Amphetamines and Trace Amines

Historical Timeline

- ~3000 BCE: Ephedra (ma huang) used for Chinese Medicine
- 1200 CE: Khat is cultivated and used. (active ingredient: Cathinone)
- 1885 CE: Nagai Nagayosi isolates ephedrine from ephedra
- 1887 CE: Lazar Edeleanu synthesizes Amphetamine (phenylisopropylamine)
- 1893 CE: Nagai Methamphetamine synthesis is reported
- 1912 CE: Meth • HCl synthesized by Akira Ogata via I2 and red Phos.
- 1919 CE: Gordon Alles reports Amphetamine’s sympathomimetic properties
- 1927 CE: Smith, Kline, French sell Benzedrine inhaler
- 1933 CE: Allies and Germans provide stimulants to soldiers
- 1940’s CE: Dramatic increase in amphetamine prescription and use
- 1950’s CE: Japanese gov. fights Yakuza in attempt to stop illicit amphetamine sales
- 1953 CE: Project MK Ultra is sanctioned
- 1960’s CE: Regulation enters trucking industry in US
- 1960’s CE: Clandestine labs skyrocket in US often run by biker gangs
- 1971 CE: Amphetamine becomes schedule II under Controlled Substances Act
- 1970’s CE: MDMA makes a resurgence
- 1980’s CE: P2P restrictions cause "cooks" to use Nagai route.
- 1990’s CE: Further restrictions lead to "cooks" using the Birch method
- 1991 CE: PiHKAL is published
- 1993 CE: Cathinone goes Schedule I
- 1996 CE: Comprehensive Meth Control Act Passed
- 2004 CE: Supplements containing Ephedrine are banned in US
- 2005 CE: Combat Meth Epidemic Act is Passed
- 2006 CE: MLB Bans Amphetamine
- 2008-13 CE: Breaking Bad Seasons 1-5
- 2017 CE: FDA Grants "breakthrough designation" to MDMA for PTSD after Phase 2 trial.
- 2018 CE: Airforce stops issuing Amphetamine to pilots.

Isolation of Ephedrine from Ma Huang
1kg of powdered Ma Huang is extracted with cold benzene and dilute sodium carbonate. The organic layer is washed with dilute HCl, which is then basified with potassium carbonate to liberate the basic residues. Extraction with chloroform followed by distillation yields 2.6g of crude ppt. Fractional crystallization of the HCl salt in alcohol was used for purification.

J. Biol. Chem. 1926, 70, 109-114.

Khat contains cathinone which has moderate stimulant properties. It is very popular around the red sea regions. Approximately 40% of Yemen's total water supply goes to the cultivation of the khat plant.

Methamphetamine is seeing a resurgence in the US. Illicit Meth today is nearly 100% pure. In 2015 nearly 6,000 people died from meth use, a 255% increase from 2005.


![Cathinone](image)
Amphetamines and Trace Amines

Catecholamines
- L-Phenylalanine → AADC → L-Tyrosine
- L-Tyrosine → AAAH → L-Dopa
- L-Dopa → AADC → Dopamine

PNMT: Phenylethanolamine N-methyltransferase
COMT: Catechol-O-methyltransferase
DBH: Dopamine beta-hydroxylase
AADC: Aromatic L-amino acid decarboxylase
AAAH: Aromatic amino acid hydroxylase

Dopamine
- Synthesized in the medulla of the adrenal glands and in neurons where it is a neurotransmitter and precursor to epinephrine and norepinephrine.
- It does not cross the BBB.
- Two known types of receptors D1-like (D1 and D5) and D2-Like (D2, D3, and D4).
- Binding to D1-like receptors is excitatory.
- Binding to D2-like receptors is inhibitory.
- D1 receptors are most common, D2 are common and D3, D4, and D5 are least common.
- Its Major functions are: Motor Control, Motivation, Arousal, Reinforcement and Reward.
- Its Minor Functions are: Sexual Drive, Nausea, and Lactation.
- Produced in the Ventral Tegmental Area (VTA) and released in the Frontal Cortex, Nucleus accumbens and Hippocampus.
- Produced in the Substantia Nigra and released in the dorsal striatum. (motor functions pathway)
- Higher levels of dopamine in pathways of the Basal Ganglia indicate easier activation. This area of the brain is responsible for initiation of behaviors. Thus dopamine plays a critical role in operant conditioning to reward signals.

