# My Favorite Molecule

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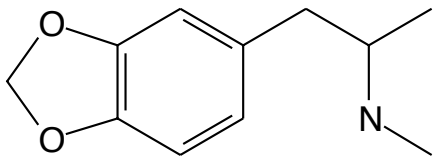


Figure 0.1: 3,4-methylenedioxymethamphetamine

## 0.1 Introduction

MDMA is a compound that over the course of three decades has accrued quite a bit of baggage. This report will attempt with all futility to remain objective and analytical. Too many books and essays have been written on this compound from the eyes of some random ignorant hippie, fueled

by numerous vague "whoa, dude" accounts, or even worse by ex-chemists who while being overgenerous with synthesis methods still do not have an appreciation as to why these processes work. The following excerpt from "PiHKAL" by Alexander T. Shulgin should shed a bit of light on the nature of this report, written by an inquiring chemist:

> "At the present time, restrictive laws are in force in the United States and it is very difficult for researchers to abide by the regulations which govern efforts to obtain legal approval to do work with these compounds in human beings.... No one who is lacking legal authorization should attempt the synthesis of any of the compounds described in these files, with the intent to give them to man. To do so is to risk legal action which might lead to the tragic ruination of a life. It should also be noted that any person anywhere who experiments on himself, or on another human being, with any of the drugs described herin, without being familiar with that drug's action and aware of the physical and/or mental disturbance or harm it might cause, is acting irresponsibly and immorally, whether or not he is doing so within the bounds of the law."

3,4-methylenedioxymethamphetamine (also known as: ecstasy, MDMA, MDM, DAVE, adam, empathy, rolls, beans, E, X, XTC, and so on, though I will refer to it from here on out as DAVE), like all compounds that make up the MD class, contains two rings; one of benzene and one heterocyclic ring. One can think of it as methamphetamine with an extra heterocyclic ring on the back end. Small changes in chemical formula will produce molecules with uniquely different effects. For example, replacing the N-methyl group with a hydrogen would turn DAVE into MDA. This single change in structure causes quite a change in psychological effects, such as the addition of hallucinogenic properties. DAVE is a white, crystalline solid with a melting range of 147-153$^o$C depending on method of synthesis. A yellowish tinge commonly seen in illegal product comes from impurities. I chose this molecule because I feel that there is much confusion and misinformation about it that should be cleared up. I do not condone the illegal use of any drug, but I do believe that DAVE has shown potential for therapeutic use and should be researched more before any definitive conclusions are made as to its scheduling. If one thing is for certain, it is that this compound is not going to disappear any time soon. The DEA made a poor decision in scheduling the drug, the results of which are seen today. Scheduling DAVE

only drove the drug underground, both increasing its use and decreasing its average purity. This drug became far more dangerous and popular *because* of the DEA.

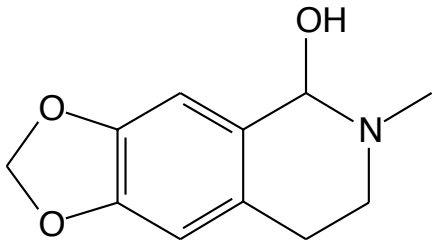


Figure 0.2: hydrastinin

## 0.2 Sources

DAVE does not occur in nature; it is known as semi-natural because a significant amount of synthesis is done by nature before man lays hands on it. The most popular starting material, isosafrole, is an essential oil obtained from sassafras plants. Its first recorded synthesis was rather uneventful and not much information (at least, in english) is given about it. In 1912 DAVE was patented by Merck Pharmaceuticals in Germany (patent #274,350) as a supposed appetite suppressant. Merck never actually marketed it and their patent has since lapsed. In reality it was simply a byproduct in the synthesis

of *Hydrastinin*, which Merck planned to market as a vasoconstrictive and styptic medicine. DAVE is listed in Merck's patent application simply as an intermediate. Also worth noting is a number of German-language sources[1], (none of which I can actually read) crediting an undergraduate German chemist, Fritz Haber, with the first actual synthesis of DAVE in 1891. The first actual synthesis with the intent of obtaining DAVE (as a product, not an intermediate) occurred in 1953 by the U.S. Army Chemical Center (contract no. DA-18-108-CML-5663) for potential use in battle. It is not known which ancient technology was used to identify this compound, but its synthesis, as described in the Merck patent, was rather straightforward.

