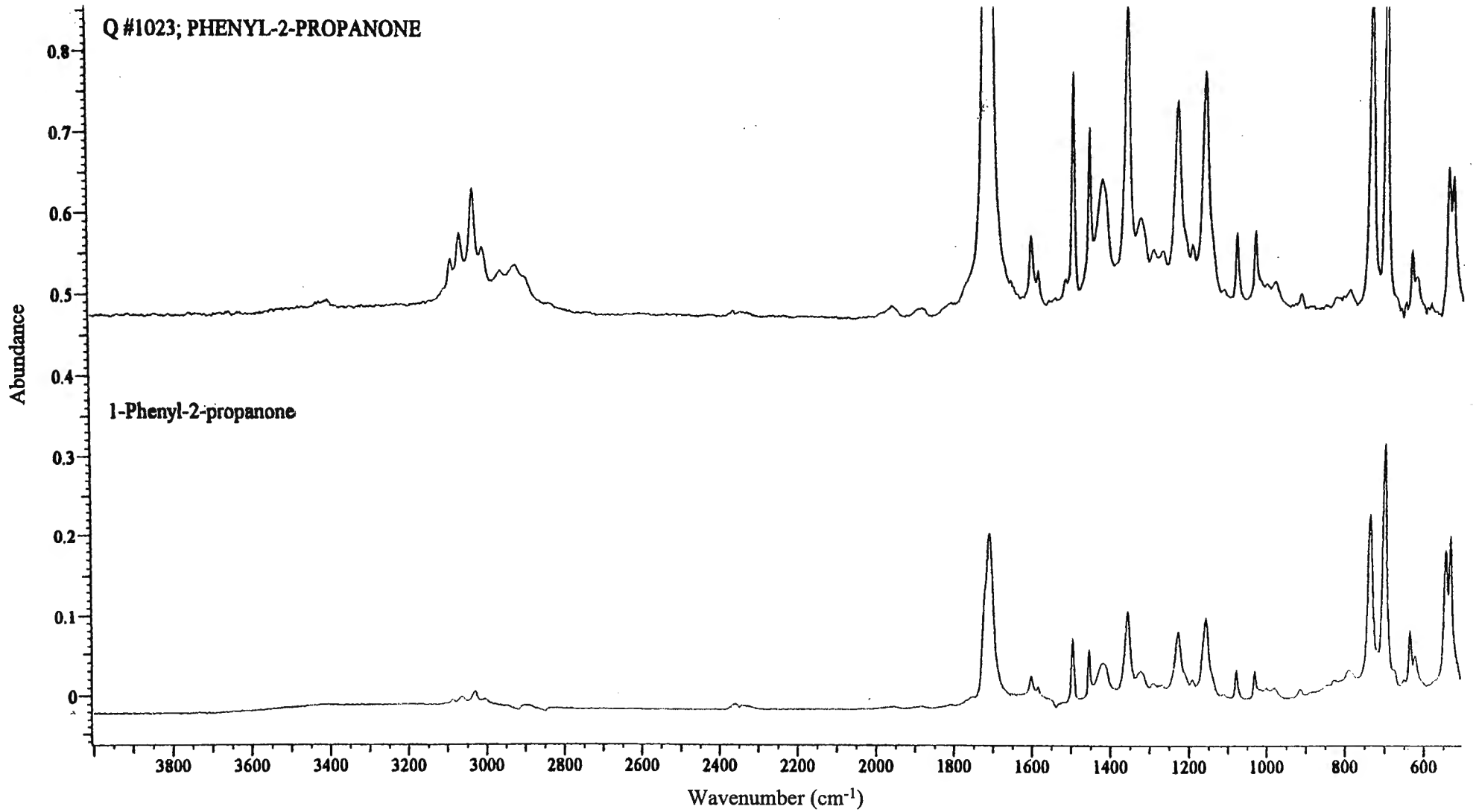


Fig. 6. FT-IR spectra. Comparison of 1-phenyl-2-propanone vs known library spectrum.

