The Sassafras Tree and Designer Drugs

From Herbal Tea to Ecstasy

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The following account reviews some aspects of the phytochemistry of *Sassafras albidum*. Its origin is found in a special topic lecture that I insert into the presentation of amine chemistry in the introductory organic course. A discussion of clandestine drug synthesis provides a far more interesting venue for presenting methodology for amine synthesis than the catalog approach that prevails in most textbooks. In the course of gathering material for this presentation, I became aware of the significance of the sassafras tree in the underground production of methylenedioxymethamphetamine (MDMA, ecstasy, XTC, Adam) **(11)** a controversial designer drug. After presenting some basic botanical information, a brief historical overview of medicinal interest in material from the sassafras tree will be given. This will be followed by a discussion of the chemical composition and utilization of the derived essential oil. The second portion of the paper examines the chemistry of amphetamines and their clandestine production. Finally, the designer drug, Ecstasy, will be discussed in detail and its link with oil of sassafras explored. Interwoven into this story will be a look at the mechanisms through which the federal government designs, enforces, and interprets legislation for chemical substance regulation.

Botanical Considerations

Taxonomically, *Sassafras albidum* is a member of the family *Lauraceae*, the laurels, which comprises approximately 40 genera and is represented by more than 2000 species. Numbered among this group are the camphor laurel and the cinnamon trees of the Orient and the West Indian avocado pear. Distribution of the *Lauraceae* is primarily throughout tropical southeastern Asia and Central and South America. In addition to sassafras, the California laurel, *Umbellularia californica*, the spicebush, *Lindera benzoin*, and redbay, *Persea borbonia*, are native to North America.

The sassafras tree ranges from Maine across southeastern Ontario to Michigan and south to Florida and Texas. Its preferred habitat is thickets, roadsides, and old fields where it typically attains heights of 20–50 feet. Perhaps its most unusual characteristic is its multivariate foliage. Unlobed, single- and triple-lobed leaves grow concurrently on the same twig. All tissue from the plant (most notably the root bark) emits a pronounced aromatic aroma.

Of the Tree that Is Brought from the Florida, Whiche Is Called Sassafras

So begins an extensive treatise on the remarkable curative powers associated with this *materia medica* in *Joyfull Newes out of the Newe Founde World*, the 1577 translation of the first European pharmacopeia to catalog materials from the
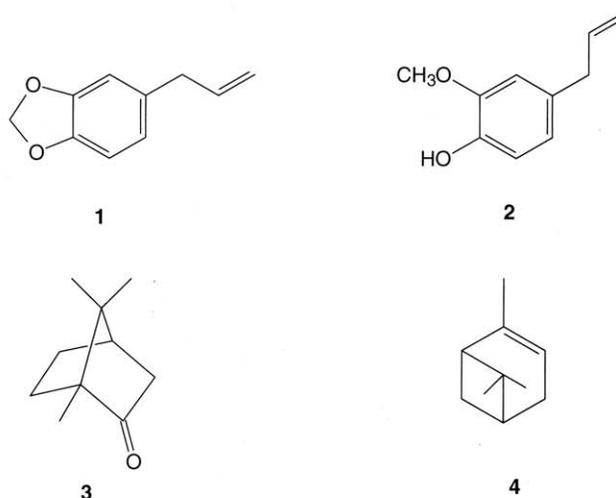

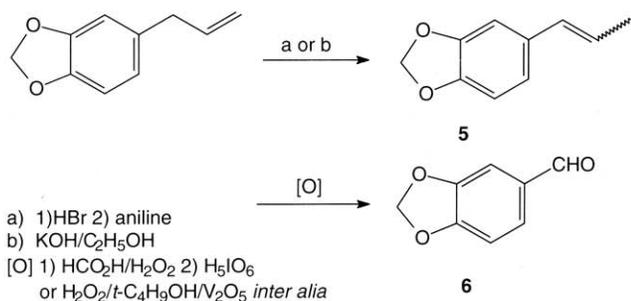Figure 1. Sassafras oil principal components.

Figure 2. Heliotropin synthesis.

a) 1)HBr 2) aniline
b) KOH/C$_2$H$_5$OH
[O] 1) HCO$_2$H/H$_2$O$_2$ 2) H$_5$IO$_6$
  or H$_2$O$_2$/t-C$_4$H$_9$OH/V$_2$O$_5$ inter alia

Americas authored eight years earlier by the Spanish physician, Nicholas Monardes (1). With a medical practice established in the coastal city of Seville, Monardes had access to herbal materials carried back to Spain by the Conquistadors, and he freely experimented with them in the treatment of his patients. In a book describing the utility of such exotic and dubious therapeutic agents as "oyle of the fig tree of hell", "blood stone", and "dragon's blood", the sassafras tree is afforded substantial attention; (only the chapter on tobacco is longer). The litany of infirmities and ailments said to respond to treatment with aqueous infusions of the root bark includes fever, liver discomfort, headache, bronchial congestion, stomach ailments, kidney stones, gout, toothache, arthritis, constipation, and infertility.

Early accounts of New World explorers unfailingly cite enormous populations of the tree all along the eastern seaboard. Second only to tobacco, sassafras root bark became a principal export to England commencing with the first permanent British settlement at Jamestown, Virginia. Alexander Brown in *The Genesis of the United States* documents a letter sent from the Council in Virginia to England in June 1607, in which a potentially detrimental preoccupation with root gathering is noted. The letter relates "our easiest and richest commodity being saxifrax roots were gathered up by the sailors with loss and spoil of many of our tools and with drawing our men from our labor" (2).

