Chapter 7
Chemical Analysis of Drugs of Abuse

Drug-Control Laws

- The U.S. federal law known as the Controlled Substances Act (CSA) will serve to illustrate a legal drug-classification system created to prevent and control drug abuse.

- This federal law establishes <u>five schedules</u> of classification for controlled dangerous substances on the basis of a drug's:

  - potential for abuse

  - potential for physical and psychological dependence

  - medical value

Controlled Substances Disclaimer

- Department of Justice (DOJ)/Drug Enforcement Administration (DEA)/Office of Diversion Control

- Definition: Title 21 Code of Federal Regulations

- List of substances and schedules: Section 1308 of the Controlled Substances Act (21 U.S.C. §801 et seq.) (CSA)

- List of Defined Abbreviations (e.g. THC: Tetrahydrocannabinols)

- http://www.deadiversion.usdoj.gov/schedules/#disclaimer

Schedules

- Schedule I drugs: have a high potential for abuse and have no currently accepted medical use (e.g., <u>heroin, marijuana, methaqualone, and LSD, etc)</u>

- Schedule II/IIN drugs: have a high potential for abuse and have medical use with severe restrictions (e.g., <u>cocaine, morphine, opium, fentanyl, PCP, amphetamine, etc)</u>

- Schedule III/IIIN drugs: have less potential for abuse and a currently accepted medical use. (products that contain less amount of codeine (Tylenol with Codeine®), buprenorphine, (Suboxone®), anabolic steroids, etc)
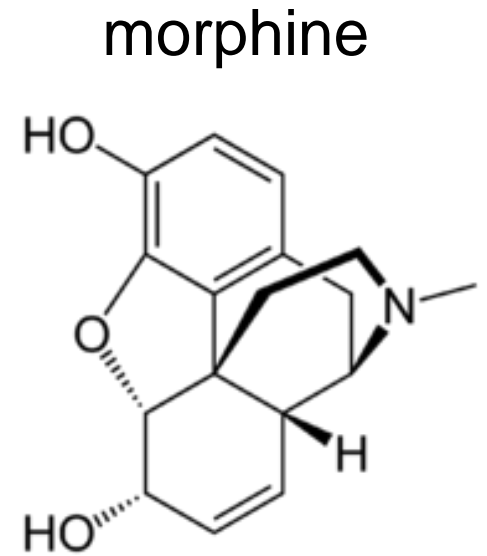
Schedules-continued

- Schedule IV drugs: have a low potential for abuse relative to substances in Schedule III (alprazolam (Xanax®), carisoprodol (Soma®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), etc)

- Schedule V drugs: have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics (cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC®, Phenergan with Codeine®), and ezogabine)

Classification

- <u>Narcotic drugs</u> (pain killers): opiates (morphine, codein), heroin, methadone, oxycondone, fentanyl, etc

- <u>Depressants</u>: substances used to calm irritability and anxiety and may induce sleep, alcohol and tranquilizers, (barbiturates, methaqualone, meprobamate, diazepam, chlordiazepoxide, ethanol)

- <u>Stimulants</u>: substances taken to increase alertness or activity, followed by a decrease in fatigue and a loss of appetite (amphetamines, cocaine, caffeine, nicotine)

- <u>Hallucinogens</u>: cause marked changes in normal thought processes, perceptions, and moods (marijuana, LSD, phencyclidine)
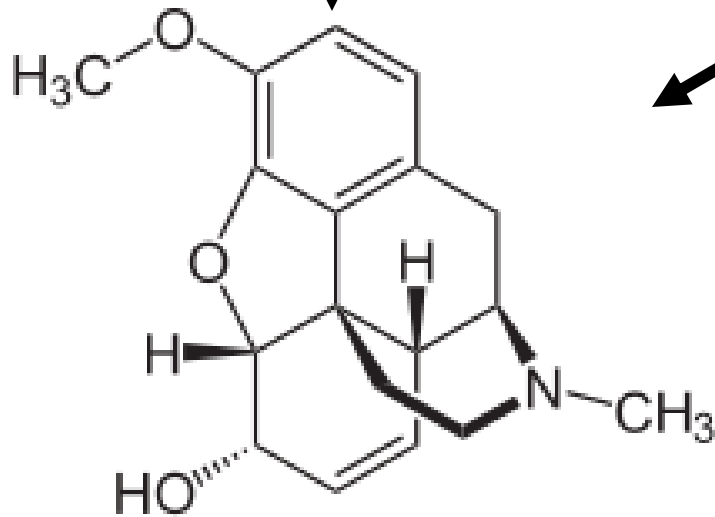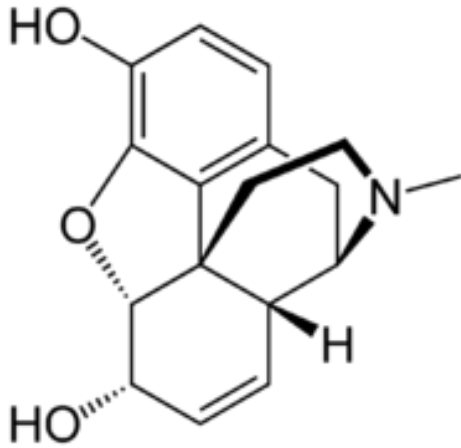
morphine