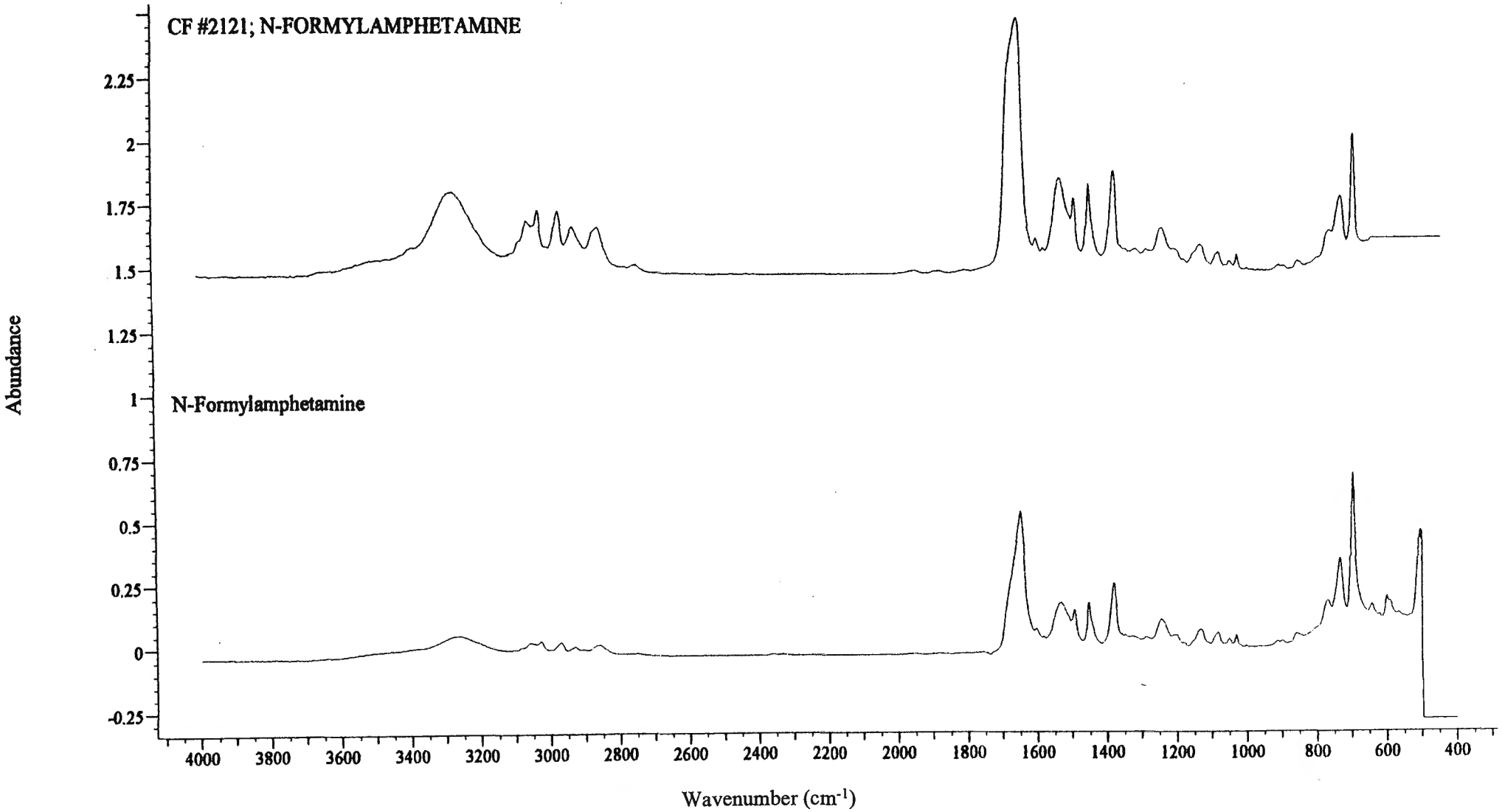


Fig. 7. FT-IR spectra. Comparison of N-formylamphetamine vs known library spectrum.

