Future Synthetic Drugs of Abuse

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It seems likely that primitive man wished at times to escape his reality and most probably found some natural drug to facilitate this desire. In fact, abuse of the coca leaf and the opium poppy is thought to have been practiced for at least the last 3400 years[96,123] and the use of peyote may have been known as early as 1000 BC[129,130]. Perhaps due in part to the long history of opiate products, one of the first derivatives of a natural drug to be used pharmaceutically was heroin. The acceptance of heroin as a pharmaceutical was primal in establishing the concept that certain structural modifications of physiologically active compounds can result in new compounds which cause biological responses which are not only similar, but are enhanced as compared to those of the parent compounds. Other works such as the structural elucidation of mescaline and the preparation of N-methyl and N-acetyl derivatives of mescaline has served to strengthen this concept and to broaden the scope of permissible derivatives[143]. In the ensuing years much knowledge has been gained regarding biologically useful derivatives of the naturally occurring drugs but, most importantly, the structures of the alkaloids and the protoalkaloids have, one by one, been elucidated. This knowledge has then allowed researchers of recent times to deduce many of the structure relationships associated with specific biological responses. The sum of this hard-won knowledge allows one to produce pharmaceutically useful compounds, which have no counterpart in nature, from off the shelf chemicals. Unfortunately there are those people who would take this body of knowledge and, rather than use it for the enhancement of medical science, use it for their own financial gain. Individuals such as these have created the so-called designer drug phenomenon.

Henderson[57] first described a synthetic drug as one which was designed by a clandestine chemist to produce a certain pharmacological response. However, today designer drugs are universally understood to belong to a group of clandestinely produced drugs which are structurally and pharmacologically very similar to a controlled substance but are not themselves controlled substances[95]. The Drug Enforcement Administration (DEA) has noted that the designer drug terminology tends to cast a somewhat glamorous aura onto the concept, and as a result, the DEA feels that it would be wise to refer to these compounds in some other manner and suggests the use of the term Controlled Substance Analogs (CsA).

In October of 1987 the United States Government amended the Controlled Substance Act in an effort to curtail the illicit introduction of new CsA's. This amendment states that any new drug which is substantially similar to a controlled substance currently listed under the Code of Federal Regulations (CFR), Schedule I or II, and has either pharmacological properties similar to a Schedule I or II substance or is represented as having those properties, shall also be considered a controlled substance and will be placed in Schedule I. The amendment further contains provisions which exempt the legitimate researcher as well as compounds that are already being legally marketed from the provisions of the amendment.

Since the CsA amendment has yet to be tested in a court of law, it is much too early to say how successful it will be in limiting the spread of the CsA phenomena. However, it is safe to assume that there will be those who believe that they can manage to evade the provisions of the CsA amendment, and much of the world has not yet even attempted to find a litigious solution to the problem of CsA's. Therefore, an attempt to identify those CsA's which would be logical candidates for synthesis by a clandestine chemist is still a pertinent exercise.

Hallucinogens

A great many compounds, when taken in sufficient quantity, will alter one's perception of reality. For the purposes of this paper, the term hallucinogen is reserved for those compounds that are characterized by the predominance of their actions on mental and psychic functions[22].

Hallucinogens can be classified according to structural similarities into four groups of compounds and into one group containing miscellaneous structures. The classifications are: indoles, phenylalkylamines, piperidyl benzilate esters, cannabinoids and miscellaneous.

The piperidyl benzilate esters have been extensively studied and relationships between psychotomimetic activity and chemical structure have been established[1,2]. The N-methyl and N-ethyl-3-piperidyl benzilate esters are controlled substances and are listed under the CFR Schedule I as hallucinogens. Benactyzine is a noncontrolled drug which is used medically as an antagonist to cholinergic nerve fibers[15]. It appears that the pharmacological effects of the piperidyl benzilate esters may not be conducive to a good trip for the user. Brown describes the pharmacological effects by explaining how thought processes are severely disrupted. He reports that speech is disorganized and incoherent, and that confusion, disorientation, and amnesia occur often and may be long lasting[22]. Perhaps these compounds should not be classified as hallucinogens but rather as incapacitating agents. Additionally, although the pharmacological effects of the piperidyl benzilates have been compared to those elicited by phencyclidine[134], there is no evidence to suggest any significant abuse of these compounds. Therefore, no further discussion will be given to the piperidyl-benzilate esters.

Given the world wide ready availability of marijuana, it is somewhat difficult to produce a viable argument for making CsA's of cannabinoids. However, ten years ago (1978) an attempt to produce CsA's from cannabis extracts was encountered in the Jacksonville, Florida area. In this case a concentrated extract of cannabis had been obtained by a soxhlet extraction. The extract had been acetylated with acetic anhydride, and in the final step, the excess acetic anhydride removed by distillation (reference is unretrievable due to its appearance in an underground periodical). The product contained neither quantities of nonderivatized cannabinoid nor any identifiable plant fragments Since this single instance, no acetalaced cannabinoid samples have been reported by a DEA laboratory. Therefore, this instance is assumed to represent an isolated occurrence and as such, will serve to terminate our discussion of cannabinoid CsA's.

Under the heading miscellaneous, one must include nearly any ingestible compound known to man, as any substance taken at toxic levels will alter one's perception of reality. Obviously a discussion of all such compounds as models for CsA hallucinogens is not within the scope of this article. However, the compound known as phencyclidine (PCP or N-(1-phenylcyclohexyl)piperidine), although developed by Parke Davis and Company (Rochester, Michigan) as an anesthetic, does produce psychotomimetic effects and is widely abused in the United States. It is listed in the CFR under Schedule II, and two of its homologs and one analog are listed under Schedule I.

Therefore, in the following discussions, the indoles, the phenylalkylamines and PCP will be considered as possible candidates for hallucinogenic CsA's.

Indoles

The literature covering indole chemistry is huge and diverse. Over 500 naturally occurring indole alkaloids were known by 1972 and accounted for nearly one fourth of all alkaloids known at that time[120]. By 1980, the number of known indole alkaloids had risen to approximately 1200[89]. Today there have been many more indoles added to the list of naturally occurring alkaloids. These alkaloids include such pharmacologically and structurally diverse compounds as tryptophan (essential amino acid), reserpine (tranquilizer), strychnine (stimulant-convulsant) harmaline (hallucinogen), serotonin (anticholinesterase and monoamine oxidase inhibitor), ergometrine (oxytocic), vinblastine (antitumor agent), and psilocybin (hallucinogen).

Only nine compounds containing the indole nucleus are controlled substances under the United States Federal Statutes. Three of these compounds are classified as ergot alkaloids, five are simple 3-(2-ethylamino)-indoles, and one is the pentacyclic

alkaloid, ibogaine. The ergot alkaloids are lysergic acid, lysergic acid amide, and lysergic acid diethylamide (LSD). The five controlled indolealkylamines are N,N-dimethyltryptamine (DMT), N,N-diethyltryptamine (DET), N,N-dimethyl-5-hydroxytryptamine (bufotenine), N,N-dimethyl-4-hydroxy-tryptamine (psilocin), and the phosphate ester of N,N-dimethyl-4-hydroxytryptamine (psilocybin).