By the 1820's, scientific scrutiny had voided the majority of the therapeutic claims indicated earlier. However, the dried root bark remained official in the U.S. Pharmacopeia through 1926 where it is indicated that the material has useful antiseptic properties, can induce a beneficial increase in sweating or be used to mask the taste or odor of other unpalatable medicines. Even today, sassafras tea produced by steeping the young roots remains a fixture in Appalachian folk culture where it enjoys repute as a "spring tonic" and "blood thinner" (3).

Sassafras Oil

North American sassafras oil consists of the volatile, steam distillable components of the roots and root bark of *S. albidum*. It is a yellow to amber liquid with a melting point of 4–6 °C. Its olfactory quality has been described as sweet-spicy, fresh, slightly camphoraceous and woody-floral with a fresh-peppery topnote. It possesses a unique sweet, woody flavor and was widely employed to flavor toothpastes and soft drinks, particularly root beer, prior to 1961.

The principal chemical constituent of the oil (≈80%) is safrole (1) (4-allyl-1,2-methylenedioxybenzene). Other significant components that have been identified include eugenol (2), camphor (3), and α-pinene (4) (Fig. 1).

Enormous quantities of safrole are used in technical perfuming to scent soaps and commercial cleansers. In addition,

piperonal (6) (heliotropin), widely employed in fine perfumes, can be prepared most economically from safrole via base-catalyzed alkene isomerization to isosafrole (5) followed by oxidative cleavage (Fig. 2). Prior to 1942, the United States relied primarily on oil of camphor, available from the Asian camphor laurel, to meet its requirements for safrole. With the entrance of the United States into the Second World War a new source had to be secured. At this point, "Brazilian sassafras oil" emerged as an important commodity. Originally, the source of this oil was incorrectly identified as *Ocotea cymbarium*. The actual source is *Ocotea pretiosa* while the oil from the previously mentioned specie is devoid of safrole (4).

Food and Drug Administration studies conducted in 1960 indicated that safrole is a weak liver carcinogen in rats. The
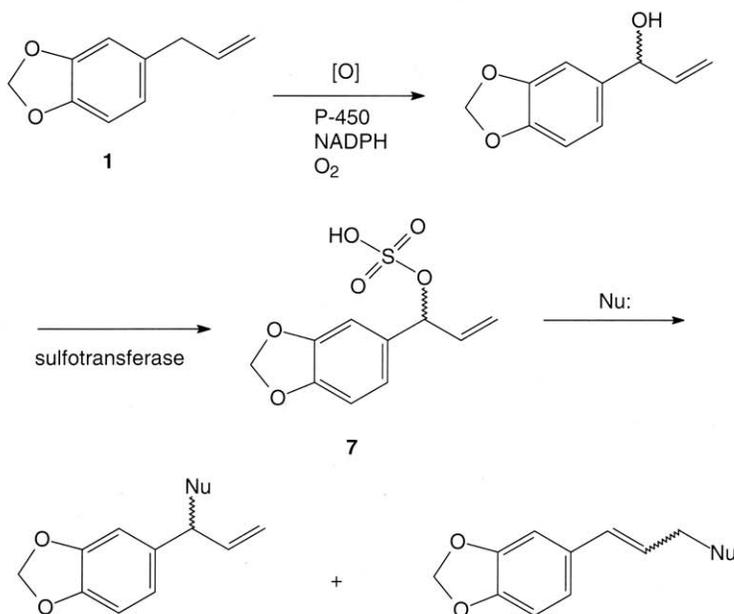

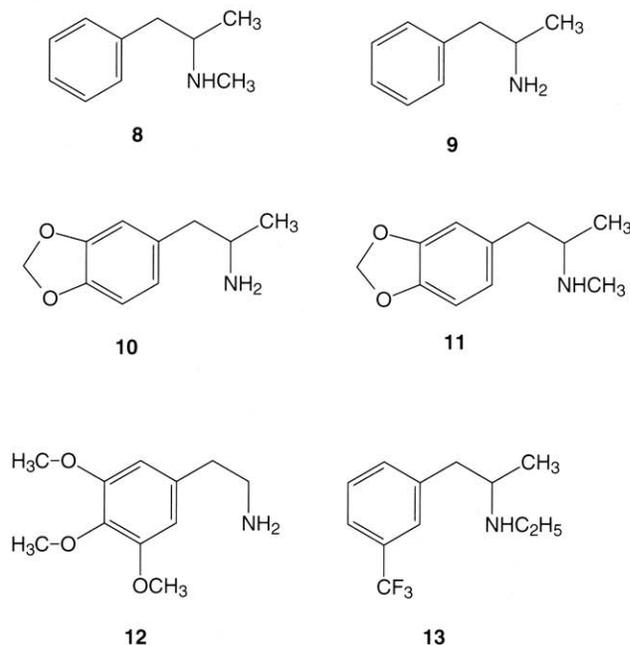Figure 3. Mechanism of chemical carcinogenesis by safrole.

Figure 4. Some phenethyl- and phenyl isopropylene incorporating drugs of abuse.