Epinephrine
- Produced in adrenal glands and neurons in the medulla oblongata.
- Regulates visceral functions like respiration.
- In fight or flight, interacts with the sympathetic nervous system: increases blood flow to muscles and cardiac output, dilates pupils, releases blood sugar.
- Binds α and β receptors but does not cross BBB.
- Not produced in the brain. Peripheral system only.
- Effects long term memory of stressful events through peripheral excitation.

Norepinephrine
- Comprehensive Physiology 2015, 5, 1-15
- Produced in the locus coeruleus (pons/brain), utilized by sympathetic ganglions along spinal cord.
- Redirected by adrenal glands back into blood, similar effects as epinephrine by binding adrenergic receptors
- Effects include: pupil dilation, increased cardiac output, adipose tissue thermogenesis, vasoconstriction, sugar production in liver, release of glucagon in pancreas.
- Directly related to alertness and wakefulness. The LC mobilizes the brain for action in fight or flight.

Above: Neural Pathway of Dopamine
Right: Norepinephrine Neural Pathway

Above: Epinephrine Produced in Adrenal gland
Amphetamines and Trace Amines

Trace Amine Biology
- 9 Genes/Pseudogenes in humans that are known to be related to trace amines.
- Genes: TAAR1, TAAR2, TAAR5, TAAR 6, TAAR8 and TAAR9
- Pseudogenes: TAAR3, TAAR4, TAAR5.
- Mostly orphan genes with little understood about their role and natural substrates.
- TAAR1 is most well understood and is found in the VTA, Frontal Cortex, hypothalamus and elsewhere.
- Binds tyramine> β-phenethylamine> dopamine=octopamine. It is also known to bind synthetic amphetamines.
- It exerts a negative control on dopaminergic activity indicating trace amines may act as neuromodulators.
- TAAR2 sometimes has a nonsenses mutation in schizophrenic patients.
- TAAR5 is most highly conserved among mammals, found in olfactory epithelium.
- TAAR6 has been associated with schizophrenia, depression and bipolar.
- TAAR8 may be stimulated by lipopolysaccharides, making it potentially unique.
- No reliable information is known on TAAR9's role.

Biomed. & Pharmacotherapy 2016. 83. 439-449
Progress in Neurobiology. 2006. 79. 223-246

Cellular Role of Dopamine

1. Using a proton gradient established by an ATPase, VMAT antiports DOPA into the vesicle and a proton to the cytosol.

- Vesicle monoamine transporter (VMAT)
- Dopamine Receptor (D1-like or D2-like)
- Dopamine Transporter (DAT) (“reuptake pump”)
- Monoamine Oxidase (MAO)

2. The vesicle travels down the axon reaching the terminal where exocytosis releases dopamine into the synapse when signaled. The extracellular dopamine binds the dopamine receptor, transmitting the signal to another neuron.

3. The Dopamine Transporter pumps DOPA into the cytosol of the presynaptic neuron. Here, the DOPA can be reused by transport into another vesicle by VMAT or destroyed by MAO.

DOPAC= Dihydroxyphenylacetic acid

Mechanisms of neurotransmitter release by amphetamines: a review.
Progress in Neurobiology. 2005. 75, 406-433
Amphetamines and Trace Amines

**Modulation of Dopamine by Amphetamine**

1. Amphetamine destroys the proton gradient in vesicles leading to dopamine release into the cytosol.

2. Amphetamine inhibits MAO, protecting cytosolic DOPA.

3. AMPH causes DAT to actively transport DOPA into the synapse, the wrong way. The exact mechanisms for this are not yet known. AMPH also slightly blocks reuptake of DOPA. This leads to an increase in extracellular dopamine recognized by nearby neurons.

4. AMPH stimulates the production of DOPA, further amplifying the drugs effects.

*Vesicle monoamine transporter (VMAT)*

*Red* Dopamine Receptor (D1-like or D2-like)

*Light blue* Dopamine Transporter (DAT) (*reuptake pump*)

*Purple* Monoamine Oxidase (MAO)

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"Therapeutic doses are normally given up to about 60 mg. ... [I have] never gone over 40 mg, but based on the experiences of others who have, [I recommend] this estimated dosing schedule: (1) Light increase in motivation: 10–15 mg. (2) 'Good' club buzz: 20–40 mg (add 1-2 drinks and [you are] set!). (3) Highway speeds: 60–80 mg (might start cleaning the club/party your [sic] at, lol). (4) TWEAKED OUT: 100–120 mg (not recommended). **Based on Instant-release pills take orally... as always tolerance and body-type depending...""