Because the major pharmacological effects of ibogaine are probably not those of a hallucinogen[127,159,168] and because only a very few illicit samples have been encountered, we will not discuss the subject further.

Ergot Alkaloids

Lysergic acid (*Compound 1, Figure 1*) is a tetracyclic compound, and as noted previously, contains an indole nucleus and belongs to the family of ergot alkaloids. Nearly all of the known naturally occurring hallucinogens have a 3-(2-ethylamino)-indole contained within the molecular structure. The assessment of a particular LSD derivative as a candidate for a future CsA involves the consideration of several points. The most important are those attempts made by other researchers to modify the structure of LSD while retaining hallucinogenic activity. To date, all attempts to modify the tetracyclic ring system have resulted in a loss of hallucinogenic activity. For instance, of the four possible C-8 stereoisomers only the dextro isomer of LSD is hallucinogenic[124]. Modification of the amide alkyl substituents also reduces hallucinogenic activity substantially[160]. Additionally, substitution with either a hydroxyl or a methoxy at the C-12 of LSD results in a compound with no hallucinogenic activity[160], whereas a comparably substituted methoxyindolealkylamine appears to always be hallucinogenic[42]. The only structural modification which results in the maintenance of hallucinogenic activity on par with LSD is the substitution of either a methyl or an acetyl to the indole nitrogen[125].

The total synthesis of LSD derivatives is not simple and requires the talents of an adept synthetic chemist[38,76,92]. Much of the LSD produced today uses ergotamine that is obtained from legitimate commercial sources (*Golden, L. personal communication*). However, if ergotamine becomes difficult to obtain from commercial sources, the ergot alkaloids can be produced easily and in large quantities by cultivating strains of the fungus Claviceps in submerged cultures[142]. Given the fact that structural modifications of the tetracyclic ring system are likely to result in a product with either little or no activity, and the fact that there will never be a shortage of ergot alkaloids for clandestine syntheses, it is quite unlikely that the total synthesis of LSD or derivatives thereof will become commonplace in the near term. One final point to consider is that the CFR lists LSD and all optical, geometrical, and positional isomers of LSD under Schedule I, and Iysergic acid and lysergic acid amide under Schedule III.

Because of previously noted pharmacodynamics and the imposing nature of a total synthesis, the immediate precursor of a LSD derivative synthesis will most certainly be a controlled substance, namely lysergic acid; therefore, much of the impetus forproducing noncontrolled LSD derivatives is lost. However, if the CsA amendment were not a consideration there would be a clear first choice via substitution of the indole nitrogen to create either 1-alkyl or 1-acyl derivatives. Derivatives of this type most probably fall under the purview of the CsA amendment. The N,N-methylpropyl isomer Of LSD has been the only derivative of LSD examined by the author. Derivatives of this type might seem to be an unlikely choice for a CsA due to a high probability of significant loss in hallucinogenic activity. However, a reduction in hallucinogenic activity may become acceptable to the U. S. clandestine chemist when he notes that lysergic acid amide is listed as a Schedule III substance in the CFR; therefore, structurally similar substances of this compound are exempted from the CsA amendment. A lucid argument can then be made that lysergic acid N,N-dimethylamide is derived from lysergic acid amide rather than LSD. Carrying this theme to the next logical step one would then assume that the 1-alkyl and 1-acyl derivatives of the N,N-dimethyl isomer would also not be controlled by the CsA amendment. At present, no known CsA of LSD has ever been encountered by the DEA.

Indolealkylamines

All of the hallucinogenic indolealkylamines can be classified as belonging to the family of compounds known as tryptamines and are substituted 3-(2-ethylamino)-indoles.

The tryptamines are a most interesting and biologically useful class of compounds. In the human body, serotonin (5-hydroxytryptamine) functions as a vasoconstrictor, inhibits gastric secretion, stimulates smooth muscle, and is naturally present in the central nervous system where it is involved in neurotransmission[44]. The 5-methoxy homolog of serotonin is considered to be hallucinogenic in humans as is the 5-methoxy homolog of gramine (3-(N,N-dimethylaminomethyl)-indole) [41]. Melatonin (N-acetyl-5-methoxytryptamine), formed by the mammalian pineal gland, appears to depress gonadal function and is known to cause contractions of melanophores. Bufotenine, the N,N-dimethyl homolog of serotonin, is classified as a very weakly active hallucinogen and is noted to have extremely unpleasant cardiovascular depressive side effects[63]. The O-methyl homolog of bufotenine, N,N-dimethyl- 5-methoxytryptamine (5-methoxy-DMT), is reported to be an extremely potent hallucinogen, but it, like all other C-5 substituted indolealkylamines, is not active if taken by mouth[22]. Both DMT and DET are well known for their hallucinogenic activity, just as both of these compounds are also inactive if taken by mouth. The N,N-dipropyl and diallyl derivatives are also hallucinogenic only if used either parenterally or by inhalation at approximately the same level as DET, whereas higher homologs abruptly become inactive[148]. The compound 6-hydroxy-DET has been determined to be a major metabolite of DET in man[149], and it does not possess hallucinogenic activity[150]. Conversely, the 4-hydroxy-N,N-dimethyltryptamines (psilocin and psilocybin), are very active hallucinogens when taken orally. The activity of psilocybin (O-phosphoryl-4-hydroxy-DMT) when taken by mouth is not related to the phosphoric acid radical since the pharmacological effects of psilocin (4-hydroxy-DMT) are identical[67]. Pharmacological information for baeocystin (4-hydroxy-N-methyltryptamine) was not found; however, one would expect hallucinogenic activity to parallel that of the N-alkyl-tryptamines and thereby would expect the drug to be weakly hallucinogenic.

It is thought that in the past most clandestine syntheses of indolealkylamines used indole as the starting material[144]. A modest literature search will convince a clandestine chemist that the use of the Fischer indole synthesis affords access to a greater variety of indole derivatives[69,119] as it will also reduce the chance that law enforcement will be alerted by his purchases of essential chemicals. Hence, in the production of indolealkylamine derivatives, the covert chemist need not be limited by the commercial availability of appropriate indole precursors.

Relative to those which lack an aryl ring substitution, there is no doubt that the activity of psilocybin/psilocin upon ingestion is due to an enhancement of gastrointestinal absorption which, in turn, must be structurally related to the presence of the C-4 hydroxyl substitution. Therefore, if the CsA amendment were not a consideration, derivatives derived from psilocin would be the obvious first choice. These derivatives are the 4-hydroxy-N,N-alkyl homologs starting with N,N-dimethyl, N,N-methyl-ethyl, and on to N,N-diallyl to give a total of 10 possible derivatives. As is also the case for hallucinogenic phenylalkylamines, alkyl substitution, not to exceed a C-3 moiety, at the position alpha to the side chain nitrogen generally will maintain hallucinogenic activity. This brings the total possible number of hallucinogenic CsA's of psilocin to 40. A somewhat removed second choice would be the same series of derivatives in conjunction with either acetylation or methylation of the indole nitrogen. This would then bring the total number of the possible 4-hydroxy-substituted tryptamine CsA's (less one for psilocin) to 119.