Food Additives Amendment (1958) to the Federal Food, Drug and Cosmetic Act includes the much discussed Delaney Clause (5), which stipulates that no known carcinogenic substance can be utilized as a food additive. In another FDA study, safrole levels in the range of 8–26.7 ppm were detected in various root beer samples (6). The use of safrole and sassafras oil as flavoring agents was proscribed on December 2, 1960. Dihydrosafrole and isosafrol were also banned (7). Further regulation was promulgated to address the commercial sale of herbal teas containing ground sassafras root bark (8) and a 1976 article in *The Journal of the American Medical Association* pointed to the dangers associated with safrole exposure through the ingestion of sassafras tea (9). Safrole is also present in lower concentrations in many spices including anise, basil, nutmeg, mace, and black pepper.

Evidence for the mechanism of safrole carcinogenicity (Fig. 3) has accumulated that implicates a two-step metabolic activation of safrole, the precarcinogen, into a highly electrophilic sulfuric acid monoester ultimate carcinogen (10). The proposed bioactivation pathway proceeds by way of enzymatic oxidation at the readily oxidized secondary benzylic/allylic position. Sulfate donation affords the potent electrophile, 1-sulfooxysafrole (7), a compound that can be viewed as a biochemical equivalent of the sulfonate esters employed by synthetic organic chemists to activate alcohol substrates toward substitution. This metabolite can form covalently linked adducts via reactions with sites on the polydentate DNA nucleophile in the initiation step of chemical carcinogenesis. *In vitro* and *in vivo* studies with model safrole derived sulfonate esters and nu-

Table 1. Controlled Substance Scheduling Criteria

Schedule	Abuse Potential	Accepted Medical Use in the United States	Dependence Creation	Examples (current level)
I	high	no		heroin, LSD, marihuana, mescaline
II	high	yes	severe psychological or physical	cocaine, methadone, amphetamine
III	< I & II	yes	mod/low psych. or phys.	barbiturates, anabolic steroids
IV	< III	yes	limited psych. or phys.	diazepine, tranquilizers
V	< IV	yes	limited psych. or phys.	pharmaceutical mixtures with narcotic pain killers

cleosides have resulted in the isolation and characterization of N-alkylated guanosine and adenosine adducts whose formation can be rationalized in terms of S_N1 and S_N2-reactions (11).

Ecstasy—Sassafras Oil in the Clandestine Drug Lab

Compounds incorporating the phenethylamine pharmacophore have been popular drugs of abuse and targets for underground synthetic chemists for over 50 years (Fig. 4). The prototypical representatives of this class, methamphetamine (8) and amphetamine (9), are central nervous system psychomotor stimulants. Current legitimate medical utilization of amphetamines is limited to the treatment of narcolepsy, a neurologically based sleep malady, and attention deficit hyperactivity disorder. Recently, the appetite-suppressing activity of these compounds has reemerged as a topic of interest with the focus on fenfluramine (13) treatment in the management of obesity (12).

Illegitimate use of amphetamines remains a significant problem. Their popularity has followed a cyclical pattern and is currently on the upswing while cocaine and crack abuse appear in decline. Their illicit preparation is based typically upon reductive amination protocols commencing with phenyl-2-propanone (P2P) or a substituted derivative. Catalytic hydrogenation, hydride reductions, dissolving metal reductions, and the Leuckart reaction have all been employed in this capacity. Reduction of ephedrine, a bronchodilator and the active ingredient in many over-the-counter cold formulas, is also a popular method (Fig. 5) (13). Control over absolute stereochemical outcome is not exerted in any of these synthetic routes and the products are, therefore, racemic mixtures of enantiomers that display significantly disparate pharmacological profiles. The stereochemical integrity of enantiomerically pure ephedrine that might be employed as a starting material is compromised under the acidic conditions of its reduction in which the dehydration product (an enamine-imine tautomeric pair) is the hydrogenation substrate. In the absence of any quality control, insufficient (or non-existent) purification protocols often result in highly impure product reaching the market. One frequently encountered imine reduction relies on an aluminum amalgam prepared from mercuric chloride. Less than fastidious purification can result in grey-tinted product that has been shown to be contaminated with up to 1300 ppm of mercury (14). Drug Enforcement Agency data for the period 1981–1987 indicate a range of methamphetamine purity from 3.7% to 97% with an average of 40%–50% for samples of less than three grams. Figures in the same report show that clandestine methamphetamine lab seizures grew from 184 in 1981 to 775 in 1987 (15).
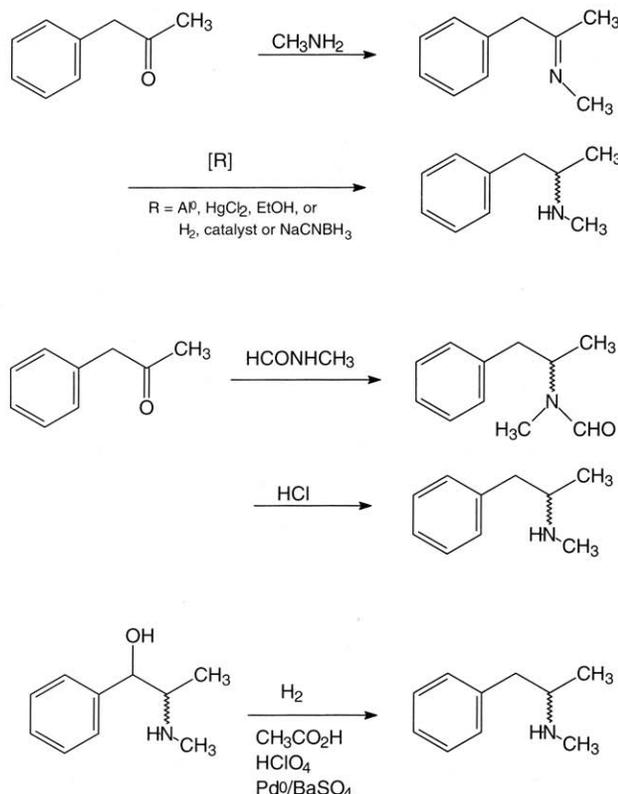