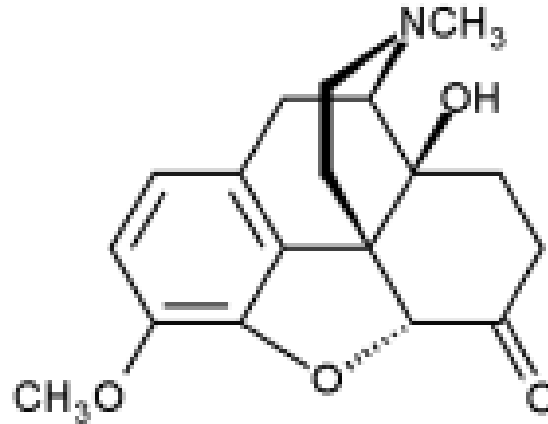extraction

chemical
reaction

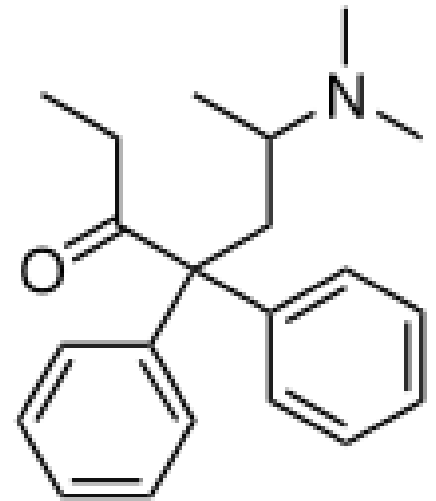extraction

chemical
reaction

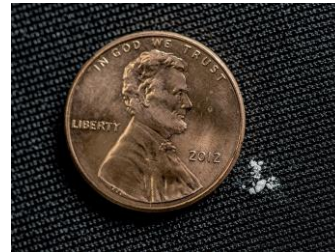codeine

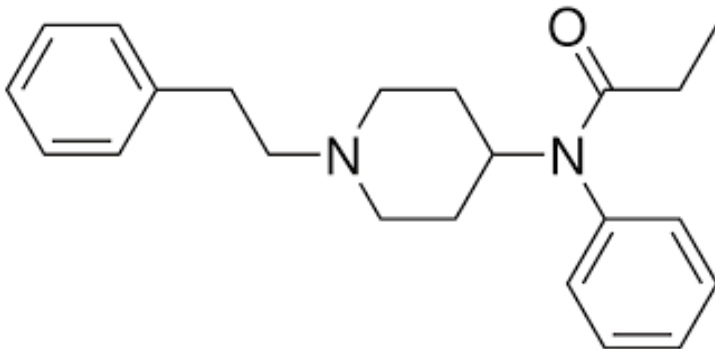heroine

© W.P. Armstrong 2004
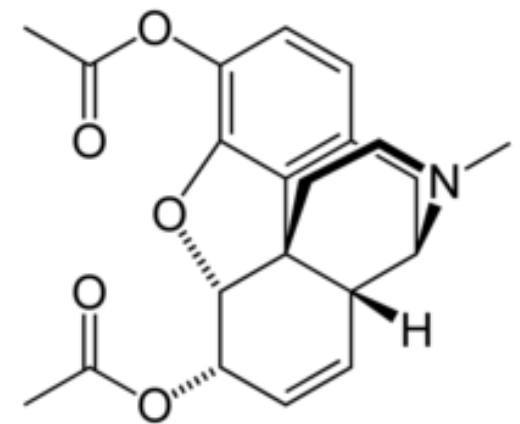
morphine

oxycondone

methadone

fentanyl

$LD_{50} = 2$ mg
~ 29,000 deaths in 2017,
USA

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Hallucinogens

- Hallucinogens cause marked changes in normal thought processes, perceptions, and moods.

- Marijuana is the most controversial drug in this class because its long-term effects on health are still largely unknown.

- The chemical substance largely responsible for the hallucinogenic properties of marijuana is known as tetrahydrocannabinol (THC).
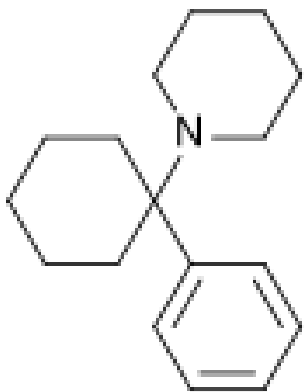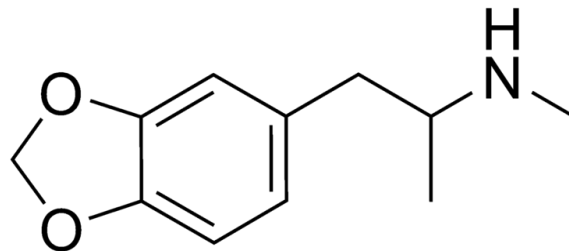
Marijuana

The Molecular Structure of THC
(delta-9-tetrahydrocannabinol)