The 5-methoxy derivatives of gramine and serotonin are first choices for future CsA's when considering the new U. S. amendment. Substitution at the alpha carbon on the side chain will probably maintain psychotropic activity only for serotonin derivatives. Hence, allowing only a methoxy substituent at the aryl C-5 position, and a substitution at the carbon alpha to the nitrogen (the nitrogen being any combination of hydrogen, methyl, ethyl, n-propyl, and allyl) 75 CsA's can be obtained. Then substitution of the indole nitrogen with either methyl or acetyl brings the total number of possible CsA's that can be argumentatively related to serotonin to 225.

An additional series of compounds that could serve as future CsA's under U. S. law are those which are substituted with alkyl groups at the carbon alpha to the side chain nitrogen. Recently, a commercially available tryptamine which has an ethyl moiety substituted at the alpha carbon has become the newest U.S. tryptamine CsA. Known as ET in the illicit CsA drug market is 3-(2-amino-butyl)indole (Etryptamine, Monase® by Upjohn; *compound 3, Figure 3*). Because ET does not appear in either Schedule I or II of the CFR and is a legally marketed product, ET and derivatives thereof are exempted from control under the CsA amendment. Pharmacokenitic data on ET indicates that it is a monoamine oxidase inhibitor[45,90] and psycho-energizer[31,118]. Hence, ET could produce some degree of hallucinogenic activity in man. In 1986 ET was reported as the she

causative agent in a fatal overdose in Duesseldorf, Germany[30]. This may be one of the few times that a CsA has originated outside of the U. S. The sample of ET which was submitted to our laboratory appears to have been obtained from the Aldrich Chemical Company (*$48.05/100g*). Unfortunately, it is not yet clear if ET is actually the substance which is producing the biological response being sought by the illicit user. It is the case that the sample of ET we examined and the batch of ET which the Aldrich Chemical Company is presently selling contains a major quantity (about 30%) of the agent shown in Figure 4 which could also be a hallucinogen[107,158].

Nomenclature for this possible hallucinogen can either be 1-methyl-3-ethyl-1,2,3,4-tetrahydroharmane, or 2,2-dimethyl-4-ethyl-2,3,4,5-tetrahydro-β-carboline. The creation of this substance most probably occurred after synthesis and during the purification of ET. Under anhydrous conditions, the reaction of acetone and ET would give the corresponding enamine which could then undergo a Mannich condensation to yield the hallucinogen[132,165]. The compound 2-methyl-8-methoxy-4,5-dihydro-β-carboline (harmaline) is considered to be a hallucinogen[59] as well as a monoamine oxidase inhibitor[23]. On the other hand, the compound 2-methyl-8-methoxy-2,3,4,5-tetrahydro-β-carboline is classified as a tranquilizer[160]. We were not able to attain any literature whatsoever on the hallucinogen shown in (*Figure 3, Compound 4*), much less any pharmacokenetic data. Hence, due to the apparently unpredictable pharmacological behavior of structurally similar β-carboline derivatives, I will not speculate as to the pharmacological properties of said substance.

Phenylalkylamines

As was observed for the simple indole alkaloids, there are several simple phenylalkylamines which play important roles in the normal biological function. Some of these are tyrosine, 3,4-dihydroxyphenylalanine (DOPA), 3,4-dihydroxytryptamine (dopamine), and norepinephrine. The naturally occurring hallucinogenic protoalkaloid, mescaline, is 3,4,5-trimethoxyphenethylamine. Structural modifications which impart hallucinogenic activity to phenylethylamines have been studied and a considerable quantity of that data is easily retrieved. The following constitutes a brief review of some of the most salient concepts relative to hallucinogenic activity chemical structure relationships within the family of phenylethylamine derivatives.

It has been found that the addition of methoxy moieties to the aromatic ring of a phenylethylamine, in general, produces compounds that are psychotomimetic[135]. Further, it has been noted that the methylenedioxy moiety can be used in the place of two adjacent ring substituted methoxy groups with C-3,4 substitution providing the most potent psychotogens[4,19,106,133]. Historically 3,4-methylenedioxyamphetamine (MDA) has probably been the most consistently abused psychotomimetic phenylethylamine. Amphetamine and methamphetamine are adrenomimetic at low to moderate dose levels; however, at high dose levels they also become psychotomimetic in man[28,97]. Additionally, it has been found that the addition of an α-alkyl moiety (up to C-3)[141] to methoxyphenylethylamines results in an increase in hallucinogenic activity and, alkyl only substitutions to the aromatic ring tend to result in a gradual loss of central activity which can be related to the increasing size or the alkyl group[52,102]. Braun et al.[20] has determined that a gradual decrease in psychotomimetic activity also occurs with the increasing size of a N-alkyl substituent. Braun also noted that upon N,N-dialkyl substitution an abrupt and significant loss of hallucinogenic activity occurs, whereas N-hydroxy substitution maintains activity.

The bases of structure-activity relationships as determined by aromatic ring substitutions are not obvious. For instance, mescaline has relatively prominent psychotomimetic properties but 3,4-dimethoxyphenylethylamine (3,4-dimethoxydopamine) is not considered to be psychotogenic, and the hallucinogenic potency of 3,4-dimethoxyamphetamine is less than that of mescaline[61]. On the other hand, the hallucinogenic potency of 3,4-methylenedioxyamphetamine is approximately three times that of mescaline[20]. Also, tyramine (4-hydroxyphenylethylamine) is devoid of hallucinogenic activity, but 4-methoxy-tyramine is weakly hallucinogenic[140]. However, 2-methoxymethamphetamine has no known hallucinogenic activity[160], and the 4-methoxyphenyl-α-methyl-ethylamine (4-methoxyamphetamine) has five limes the psychotropic activity of mescaline[136]. To complicate the situation further, one work reported the synthesis of 4-substituted methamphetamine derivatives using both ring activating and ring deactivating substituents of quite different atomic volumes, and found hallucinogenic activity present for all derivatives. The compounds in question are 4-bromo-, 4-amino-, 4-chloro-, 4-nitro-, 4-iodo-, and 4-hydroxymethamphetamine[91]. It is a little surprising that substituents of such radically different atomic

volumes and electronegativities would all give 4-substituted phenylisopropylamine derivatives having psychotropic activity. In contrast, another study of hallucinogenic activity as a function of aromatic ring substitution, found the compound 2,5-dimethoxy-4-methylamphetamine to be some eighty times more potent than mescaline but upon going to the 4-ethyl derivative, quite a trivial change, nearly all hallucinogenic activity was supposedly lost[134]. Despite these seeming inconsistencies, many of the necessary structural requirements for producing hallucinogenic phenylethylamine can be understood bynoting the common structural features of these psychotogens. The structure activity relationships noted above can be found in a single source review article by Shulgin[136].

