Idaho State Police
Forensic Laboratory Training Manual
Stimulants

1.0.0 Backround

The most commonly encountered stimulants are the amphetamines. These compounds are widely used and abused, primarily for their stimulant effect; however, many people have been introduced to the amphetamines because of their anorectic effect. Amphetamines are habituating rather than addictive and abusers develop a tolerance for the compounds. Amphetamines (also called phenylisopropylamines or phenethylamines) have the general structure shown in Figure 1.

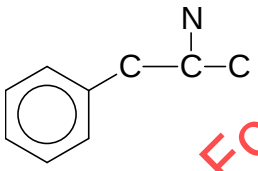
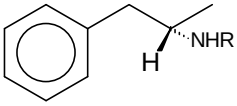


Figure 1

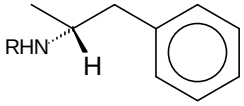
The different compounds in this family arise from: (1) substitutions on the propane chain; (2) substitutions on the nitrogen atom; (3) substitutions on the benzene ring; (4) combinations of one or more of (1) through (3). Pages 627 and 628 of reference 3 give the structures of some of the more common of these compounds. In general, substitutions on the propane chain and the nitrogen atom affect the stimulant properties of the compounds while substitutions on the benzene ring give hallucinogenic properties. With a couple of exceptions, the ring substituted compounds will be addressed in the hallucinogen section.

1.1.0 Amphetamine and Methamphetamine

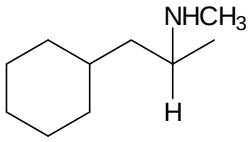
Two of the most frequently encountered stimulants in the forensic laboratory are Methamphetamine and Amphetamine, which are Schedule II controlled substances. Both of these compounds have one chiral center and hence there are two possible stereoisomers for each as shown in Figure 2.



2S configuration
R=H, d-Amphetamine
R=CH3, d-Methamphetamine



2R configuration
R=H, l-Amphetamine
R=CH3, l-Methamphetamine



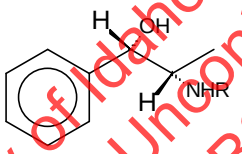
Propylhexedrine

Figure 2

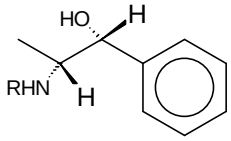
The dextro forms are approximately 10 times more potent than the levo forms. The levo form of methamphetamine works well as a bronchadialator and, until recently, could be purchased over the counter in Vick's inhalers. Benzedrex brand inhalers contain Propylhexedrine that is a Schedule IV controlled substance when not in the inhaler form.

1.2.0 Ephedrine, Pseudoephedrine, Phenylpropanolamine and Cathine

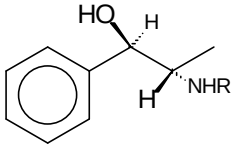
The 1-Hydroxy-phenethylamines have two chiral centers so there are four possible structures for each as shown in Figure 3.



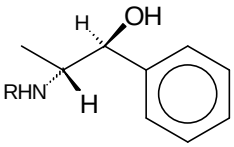
1S,2S configuration
R=H, Cathine
R=CH3, d-Pseudoephedrine



1R,2R configuration
R=H, l-Norpseudoephedrine
R=CH3, l-Pseudoephedrine



1R,2S configuration
R=H, l-Norephedrine
aka l-Phenylpropanolamine
R=CH3, l-Ephedrine



1S,2R configuration
R=H, d-Norephedrine
aka d-Phenylpropanolamine
R=CH3, d-Ephedrine

Figure 3

Ephedrine is a naturally occurring stimulant found in the Ma Huang (Ephedra vulgaris) plant. d-Pseudoephedrine is a decongestant and l-Ephedrine is a bronchadialator. Both can be found in many over the counter cold preparations. Older methods of manufacturing methamphetamine including those that start with phenylacetone yield a mixture of dextro and levo forms. Reduction of d-Pseudoephedrine or l-Ephedrine yields the more potent dextro-Methamphetamine. For this reason there is a great demand by illicit methamphetamine manufacturers for ephedrine and pseudoephedrine. In an attempt to reduce the clandestine manufacture of methamphetamine, certain laws have been enacted to control the possession of "bulk" ephedrine and pseudoephedrine. Controls have also been placed on preparations having ephedrine as the only active ingredient. Because of its decongestant properties, phenylpropanolamine (PPA) can be found in over the counter cold preparations such as Contact. PPA also has anorectic properties and can be found in diet pills such as Dexatrim. Because the reduction of PPA yields amphetamine, it is sometimes encountered in clandestine laboratories. The 1S,2S configuration known as cathine is a Schedule IV controlled substance. Cathine is found in various European drug preparations, but is rarely encountered in the United States.

1.3.0 Cathinone and Methcathinone

Figure 4

Cathinone is a naturally occurring stimulant found in the Khat plant. Khat is an evergreen shrub that grows at high altitudes in East Africa and on the Arabian Peninsula. After the leaves of the Khat plant are picked, the cathinone rapidly converts into cathine. Methcathinone is synthetically produced from the oxidation of ephedrine or pseudoephedrine. Care must be taken in the analysis of cathinone and methcathinone. The use of a too alkaline reagent during extraction will convert the cathinones into their corresponding 1-Hydroxy-phenethylamines. In addition, the retention times and mass spectra of the cathinones are very close to those of the corresponding 1-Hydroxy-phenethylamines. There are several derivatives of cathinone with a variety of substitutions, at the ring structure, at the two positions off of the amine or at the tail end of the carbon chain.