Figure 5. Some commonly utilized routes for clandestine methamphetamine production.

a) Ac$_2$O, pyridine
b) CH$_3$CO$_2$H, ThO$_2$, combustion tube
c) CH$_3$CH$_2$NO$_2$, n-BuNH$_2$
d) Fe(0), HCl
e) CH$_3$CO$_2$CH$_2$CH$_3$, CH$_3$CH$_2$O$^-$
f) H$_2$SO$_4$
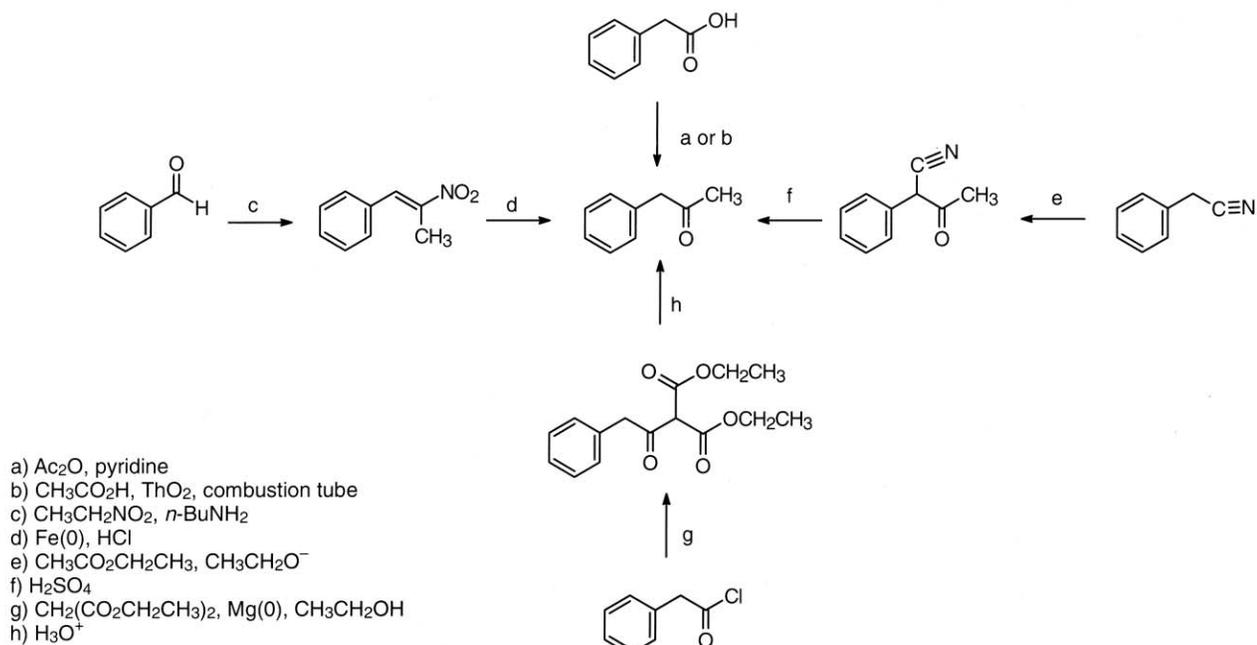g) CH$_2$(CO$_2$CH$_2$CH$_3$)$_2$, Mg(0), CH$_3$CH$_2$OH
h) H$_3$O$^+$

Figure 6. Methods used in illicit P2P production.

Attempts to attack the substance abuse problem in the United States by legal proscription began in earnest with omnibus drug legislation, the Comprehensive Drug Abuse Control Act of 1970 (16). Included among its many provisions were regulations for controlling the possession, manufacture, and distribution of controlled substances. A classification scheme consisting of five schedules was established and populated with roughly 150 compounds and mixtures (Table 1). Provision was made to allow the Attorney General to amend the list through addition, deletion, or rescheduling. Scheduling a previously uncontrolled compound would require both a public hearing and a finding by the Secretary of Health, Education, and Welfare (now Health and Human Services) grounded upon a scientific review that spoke to the need to regulate the substance and the appropriateness of the scheduling level. This was to ensure that clinical investigation of potentially useful psychoactive agents would not be impeded unnecessarily.

It also was apparent that an effective national drug control policy would have to limit access to chemicals utilized in the synthesis or processing of drugs of abuse. Accordingly, so-called *immediate precursor chemicals*, those that by simple chemical conversion could be transformed into controlled substances, could be scheduled at or above the level of the psychoactive substance itself. Regulations were subsequently imposed on commerce involving two additional categories of chemicals. *Precursor chemicals* are initial starting materials for multi-step syntheses of controlled substances (an example is anthranilic acid, used in methaqualone synthesis). *Essential chemicals* are defined as solvents, reagents, or catalysts required for the production of scheduled drugs (examples include acetic anhydride and 2-butanone). Transactions involving these categories of chemicals are subject to strict record-keeping provisions, restricted in sale to clearly identified and authorized parties and subject to volume limitations.

