The Sassafras Tree and Designer Drugs

From Herbal Tea to Ecstasy

Larry G. French
St. Lawrence University, Canton, NY 13617

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. The course of gathering material for this presentation, I became aware of the significance of the sassafras tree in the underground production of methylenedioxyamphetamine (MDMA, ecstasy, XTC, Adam) (11) a controversial designer drug. After presenting some basic botanical information, a brief historical overview of medicinal use 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. Intertwined 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.

Figure 1. Sassafras oil principal components.
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 Ooctea cymbertiunm. The actual source is Ooctea preussica while the oil from the previously mentioned species is devoid of safrole (4).

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

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 1963.

The principal chemical constituent of the oil (=50%) 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,
Table 1. Controlled Substance Scheduling Criteria

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Abuse Potential</th>
<th>Accepted Medical Use in the United States</th>
<th>Dependence Creation</th>
<th>Examples (current level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>high</td>
<td>no</td>
<td>severe psychological or physical</td>
<td>heroin, LSD, mescaline</td>
</tr>
<tr>
<td>II</td>
<td>high</td>
<td>yes</td>
<td>moderate to severe psychic or physical</td>
<td>cocaine, methadone, amphetamine</td>
</tr>
<tr>
<td>III</td>
<td>&lt; I &amp; II</td>
<td>yes</td>
<td>limited psychic or physical</td>
<td>barbiturates, anabolic steroids</td>
</tr>
<tr>
<td>IV</td>
<td>&lt; III</td>
<td>yes</td>
<td>limited psychic or physical</td>
<td>diazepam, tranquilizers</td>
</tr>
<tr>
<td>V</td>
<td>&lt; IV</td>
<td>yes</td>
<td>limited psychic or physical</td>
<td>pharmaceutical mixtures with narcotic pain killers</td>
</tr>
</tbody>
</table>

Cloesides have resulted in the isolation and characterization of N-alkylated guanosine and adenosine adducts whose formation can be rationalized in terms of $S_{N2}$ and $S_{N1}$-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 disorder, 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). Illicit 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 exercised 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.

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Attempts to attack the substance abuse problem in the United States by legal prescription 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 500 compounds and mixtures (Table 1). Provision was made to allow the Attorney General to amend the list through addition, deletion, or rescheduling. Scheduling of 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 antranilic 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 vinyl nitro 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 daunting by the movement of production facilities into rural northern border states. Remote locales, reagent 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 (analogues) (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 anorectic 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, alkoxyl, and methylendioxy 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-Trimethoxyphenyl is the maximum hallucinogenic properties (mescaline (12)). Nitrogen alklylation is associated with a diminution of hallucinogenicity. The analogous primary amine, 3,4-methylendioxyamphetamine (MDA) (10) is a moderately potent hallucinogen; whereas, ecstasy appears to be non-hallucinogenic. Also of note is the reversal of normal stereochrmical 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 Diversions 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 1983, the ranks of controlled substances permanently or temporarily scheduled had swollen from the original 150 to more than 300 (32). This growth can be attributed primarily to the introduction of CSAs 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 arrived...

\(^1\)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.
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 (36). 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. 9) (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 methylvanil 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

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**Table 2. Some Components of the Sassafras Oil Bromination Mixture**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>camphor</td>
<td>impurity in starting material</td>
</tr>
<tr>
<td>safrole</td>
<td>unresolved starting material</td>
</tr>
<tr>
<td>cis-isosafrole</td>
<td>H⁺ catalyzed alkene isomerization of safrole</td>
</tr>
<tr>
<td>trans-isosafrole</td>
<td></td>
</tr>
<tr>
<td>2-methoxysafrole</td>
<td>arylselenylation of 2-bromosafrole</td>
</tr>
<tr>
<td>2-hydroxysafrole</td>
<td></td>
</tr>
<tr>
<td>2-bromosafrole</td>
<td>Markovnikov ion addition of HBr to safrole</td>
</tr>
<tr>
<td>3-bromosafrole</td>
<td>anti-Markovnikov radical addition of HBr to safrole</td>
</tr>
<tr>
<td>2-bromoerugenol</td>
<td>Markovnikov ion addition of HBr to erugenol</td>
</tr>
<tr>
<td>4-[(bromomethyl)phenyl]-1,2-dimethoxybenzene</td>
<td>Markovnikov ion addition of HBr to 4-allyl-1,2-dimethoxybenzene</td>
</tr>
<tr>
<td>4-[(bromomethyl)phenyl]-1,2-dimethoxybenzene</td>
<td>anti-Markovnikov radical addition of HBr to 4-allyl-1,2-dimethoxybenzene</td>
</tr>
</tbody>
</table>

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*In the early 1980's a number of abusers of the meperidine analog, 1-methyl-1-phenyl-4-propionoxygen-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 2.2%, 1-methyl-1-phenyl-2.5.6-tetrahydrotriphenyl (MPTP), which can form via dehydration of the benzyl alcohol utilized in the final acylation step in the MPPP synthesis, was responsible for the potent neurotoxicity. See ref. 14 and 36.
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 raid 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, methyleneedioxystyrone, 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 Markownikov’s addi- tion 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 unspeciated 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 17a 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-

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 Substances Act of 1986 (47) imposes criminal penalties on non-exempted individuals engaged
Nominations Being Solicited for the Fifth Braisted Memorial Award

Nominations for the Fifth Braisted Memorial Award, which is administered by the ACS Division of Chemical Education through its International Activities Committee, are now being solicited. The primary criterion for eligibility for the award is significant contribution to the advancement of chemical education internationally—a criterion that clearly describes an important part of Bob Braisted's life. Anyone wishing to nominate an eligible person should send a nominating letter (in English), not exceeding two typed pages in length (single spaced), which describes the candidate's contributions to chemical education, with particular reference to the international aspects of these contributions. A curriculum vitae and other supporting documentation (10 pages, maximum) should be attached to the nominating document, and a second nominating letter is required. The nominee must not be a citizen or resident of the United States, but the nominator and co-nominator may be from any country. The nominating documents should be sent to the Committee Chair, Professor Ram S. Lamba, Department of Chemistry, Inter American University of Puerto Rico, Hato Rey, PR 00919 U.S.A., in time to reach him by November 30, 1985. He will forward all nominating documents to the Braisted Award Subcommittee of the DIVCHED International Activities Committee. It is intended that the name of the award recipient shall be announced before March 31, 1986.

The previous four Braisted Memorial Awards were presented to David Waddington (of the United Kingdom), Aleksander Ferkov (of Yugoslavia), Ennio Maiorino (of Brazil), and Y. Y. Sano (of Japan). The Fifth Braisted Award is to be presented at the Fourteenth Biennial Conference on Chemical Education, which will be held at Clemson University in Clemson, SC in 1986. The Braisted Memorial Award consists of economy class air fare from the recipient's home city to the Biennial (Clemson, SC, in this case), living expenses at the Biennial Conference, a one year membership in the Division of Chemical Education, and a one-year subscription to the Journal of Chemical Education. The recipient is expected to present the Braisted Memorial Award Lecture at the Biennial Conference on Chemical Education and participate in some other relevant activity at the Biennial.