The following phenylalkylamines are listed under Schedule I of the CFR as hallucinogens:

1. 4-Bromo-2,5-Dimethoxyamphetamine (DOB)
2. 2,5-Dimethoxyamphetamine (2,5-DMA)
3. 4-Methoxyamphetamine (PMA)
4. 5-Methoxy-3,4-Methylenedioxyamphetamine (MMDA)
5. 4-Methyl-2,5-Dimethoxyamphetamine (DOM, STP)
6. 3,4-Methylenedioxyamphetamine (MDA)
7. 3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy)
8. 3,4,5-Trimethoxyamphetamine (TMA)
9. 3,4,5-Trimethoxyphenethylamine (Mescaline)

The majority of the hallucinogenic phenylethylamines which are presently controlled under U. S. law were first encountered in a relatively short period of time in the latter part of 1960. Since that time the emergence of new CsA's Of psychotogenic phenylethylamines has continued but at a much reduced pace. Starting in 1972, several samples of MDMA were analyzed by DEA laboratories. Apparently MDMA was readily accepted by the user and abuse has continued to increase. Presently in the U. S. and Canada there are at least four other CsA's of psychotogenic phenylethylamines in the illicit market. These are N-hydroxy-3,4-methylenedioxy- amphetamine (N-hydroxy MDA), N-ethyl MDA (EVE, MDEA), 4-ethoxy-2,5-dimethoxyamphetamine (MEM)[7], and 4-bromo-2,5-dimethoxyphenylethylamine (DBMPEA) (*Sapienza, E personal communication; Allen, A. personal communication*). Upon placing MDMA under legal controls, the N-ethyl homolog of MDA (EVE) was immediately introduced as a replacement for MDMA. However, it seems that EVE has not been well accepted by the user, apparently because EVE has a lower potency than MDMA; therefore requiring a larger dose to produce psychotropic effects and often resulting in making the user ill[83].

Assuming the ready availability of the appropriate chemical precursors, and assuming a lack of concern for the legal provisions enacted by governments for the purpose of controlling CsA's, choices for CsA's of ring substituted phenylethylamine psychotogens are numerous. Previously cited literature provides many such CsA possibilities with at least ten aromatic ring substituted amphetamines (*Compounds numbered 5-15, Figure 4*) having potencies greater than mescaline (*Compound 5*). Other CsA's can be obtained from compounds 6 through 15 by modification of the α-alkyl side chain to either C-2 or C-3 alkyls, and mono-substitution or the nitrogen with either hydroxy or short chain alkyl. These modifications result in a total Of 160 possible CsA's based only upon the ring substitutions of the aforementioned compounds. Additionally, tile ring substituted phenylisopropylamines which are presently controlled substances, can be modified in the same manner, and after excluding controlled substances and N-hydroxy MDA, there are 118 more possible derivatives, giving a total of 278 possible new CsA's. Each time a new ring substitution is introduced, such as MEM, then this number is increased by 16.

If the U. S. CsA amendment is a consideration, then psychotomimetic phenylethylamines could be created from compounds which are structurally related to dopamine, adrenaline (N-methyl-3,4-di-hydroxyphenyl-β- hydroxyethylamine), and norepinephrine (3,4-dihydroxyphenyl-β-hydroxyethylamine). A case in point is the compound macromerine, N,N-dimethyl-3,4-dimethoxyphenyl-β-hydroxyethylamine, a known psychotogen[60]. Some other compounds which could be used as CsA models are synephrine (N-methyl-4,β-dihydroxyphenylethylamine), phentermine (α,-α-dimethylphenylethylamine), 4-chlorophentermine, mephentermine (N,α,α-trimethylphenylethylamine), phenelzine (phenylethylhydrazine), and tranylcypromine (2-phenylcyclopropylamine). Structural modifications of these compounds could provide quite a few additional CsA's. Because of the sheer size of the task, no attempt was made to determine the total number of possible CsA's

that could be derived by using these compounds as models. However, the magnitude of the possibilities become evident when one calculates tile possible CsA's which, could be obtained using just dopamine (*Compound 16*, *Figure 5*) as the model compound, as is demonstrated in the following paragraph.

The total number of possible CsA's were limited by the following considerations:

1. Ring substitution at *C-3,4* is dimethoxy
2. Ring substitution to sites *C-2,5,6* were limited to combinations of CH_3-, Br-, Cl-, and CH_3O-,
3. Substitution on the amine nitrogen and the alpha carbon were limited to the following:
    1. Of the three ring sites available for substitution, no more than two were allowed for any given structure
    2. Single substitution on the ring at *C-2* to give 2,3,4-trisubstituted derivatives was disallowed
    3. Mixed halide structures were excluded
    4. Ring substitutions which would result in any derivative which is presently a controlled substance were disallowed.

Given these considerations there are 47 structures which can be drawn. Each one of these can then exist as 16 derivatives obtained by substitution as shown above at the alpha carbon and nitrogen. The multiplication product of these two values provides the total number of possible hallucinogenic CsA's (752) which, one could argue, are structurally related to dopamine.

Research targeted at the determination of structure-psychotropic activity relationships has waned in recent years. Perhaps in future years it will be the clandestine chemist who will fill in the blanks.

Phencyclidine

The synthesis of phencyclidine (PCP) was first reported in 1958[26] and patent rights were granted to Parke, Davis & Co. in 1960 and 1963 for medical use as an anesthetic[110,111]. PCP first came to the attention of DEA, then the Bureau of Narcotics and Dangerous Drugs, as a drug of abuse inthe latter part of the 1960's. Pharmacologically, PCP has been described as a pseudo hallucinogen which has many of the characteristics of a depressant drug[104]. Without question, PCP deserves a special niche in any discussion of drugs of abuse if for no other reason than the notoriously bizarre effects it has been known to have upon some of the abusing population[113].

The now so very familiar synthesis using 1-(1-piperidyl)cyclo-hexyl carbonitrile and phenyl Grignard reagent was published by Maddox et al. in 1965 and, either fortunately or unfortunately depending upon one's point of view, the accompanying pharmacological data was useless as it could not be correlated to the compounds synthesized[99]. However, pertinent literature is not hard to find as both the original U. S. patent[43] and later studies have provided a pharmacological basis for the production of CsA's of PCP[87,88].

It does not appear to be possible for one to generate a CsA model structure that will not fail under the CsA amendment provision which stipulates that the term "controlled substance analogue" means a substance-the chemical structure of which is substantially similar to the chemical structure of, in this case, PCP. This is the result of the fact that a one carbon separation between an aryl system and the amine nitrogen, and the fact that the central carbon between these moieties is in a ring system appear to be principal requirements for PCP-like pharmacological activity. Other activity structure relationships are:

1. Substituents which decrease lipophilic character generally decrease potency
2. Aryl substitution with 2-thienyl generally increases potency
3. Substitutions onto the aryl system decreases potency
4. To maintain potency N,N-dialkyl substitutions should be either piperidino or pyrrolidino ring systems
5. N-ethyl is the most potent N-alkyl monosubstitution and potency falls off rapidly with either an increase or decrease in the alkyl chain size
6. Substitution on the beta carbon of either the cycloalkyl or the cycloalkylamino rings will most likely be synthetically

difficult due to steric considerations.