*Pharmacol Rev. 2014, 66, 193–221*
Theories of Dopamine Receptor Evolution

- D₁-Like and D₂-Like receptors are thought to have completely independent lineages indicating that the ability to bind dopamine was acquired twice.
  - D₁-Like: DRD₁, DRD₅, DRD₁C, DRD₁E.
    - Lack of introns.
    - Activates Gα₁₅/16 G-proteins causing cAMP production.
    - D₂ has sister relationships with D₃ and the D₁C/E clade.
    - D₁C and D₁E have a sister relationship.
    - Over time, the binding pocket of D₁ has become more refined for DOPA.
  - D₂-Like: DRD₂, DRD₂L, DRD₃, DRD₄RS.
    - Up to 6 introns.
    - Activates Gα₁₅/16 G-proteins inhibiting cAMP production.
    - D₂ has sister relationships with D₃.
    - D₄ and the D₂/3 clade have a sister relationship.

ADHD and Amphetamines

- Amphetamines have become the first-choice treatment for ADHD.

Attention Deficit Hyperactivity Disorder (ADHD)

- Today, 4-10% of children are affected in US. Boys are 2X diagnosed compared to girls.
- Three categories: Predominantly inattentive (ADHD-PI), Predominantly Hyperactive-Impulsive (ADHD-PI), and Combined type (ADHD-C).
- 30-50% of people have ADHD symptoms continue into adulthood.
- Genetics determine roughly 75% of cases, indicating a genetic component although ADHD is very poorly understood today.
- Difficult to diagnose because the behaviors exist on a continuum, leading to its controversy as a diagnosis.

Genetic Variance

- Some individuals with ADHD possess DAT and/or DRD₄ variants and decreased levels of D₂/D₃ receptors. This makes them effectively less receptive to dopamine signals.
- Some studies have found differences in brain structure in the left frontal cortex and regions responsible for long-term memory.
- Some potential, not yet clinically validated biomarkers are:
  - Phenylethylamine levels in urine
  - Platelet levels of MAO
  - Zinc and Iron levels.

Prenatal Stress in Mothers

- A variety of neurodevelopmental and behavioral phenotypes may be associated with prenatal stress, including ADHD.
- Individual fetuses may respond differently to prenatal stress hormones. Some may show no effect based on their genetic composition.
- Some researchers theorize that this could be an evolutionary mechanism to make offspring better prepared for the environment they are entering by responding to the mother’s signaling.

Evolution and ADHD

- Many theories exist based around the idea that ADHD gave a selective advantage to either individuals or groups with individuals who were more vigilant, more risk taking, more exploratory, more energetic, or more impulsive.
- Some speculate that it may have been an individual disadvantage, but an advantage to the group.
- The most culturally popular is the "Hunter vs. Farmer Hypothesis" first suggested by Thom Hartmann in his book Attention Deficit Disorder: a Different Perspective. Thom Hartmann is a political commentator and his book was not a scientific work. Nevertheless, it postulated a theory that some researchers have adopted.
- The idea is that Hunters had to be vigilant and hyperfocused on their environment to catch prey and not become prey. When humans became farmers this was no longer an advantage in a sedentary society and became a maladaptation that some humans still have today.

During the two episodes of vertebrate whole genome duplication, 4 copies of D₁-like and D₂-like receptors were produced (8 total). In both the D₁ and D₂ lineages, one of the copies was lost. Later, in the gnathostome ancestor, the DRD₁C/E ancestor was duplicated. Also in the gnathostome ancestor, the DRD₂/2L and DRD₄/4RS ancestors were duplicated giving rise to the 5 D₂-like receptors we know today.

- Note: Research on this topic is still very active and the theories presented may change. Additionally, an opinion exists that eukaryotic cells acquired cell-cell signaling machinery through late horizontal gene transfer from bacteria (similar to the way eukaryotic cells gained mitochondria).