©2001 HowStuffWorks
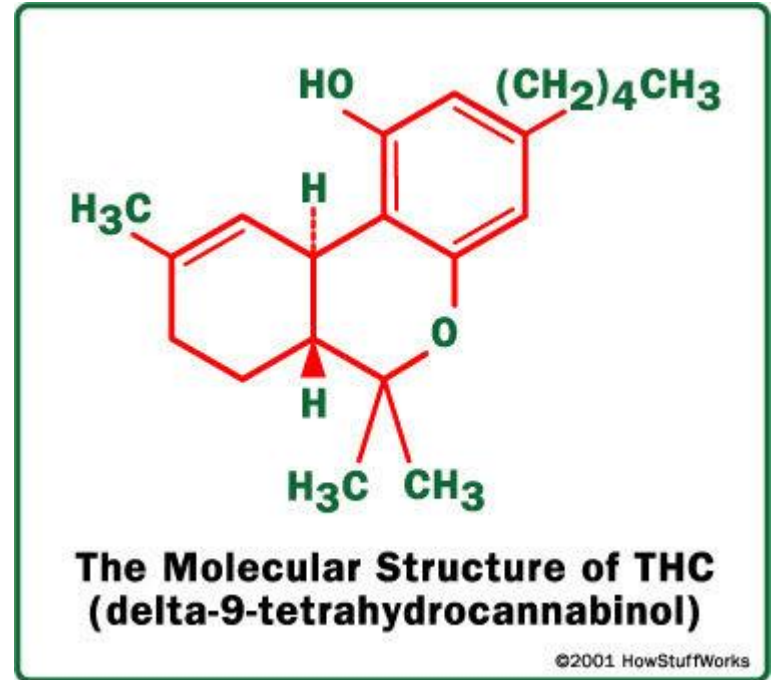
THC

Other Hallucinogens
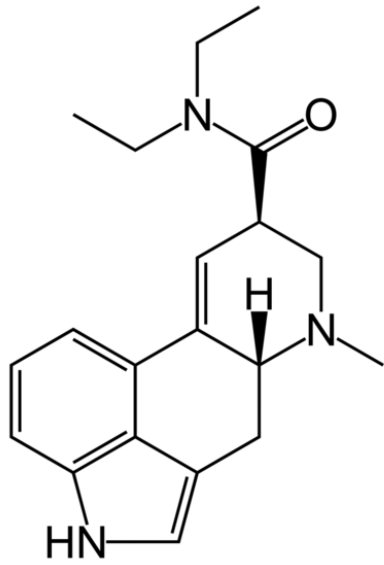

LSD

PCP

MDMA (Ecstasy)

Stimulants

- Stimulants are substances taken to increase <u>alertness or activity</u>, followed by a <u>decrease in fatigue and a loss of appetite</u>.

- Sometimes disguised as agents that help weight loss

Stimulants

- Amphetamine and methamphetamine (METH or ice or crystal), often injected intravenously, cause an initial "rush," followed by an intense feeling of pleasure.

Amphetamine

(METH)

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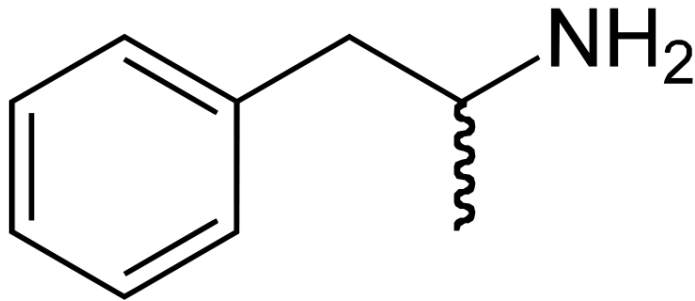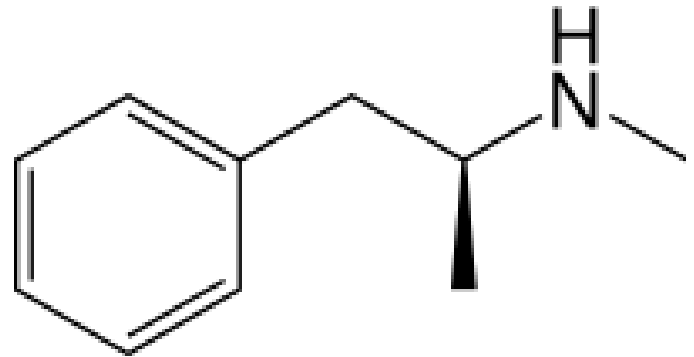
Pseudoephedrine HCl
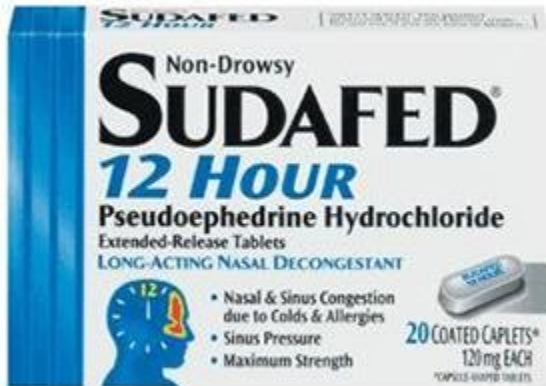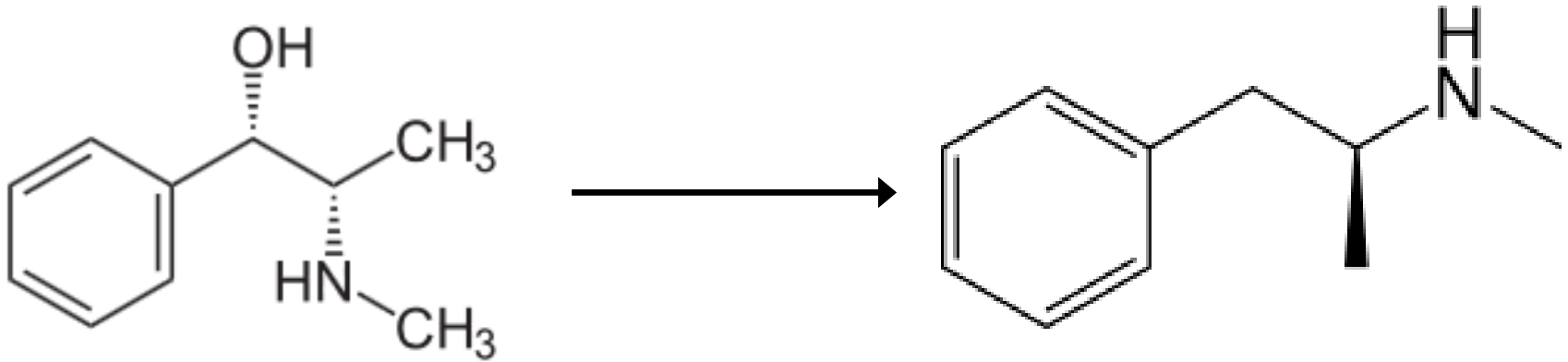
Sudafed

Stimulants

- Cocaine, extracted from the leaves of *Erythroxylon coca*, causes increased alertness and vigor, accompanied by the suppression of hunger, fatigue, and boredom.