Because of factors noted above, there appears to be a relatively small probability of a PCP CsA appearing in the illicit marketplace that will not fall under the purview of the U. S. CsA amendment. However, it is also the case that under U. S. law there is a reporting requirement placed upon the purveyors of piperidine. Since the implementation of the piperidine reporting requirement it has become much more difficult for the clandestine chemist to safely acquire this chemical precursor of PCP. Therefore, a market force has been introduced that will almost certainly result in the production of PCP CsA's which will not contain a simple piperidino moiety. This thought, taken with the previously discussed activity-structure relationships, allows one to suggest the 50 structures depicted in Figure 6 as being representative of future CsA's of PCP. Of these 50 compounds, two have already been placedin the CFR Schedule I: N,N-(1-phenylcyclohexyl)-ethylamine and N-(1-phenylcyclohexyl)-pyrrolidine.

Stimulants

Relative to medical usage, a stimulant is defined to be an agent that arouses organic activity, strengthens the action of the heart, increases vitality, and promotes a sense of well being. However, as per the medical definition, the effects produced by a stimulant may not be a very accurate term for the effects sought by those who abuse these compounds. For instance, at dose levels usually equated with heavy abuse, both amphetamine[5,50] and methamphetamine[97] are thought to be psychotogenic. Therefore, several of the amphetamines could be discussed as hallucinogens; however, it seems most likely that a substantial portion of the abuse of stimulant drugs is performed with the intention of inducing a state of euphoria[22]. Historically, the abuse of stimulants (euphoriants) has been largely confined to amphetamine, derivatives thereof, and cocaine. Some of the amphetamine derivatives which have been controlled under U. S. law are methamphetamine, N-ethylamphetamine, fenethylline, phenmetrazine (preludin), phendimetrazine, benzphetamine, chlorphentermine, clortermine, diethylpropion, methylphenidate, pemoline, and amphetamine. Other derivatives of amphetamine which have been encountered in samples submitted to DEA laboratories, but have not yet been brought under legal controls, are bis-methamphetamine, fencamfamine[108], N,N-dimethylamphetamine (dimephenopan) (*A. Allen, personal communication*), and an analog of pemoline, 4-methylaminorex (U4Euh)[72]. Since Pemoline is listed under Schedule IV of the CFR and 4-methylaminorex is clearly an analog Of pemoline, it falls outside of the guide-lines set forth in the CsA amendment; therefore, 4-methylaminorex is not controlled under U. S. law. It is equally clear that *bis*-methamphetamine and N,N-dimethylamphetamine do fall under the CsA guidelines and would be considered controlled substances under tile CsA amendment. However, it may be that N,N-dimethylamphetamine may not enjoy a long history in the clandestine market as at least one work states that it is considerably less potent than methamphetamine[126].

Most of the adrenomimetic activity-structure relationships were delineated in the previous discussion on psychotomimetic phenylethylamines. The principle difference between the pharmacological action, as related to structure for these two classes of compounds, is determined by the nature of the substituents on the aryl system. In general it is noted that substituents on the aryl system which are ortho-para directors tend to produce psychotogenic compounds with methoxy substituents often producing the most pharmacologically active hallucinogens. However, there are several exceptions to this general statement, not the least of which is exemplified by substitution on the phenyl ring of the electrophilic hydroxy moiety which in nearly every case either eliminates or greatly reduces hallucinogenic activity. On the other hand, adrenomimetic activity is clearly enhanced by branching of phenylethylamine at the carbon alpha to the amine nitrogen and is maintained at reasonable levels by substitution to the nitrogen as shown in table II. Both N-ethylamphetamine and N,N-dimethylamphetamine have appeared in the illicit market and clearly follow the points made above. However, a market factor has been introduced by the fact that phenyl-2-propanone (P2P) has been listed under the CFR as a Schedule II substance. Hence, it makes little sense for the clandestine chemist to produce CsA's of phenylethylamines which have potencies that are less than methamphetamine if he is going to produce his CsA's in a synthesis that uses P2P. The recent illicit use of 4-methylaminorex may well be the result of the clandestine chemist trying to circumvent the legal problems associated with P2P. On the other hand, the sum total of methamphetamine still being covertly produced suggests that the control of P2P has not appreciably reduced the drug's availability in the illicit marketplace.

As before, if the chemist is not concerned about the CsA amendment, the structural possibilities offered by Table II, less the

three controlled substances that are included, provides for thirteen possible future stimulant CsA's. It would seem that the single most logical next stimulant CsA would be N-methyl-α-ethyl-phenyl- ethylamine. This compound should be pharmacologically very similar to methamphetamine and synthesis could employ 1-phenyl-2-butanone instead of P2P. Alternatively, the use of 1-(4-fluorophenyl)propan-2-one, in place of P2P, would almost certainly give a product with adrenomimetic properties, and may in fact be considerably more potent than methamphetamine.

The clandestine chemist of limited chemical sophistication may not notice the structural similarity of such compounds as methylphenidate, phenmetrazine, 4-methylaminorex, and amphetamine. If he does recognize the constancy of the phenylisopropylamine substructure in these compounds he may well explore the literature in an effort to determine the structural outer limits for the phenylisopropylamine stimulants. At what may be near these structural outer limits he will find a class of compounds which are correctly referred to as conformationally rigid phenylethylamines. Some of the conformationally rigid phenylethylamines are fencamfamine, tranylcypromine (2-phenylcyclopropylamine), 2-phenyl-cyclohexylamine[138], 2-amino-3-phenyl-*trans*-decalin, and 2-aminotetralin[8]. The potency of most of these compounds is highly dependent upon stereochemistry. Those isomeric forms which most closely approximate the anti periplanar conformation observed for amphetamine in solution are the most potent stimulants. Hence, *trans*-tranylcypromine is considerably more potent than is the *cis* isomer[48]. The most active isomer of these compounds does not approach the potency of the simple phenylisopropylamines. Given this reduction in potency for the most active isomers one would think that, in order to obtain amiable product for the illicit market, a stereo specific synthesis would be required. This feature, along with a lowered potency for even the more active isomers, may very well exclude the conformationally rigid phenylethylamines from the synthetic repertoire of the surreptitious chemist. Hence, it is a reasonable expectation that those conformationally rigid phenylethylamines which will be abused in the future will be obtained by diversion of limit supplies rather than by clandestine syntheses.

Unfortunately, it seems to be an axiom that any compound which has any possibility of altering man's perception of himself or his surroundings will at some time be abused. Propylhexadrine, although not an extreme example, is nevertheless an example of a compound which has been abused although adrenogenic potency is far less than that of methamphetamine[39]. Therefore, one must expect some abuse of the conformationally rigid phenylethylamines to occur. It would be my guess however, that the extent of such abuse will never be large.

The parent structure for 4-methylaminorex has been known since 1889[37] and many derivatives thereof have been studied for pharmacological activity. Pemoline (2-amino-5-phenyl-2-oxazolin-4-one)[68,154] is presently a controlled substance in the U. S., is classified as a stimulant, and is listed under Schedule IV of the CFR. Poos (*personal communication*) synthesized and performend pharmacological studies for some twenty seven 2-amino-2-oxazoline isomers of which aminorex and 4-methylaminorex were two. In this work, aminorex and 4-methylaminorex, regardless of the steroisomer employed, were found to have anorectic activity on par with d-amphetamine. However, adrenomimetic activity of 4-methylaminorex was determined to be less than that of amphetamine and similar to phenmetrazine[112]. It has been suggested that the effectiveness of stimulant drugs as appetite suppressants are the result of the fact that the user forgets to eat and that this behavior is in direct proportion to the adrenomimetic activity of the drug[29]. Contrary to previously cited work this suggests that aminorex may in fact be as potent an adrenomimetic as amphetamine. In any case, Poos (*personal communication*) highlighted eight compounds which may have adrenomimetic activity similar to those of amphetamine and methamphetamine.