PeerJ 2018 DOI: 10.7717/peerj.4593; Biol. of the Cell 2003, 95, 489-502
Trends in Genetics 2004, 20, 292-299

The Lancet Psychiatry 2018 5, 727-738
JAMA 2009, 302, 1084-1091
Nature Reviews: Neuroscience 2008, 9, 957-964
Current Opinion in Genetics and Development 2007, 17, 234-238
Amphetamines and Trace Amines

Performance Enhancing Effects?
• Evidence shows that Amphetamine stimulants can have positive effects on Physical Performance.
  • Increase in physical strength
  • Decrease in muscle fatigue
  • Increase in endurance
  • Decreased reaction time
  • Increased alertness and focus
  • Increased acceleration

• Because of these performance effects and their dangerous side effects, most professional and collegiate sports have banned amphetamines.

• In addition to their positive effects, there are several side effects which can hurt performance
  • Decreased heat tolerance (disrupts thermoregulation leading to increased core temperature).
  • Increased risk of cardiac arrhythmias, dyskinesia, seizures, hallucinations.
  • If too much is taken it can negatively impact focus, reaction time, and decision making. These negative effects can prove fatal under physical exertion.

Cognitive Enhancers: A Limitless Pill?
• Research is inconclusive on the impact of phenylethylamines on short and long term memory and focus in healthy individuals. Meta-studies find evidence of bias in the results and draw inconclusive conclusions.

• Results are highly dose dependent on an individual level. High doses hinder performance broadly.

• Modafinil has gained attention recently as a safer amphetamine with potentially small cognitive enhancing effects. However, this has yet to be proven.

• Amphetamine (Adderall) and Ritalin (Methylphenidate) are frequently employed as study drugs by college and high school students.

• Between 5 and 35% of students college students use phenylethylamines illegally.

• Between 3 and 10% of grade school students use phenylethylamines illegally.

Use to Fight Fatigue
• Amphetamines have been used historically and contemporarily to fight fatigue in militaries (particularly in aviation), long-haul trucking, oil rigs, med. residency, etc.

• While controversy exists in the literature on the extent to which phenylethylamines have been used in the military, clear documentation of their widespread useage in WWII exists.

• Recently, Modafinil has been gaining attention and usage by militaries around the world, US included.

• They are most often used in aviation for long bombing missions. Although, they are also used in long ground missions, particularly in the special forces.

Addict. Behav. 2017 245-249
27, 1069-1089
Addiction. 2013 109, 547-557

On Left: Yerkes-Dodson Theory

Optimal Level of response and learning

Level of "arousal function" (nonspecific cortical bombardment)

Deep sleep

Point of waking

Increasing alertness, interest, positive emotion

Increasing emotional disturbance, anxiety

All Studies Combined Flight

Analyzing the effect of stimulants vs. placebo on flight performance

"Overall, modafinil maintained flight accuracy within approximately 15-30% of baseline levels, whereas performance under the no-treatment/placebo condition declined by as much as 60-100%.
Benefits were most noticeable after 24 to 32 h of continuous wakefulness"

"Bennies" are used by a seal fighting in the Vietnam War in the novel Men with green Faces

Jacobson's "miracle tissue regenerator" shots, consisted of amphetamines, animal hormones, bone marrow, enzymes, human placenta, painkillers, steroids, and multivitamins. Although, he had many important and famous clients, his most famous was JFK who received his "miracle tissue regenerator" shot on over 30 occasions.

"I don't care if it's horse pish! It's the only thing that works."

- JFK

Aviat Space Environ Med. 2004 75 9, 777-784.
Psychopharmacology 2000, 150, 272-282
J. Interdisciplinary Hist.. 2011, 205-233
Bulletin of Anesthesia History. April 2011, 21-32

On Right: Yerkes-Dodson Theory

Max Jacobsen (Dr. Feelgood)
Disclaimer:

The following information was legally obtained under the First Amendment of the US Constitution. HOWEVER, attempting to act on this information through the purchasing of precursor chemicals with intent to manufacture, synthesis of controlled substances or their derivatives, and consumption of these chemicals are **all felony crimes** and should not be committed. ADDITIONALLY, many of these chemicals are highly **reactive** and many of the portrayed chemical reactions produce **dangerous** gases and other byproducts. These reactions **should NOT be attempted** for safety reasons.
Amphetamines and Trace Amines

Most Common Methods of (Meth)Amphetamine Synthesis

**P2P Methods**

**Leuckart (Oldest Method)**

\[
\text{Ph} + \text{HNO}_2 \xrightarrow{\text{acetic acid then HCl}} \text{R=H AMPH} \quad \text{R=Me METH}
\]