In February 1980, P2P was classified as a schedule II substance due to its status as a immediate precursor chemical in amphetamine syntheses. Not surprisingly, the combination of a large profit motive and ethical shortfall bred great ingenuity on the part of clandestine drug lab operators. In the 18 months immediately following the disruption in P2P supply, at least five different synthetic routes to the critical starting material were in place in raided labs (Fig. 6) (13). Four of these routes involve one carbon homologations of phenylacetic acid or an equivalent. The other relies on a Knoevenagel condensation with benzaldehyde and subsequent dissolving metal reduction of the vinylnitro compound so obtained. Soon the ranks of scheduled substances expanded as precursors of precursors were added. Methamphetamine production via reduction of ephedrine extracted from commercial cold medications also gained in favor. Law enforcement was further daunted by the movement of production facilities into rural northern border states. Remote locales, meager DEA resources, and access to precursor materials smuggled across the border from Canada, where chemical control measures are less mature than in the United States, create an ideal environment for this criminal enterprise (17).

Another option once available to the illegal producer seeking to remain a step ahead of the law is the synthesis of "designer drugs", a term that probably suggests a greater degree of chemical and pharmacological prowess on the part of the criminal than is merited and one that glamorizes potentially deadly substances. Designer drugs are synthesized compounds, at one time exempt from DEA control because of their unique chemical structures, that are often marketed aggressively. They closely resemble previously popular and scheduled drugs (controlled substance analogs, CSA's) (18) and are seldom, if ever, novel compounds. Preparative routes and biological activity profiles normally are to be found in the medicinal chemistry literature. Potential target compounds have been identified in reviews such as "Drugs of Abuse in the Future" (19) and "Future Synthetic Drugs of Abuse" (20). Additional papers are available that include surveys of published procedures for the synthesis of controlled substances and potential CSA's, some of which include evaluation of their relative merits as well as adaptations to simplify synthetic routes, eliminate special equipment requirements or substitute yet unregulated starting materials. In many cases detailed experimental information is provided. The hallucinogen, phencyclidine (14) (angel dust), functioned as a lead compound for illicit CSA production in the 70's. Underground pharmaceutical efforts in the 80's centered primarily on analogues of meperidine (Demerol) (15) and fen-

tanyl (**16**), potent synthetic heroin surrogates (analgesics) (Fig. 7), as well as on derivatives of the stimulant and hallucinogenic amphetamines.

MDMA (**11**), a designer amphetamine, initially noted in the recreational drug-using population in 1970, saw a surge of popularity in the mid 1980's (*21*). Certainly not a new compound, MDMA had first been described in the German patent literature in 1912 where its synthesis from safrole and evaluation as an anoretic agent are described (*22*). In the mid 1980's, a small group of psychotherapists became intrigued with this compound's seemingly unique psychopharmacological profile and began to make it available to their patients. Supplies of the compound came exclusively from underground sources. Although scientifically sound, controlled experiments were not conducted (nor were relevant toxicological studies), a body of anecdotal evidence accumulated that suggested to some that this agent might be a singularly effective chemical adjunct in psychotherapy and represent the first example of a new class of drugs dubbed entactogens (*23*). Subjective effects reported by users included a sense of euphoria, increased empathy and communicativeness, and heightened alertness and self-awareness. Undesirable side effects, evident the day after use, were also noted by some. These included drowsiness, muscle aches, and a diminished ability to concentrate (*24*). A small circle of proponents was convinced that the compound was worthy of further study to determine its efficacy in promoting interaction in the psychotherapeutic setting. An MDMA conference was held in Oakland, California, in 1986 where papers were presented by private practitioners who were dispensing MDMA to their patients as well as by faculty from schools of medicine, pharmacy, and public health. Others were irresponsibly touting it as a social lubricant (alcohol without a hangover), a mind-expanding agent (an innocuous LSD substitute), and a New Age soma.[1] Some were reaping huge financial rewards.