Shown below and listed in decreasing order of anoretic activity they are:

1. 2-Amino-5-(4-fluorophenyl)-2-oxazoline
2. 2-Amino-5-(4-Chlorophenyl)-2-oxazoline
3. 2-Amino-5-(3-trifluoromethylphenyl)-2-oxazoline
4. 2-Amino-5-(4-bromophenyl)-2-oxazoline
5. 2-Amino-5-phenyl)-2-oxazoline **[***Aminorex***]**
6. 2-Amino-5-(4-trifluoromethylphenyl)-2-oxazoline
7. 2-Dimethylamino-4-methyl-5-phenyl-2-oxazoline
8. 2-Amino-4-methyl-5-phenyl-2-oxazoline **[***4-Methylaminorex***]**.

Although not mentioned in this work, one would immediately assume that the 4-fluorophenyl- and 4-chlorophenyl derivatives of compounds 7 and 8 would also have significant anoretic activity. Given the astoundingly simple synthetic process required to produce these compounds, and the fact that the 4-halogen substituted aryl derivatives would require precursors unlikely to titillate the interest of law enforcement agencies, these compounds will most probably be made in future clandestine syntheses. It is also conceivable that some enterprising clandestine chemist will wonder if appropriately substituted methoxy derivatives will have psychotomimetic properties.

The literature contain many references to stimulant drugs of variant structures which may not spark the interest of the less knowledgeable clandestine chemist. However, nearly all of these compounds can be accessed through literature searches for either derivatives of phenylethlamines or stimulant compounds. Several compounds which serve as examples are fenmetramid[73], prolintane, 1-(α-propyl-phenylethyl) pyrrolidine[55,62], pyrovalerone (1-(4-methyl-phenyl)-1-oxo-2-pyrrolidino-n-pentane)[56], N,3,3-trimethyl-1-(m-tolyl)-1-phthalanpropylamine[40], zylofuramine (α-benzyl-n-ethyl- tetrahydro-D-threo-furfurylamine)[51], a series of N-substituted phentermine compounds[18], 4-hydroxyamphetamine[65,66,100], N-methylephedrine[139], nylidrin, N-(1-methyl-3-phenylpropyl)-2-hydroxy-2-(4-hydroxyphenyl-1-methyl-ethylamine[155], pheniprazine, α-methyl-phenylethyl-hydrazine[169], and N,N-diethyl-2-phenylcyclopropylamine (SKF). All of these compounds are derivatives of phenylethylamine with the exception of N,3,3-trimethyl-1-(m-tolyl)-1-phthalanpropylamine which is a 3-phenyl-3-propylamine substituted onto a phthalane at C-1. A number of closely allied derivatives of this compound have been examined and are classified as weak stimulants.

Fenmetramide is noteworthy in that it is a 2-one derivative of phenmetrazine. Any and all of these compounds are subject to abuse; however, the synthesis of simple phenylethylamine derivatives would not appear to offer the clandestine chemist any advantage over the synthesis of methamphetamine. The reasons for this statement are that pharmacological studies have not identified other phenylethylamine structures with stimulant activity appreciably greater than methamphetamine and that either P2P or the β-hydroxy-phenylisopropylamines are the preferred precursors. However, in any case, the U. S. CsA amendment should apply for all compounds containing the phenylethylamine substructure.

The stimulant drugs phenmetrazine (Preludin) and methylphenidate (Ritalin) are controlled under Schedule II of the CFR. These compounds rank approximately half-way between caffeine and amphetamine in potency[47,105,156]. The published synthesis of phenmetrazine, which would seem to be most amenable to the clandestine laboratory, is given in the work by Otto[109]. The reaction involves the acid-catalyzed cyclization of N-hydroxyethylnorephedrine (N-hydroxyethyl-phenylpropanolamine). However, this reaction places severe limits on the production of CsA's because suitable precursors are limited. For instance, phenmetrazine CsA could be prepared from compounds such as N-ethyl-2,2-hydroxyphenyl-1-methylethylamine, 1,1-hydroxyphenyl-2-aminobutane, etc, but limited commercial availability would generally require synthesis of these compounds. Additionally, the product CsA would clearly be perceived, even by the untrained, as being structurally similar to phenmetrazine and thereby would be a controlled substance under the CsA amendment. Further, the corresponding phenylethylamine which could be made from these precursors, although also under the purview of the CsA amendment, would most probably have greater adrenergic activity than the phenmetrazine derivative. Hence, clandestine production of phenmetrazine CsA's would most likely be an uncommon event.

Pipradrol (*compound 38, Figure 12*) is a controlled substance under CFR Schedule IV and can be considered to be an analog derivative of methylphenidate. Methylphenidate can be synthesized by the method of Hartmann and Panizzon[53]. The product exists as two diastereoisomeric enantiomer pairs, one of which is the active stimulant, *threo-dl*-methylphenidate[163], while the other is inactive as a stimulant. *Threo*-methylphenidate accounts for only 20% of the final reaction product[121,122]. The synthesis of pipradrol may be more amenable to the clandestine laboratory as it is a relatively simple synthesis and isolation of the final product is straightforward. An appropriate C-2 substituted, N-protected piperidine is a suitable precursor for what is essentially a two step synthesis[153,164]. Numerous derivatives of methylphenidate and pipradrol have been synthesized with the result that structure activity relationships have been well defined.[10,33,54,93,103,116,128,131,152,166,167] There is little incentive, beyond the not inconsiderable pressure of an already existing and ready market, for producing clandestine CsA's of methylphenidate. However, there are a number of pipradrol derivatives described in the last cited references which are

suitable for clandestine production. A best bet for a future CsA is the most potent adrenomimetic compound in this series, 2-diphenyl-methylpiperidine[157], which is estimated to be as potent as methamphetamine[146]. In a very similar article to this paper, "Drugs of Abuse in the Future," Shulgin[137] suggested that levophacetoperane (*compound 40, Figure 12*) could well be a future clandestine CsA. However, this compound shares the same limitations for clandestine synthesis as does methylphenidate, in that only one diastereoisomer is active[75] and it is less potent than methylphenidate[32].

Although the phenylisopropylamine substructure is an integral part of most known stimulants, the well known and much abused stimulant, cocaine, does not share this structural feature. The cocaine molecule instead compares more closely to the structure of acetylcholine. The synthesis of cocaine has recently been revisited by Casale and many of the procedural techniques are explained in sufficient detail so that any competent organic chemist can now make the C-3 equatorial cocaines[25]; however, it is still a tedious and demanding synthesis, and in my opinion will only be encountered on rare occasions in clandestine laboratories. The particular pharmacological behavior of cocaine is unquestionably due in major part to the stereochemistry of the molecule as determined by the fused bicyclic tropane ring system[27]. Given the present difficulties associated with the synthesis of the tropanes and the ready availability of the natural product, it is unlikely that a synthetic CsA of this compound will appear in the near future. However, it is the case that certain modifications of natural cocaine can result in products having substantially greater potencies than cocaine. The compounds 2-carbomethoxy-3-(4-fluorophenyl)tropane and 2-carbomethoxy-3-phenyl-nortropane are both some 60 times more potent than cocaine[27]. These compounds could well be of interest to some clandestine chemists as taking one kilogram or cocaine and converting it into a product some sixty times more potent would obviously be quite cost effective.