**Reductive Amination**

\[
\text{Ph} + \text{RNH}_2 \xrightarrow{\text{MeOH; then [H]}} \text{R=H AMPH} \quad \text{R=Me METH}
\]

Various reductants can be used to reduce the Schiff Base. Common ones are:
- Aluminum amalgams (from aluminum foil)
- Hydrogen (Pt/C, Raney Ni, Pd/BaSO4)
- Metal Hydrides are occasionally used (NaBH4 and LiAlH4)

Advantages of a P2P production method include its scalability. Resolution
can be achieved using d-tartaric acid and ethanol.

The major disadvantage is the required synthesis of P2P given its scheduled
status.

**(Pseudo)Ephedrine Methods**

**Nagai Method (HI, Red Phosphorus)**

**Moscow Method** (I2, H2O, Red Phosphorus)

**Hypo Method** (H3PO2, HI)

Through the course of the reaction HI dissociates at high
temperature to H2 and I2. It is
in this way that it acts as a
reductant in the reaction. Red
Phosphorus reacts with the I2
produced to generate PI3,
which is hydrolyzed to
regenerate HI and form
phosphoric acid.

*J. Organomet. Chem 1997, 529, 295-299*

Role of Red Phosphorus and I2 in Nagai-type methods

**Chlorination/Reduction**

\[
\text{OH} \quad \xrightarrow{[X]} \quad \text{Me} \quad \xrightarrow{[\text{Cat}]} \quad \text{Me}
\]

\[ [X]= \text{SOCl}_2, \text{PCl}_3, \text{PR}_3, \text{PCl}_5, \text{etc} \]
\[ [\text{Cat}]= \text{Pd/C}, \text{Pt/C}, \text{Pd/BaSO}_4 \]

Advantages of this route: Chiral Pool materials
Disadvantages: Dangerous impurities, Reactive reagents, Harder to obtain materials.

Above: "Poor Man's Hydrogenation Device" made from
a stainless steel fire extinguisher.

On Right: An example of how to build a low pressure
bomb for hydrogenation out of a champagne bottle

**Birch Reduction and the "Shake and Bake"**

Traditional Birch requires free base, and can provide a very
pure product. The main problem is the aquisition of ammonia.
This must usually be bought as fertilizer or stolen.

All the contents are placed in a soda bottle, shaken, and occasionally vented to prevent
explosion. It has become the most popular method of synthesis for personal use in US.
Yields are in the mid 30% range.

Shake and Bake method is VERY dangerous:
youtu.be/oCZgG3VJdTQ
Amphetamines and Trace Amines

**Most Common Methods of (Meth)Amphetamine Synthesis (Cont.)**

Friedel-Crafts and Ritter Syntheses

- **Rxn is messy and low yielding.**
  - **JACS 1946, 68, 1009-1011**
- **Ritter Reaction:**  
  - **JACS 1948, 70, 4045-4050**
- 3 main methods of allylbenzene synthesis:
  - PhMgBr + AllylBr
  - PhMgBr, AllylBr, Cul
  - Cinnamaldehyde + Tosylhydrazine then NaBH₄
  - **JOC 1978, 43, 2310**

**Other common methods of synthesis**

- **NO₂** LAH → **NH₂**
- **R= NH₂ or N₃**
- **Several Steps**
- **OH** → **Me NH₂**

**Key Resources for Synthesis info:**

- **Secrets of Methamphetamine Manufacture 7th ed.**
  - Uncle Fester
- **Total Synthesis II**
  - Strike
- **PIHKAL by Shulgin**
  - **Forensic Science International 42, 1989, 183-199**
  - erowid.org

**3,4-Methylenedioxy methamphetamine (MDMA) (aka Molly, E, Ecstasy, Adam)**

- Synthesized 1912, rediscovered around 1950-60
- Tested on animals by the CIA in the MK Ultra program
- Used as a party drug to replace MDA ("the love drug")
- Shulgin was instrumental for its growth in popularity in the US.
- It became a Schedule I drug in 1985
- It can lead to death due to its body temperature elevating effects.
- Recently given "breakthrough designation" by FDA after Phase 2 trial for PTSD
- Biologically, it modulates the release of serotonin, norepinephrine and dopamine.
- It decreases activity in the amygdala, the fear center of the brain.