- *Crack* is a powder cocaine mixed with baking soda ($NaHCO_3$) and water, then heated.

- *Crack* is often smoked in glass pipes, and, like cocaine, stimulates the brain's pleasure center.
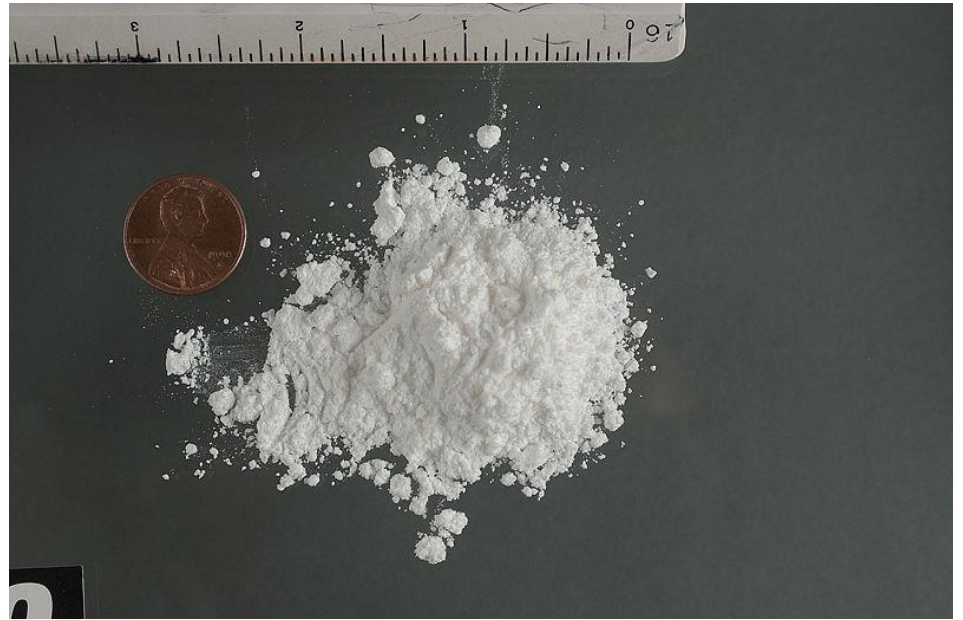
power cocaine (HCl salt)
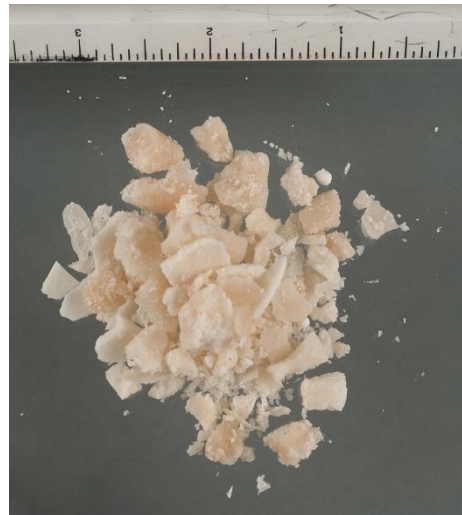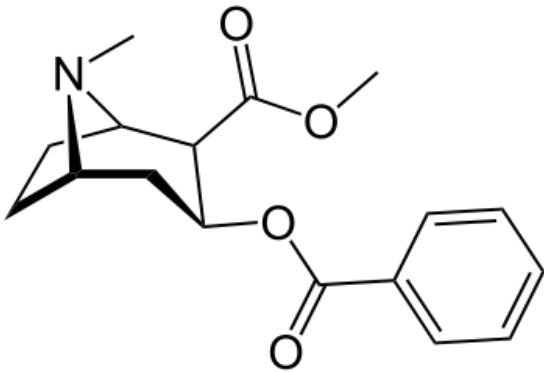
Crack (mixture with sodium bicarbonate and powder cocaine)

Toluene in glue damages brain permanently
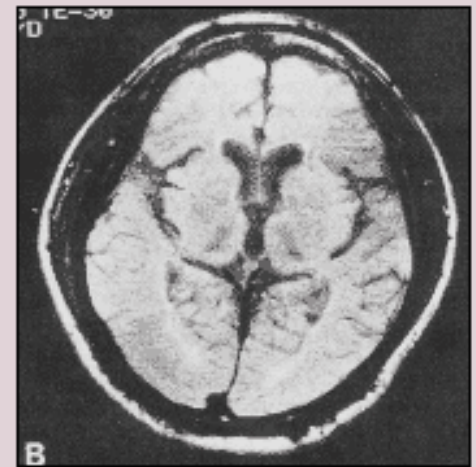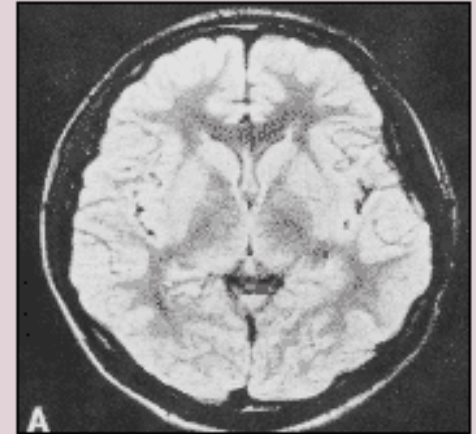
Courtesy of Neil Rosenberg, M.D.