In "Drugs of Abuse in the Future," Shulgin[137] directed attention to another stimulant which also does not contain the phenylethylamine substructure and, in fact, is reminiscent of the depressant glutethimide. The compound is known commercially as Bemegride, 4-ethyl-4-methylpiperidine-2,6-dione, and was first synthesized by Thole and Thorpe in 1911[151]. The principal medical use is as an analeptic in barbiturate poisoning. As a stimulant, bemegride is approximately equal to phendimetrazine and pemoline in potency. Although glutethimide and bemegride are structurally similar, their pharmacokinetics are diametrically opposed. Hence, bemegride cannot be described as a CsA. Bemegride, by virtue of being a stimulant, has an obvious potential for abuse, although under the conditions of abuse, rather large quantities of the drug will be required. Increasing the possibility of bemegride abuse are the facts that the synthesis of the compound is not difficult and, of course, does not use either a controlled or watched substance as a precursor[11].

Sedatives-Depressants

Depressants include such diverse chemical entities as methaqualone, 5,5-disubstituted barbituric acids, glutethimide and methyprylon, benzodiazepines, chlorhexadol, chloral hydrate, paraldehyde, meprobamate, and ethyl alcohol to name a few. Historically in the U. S., the abuse of depressants, alcohol aside, has been in major part confined to the barbiturates, methaqualone, and the benzodiazepines. Barbiturate abuse peaked in the mid 1970's and has since become near nonexistent, in part no doubt, to the well deserved bad press that the barbiturates garnered. The abuse of methaqualone peaked around 1980 and has also declined steadily since that time. However, much counterfeit "lude" is still being sold, but instead of containing methaqualone, the tablets now often contain diazepam. Diazepam has become the most prevalent depressant drug of abuse and its use is apparently continuing to rise. It is somewhat peculiar that of the many benzodiazepines known and readily available in the legal commercial market, diazepam is by far the most extensively abused. The factors controlling this apparent user preference for diazepam is certainly related, in part, to simple product recognition; however, it is my perception that the dominant factor is the ease with which the drug can be diverted from the legitimate market. In 1985 the legitimate diazepam market consisted of 5 billion tablets[34] (*Franzosa 1985*) and since that time generic diazepam tablet production has increased along with even greater product availability for diversion into the illicit market (*Franzosa, E. personal communication*).

A typical benzodiazepine synthesis is not be considered difficult and a methaqualone synthesis is quite straightforward[46] (Grimmel et al. 1946). Further, there is a great abundance of literature from which the clandestine chemist can draw in deciding upon a CsA based upon either the benzodiazepines or methaqualone itself. However, with the very notable

exception of methaqualone, the clandestine syntheses of depressant drugs in the U. S. have been extremely rare (Franzosa, E. personal communication). It is not likely that a clandestinely synthesized benzodiazepine CsA will be encountered as long as the huge, easily diverted legitimate supplies are at hand.

The use of methaqualone is in decline, but it will be with us as an abused substance for still some time. Given the very large numbers associated with the clandestine synthesis of methaqualone, it is perhaps surprising that only two CsA's of methaqualone, have been analyzed at this laboratory. Again, past history would suggest a high probability for the appearance of new CsA of methaqualone in the future. A CsA of methaqualone will by necessity have the 3-aryl-quinazoline structure, and as a result will fall under the CsA amendment. One would shell predict that the driving force behind any future clandestine synthesis of a methaqualone CsA will revolve around attempts to use precursor materials which will not alert law enforcement lo the existence of the clandestine laboratory. A literature review for CsA candidates will quickly surface several possibilities[16,17,24,70,74,84,85,115,145]. One of the most intriguing methaqualone CsA's from the perspective of a clandestine chemist would have to be the halo- and thio- derivatives described by Joshi et al.[86]. Two of the compounds from this work possess depressant activity greater than methaqualone and would be particularly well suited to clandestine synthesis.

Analgesics

Literature covering the analgesics is so voluminous that a review of the published data on the subject is far beyond the scope of this work. Most of the potent analgesics are modeled after features found within the structure of morphine and some literature detailing these structural features has been published by Paul Janssen[77,78,79,80,81]. Despite a significant passage of time, the structure activity relationships established in these works still comprise a very sizable portion of our empirical knowledge on this subject.

Some 13 years ago, Shulgin[137] provided a short overview of many of the known major classes of analgesics. The following constitutes a similar listing:

1. Morphines
2. Morphinans and isomorphinans
3. Benzomorphans
4. Pethidines (meperidines), prodines, and ketobemidones
5. Fentanyls
6. 3,3-Diphenylpropylamines (methadone, propoxyphene)
7. Thiambutenes
8. Phenampromide and 1-dialkylaminoethyl-2-(4-alkyloxy)benzyl-5-nitrobenzimidazols
9. Pirinitramide derivatives

Numerous works have dealt with the syntheses and pharmacological testing of derivatives of the structures listed above. Synthetic procedures have been improved and refinements aimed at the tailoring of specific analgesics to fulfill certain medical needs have been addressed. However, it has been since 1975 that no work has been found introducing a new class of analgesics of either unusual potency or particularly well suited to synthesis in clandestine laboratories. There has been discovered one compound which may be of minor interest in that it is an analgesic with potency similar to morphine and can be described as a ring condensation product of N,N',3-trimethyl-5-hydroxytryptamine[21]. In any discussion of synthetic analgesics one must include the so called Bentley compounds. These compounds are not, in the purest sense, synthetic analgesics as they are C-ring etheno Diels Alder adducts of thebaine[12]. Etorphine (*compound 47*, *Figure 14*) is perhaps the best known compound in the series and has analgesic activity approximately 1000 times that of morphine[13,71]. Although reaction conditions appear to be critical, the synthesis of etorphine derivatives involves what is essentially a two step reaction with methylvinylketone and an appropriate organometallic reagent[49,64]. Hence, the only expected difficulty in the clandestine synthesis of these compounds would lie in the initial acquisition of the thebaine. Therefore, it is somewhat surprising that either etorphine or derivatives thereof have not become a contributor to illicit analgesic supplies. On the other hand, if etorphine were to be admixed with some less potent analgesic, such as heroin, it is doubtful that it would ever be detected. In his 1975 article, Shulgin pointed to meperidine, prodine, and ketobemidone as possible models for "Drugs of Abuse in the

Future." There are some who think that Shulgin's comments were somewhat of a self fulfilling prophecy as it is felt that his article is well worn within the circles of clandestine laboratory operators (*Sapienza, F. personal communication*). Supporting this premise, at least to some extent, is the fact that the appearance of the first known fentanyl, China While, did not occur until 1979 (*Henderson, G. I.. personal communication*). However, it is also the case that desmethylprodine (MPPP) was first encountered in a DEA laboratory sample submission in July of 1973 (*Kram, T. personal communication*), a full two years before Shulgin published his article.