Structure/activity relationships in the phenylisopropylamine series for both CNS stimulatory and hallucinogenic properties have been well defined (*26*). The substitution of hydroxy, alkoxy, and methylenedioxy functionality in the aromatic ring is associated with the addition of hallucinogenic activity. The potency of this effect is determined by the number, type, and relative substitution pattern. 3,4,5-Trisubstitution confers the maximum hallucinogenic properties (mescaline (**12**)). Nitrogen alkylation is associated with a diminution of hallucinogenecity. The analogous primary amine, 3,4-methylenedioxyamphetamine (MDA) (**10**) is a moderately potent hallucinogen; whereas, ecstasy appears to be non-hallucinogenic. Also of note is the reversal of normal stereochemical correlates with bioactivity. In the hallucinogenic amphetamines, greater sensory distorting activity resides in the (R)-enantiomer; whereas, the more potent entactogenic properties of MDMA are found in the (S)-enantiomer. Parasympathetic stimulatory activity is stronger in the (S)-form. This observation has led to the suggestion that a novel mode of action through which ecstasy alters perception may exist. Evidence suggests that some of MDMA's subjectively desirable effects may be associated with stimulation of serotonin release in the brain (*27*). Studies with baboons and rhesus monkeys show that these species will self-administer this substance by injection—a result that suggests abuse potential in humans (*28*).
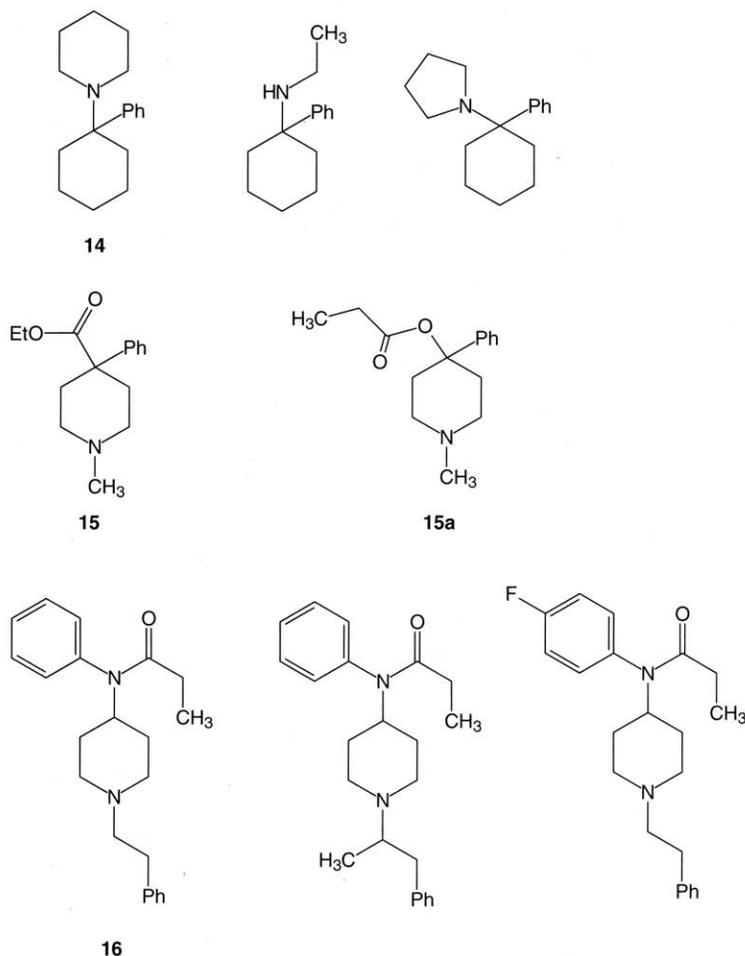

Figure 7. Hallucinogenic and analgesic drugs of abuse and some encountered CSAs.

The Drug Enforcement Agency first responded to the emergence of MDMA as a widely used recreational drug in July 1984, with a proposal that it be categorized as a schedule I substance, the classification reserved for drugs with significant abuse potential and no accepted medical utility (*29*). A legal basis for emergency scheduling was provided two months later by the Dangerous Drug Diversion Control Act of 1984 (*30*) that enables temporary scheduling of drugs where an immediate threat to the public health exists. Such emergency scheduling can be initiated by the Attorney General with publication in the *Federal Register* of the intent to regulate and a supporting rationale. It comes into effect 30 days thereafter. Scheduling in this manner is for one year with the possibility of a six-month extension and is not subject to judicial review. This authority was invoked on five occasions to deal with 13 drugs in the first year after coming into force. As of April 1993, the ranks of controlled substances permanently or temporarily scheduled had swollen from the original 150 to more than 300 (*31*). This growth can be attributed primarily to the introduction of CSA's and the recognition of the problem of anabolic steroid abuse that led to the schedule III regulation of these compounds.

In early 1985, DEA officers in Dallas were estimating that 50,000–100,000 tablet-form MDMA doses were arriv-

[1]Such claims were reported in both the popular press and a rather extensive underground press that developed around this substance. A substantial compilation of such references can be found in ref. *25*.
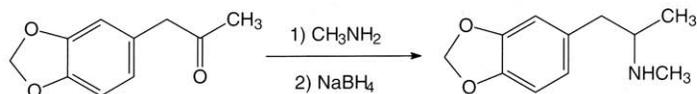
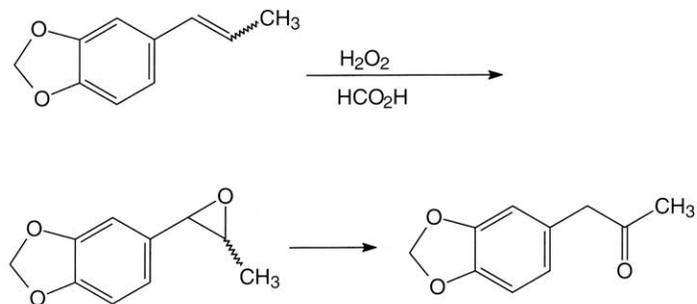Figure 8. Reductive amination route to MDMA.

Figure 9. Preparation of 3,4-methylenedioxyphenyl-2-propane.

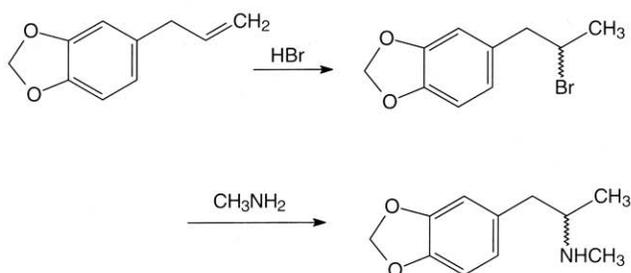
Figure 10. Synthesis of MDMA from safrole.

ing per month and selling on the street and in the dance clubs for $15–$25 a dose. Authorities were actually receiving phone calls from citizens being recruited as distributors inquiring into the legality of the enterprise (at the time, MDMA was not controlled). Meanwhile, a darker side of MDMA use was emerging. The report of five ecstasy-related fatalities in Dallas county in a nine-month period appeared (32). Neuropharmacological studies in rats and primates suggested moderate neurotoxicity associated with the administration of the drug. A deleterious impact on serotonergic neural systems involving depletion of the neurotransmitter, 5-hydroxytryptamine, and its metabolites was noted (33).