Brain images show marked atrophy (shrinkage) of brain tissue in a toluene abuser (B) compared to a nonabusing individual (A). Note the smaller size and the larger empty (dark) space within the toluene abuser's brain. (The white outer circle in each image is the skull.)

Drug Identification (Seized Drugs)

- The challenge or difficulty of forensic drug identification comes in selecting analytical procedures that will ensure a specific identification of a drug.

- This plan, or scheme of analysis, is divided into two phases.

  - <u>Screening test</u> (preliminary test): nonspecific and preliminary in nature to reduce the possibilities to a manageable number

  - Confirmation test: a single test that specifically identifies a substance.

Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG)

- Recommend minimum standards for the forensic examination of seized drugs and to seek their international acceptance.

- Drug monographs (chemical and physical properties, FTIR, NMR, Mass data, etc)

- Developed questions as a resource and training tool

- Provided workshop, meeting, etc

- http://www.swgdrug.org/

Categories of Analytical Techniques

Category A	Category B	Category C
Infrared Spectroscopy	Capillary Electrophoresis	Color Tests
Mass Spectrometry	Gas Chromatography	Fluorescence Spectroscopy
Nuclear Magnetic Resonance Spectroscopy	Ion Mobility Spectrometry	Immunoassay
Raman Spectroscopy	Liquid Chromatography	Melting Point
X-ray Diffractometry	Microcrystalline Tests	Ultraviolet Spectroscopy
	Pharmaceutical Identifiers	
	Thin Layer Chromatography	
	Cannabis only: Macroscopic Examination Microscopic Examination	

When a validated Category A technique is incorporated into an analytical scheme, at least one other technique (from either Category A, B or C) shall be used.

When a Category A technique is not used, at least three different validated techniques shall be employed.

Two of the three techniques shall be based on uncorrelated techniques from Category B.

Biological Samples

- Biological samples (drug test)
  - **Urine (most common)**
  - **Blood (most accurate)**
  - **Oral Fluid/Saliva**
  - Breath air (alcohol)
  - Sweat
  - Hair

Why You Need Drug Test

- Workplace requirement (urine)
  - Federal Workplace: Confirm by mandate: (YR 1986)
    - Executive Order 12564 >> Drug-free Federal workplace
    - Tested in certified labs by Substance Abuse and Mental Health Services Administration (SAMHSA)
  - Non-Federal Workplace: No guidelines
- Legal: Court requirement (urine)
  - Very strict by policy
- Forensic: Crime investigation (many samples)
  - Very strict by policy
- Medical/clinical (urine)
  - Verify drug dependency and monitor treatment progress
- Sports: Doping test (urine)