The probability that CsA's of prodine will constitute any appreciable quantity of the clandestine analgesic market in the future is relatively remote. The well publicized neuro-toxicity of the prodine dehydration product, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[36,94,101,114], coupled with a limited scope of derivatives having appreciable analgesic activity[9,14,98,170] would seem to remove prodine from consideration as a model for CsA's. The fact that the 3-allyl analog of MPTP is not thought to be neurotoxic[21] and the corresponding prodine analog has greater analgesic activity than does β-prodine[171] may be of some interest to the clandestine laboratory operator. However, allylprodine (*compound 49, Figure 15*) is already controlled under Schedule 1. A prodine derivative which may be found in a future clandestine laboratory is α-promedol[35]. Analgesic activity for the unresolved stereoisomers of promedol is approximately ten times that of morphine, but there is some increased difficulty associated with the synthesis and neurotoxicity for it's MPTP analog is a real possibility. It is also the case that α-promedol is listed in CFR Schedule I under the name of trimeperidine.

In any event, the syntheses of prodine CsA's arc fraught with considerable risk from the inadvertent production of either MPTP or an as yet unexplored congener also having neurotoxic properties. It is worth noting that at one time MPTP was tested for use as an insecticide and that there are reports of workers handling MPTP who have suffered full blown Parkinsonian symptoms (*Shafer, J. personal communication*).

Meperidine (pethidine, demerol) is approximately 50% as potent an analgesic as is morphine and has a safety margin of only 4.8 as compared to 71 for morphine[82] Hence, one would assume that the continued abuse of meperidine is most probably related to the east with which it can be diverted from commercial channels rather than it's applicability to drug abuse per se. It has been noted that there are some 4000 compounds which may be related chemically to meperidine. It should be pointed out that of these 4000 compounds, many are not classified as analgesics, and they must also include the closely allied prodine and ketobemidone derivatives. The most potent analgesics of the meperidine class of compounds, as is the case with the prodine class of compounds, all appear to already be controlled under Schedule I and the less potent but clinically useful derivatives controlled under Schedule II. The most interesting compound from the view point of clandestine synthesis would have to be phenoperidine, as analgesic activity is approximately 30 times that of morphine and the safety margin is increased, relative to meperidine, quite substantially[82]. Fentanyl is an analgesic of high potency, approximately 300 times that of morphine, which was developed by Janssen in 1962[80] and is N-[(2-phenylethyl)-4-piperidyl]-N-phenyl-propanamide. The first CsA of fentanyl came to the attention of law enforcement in late 1979 but was not identified until 1981[3]. In the next three years a procession of new fentanyl CsA's appeared in the illicit drug market. The abuse of fentanyl CsA's peaked in 1985 and has since decreased dramatically[58], a phenomena which was the result of DEA successfully terminating the operation of the responsible laboratories. However, the ripple effect is still being felt as international and national meetings have been held to discuss the problems presented by CsA's. Also, legislation, such as the U.S. CsA amendment, has been passed in order to allow law enforcement to deal more efficiently with the analog problem.

It is the author's opinion that fentanyl CsA's will be back as the future analgesic drugs of abuse. The thoughts behind this statement are that the published synthesis schemes for the fentanyl compounds allow for the use of wide variety of precursors as discovered by the confiscated notes from an anonymous clandestine laboratory that synthesized a drug, based on information presented in two separate volumes of the Journal of Organic Chemistry[6,79,117,161,162]. Also, several fentanyl derivatives have such high potencies that the quantities required to be synthesized are trivial. For instance, carfentanil (*compound 53, Figure 17*) is approximately 4000 times as potent as heroin and has an extremely favorable therapeutic index[82]. Hence, an easy week's work for two chemists could provide 1 (one) kilogram of carfentanil which would be equivalent to four metric tons of pure heroin.

In the course of this article, several points have been made concerning those forces which will control the appearance of future synthetic drugs of abuse. The most important of these factors is user acceptance of the marketed drug. Needless to say, the typical clandestine drug dealer and/or chemist is not overly concerned with the health of the user. However, they are concerned with having a ready market for their product. A reputation for selling "bad stuff" would not be conducive to good business. A recent example of this can be found in MPPP.

The second most important market controlling factor is law enforcement control of the industry. A recent example would be the effects produced when P2P was placed under legal controls. The response so far has been two-fold; first there has been a concerted move to either more fundamental precursors or to synthetic routes utilizing β-hydroxyphenylethylamines, and second, there has been an apparent increase in the abuse of 4-methylaminorex. Hence, the methamphetamine market is in a state of flux as a direct result of law enforcement activity and either a CsA will be found which will provide both the user and the clandestine drug chemist with the same advantages as methamphetamine or a new precursor synthesis scheme will be found which will offer nearly the same advantages as P2P. It is axiomatic that for drugs of moderate potency arid high consumer demand, such as methamphetamine, a synthesis scheme must be relatively straightforward as it must be amenable to the limited expertise available in the clandestine laboratories in order to meet consumer demand.

In this work, only an occasional attempt was made to address the difficulties associated with the practical synthesis of the various derivatives discussed. Some of the compounds discussed do not have conveniently configured precursors that are commercially available. Hence, synthesis of some of these compounds require using the precursors earth, fire, and water. Additionally, as the number and complexity of substitution on any given chemical structure increases, there is a corresponding increase in the number of byproducts and a decrease in the ultimate yield of target compound. In total then, some of the compounds mentioned in this work are not practical, especially considering the clandestine laboratory, given the present state of synthetic knowledge. However, as time moves on, more efficient and direct methods of synthesis will be found and made available to the informed reader through the scientific literature. This point is easily exemplified even by the work of our own forensic scientists[25,147]. The clandestine chemist of the future will be more sophisticated than those of the present and compounds not yet conceived of will be within their reach.

Consumer preferences and law enforcement activities are the two dominate forces affecting today's illicit drug markets. While staying within the confines of consumer demand, the clandestine chemist of the future will synthesize those drugs having the highest possible potency in an effort to limit his exposure to law enforcement activities and to expand his illicit business as well.

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Definitions

Analgesic
: **1)** Causing analgesia or freedom from pain.
: **2)** A pain relieving remedy.

Analog
: Compound with similar electronic structure but different atoms.

Controlled Substances
: Those drug substances which are listed as of January 1, 1988 under schedules I through V of the United States Title 21 Code of Federal Regulations (CFR) section 1300 to end.

Derivative
: An organic compound containing a structural radical similar to that from which it is derived, for example, benzene derivatives containing the benzene ring.

Homolog

Member of a series of compounds whose structure differs regularly by some radical, for example, methylene, from that of its adjacent neighbors in the series.

Schedule I

Schedule I is a listing of those substances which are controlled under U. S. federal laws, are deemed to have a high potential for abuse, and for which there is no accepted medical use.

Schedule II

Schedule II is a listing of those substances which are controlled under U. S. federal laws, are deemed to have a high potential for abuse, and for which there is a accepted medical use.

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