Gas Chromatographic and Mass Spectral Analysis of Amphetamine Products Synthesized from 1-Phenyl-2-Nitropropene

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Abstract
The conversion of 1-phenyl-2-nitropropene to amphetamine is investigated under a variety of reaction conditions using gas chromatography–mass spectrometry (GC–MS). This versatile intermediate is prepared by treating benzaldehyde with butylamine and nitroethane. GC–MS analysis revealed that amphetamine is produced as the major product upon catalytic reduction of 1-phenyl-2-nitropropene. However, a number of partial reduction products are also present in the mixture. Reduction of the nitropropene with a 5 molar excess of lithium aluminum hydride yields 1-phenyl-2-propanoxime as the major component. A variety of other partial reduction products and products of competing reactions are also present in this product mixture, as well as amphetamine. When this reduction is carried out with a large excess of lithium aluminum hydride, amphetamine is formed as the major product. 1-Phenyl-2-nitropropene is also converted to the ketone, 1-phenyl-2-propanone, by partial reduction and hydrolysis. Amination of this ketone under Leuckart and reductive amination conditions provide amphetamine as the principle product. GC–MS analysis reveals that these samples also contain several by-products characteristic of these routes of synthesis.

Introduction

Amphetamine and methamphetamine remain popular drugs of abuse in the United States and abroad (1). Although a variety of synthetic methods are known for the production of amphetamine-type compounds (2), one of the most common approaches used by clandestine laboratory operators involves the amination of phenyl-2-propanone (P-2-P) under reducing conditions (Scheme 1, Method A). This typically involves heating P-2-P with formamide for amphetamine or methylformamide for methamphetamine to yield the racemic amphetamine products. Furthermore, this process can produce several other by-products including 4-methyl-5-phenylpyrimidines and α-benzylphenethylamines (2). The 4-methyl-5-phenyl-pyrimidines form as a result of competing reactions in the amination process. The α-benzylphenethylamines form from amination of dibenzylketone, an impurity introduced in the clandestine preparation of the P-2-P precursor. Because P-2-P is controlled, clandestine chemists often prepare this precursor by treating phenylacetic acid with acetic anhydride (3) (Scheme 1, Method A). In the course of this synthesis, dibenzylketone forms in a competing reaction and is usually not removed prior to using the P-2-P product mixture in amination reactions. Thus, both amphetamines and α-benzylphenethylamines are obtained upon amination of the crude P-2-P intermediate (4).

Another route commonly used by clandestine chemists for the synthesis of amphetamine-type compounds involves hydrogenolysis of 1-phenyl-1-hydroxy-2-propanamine precursors such as the ephedrines, pseudoephedrines, norephedrines, norpseudoephedrines, or the corresponding 1-phenyl-1-chloro-2-propanamines (Scheme 1, Method B) (2,5,6). The products formed using this approach will have the same stereocchemical configuration at the 2-position as the starting 1-phenyl-1-hydroxypropanamine, and thus they may be obtained as a single enantiomer, unlike the amination method (5,6). Also, amphetamine products prepared by this route may contain contaminants or by-products unique to this method such as the intermediate, 1-phenyl-1-chloropropanamine. Based on these considerations, it is clear that the synthetic origin of illicitly manufactured amphetamine products may be determined by identification of the stereochemical configuration of the amphetamines and identification of contaminants and by-products present in the sample.

In recent years, there have been an increasing number of reports of alternative methods for the preparation of amphetamine-type compounds (7,8). One alternative approach encountered frequently involves the use of the versatile precursor 1-phenyl-2-nitropropene (β-methyl-β-nitrostyrene) (6). This precursor can be prepared in a simple reaction using readily available and uncontrolled starting materials, such as benzaldehyde, nitroethane, and a base. Once formed, this precursor may be converted directly to amphetamine under re-
Reducing conditions or used to synthesize P-2-P, which may be aminated to yield amphetamine derivatives (Scheme 2). In this report, a number of methods that may be used to convert 1-phenyl-2-nitroprene to amphetamine have been studied.