Window of Detection for Various Matrices

Period of Detection for Each Sample (in Days)
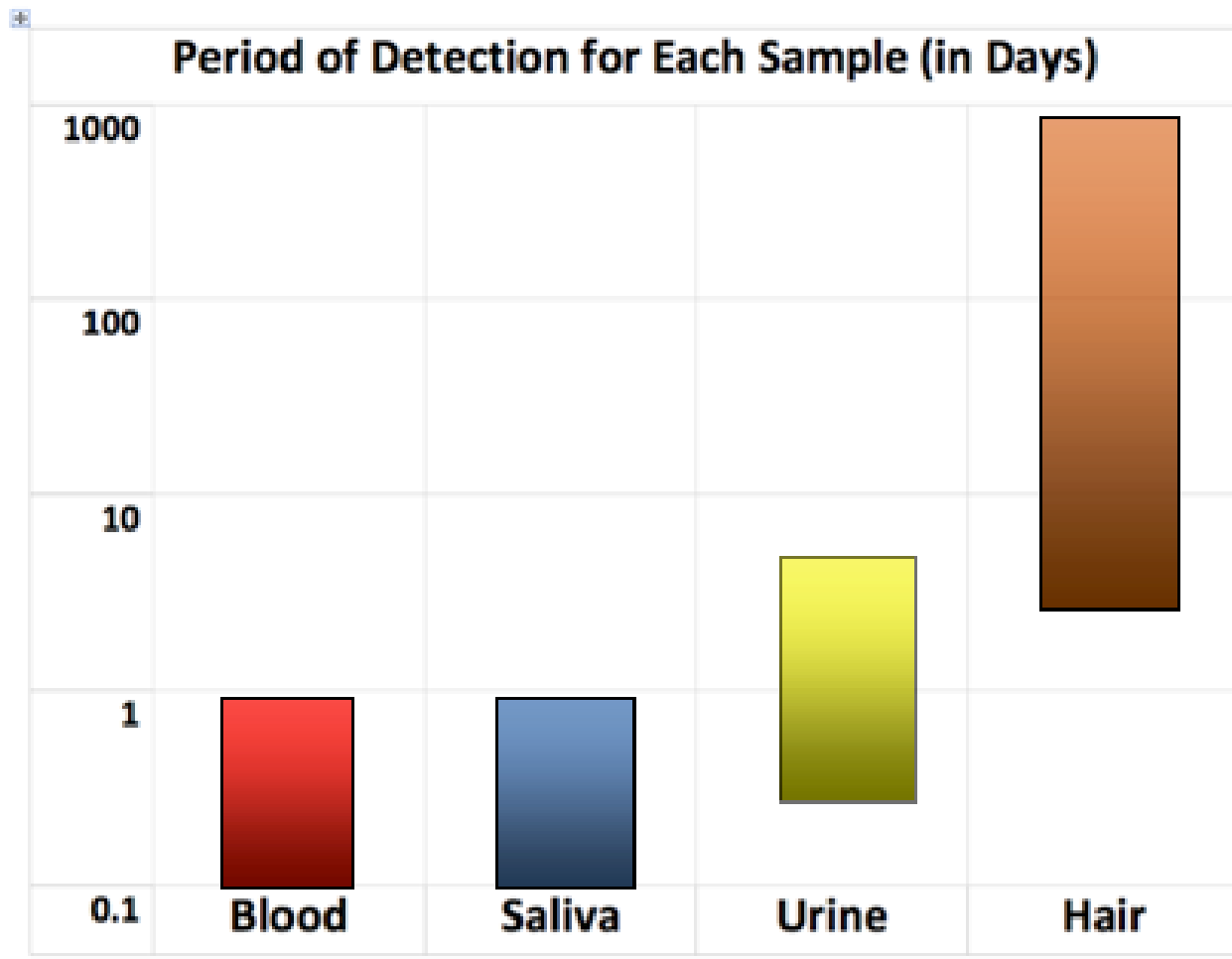
Very broad estimates that depend on substance, the amount and frequency, other factors