Prompted by reports of escalating usage (primarily in California, Texas, and Florida) and the new toxicity data and perhaps sensitized by the recent tragedy experienced by abusers of the demerol analog, MPPP (15a),[2] DEA temporarily placed MDMA into schedule I on May 31, 1985. The emergency scheduling of MDMA generated much litigation in the ensuing five years. The constitutionality of the emergency scheduling provision was challenged on separation of powers grounds. A series of conflicting court decisions followed. Ultimately, the Federal Courts ruled

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[2]In the early 1980's a number of abusers of the meperidine analog, 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP (15a)) experienced a rapid onset of profound Parkinson's disease symptoms. It was soon discovered that an impurity present in amounts up to 3.2%, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), which can form via dehydration of the benzylic alcohol utilized in the final acylation step in the MPPP synthesis, was responsible for the potent neurotoxicity. See ref. 14 and 34.

that these provisions did not unconstitutionally delegate legislative powers to the Attorney General nor did the temporary preclusion of judicial review violate nondelegation doctrine.

At the time emergency scheduling came into force, hearings were underway that would determine MDMA's ultimate scheduling level. Proponents argued for schedule III classification that would have enabled clinical testing to proceed. This position was endorsed by the DEA's administrative law judge. However, nearly two years later, in November 1986, MDMA was permanently placed into schedule I (35). A subsequent appeals court decision invalidated this assignment and MDMA again became unregulated. Re-review and reclassification into schedule I soon followed and has not been successfully challenged.

Stepping out of the courtroom and back into the garage, trailer or kitchen, the stories of *Sassafras albidum* and ecstasy now merge. As in the synthesis of the pure stimulant phenylalkylamines, early clandestine preparation of the hallucinogenic analogs typically relied on reductive amination of an imine produced from the appropriately substituted phenyl-2-propanone (Fig. 8) (36). Although P2P had been controlled previously, a sizable number of ring substituted derivatives remained commercially available. 3,4-Methylenedioxyphenyl-2-propanone was not regulated until March 1989.

As had previously been demonstrated, the control of a required precursor had not usually been sufficient to curtail synthesis of high demand drugs, and underground labs again turned to in-house synthesis of the needed starting materials. One such route was based on oxidation of isosafrole to the key ketone via epoxidation/rearrangement with hydrogen peroxide in formic acid (Fig. 9) (37). As part of the 1990 Anti-Crime Act, isosafrole, safrole, and methylamine were deemed precursor chemicals and controlled (38).

Sassafras root bark is not readily controllable and those who cannot collect their own can still purchase the product at health and natural foods stores. The root bark contains up to 8% by weight of safrole rich essential oil. It was not surprising that a clandestine producer would seek to exploit this natural source of starting material. In fact, the

Table 2. Some Components of the Sassafras Oil Bromination Mixture

Compound	Source
camphor	impurity in starting material
safrole	unreacted starting material
cis-isosafrole	H+ catalyzed alkene isomerization of safrole
trans-isosafrole	"
2-methoxysafrole	solvolysis of 2-bromosafrole
2-hydroxysafrole	"
2-bromosafrole	Markovnikov ionic addition of HBr to safrole
3-bromosafrole	anti-Markovnikov radical addition of HBr to safrole
2-bromoeugenol	Markovnikov ionic addition of HBr to eugenol
4-(2-bromopropyl)-1,2-dimethoxybenzene	Markovnikov ionic addition of HBr to 4-allyl-1,2-dimethoxybenzene
4-(3-bromopropyl)-1,2-dimethoxybenzene	anti-Markovnikov radical addition of HBr to 4-allyl-1,2-dimethoxybenzene
safrole dimer	?

first synthesis of MDMA reported in the chemical literature involves treatment of safrole with aqueous hydrobromic acid followed by displacement with methylamine (Fig. 10) (22). Although access to the original patent (in German) or a later paper in the Polish pharmaceutical literature (39) (in Polish) is certainly not convenient, the *Chemical Abstract* of the *Acta Polon. Pharm.* paper contains the required experimental details in English.

In 1991, a paper appeared in the *Journal of Chromatographic Science* describing the forensic analysis of samples seized from a raided laboratory. This analysis revealed a process in development for ecstasy manufacture based on steam distillation of sassafras root bark (40). Capillary GC–MS analysis of the essential oil starting material revealed the presence of camphor, methylenedioxystyrene, eugenol, 4-allyl-1,2-dimethoxybenzene, and a trimethoxy substituted allylbenzene in addition to the major component, safrole. Hydrobromination of the crude extract with HBr had been carried out to afford a complex product mixture. GC–MS analysis of this highly impure material revealed more than two dozen compounds about half of which could be identified unequivocally via comparison with standards and/or fragmentation pattern analysis (Table 2). Predicting the expected product composition constitutes an excellent review exercise for the introductory organic group. Two of the three most abundant products were identified as 2-bromosafrole, the product of Markovnikov ionic addition to the allyl benzene and 3-bromosafrole that presumably arises via the competitive radical addition pathway. It is probably safe to assume that the lab operator did not take steps to prevent this side reaction.