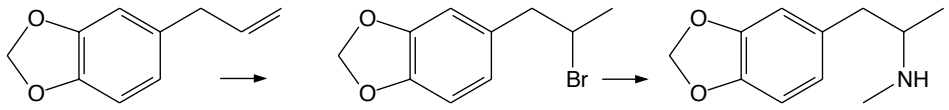


Figure 0.3: Original Synthesis Route

[1]This is actually heresy in that only one source made mention of it and this source offered no links to cited German-language documents

## 0.3 Uses

While originally labeled an appetite suppressant, DAVE has been known to do a lot more. This section will be broken into three subsections; psychological effects, physical effects, and miscellaneous or unsubstantiated effects.

### Psychological Effects

DAVE is predominantly responsible for a feeling that "everything is alright". Unlike many other mind-altering substances such as alcohol which makes one think inward, those under the influence of DAVE pay more attention to others and genuinely listen. Originally this drug was going to be called *empathy*, a much more accurate name. The name *ecstasy* was chosen because it sounded more appealing to consumers. DAVE is also known to make one more creative, perform better orally (in speech, okay), much less inhibited, more forgiving, more aware of ones own senses, euphoric, more likely to create emotional (but sometimes inappropriate) bonds, restless, and nervous. Effects upon "coming down" include sadness, full-blown depression, short-term memory loss, nostalgia, and mental fatigue. Those for and against DAVE still generally agree on these psychological effects.

## Physical Effects

Minor physical effects of taking DAVE include increase in energy, visual distortion (generally brighter and more colorful), appetite loss, nystagmus, mild hallucinations (generally with higher doses), increased heart rate and blood pressure, inability to regulate temperature, jaw clenching, muscle tension, erectile dysfunction (though this is more of a psychological side-effect), hyperthermia, dehydration, hynatremia, nausea, vomiting, headaches, dizziness, loss of balance, vertigo, hangover (for days or weeks), fatigue, liver toxicity (rare), and death (very rare, only in high doses). Note that while it is possible to overdose and die from taking DAVE it would require a ludicrous amount of it. Most other prescribed drugs could do the job in $\frac{1}{50}^{th}$ of the lethal DAVE dose by mass. This compound is actually one of the safest drugs one could take, from a physical perspective.

## Miscellaneous or Unsubstantiated Effects

DAVE has been suspected in disrupting natural serotonin metabolism. In the short term this has been found true. However, no long-term data has given a definitive answer as to whether or not long-term exposure causes reduced serotonin metabolism and, more importantly, no detrimental effects

have been observed for processes controlled by serotonin, such as regulation of self-esteem or sleep. On the contrary, moderate use of DAVE has induced positive results on self-esteem. One must remember, however, that these tests generally follow a more expedited system. Normal use ($2.0\frac{mg}{kg}$) of DAVE with week-long intervals of abstinence (when used more often the positive effects quickly disappear) has shown negligible differences in serotonin levels. Along the same lines, DAVE intake has been suspected as a neurotoxin. Several accredited reports have shown it is in fact a neurotoxin in small animals, such as rats, but a normal dose (see above) has proved at worse inconclusive, and at best safe. Only heavy use involving unreasonable amounts of DAVE produced similar neurotoxic effects in humans. It is also worth mentioning that DAVE has not found to be addictive. In fact, it has been shown to decrease ones other addictive tendencies, such as alcoholism, though not to a great degree. As a last note, currently only 20% of ecstasy on the street is purely MDMA. Supposed XTC tablets have been shown to carry several other substances, such as Diphenhydramine, Caffeine, Procaine, Methamphetamine, Aspirin, Acetaminophen, Ephedrine, Ketamine, and several other impostor substances. See http://www.ecstasydata.org/ for an astoundingly long list of tablets and their actual contents.

## 0.4 Known Syntheses

This section will be divided into two subsections due to the illegal nature of the compound. Subsection one takes a close look at two prominent syntheses used prolifically before MDMA became scheduled, perhaps best explored in *PiHKAL: A Chemical Love Story* co-written by Dr. Alexander Shulgin. Subsection two will hilight several newer synthetic routes employed in clandestine labs worldwide.