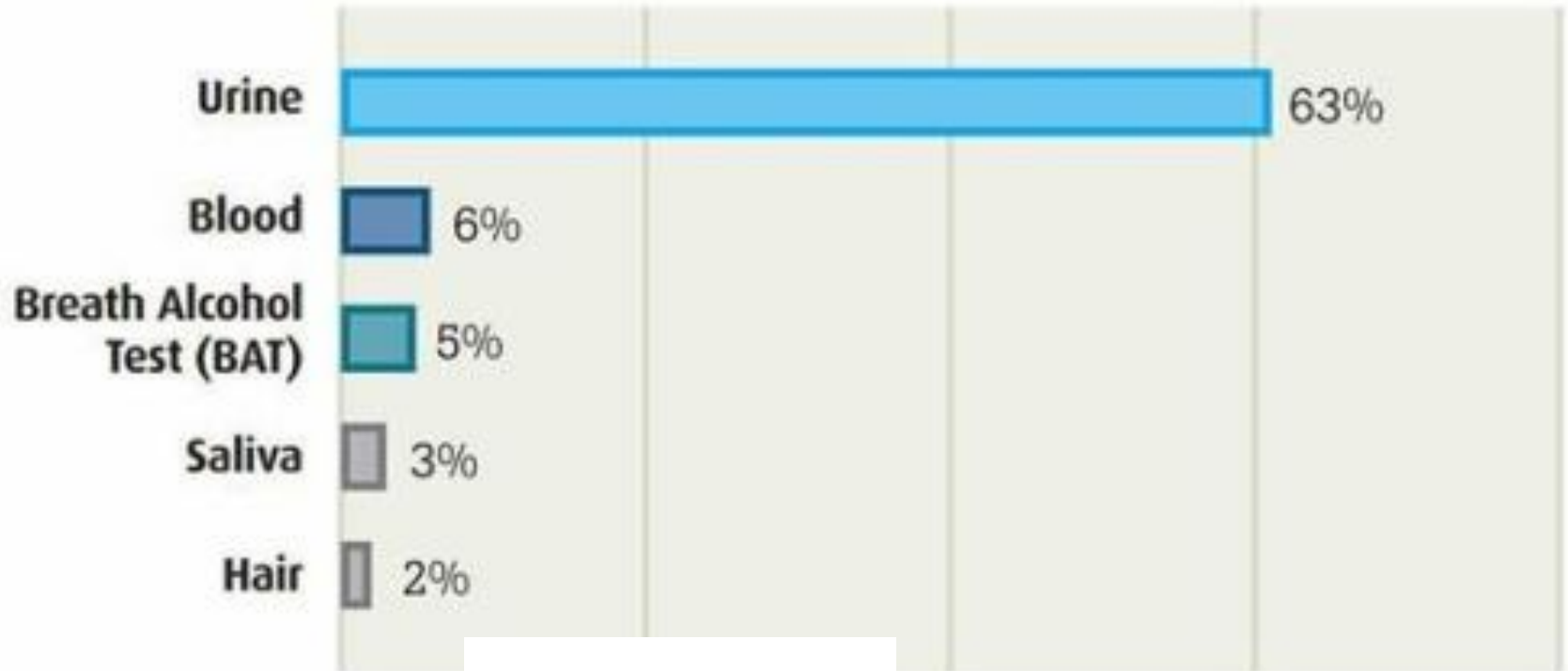
THC Distribution in a Body
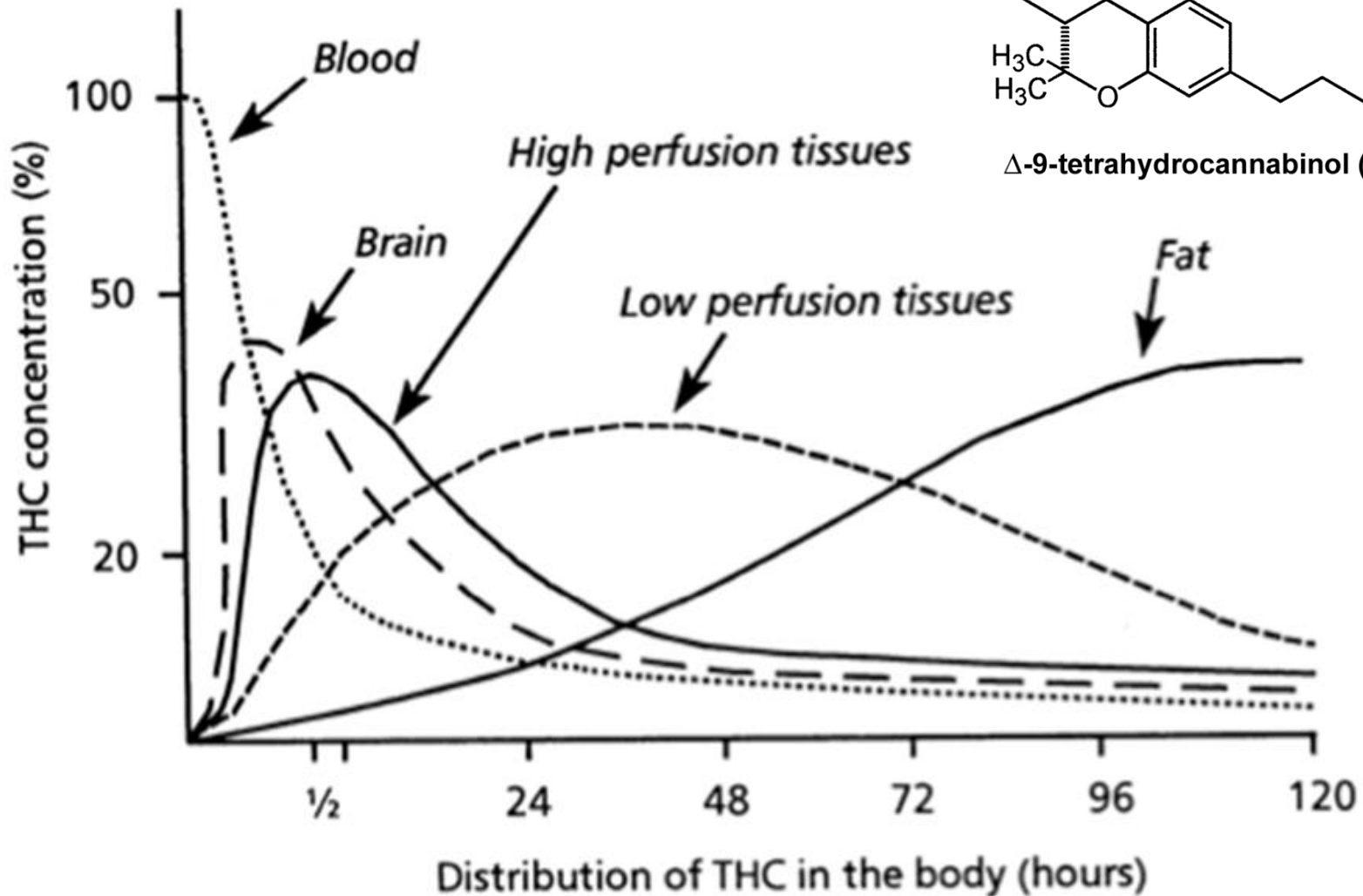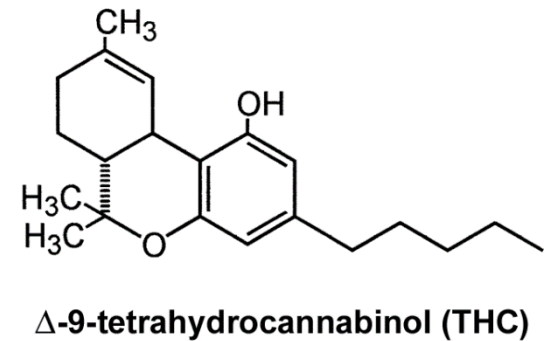
Types of Drug/Alcohol Test Required by the Organization