Gas chromatographic–mass spectral (GC–MS) analyses of the products obtained from these reactions allow for complete determination of product composition and provide analytical profiles that may be of value for the identification of amphetamine products synthesized from 1-phenyl-2-nitroprene.

**Experimental**

**Reagents and chemicals**

All reagents used for the synthetic studies were obtained from Aldrich Chemical (Milwaukee, WI). The solvents used were purchased from Fisher Scientific (Fair Lawn, NJ).

**Gas chromatography–mass spectrometry**

GC–MS analyses were performed using a Hewlett-Packard 5970B mass selective detector (Wilmington, DE). The ionization voltage was 70eV, and the source temperature was 220°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-m × 0.20-mm i.d. fused-silica column with a 0.33-µm film thickness of methylsilicone (HP-1). The column temperature was held at 70°C for 2 min and programed to 170°C at a rate of 10°C/min and from 170°C to 275°C at a rate of 25°C/min with a hold time of 2 min. The injector port temperature was 175°C.

**1-Phenyl-2-nitroprene**

A solution of benzaldehyde (7.1 mL, 70 mmol) and butylamine (26 mL, 256 mmol) in benzene (150 mL) was stirred at reflux for 6 h using a Dean–Stark trap to remove water. The reaction mixture was evaporated to dryness to yield the imine as a yellow oil. The oil was dissolved in glacial acetic acid (20 mL), and nitroethane (5.0 mL, 70 mmol) was added. This mixture was stirred at reflux for 1 h, then cooled to room temperature, poured over crushed ice (100 mL), and acidified to pH 1 (with concentrated HCl). The resulting dark green precipitate was isolated by filtration, washed with water (50 mL), and recrystallized from 2-propanol to yield 1-phenyl-2-nitroprene as yellow needles (6.9 g, 61%).

**Catalytic reduction of 1-phenyl-2-nitroprene**

A solution of 1-phenyl-2-nitroprene (200 mg, 1.2 mmol) in ethanol (50 mL), containing concentrated HCl (3 drops) and 5% palladium on carbon (100 mg), was shaken under a hydrogen atmosphere (48 psi initially) on a Parr apparatus for 16 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to yield an orange oil that was analyzed directly by GC–MS.
LAH reduction of 1-phenyl-2-nitropropane

A solution of 1-phenyl-2-nitropropane (1.2 g, 7.4 mmol) in dry THF (15 mL) was added dropwise over a period of 15 min to a cold (ice bath), stirred suspension of lithium aluminum hydride (LAH) (1.4 g, 37 mmol) in dry THF (30 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 30 min and then at reflux for 1 h. The reaction mixture was cooled in an ice bath, and the LAH was decomposed by the slow, successive addition of water (1.4 mL), 2N NaOH (1.25 mL), and water (4 mL). The resulting white suspension was filtered, and the filtrate was evaporated under reduced pressure. The resulting yellow oil was dried under high vacuum and analyzed directly by GC–MS. The LAH reduction was repeated using a 20-fold excess of LAH (5.6 g, 148 mmol).

Synthesis of phenyl-2-propanone from 1-phenyl-2-nitropropane

A mixture of 1-phenyl-2-nitropropane (1.63 g, 10 mmol), powdered iron (3 g), FeCl₃ (0.6 g), and concentrated HCl (4 mL) in toluene (5 mL) and water (5 mL) was stirred vigorously at 75°C for 18 h. The resulting dark green suspension was cooled to room temperature and gravity filtered; the layers were allowed to separate. The aqueous layer was washed with an additional portion of toluene (10 mL), and the toluene extracts were combined and washed successively with 3N HCl (25 mL), water (25 mL), saturated sodium bicarbonate (25 mL), and water (25 mL). The toluene solution was gravity filtered and dried over anhydrous magnesium sulfate. Filtration followed by evaporation of the filtrate solvent yielded phenyl-2-propanone as an orange oil, which was analyzed by GC–MS and used without further purification in subsequent reactions.