### Early Routes

The most heavily used (and therefore most quickly stopped) route to DAVE came from piperonal (see figure 0.3). This was a favored method among chemists while synthesis was still legal. Personally, I did not understand why this synthesis would be favored, as it requires an extra step over the isosafrole-related path, but it makes more sense when one considers how readily available piperonal was before it was scheduled. From piperonal one gets 1-(3,4-methylenedioxyphenyl)-2-nitropropene and from that comes 3,4-methylenedioxyphenylacetone, or simply MDP2P. An alternate path to MDP2P comes from isosafrole and proceeds in one long step. This specific reaction is analyzed in section 0.5. From here we use a two-step reaction

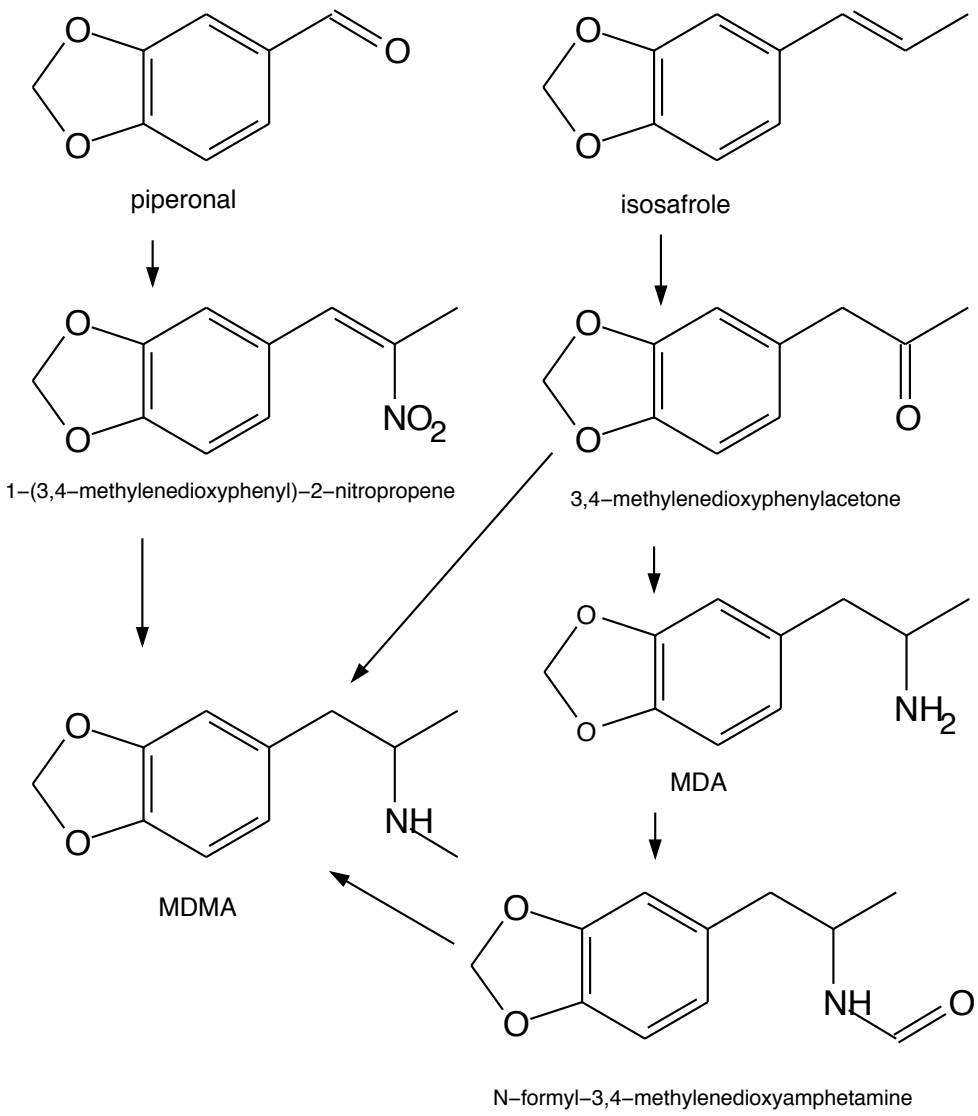


Figure 0.4: early synthesis routes

that utilizes the electronegative properties of aluminum. In the first part the carbonyl group is replaced with an imine. Next, hydrogen is added across the double bond, thus reducing this imine, leaving the expected product.