2.0.0 ANALYTICAL APPROACH

2.1.0 Extraction/Separation:

Amphetamines can be separated from excipients by routine acid-base extraction techniques. Nitrogen substituted amphetamines can also be isolated by ion-pairing techniques.

2.2.0 Gas Chromatography:

The compounds presented in this section are generally quite volatile; therefore, their Gas Liquid Chromatography (GLC) retention times are fairly short. In addition, these compounds "tail" badly in capillary systems with dirty injectors. In general, the greater the polarity of the column, the better the peak symmetry. Either a methylsilicone (OV-1) or a 5% phenyl methylsilicone (OV-5) capillary column will provide suitable resolution and peak shape.

2.3.0 Mass Spectrometry:

Mass Spectrometry (MS) fragmentation patterns of these compounds are similar. The molecular weights are generally less than 160 with the phenyl ring comprising approximately half of weight. The electron impact mass spectral base peak usually includes the nitrogen and its substituents -- *m/z* 58 for methamphetamine and ephedrine, *m/z* 44 for amphetamine and phenylpropanolamine, etc. Molecular ions are usually weak or absent. Chemical ionization mass spectrometry gives more information about the identity of these compounds, since the M+1 ion is quite intense (in most cases).

2.4.0 Derivatizations:

In order to improve chromatographic properties, separate isomers and make the mass spectrums more distinguishable, a number of derivatization techniques can be performed. References 13 -16 give several examples. A derivatization technique that was employed in this laboratory involves adding acetic anhydride to the free base amine to create the acetyl derivative of the original compound as shown in Figure 5.

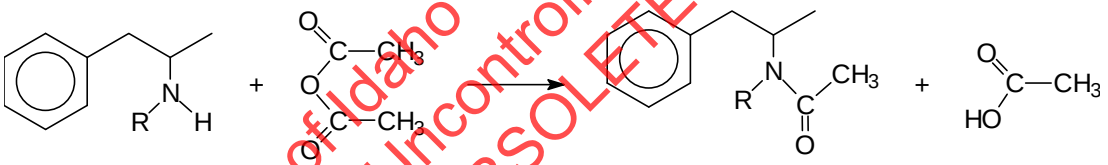


Figure 5

The addition of the acetyl group adds 42 amu's to the weight of several key ions in the mass spectrum.

2.5.0 Infrared Spectrophotometry:

Because of the volatility of their free bases, infrared spectra of the amphetamines are generally run as the acid salts. Some of the most useful acid salt forms are the hydrochloride, tartrate, and oxalate. The hydrochloride salts of some amphetamines, when ground with KBr, absorb large quantities of moisture from the atmosphere, thus giving rise to broad, intense absorbance bands in the region above 2500 cm^{-1}. This problem can be avoided by using the tartrate or oxalate salts; however, the intense absorbance bands of the tartrate or oxalate moieties then become the dominant features in a spectrum. Another technique, which can be used to avoid the moisture problem, is derivative formation. One of the most useful of the derivatizing reagents for primary and secondary amines is phenylisothiocyanate (PIT). The amphetamine

PIT derivatives are nonhygroscopic, and the infrared spectra of the derivatives furnish positive identification of the original amine. An added benefit of this derivative is that the IR spectra of the *d*- or *l*- enantiomers of the amphetamines differ from those of the racemic mixture.

3.0.0 EXERCISES

1. Obtain Pseudoephedrine HCl, pseudoephedrine base, and ephedrine. Obtain IR's and compare.

4.0.0 QUESTIONS

1. List the legitimate use(s) for Methamphetamine?
2. List legitimate use(s)s for Methylphenidate? What is a pharmaceutical product that contains Methylphenidate?
3. Draw the structure of amphetamine and next to it draw the structure of Methylphenidate. Draw these structures in a manner that shows they share the same basic structure.
4. Is the l-methamphetamine in Vicks Inhalers controlled?
5. Name two products that contain: Phenylpropanolamine, Pseudoephedrine, Ephedrine.
6. What molecular structure gives rise to the *m/z* 58 ion in the mass spectrum of methamphetamine and the *m/z* 44 ion in the mass spectrum of amphetamine?
7. Define the following terms: Molecular Formula, Empirical Formula, Stereoisomers, Chiral Center, Enantiomers, Diastereoisomers, Racimate
8. Give ways that pseudoephedrine can be distinguished from ephedrine.
9. What spot tests can be used to indicate the presence of the following compounds and what colors would you expect? Methamphetamine, Ephedrine, Phenylpropanolamine
10. What spot test would differentiate between methamphetamine and amphetamine?
11. Obtain electron impact mass spectra of methamphetamine, amphetamine, phentermine, phenylpropanolamine, and ephedrine. Can they be differentiated by this technique?
12. List the ions that differentiate methcathinone from ephedrine.
13. An unknown sample is subjected to GC/MS analysis and at least one aziridine peak is detected. Give two possible explanations for the presence of this aziridine.

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6.0.0 HISTORY

Prior to revision 3 modules in the training manual did not have individual history pages.

Revision #	Issue or review date	History	Author or Reviewer
3	7/08/11	Added 6.0.0, dropped some references changed 1.3.0	David Sincerbeaux