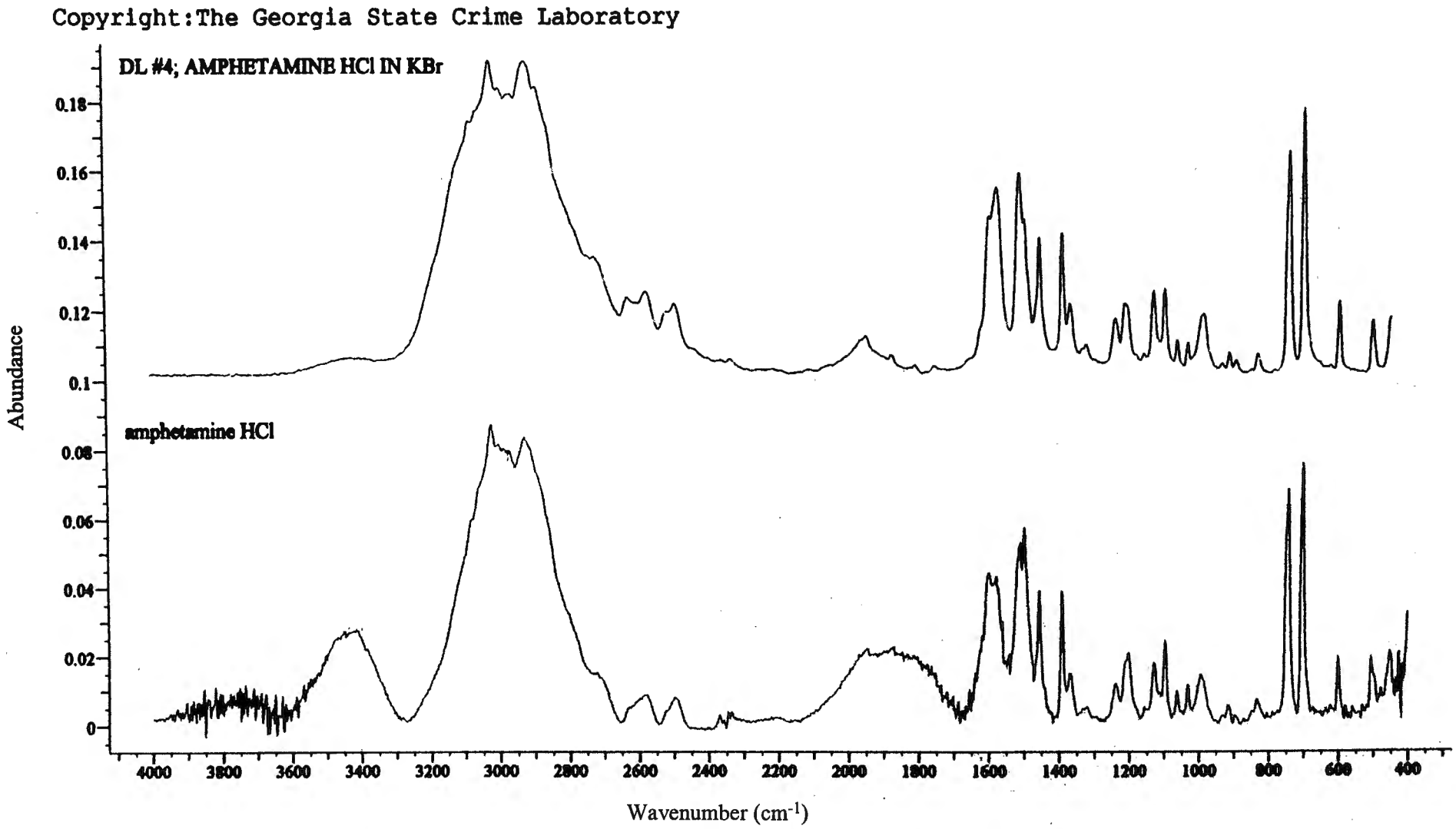


Fig. 8. FT-IR spectra. Comparison of Amphetamine vs known library spectrum.