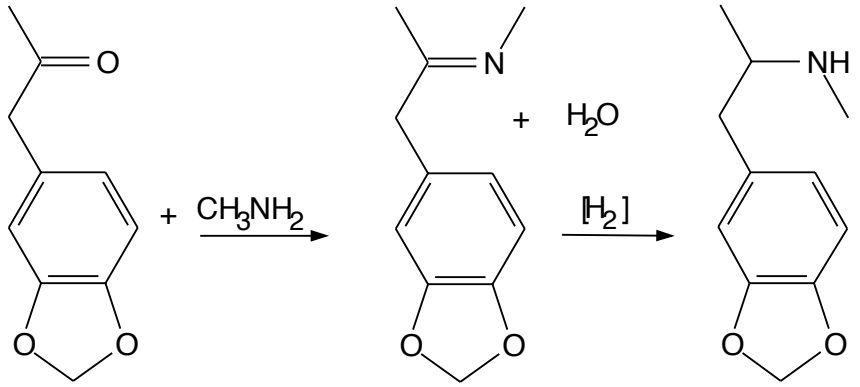


Figure 0.5: MDP2P to MDMA

## Modern Routes

There are several modern routes employed to synthesize DAVE, most of which were made due to DEA's scheduling of several popular precursors. Some of these routes start with the previously mentioned isosafrole-to-MDP2P route and then branch off into several separate methods to obtain DAVE. These routes will be listed graphically and with little explanation. My rationalization for this lack of detail has to do with the fact that none of these reactions give better yields than the "Early Routes" and were simply

thought up to circumvent current laws. That is to say, by underground chemists looking to make money. Any licensed chemist would simply follow one of the original syntheses. Not shown but constantly mentioned is a synthesis from MDP2P to DAVE by way of raney nickel catalysis. Several sources listed this synthesis, none of which explained it in any detail.