Reductive amination of phenyl-2-propanone

A mixture of phenyl-2-propanone (0.827 g, 6.2 mmol), ammonium acetate (4.9 g, 63.3 mmol), and sodium cyanoborohydride (0.503 g, 8.0 mmol) in methanol (35 mL) was stirred at room temp for 48 h. The pH of the mixture was maintained at neutrality by dropwise addition of concentrated HCl during the course of the reaction. The reaction mixture was evaporated to dryness to yield a yellow semisolid that was suspended in water (25 mL) and then acidified to pH 1 by slow addition of concentrated HCl. The acidic suspension was washed with methylene chloride (2 x 20 mL) then made basic (pH 10) by the addition of NaOH pellets. The resulting basic aqueous suspension was extracted with methylene chloride (2 x 30 mL). The combined methylene chloride extracts were washed with water (50 mL), dried over magnesium sulfate, and evaporated to dryness to yield amphetamine as a yellow oil, which was analyzed by GC–MS.

Leuckart amination of 1-phenyl-2-propanone

A solution of 1-phenyl-2-propanone (0.827 g, 6.2 mmol) and

![Scheme 4. Catalytic hydrogenation of 1-phenyl-2-nitropropane.](image)

**Figure 1.** GC–MS analysis of the products obtained from catalytic hydrogenation of 1-phenyl-2-nitropropane: A, chromatogram; B, mass spectrum of P-2-P; C, mass spectrum of amphetamine; D, mass spectrum of 1-phenyl-2-ethoxypropane; E and F, mass spectra of isomers of 1-phenyl-2-propanoxime. (Continued on page 514.)
formamide (3.5 mL) was heated at 160–170°C for 16 h. The mixture was cooled to room temperature, and 30% hydrogen peroxide (5 mL) was added. After stirring for 15 min, the reaction mixture was extracted with benzene (2 × 25 mL), and the combined benzene extracts were evaporated under reduced pressure to yield a dark oil. The oil was dissolved in a solution of methanol (5 mL) and 15% HCl (5 mL) and stirred at reflux for 2 h. The reaction mixture was evaporated under reduced pressure, and a sample of the crude product was analyzed directly by GC–MS. The remaining product was dissolved in water (25 mL) and washed with methylene chloride (2 × 20 mL). The aqueous solution was then made basic (pH 10) by the addition of NaOH pellets and extracted with methylene chloride (2 × 25 mL). The combined methylene chloride extracts were evaporated to yield the product amine as a yellow oil, which was analyzed by GC–MS.

Results and Discussion

The 1-phenyl-2-nitroprene intermediate used in these studies was synthesized from benzaldehyde in a two-step process, as shown in Scheme 3. Initially benzaldehyde was treated with butylamine, and the resulting imine was heated at reflux with nitroethane and acetic acid to yield 1-phenyl-2-nitroprene. It is reported (6) that 1-phenyl-2-nitroprene also may be prepared by simply mixing benzaldehyde, butylamine, and nitroethane and allowing the mixture to stand at room temperature for several days. In the present study, it was found that mixtures containing equimolar amounts of benzaldehyde and nitroethane in the presence of a catalytic amount of butylamine resulted in the formation of 1-phenyl-2-nitroprene within 24 h. Mixtures containing butylamine concentrations equal to or exceeding the concentration of benzaldehyde and nitroethane, however, did not yield the product. GC–MS analysis of these reactions revealed only the presence of the intermediate benzaldehyde butylamine. It is possible that higher concentrations of butylamine may either interfere with the attack of nitroethane on the intermediate imine or hinder the elimination reaction (of butylamine) following nitroethane attack (Scheme 3).

The direct reduction of 1-phenyl-2-nitroprene to amphetamine under several conditions was investigated by GC–MS. One approach studied involved hydrogenation using a palladium catalyst (Scheme 4). The results of the GC–MS analysis of the products formed from this approach are shown in Figure 1. The major product present in the catalytic product mixture is amphetamine (4.94 min, Figure 1C), as indicated by the characteristic mass spectrum (molecular ion of low abundance at 135 and a base peak at 44 amu). The other components present are characteristic of incomplete reduction or competing reactions. The
components at 7.84 and 7.90 min (Figures 1E, 1F) have similar mass spectra with a molecular ion at 149 and a base peak of 91 amu. These spectra are suggestive of partial reduction products, such as (E)- and (Z)-1-phenyl-2-propanoxime, or possibly the tautomer of the oximes, 1-phenyl-2-nitrosopropane. All of these compounds have a molecular weight of 149 and would be expected to fragment at the C1–C2 carbons to yield the benzyl cation (m/z 91) as the base peak. To confirm these assignments, a standard sample of 1-phenyl-2-propanoxime was synthesized by treating P-2-P with hydroxylamine in the presence of base. GC–MS analysis of this standard revealed two major components with similar retention times and mass spectra identical to the partial reduction components of the original reaction (see Scheme 4).