**Synthesis of MDMA**

- Many MDMA Syntheses are similar to the (meth)amphetamine analogs. They use commercial materials to arrive at a P2P equivalent:
  - Halhydrations, Wacker, Condensations, and epoxidations are all utilized

**MDP2P**

- **Starting from Safrole**
  - 1. HBr
  - 2. NaI
  - 3. MeNH₂

**Step 1 Name?**

- 1. PdCl₂[(O)]
  - H₂O, DMF
- 2. MeNH₂, NaBH₄

**Base or TM's can be used for this isomerization**

**Starting from isosafrole**

- 1. RCO₂OH
  - 2. H₂SO₄

**Name?**

**From Piperonal**

- 1. EtNO₂, base
  - 2. Fe, HCl

**Piperonal can derived from Piperine extracted from black pepper.**

**"The 2C Series"**

- R= Br 2C-B
- Cl 2C-C
- F 2C-F
- Bn 2C-Bn
- Me 2C-D
- Et 2C-E
- Ipr 2C-IP
- NO₂ 2C-N
- OMe 2C-O
- Ph 2C-Ph
- SEt 2C-T-2

- A series discovered by Shulgin. 2C-B, 2C-D and 2C-E are popular, but many in the series have not been extensively tried. None have been safely tested.

**"The 3C Series"**

- 1. Base, RX
  - 2. MeNO₂, NH₂OAc
  - 3. LAH

- 2C-G-5
Amphetamines and Trace Amines

Stephen Harwood

"The DOx Series"
- Another Series of Amphetamines pioneered by Shulgin.
- These compounds have high selectivity as 5-HT partial agonists, thus they modulate serotonin levels in the brain.
- They have long lasting effects.
- DOB, DOC, and DOM are a few of the flagship members.
- The R-enantiomer displays dramatically more activity.
- Many are unscheduled in US due to low use.

**Step 1 Name?**
Novel Synthesis of 2,4,6-DOM reported by "Labrat"

JOC. 1990, 55, 5386-5390
Tet. Lett. 1989, 30, 1689-1690
Synthesis. 1985, 202

*(with 3 mg) In the middle of the experience I found that I was able to separate components of complex things so as to evaluate them separately. There is no need to respect their normal purpose. The sharpness of observation is enhanced, but one can focus at every different depth of a thing or a concept. Colors are not just brighter; there are more of them. There is a profoundness of meaning inherent in anything that moves. A line of thought or a bit of personal history ties the thinker to the objects that had been thought of, or once experienced. It is this relationship that will prove productive. Not like in a movie which is circular in its totality, but as in true life where the future is the result of your own involvement with everything about you."

--Shulgin PIHKAL on the effects of DOM

NOTE: DOB has considerable toxicity in humans and rats. People have gone into coma and have died from ingesting too large amounts of DOx compounds. It is not recommended these compounds be consumed

Baran Group Meeting
1/11/2020

Shulgin's "Essential Amphetamines" and the "Magical Half-Dozen"
- Essential Amphetamines compounds differ from natural product oils by an amine group.
- Magical Half-Dozen (All Schedule I) are Shulgin's top compounds. Very Popular among psychonauts and clandestine chemists

**"Death"; "Dr. Death"**
- Selective serotonin release agent very dangerous!
- DOB-like

**2,5-DMA**
- Amphetamine-like tested by Army chem. warfare group

**MDA**
- Serotonin release agent
- 5-HT agonist
- Empathogen

**MDA-2**
- Discovered 1955 by Canadian researchers
- Most active "TMA" mescaline-like

**3,5-DMA**
- Mescaline-like

**H2N**
- 5-HT agonist recurring visuals: stripes, fractals, "cobweb" "geometricization"

**Mescaline**
- LSD-like first tetroxy-amph explored in Man.
- "I am into it; it is much like MDA"- Shulgin
- 30mg dose was uninspiring

**DMMDA**
- "Nexus, Tonies, Spectrum, Venus" with LSD "banana split" with E "party pack" 5-HT partial agonist
- MDMA-like
- "Chemical may be overly intense for those not well experienced with psychedelics"
- Two deaths have been attributed to 2C-E

**TMA-2**
- Tool for introspection.
- Experience more affected by physical disturbances than 2C-T-7

"serenity, tranquility, and peace, (STP)" Slow onset!
(Prodrug?) 5-HT partial agonist MDMA-like

"Visually like mescaline but less sparkly". Spiritual experiences. Dangerous!