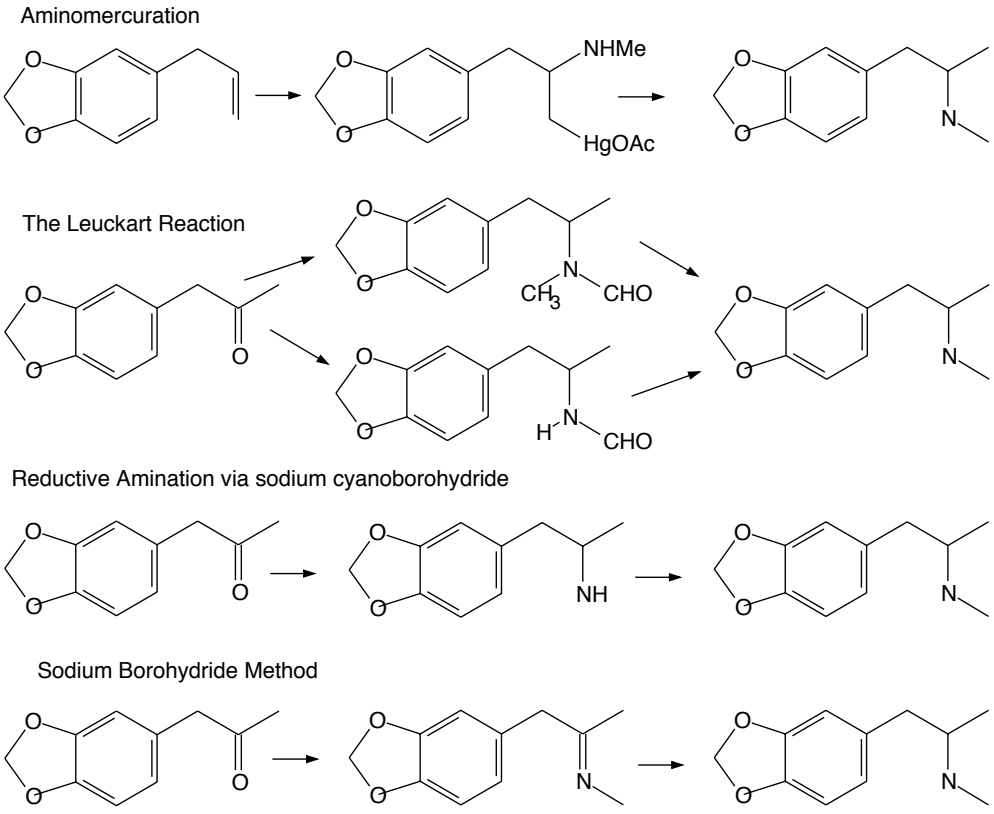


Figure 0.6: Modern Synthesis Routes

## 0.5 Specific Reaction Analysis

The most significant reaction in the known synthesis of DAVE occurs in the beginning, with isosafrole. Without argument, the most important intermediate is MDP2P, which is the basis for all chemicals in the MD-series. Therefore, the most significant reaction would have to be the one widely used to synthesize this intermediate. In this multiple-step reaction, a peroxyacid is created in situ and used in an epoxidation reaction, turning isosafrole's only susceptible double bond into a three-membered heterocyclic ring. At this point, the ring is cleaved and base is added, forming a 1,2 diol. Next, acid is added to selectively remove the unneeded OH group and form an enol. The enol quickly tautomerizes into a ketone and the reaction is complete. This reaction must be externally cooled and kept at a temperature around $40^{o}$C as the formic acid is added slowly. Acetone is used as a solvent. See *PiHKAL* under "#109 MDMA" for more exact synthesis instruction. The mechanism for this reaction is as follows:

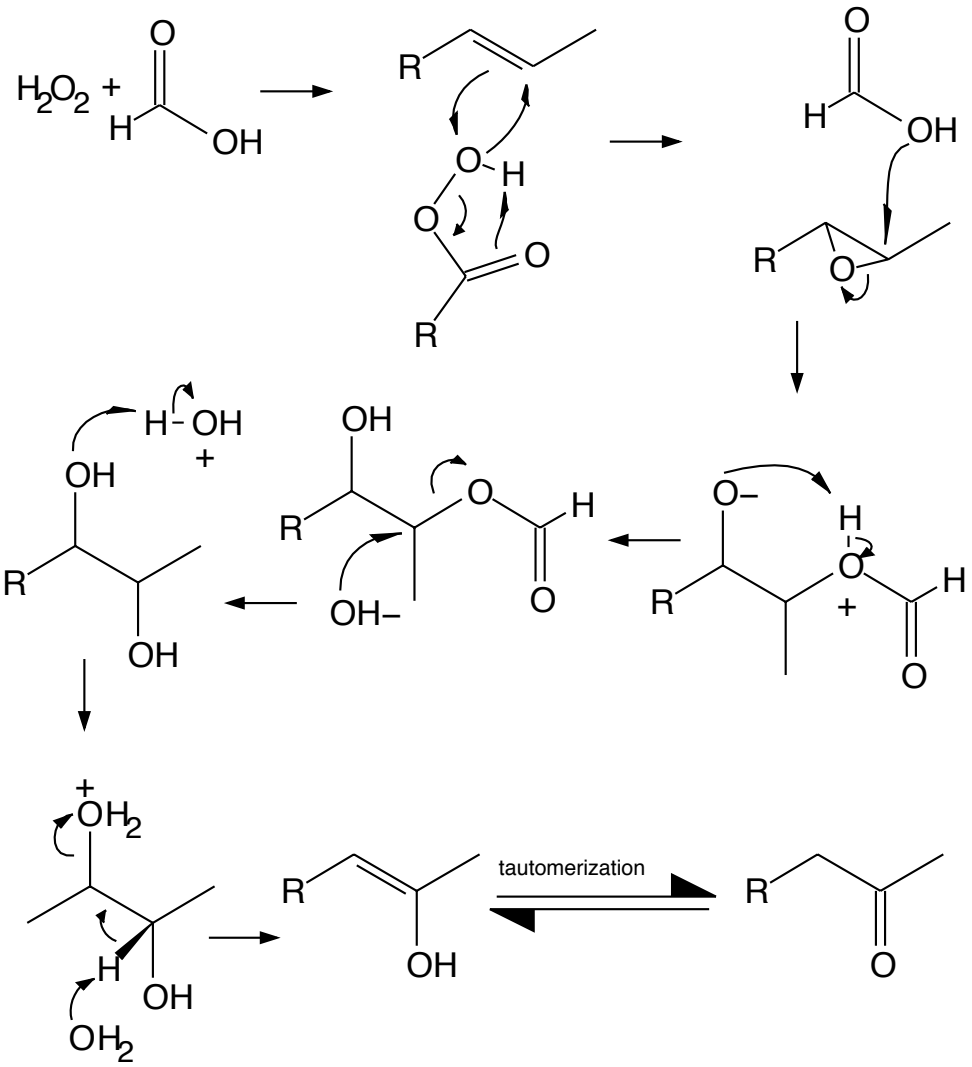





Figure 0.7: Mechanism