Two minor components in the product mixture obtained from catalytic reduction of 1-phenyl-2-nitropropane appear at 4.80 (Figure 1B) and 5.69 min (Figure 1D). The earlier eluting component has retention properties and a fragmentation pattern similar to P-2-P. This compound could form during the course of the reaction by hydrolysis of the oxime by-products or hydrolysis of 1-phenyl-2-aminopropane, an unstable intermediate formed by initial reduction of the nitro moiety of 1-phenyl-2-nitropropane (Scheme 4). The other component eluting at 5.69 min (Figure 1D) shows major fragments at m/z 45, 73, and 91, as well as a molecular ion at m/z 164. These data suggest an unsubstituted benzyl group (m/z 91), an ethoxy group (m/z 45), and either a carbethoxy group (COOEt, m/z 73) or a two-carbon fragment attached to an ethoxy group (C2H5OEt, m/z 73). The two most likely structures for these mass spectra are the ethyl ester of phenylacetic acid or 1-phenyl-2-ethoxypropane. Because the hydrogenation reaction was done using ethanol as the solvent, the ethoxy group could have been added to either phenylacetic acid or P-2-P during the reduction reaction. P-2-P was identified as a component of the reaction product, and therefore 1-phenyl-2-ethoxypropane can be envisioned as a reduction product of P-2-P diethyl acetal or hemiacetal (Scheme 5). Phenylacetic acid was not identified in this reaction mixture, and its ethyl ester is a less likely structure for the peak at 5.69 min. The ethyl ester was prepared by heating a mixture of phenylacetic acid and ethanol at reflux in the presence of a catalytic amount of sulfuric acid. The product ester showed a retention time of 6.90 min and a mass spectrum with a base peak at m/z 91 and a molecular ion at 164 amu with no major fragments at m/z 45 or 73. A second experiment was conducted by allowing a sample of P-2-P to undergo hydrogenation in ethanol in the presence of a catalytic amount of HCl—conditions identical to those used for the catalytic reduction of 1-phenyl-2-nitropropane. GC–MS analysis of the product mixture revealed a compound with a retention time and mass spectrum essentially identical to the peak at 5.69 min in the original reduction reaction. These data confirm that this compound is 1-phenyl-2-ethoxypropane and may form from a competing hydrolysis reaction.

Figure 2. GC–MS analysis of the products obtained from LAH (5-fold) reduction of 1-phenyl-2-nitropropane: A, chromatogram; B, mass spectrum of 1-phenyl-2-aminopropane; C, mass spectrum of 1-phenyl-2-nitropropane; D, mass spectrum of 1-phenyl-2-nitropropane; E, mass spectrum of BHT. F, mass spectrum of amphetamine benzaldehyde imine; G, mass spectrum of amphetamine P-2-P imine. (Continued on page 516).
during the catalytic reduction of 1-phenyl-2-nitroprene.

A second approach investigated for the direct formation of amphetamine involved treating 1-phenyl-2-nitroprene with varying amounts of a reducing agent, lithium aluminum hy-

dride (LAH). The results of the GC–MS analysis of the products formed from treatment of 1-phenyl-2-nitroprene with a 5-
molar excess of LAH are shown in Figure 2. Although am-
phetamine (5.07 min) is present in the product mixture, the
major component appears to be 1-phenyl-2-
propanoxime (8.25 min), indicating incom-
plete reduction. Again, this was confirmed by
comparison with the standard sample of 1-phenyl-2-propanoxime. Several additional
components in the product mixture also are
suggestive of incomplete reduction, inc-
cluding 1-phenyl-2-aminopropene (5.80
min, Figure 2B), 1-phenyl-2-nitroprene
(7.68 min, Figure 2C), and the starting ma-
terial, 1-phenyl-2-nitroprene (9.36 min,
Figure 2D, Scheme 6).