**DOB**
- "Chemical may be overly intense for those not well experienced with psychedelics"
- Two deaths have been attributed to 2C-E

**2C-T-2**
Amphetamines and Trace Amines

**Use as Auxiliaries**

(+)-Norephedrine via: 

```
(-)-pseudoephedrine
```

**Use as Ligands**

```
   R= H, Me, iPr, Ar etc.
```

For Noyori Reduction, >95% conv. 40-97% ee

Carpentier, J.-F.

**R.B. Woodward’s Lysergic Acid Synthesis**

```
Et₃N
```

14 steps total. *JACS* **1956**, *75* 5256

**Honorable Mention: Lysergic Acid Diethylamide (LSD)**

- Extremely potent entheogen (µg doses)
- Both Serotonergic and Dopaminergic
- Imported into US by CIA for MK Ultra
- Fueled 1960’s counter culture.
- Discovered 1938 by Albert Hofmann

**Lysergic Acid**

```
[6-10]
```

**Substituted alkenes:** Carreira, E. *JACS* **2000**, *122*, 1806-1807

**Terminal alkenes:** Carreira, E. *Org. Lett.* **2000**, *4233-4236

**Reviews on (pseud)ephedrine auxiliaries:**

Myers Chem 115 on Asymmetric Alkylation

*Current Organic Synth.* **2018**, *15*, 38-83

**Epoxides come from “top” face via proposed Li coordination**

- Hydroxide blocks top face in alkylation


See also: ACS Catal 2017 6162 ref 14c and 17.
Amphetamines and Trace Amines

The "Battle" Against Clandestine Chemistry

"Small Toxic Networks" (STN's)
- Centered around individual cooks
- More primitive precursor acquisition strategies
- STN's grew domestically in number until 2006 Combat Meth Act.
- Rarely turn large profits, enough to sustain cooking and personal use.
- STN's are difficult to disrupt. Loose associations for tradecraft, not much intranetwork contact.
- Decentralization of information on internet has helped spread clandestine methods.
- The recent "Shake and Bake" method led to an increase in STN's

"Mexican-Run Drug Trafficking Organizations" (MDTO's)
- Today, only 20% of meth is made domestically. The rest is from Global Production Networks.
- These networks obtain precursors from international sources and produce on an industrial scale.
- They have several cells which operate as a conglomerate: Production, Smuggling, Trafficking, and Distribution.
- After the Chemical Diversion and Trafficking Act of 1988, MDTO's appeared in Southwestern US.

**Super Labs** are capable of 10 lbs to 100 lbs batches and operate continuously.
- DEA works internationally to halt supply of precursor chemicals.
- Super labs moved out of US and down south after constriciting pseudo supply.
- After global restriction of pseudo, the Mexico based labs switched back to the P2P production method.

Opinions of Policy Experts
- Specifics are debated but there is a general consensus:
  - Make Pseudo and epinephrine prescription medication only.
  - More restricted control of P2P and its precursors internationally, including rarer precursor chemicals which MDTO's have access to.
- Some Experts suggest a re-examination of federal funding distribution is necessary. Vermont, 9 lab busts in 10 years receives the same amount of funding as Tennessee with 14,836 busts (half of all busts). Thats $648,709 per bust vs. $388 per bust.
- Additionally, experts disagree on how pseudo should be controlled: Local regulation (State level) or Federal regulation?

“At that moment, when I had the TV sound off, I was in a 382 mood; I had just dialed it. So although I heard the emptiness intellectually, I didn’t feel it. My first reaction consisted of being grateful that we could afford a Penfield mood organ. But then I realized how unhealthy it was, sensing the absence of life, not just in this building but everywhere, and not reacting—do you see? I guess you don’t. But that used to be considered a sign of mental illness; they called it ‘absence of appropriate affect.’ So I left the TV sound off and I sat down at my mood organ and I experimented. And I finally found a setting for despair. So I put it on my schedule for twice a month; I think that's a reasonable amount of time to feel hopeless about everything, about staying here on Earth after everybody who's smart has emigrated, don’t you think?”
—Philip K. Dick, *Do Androids Dream of Electric Sheep?*

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*Philip K. Dick’s High Life* by Stephen Bitsoli, The Fix, 2017

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