Conspicuous in its absence is the isomeric 1-bromosafrole that one would expect to form via carbocationic rearrangement to the relatively stable secondary benzylic carbocation. However, the investigators observed a third major product of high retention time that yielded a molecular ion at m/z 324 and a base peak resulting from the loss of 29 amu and suggested an unspecified safrole dimer. A speculative rationale that accounts for the high molecular weight product and the lack of any rearranged bromosafrole follows (Fig. 11). It is possible that either the 1-bromosafrole or the carbocation intermediate leading to it is intercepted in a Friedel–Crafts alkylation with safrole affording **17 a** or **17b**. Loss of the ethyl group during fragmentation would afford the exceptionally stable dibenzhydryl cation with m/z 295.

Although no MDMA was found on the premises it was anticipated that a successful synthesis would conclude with treatment of the crude bromination mixture with methylamine. The Auburn/Alabama Department of Forensic Sciences team has found that this reaction is viable, although a highly impure product results.

Epilogue

Interest in the recreational use of MDMA has not completely subsided. A small group of psychiatrists and therapists continue to call for clinical evaluation of the compound (41). The youth rave culture that originated in Britain and has since spread into some major U.S. metropolitan centers (42) has adopted ecstasy as the drug of choice to complement its grueling dance parties. Recent papers in the British medical literature have spoken to this phenomenon and chronicled a disturbing number of adverse, sometimes fatal, complications associated with MDMA abuse (43). Renal failure, liver toxicity, and hyperpyrexia have been observed in users. More severe psycho-
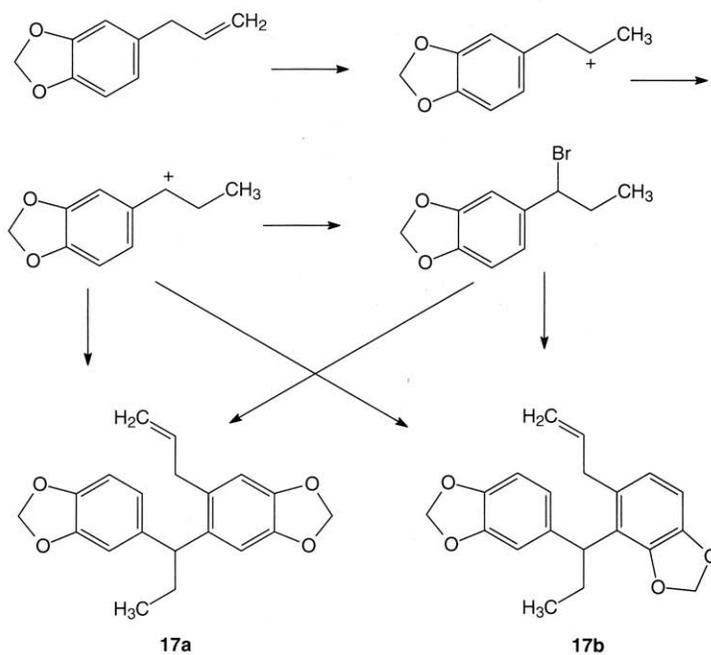

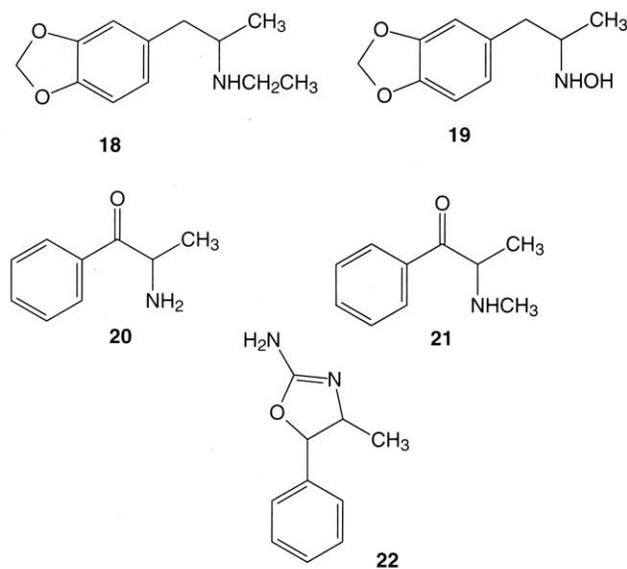Figure 11. Possible identity and mechanism of formation of safrole dimer.

Figure 12. Some recently encountered amphetamine CSAs.

logical disturbances, including psychosis, depression, and panic disorders, also have been documented.

A significant number of structurally creative amphetamines have been introduced by the underground pharmaceutical industry since the emergence of ecstasy (Fig. 12). These include derivatives of MDMA **(18, 19)** (44), cathinone and analogs **(20, 21)** (45) as well as the oxazoline incorporating 4-methylaminorex **(22)** (46). Legislative measures to combat the designer drug problem evolved rapidly. When it became apparent that even the emergency scheduling provision was insufficient in keeping pace with the problem, a remedy not based on the regulation of specific chemical substances was crafted. The Controlled Substance Analogue Enforcement Act of 1986 (47) imposes criminal penalties on non-exempted individuals engaged

in the manufacture or sale of compounds intended for human consumption that have chemical structures *substantially similar* to those of controlled substances in schedules I or II or have, or are represented as having, stimulant, depressant, or hallucinogenic effects substantially similar to or greater than those of schedule I or II drugs. Thus, escaping criminal penalties has been effectively removed as a motivation for the production and distribution of novel drugs of abuse. The ability to obtain a huge return on investment producing a single batch of a highly potent agent with extraordinary market value; avoiding the law enforcement encounters involved with international smuggling operations; and the flexibility to switch targets in response to starting material availability all continue to provide impetus to this endeavor.

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