Other minor components present in the
LAH product mixture appear to be P-2-P
(small peak eluting before amphetamine),
amphetamine benzaldehyde imine (13.07
min, Figure 2F), amphetamine P-2-P imine
(13.98 min, Figure 2G), and di-tert-butyl-
hydroxytoluene (BHT, 10.46 min, Figure
2E). P-2-P may form from hydrolysis of
1-phenyl-2-propanoxime or 1-phenyl-2-
aminopropene or both during the reaction
or subsequent workup. GC–MS analysis of a
portion of this sample extracted for basic
components (Figure 3) also showed the
presence of P-2-P, suggesting its source as
hydrolysis of the basic 1-phenyl-2-aminopropene following or during extraction. Am-
phetamine P-2-P imine could be produced
by reaction of amphetamine with P-2-P gen-
erated during the reaction. Also, it is pos-
sible that some 1-phenyl-2-nitroprene
may be hydrolyzed during the reaction or
workup to yield benzaldehyde, and reaction
of benzaldehyde with amphetamine would
result in the production of amphetamine
benzaldehyde imine. Standard samples of
the amphetamine imines of benzaldehyde
and P-2-P were prepared by allowing am-
phetamine to react with the appropriate car-
bonyl compounds under dehydrating con-
ditions. These products were analyzed by
GC–MS, which confirmed the identity of
these imines in the LAH reduction product
mixture. The standard sample of benzalde-
hyde imine has chromatographic retention
properties and a mass spectrum that
matches those observed for the component
eluting at 13.07 min (Figure 2F), and the
standard sample of amphetamine P-2-P
imine matches the properties of the com-
pound eluting at 13.98 min (Figure 2G).
These two imines show major fragments
(base peaks) from the loss of the benzyl

Figure 2 (Continued). GC–MS analysis of the products obtained from LAH (5-fold) reduction of 1-
phenyl-2-nitroprene: A, chromatogram; B, mass spectrum of 1-phenyl-2-aminopropene; C, mass
spectrum of 1-phenyl-2-nitroprene; D, mass spectrum of 1-phenyl-2-nitroprene; E, mass spectrum of
BHT; F, mass spectrum of amphetamine benzaldehyde imine; G, mass spectrum of amphetamine
P-2-P imine.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reagent</th>
<th>Reaction</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td>LiAlH₄</td>
<td>(5-FOLD) THF</td>
</tr>
<tr>
<td>1-Phenyl-2-propanoxime</td>
<td>+</td>
<td>1-Phenyl-2-aminopropene</td>
</tr>
<tr>
<td>1-Phenyl-2-nitroprene</td>
<td>+</td>
<td>1-Phenyl-2-aminopropene</td>
</tr>
<tr>
<td>1-Phenyl-2-aminopropene</td>
<td>+</td>
<td>P-2-P</td>
</tr>
<tr>
<td>1-Phenyl-2-propanol</td>
<td>+</td>
<td>P-2-P</td>
</tr>
</tbody>
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fragment from the amphetamine side of the molecule; this yields a mass of m/z 132 for the benzaldehyde imine and m/z 160 for the P-2-P imine (Scheme 7). Finally, the BHT present in the LAH reduction product mixture (10.46 min, Figure 2E) represents a contaminant derived from the reaction solvent, tetrahydrofuran (THF). BHT is added to commercial THF to scavenge free radicals and is present in a concentration of less than 0.5%. This contaminant is eliminated from the LAH product mixture after extraction of the basic products (Figure 3).

Because treatment of 1-phenyl-2-nitropropene with a five-fold molar excess of LAH resulted in a complex product mixture largely because of incomplete reduction of the starting material, the reaction was repeated using a large excess (20-fold) of hydride. The results of the GC–MS analysis of this reaction are shown in Figure 4 and indicate that, in the presence of a large excess of LAH, amphetamine (5.12 min) is obtained as the major product. The other component (10.48 min) present in significant quantities in this product mixture again is the BHT that was present in the reaction solvent.