Urine	63%
Blood	6%
Breath Alcohol Test (BAT)	5%
Saliva	3%
Hair	2%

Cocaine Metabolites

(~10% of dose)
Norcocaine

CYP3A4

BChE/hCE-2

Cocaine

BChE/hCE-1/2

Ecgonine
methyl ester

(~50% of dose)

BChE/hCE-1

Norecgonine methyl ester

Liver
Butyrylcholinesterase (BChE)
Cytochrome P450 3A4 (CYP3A4)
Human Carboxylesterases (hCE-1/2)

Benzoylecgonine

(~40% of dose)
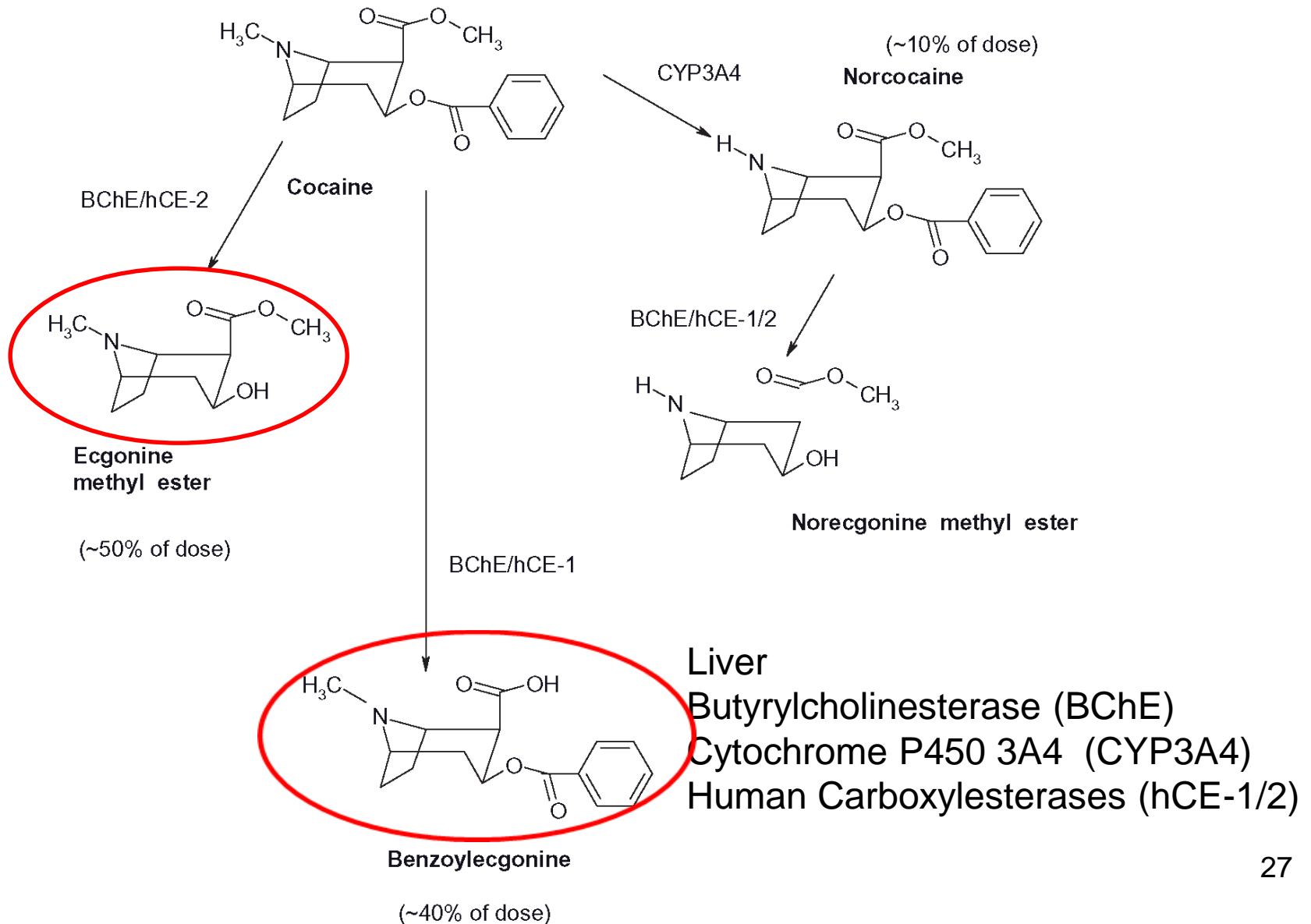
Drug Derivatization

Why: Most drugs containing polar groups (-OH, -COOH, -NH$_2$, -NRH, etc) are less volatile and sometimes does not pass GC columns

Goal: Convert polar/hydrophilic compounds to less polar/hydrophobic compounds

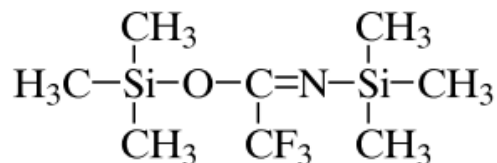How: Chemical derivatization
Popular techniques:
Alkylation
Acylation
Silylation

Silylation

No.	Reagent[a]	Compounds	Derivatives
1.	$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle Cl}{Si}}-CH_3$ (TMCS)	R–COOH	
2.	$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{Si}}-\overset{H}{N}-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{Si}}-CH_3$ (HMDS)	R–OH	$R-O-Si(CH_3)_3$ $R-\overset{O}{\overset{\|}{C}}-O-Si(CH_3)_3$
3.	$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{Si}}-O-\overset{\displaystyle CH_3}{C}=N-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{Si}}-CH_3$ (BSA)	R–OH R–NH$_2$ $R_1-\overset{}{\underset{\displaystyle R_2}{NH}}$ $R-\overset{O}{\overset{\|}{C}}-NH_2$ R–COOH	$R-O-Si(CH_3)_3$ $R-\overset{}{\underset{\displaystyle Si(CH_3)_3}{N}}-Si(CH_3)_3$ $R_1-\overset{}{\underset{\displaystyle R_2}{N}}-Si(CH_3)_3$ $R-\overset{O}{\overset{\|}{C}}-\overset{Si(CH_3)_3}{\underset{}{N}}-Si(CH_3)_3$ $R-\overset{O}{\overset{\|}{C}}-O-Si(CH_3)_3$

Silylation

4.

$$H_3C-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{Si}}-O-\underset{\underset{CF_3}{|}}{C}=N-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{Si}}-CH_3$$

(BSTFA)

Same as BSA, leaving group

$$F_3C-\overset{\overset{O}{||}}{C}-\overset{\overset{H}{|}}{N}-Si-(CH_3)_3$$
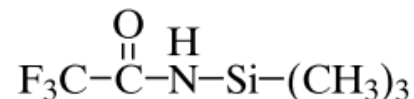
more volatile than that of BSA

5.

$$F_3C-\overset{\overset{O}{||}}{C}-\underset{\underset{H_3C}{|}}{N}-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{Si}}-CH_3$$

(MSTFA)

Same as BSA, leaving group

$$F_3C-\overset{\overset{O}{||}}{C}-\overset{\overset{H}{|}}{N}-CH_3$$

is very volatile

6.

$$\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{N-Si}}-CH_3$$
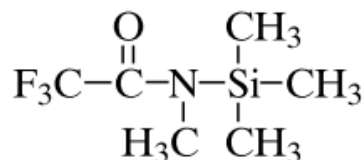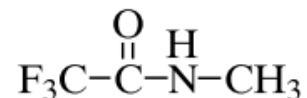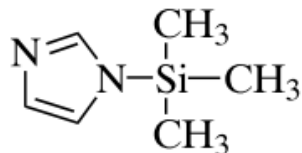
(TMSI)

R−OH
(steroids)

R−COOH

R−O−Si(CH$_3$)$_3$

$$R-\overset{\overset{O}{||}}{C}-O-Si(CH_3)_3$$

No reaction with amines

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[a] HMDS, hexamethyldisilazane; BSA, *N,O*-bis(trimethylsilyl)acetamide; BSTFA, *N,O*-bis (trimethylsilyl)trifluoroacetamide; MSTFA, *N*-methyl-*N*-trimethylsilyltrifluoroacetamide.

Silylation by BSTFA

Will do lab/demo

Benzoylecgonine (cocaine metabolite)

BSTFA