The conversion of 1-phenyl-2-nitropropene to the key amphetamine/methamphetamine precursor, 1-phenyl-2-propanone (P-2-P), was also investigated. This transformation is accomplished by reaction of 1-phenyl-2-nitropropene with iron and HCl in the presence of a catalytic amount of ferric chloride and a two-phase solvent system (toluene/water). During the course of this reaction, the nitro group is reduced to form 1-phenyl-2-aminopropane that tautomerizes to the imine and undergoes hydrolysis to P-2-P (Scheme 8). Figure 5 shows the results of the GC–MS analysis of the product obtained when 1-phenyl-2-nitropropene is subjected to these reaction conditions. This analysis suggests that the reaction proceeds relatively cleanly to yield P-2-P as the major product (4.92 min). A minor by-product with a retention of 5.41 min is also present in the product mixture, and this compound has a mass spectrum consistent with benzaldehyde. Benzaldehyde may form in a competing reaction in which 1-phenyl-2-nitropropene is hydrolyzed prior to reduction.

The P-2-P formed from 1-phenyl-2-nitropropene was subjected to amination under Leuckart and reductive amination conditions (Scheme 2), and the products of these reactions were analyzed by GC–MS. In the Leuckart reaction, the crude P-2-P product was heated with formamide and subjected to the standard hydrolytic workup. The basic compounds formed
during this reaction were isolated by extraction, yielding the product mixture shown in Figure 6. The major product obtained from this reaction was amphetamine (5.25 min), as expected. A minor component eluting at 9.89 min (Figure 6C) has a molecular weight and fragmentation pattern consistent with 4-methyl-5-phenylpyrimidine, a by-product commonly observed in amphetamine samples prepared from P-2-P by the Leuckart method. The other minor component at 6.98 min has a molecular weight of 163 and a base peak at 91 amu (Figure 6B). This compound was found to be the propylimine of amphetamine by GC–MS analysis of a synthetic standard. This by-product probably formed as a result of exposure of the amphetamine to acetone prior to GC–MS and thus represents a by-product of the workup rather than a by-product characteristic of this synthetic method.

The reductive amination reaction was also performed by treating P-2-P with ammonium acetate in the presence of sodium cyanoborohydride. The basic compounds formed during this reaction were isolated by extraction, yielding the product mixture shown in Figure 7. Again, as anticipated, the major component in this product mixture is amphetamine (5.13 min) and a trace amount of 1-phenyl-2-propanoxime (7.91 min). This compound probably was formed during the synthesis of P-2-P from 1-phenyl-2-nitropropene and carried through to this point in the synthesis. The other component in this mixture (at approximately 5.7 min) has a retention time similar to 1-phenyl-2-aminopropane, a by-product detected in the product mixture formed from the LAH reductions of 1-phenyl-2-nitropropene (Figure 2B). The mass spectrum of this component, however, differs significantly from that of 1-phenyl-2-aminopropane and is consistent with the ethylimine of amphetamine (molecular ion of 161 and a base peak of 70 amu). This imine may have formed as a result of exposure of the product mixture to ethanol prior to GC–MS analysis. It has been demonstrated (9) that ethanol contains small amounts of acetaldehyde, and this aldehyde may condense with primary amines, such as amphetamine, to yield the corresponding ethylimine. Thus the additional component eluting at 5.7 min is not the by-product of this specific synthetic method but an artifact of the workup procedure.
Conclusion

From these studies, it is apparent that the samples of amphetamine and even methamphetamine prepared using 1-phenyl-2-nitroprene as a precursor may contain several unique by-products and contaminants characteristic of this route of synthesis. For example, amphetamine samples synthesized from this precursor may contain significant quantities of 1-phenyl-2-propanoxime, particularly if the reaction conditions used do not allow for complete reduction. Other minor impurities unique to this route would include 1-phenyl-2-aminopropene, amphetamine benzaldehyde imine, and the amphetamine-P-2-P imine condensation products. These contaminants may indicate that 1-phenyl-2-nitroprene was used as the key precursor, even if no nitroprene is detected in the amphetamine sample.

References


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