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Invited Review

Arylethylamine psychotropic recreational drugs: a chemical perspective

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Abstract

The arylethylamines substituted in the aryl ring, side-chain carbons and on the terminal amine, comprise a large number of human mood and behaviour altering chemicals. Some of these psychotropic drugs have been used since pre-history, but in many states are proscribed and are consequently subject to clandestine synthesis and illegal traffic world-wide in the forms particularly of amphetamines and to a lesser extent tryptamines. The chemistry employed in the synthesis of these compounds is dictated often by the available precursors and relies usually on relatively simple, unsophisticated conversion reactions to a suitable product. The internet web sites and documentation of the recreational drug culture have been studied alongside the professional scientific and regulatory literature. The review demonstrates the great complexity of the chemistry and neuro-pharmacology of these chemicals and the challenge faced by legislative bodies to control their traffic and use for the sake of social welfare. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Phenethylamines; Amphetamines; Tryptamines; Clandestine synthesis; Psychotropic

1. Introduction

Recreational drugs have always played a part in human society. Mankind has found in its search for food and through curiosity, natural products to stimulate the senses, evoke euphoria, alleviate hunger and pain and to provide through dreams and hallucinations an escape from what was often a bleak and brutish reality. Societies adopted some of the psychotropic (mood changing) drugs for recreation, witchcraft and religious rites. Knowledge and possession of these drugs created influence and wealth. It is likely that the properties of most plants and their preparations were well known to the indigenous populations and doubtless they were traded like everything else. How much traffic there was in early times amongst the common people in recreational drugs other than alcohol is not clear. As history evolved, so did the trade in recreational drugs: opium, coca leaves, betel, cannabis, tobacco, coffee and tea dominated the scene in different parts of the world, along with the ubiquitous alcohol.

Governments throughout history have tried, usually for financial gain through taxation but also for more altruistic motives of industrial output, social welfare and stability, to control the consumption of alcohol and most other recreational drugs, from coffee to cocaine. In more recent times, this was a feature of the various prohibitions and licensing laws introduced to try (and fail) to control the consumption of gin in the eighteenth and nineteenth century in Britain. Only by permitting access to a reasonable quality product through controlled distillery outlets, and the wide availability of less injurious beers, was the black market in gin suppressed and the social damage brought under control. Fundamentalist religious and social reformers played an important role too in creating an ethos of abstinence from alcohol that carried forward into the nineteenth and twentieth century. Present day commentators are drawing an analogy between the situation then with gin and the currently burgeoning problems with the drugs of today [1].

Indeed, as synthetic chemistry rapidly developed in the nineteenth century, more potent synthetic drugs,

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notably heroin and later the amphetamines started to appear. With this development, grew concern about the direction of society with respect to these substances and what collective harm could come from them. That concern resulted in a wave of legislation worldwide during the twentieth century to prohibit the traffic and use of many substances considered harmful to health and the social fabric. This move was fuelled also by the developing trends in social and religious fundamentalism, vested commercial and political interests, as described in a sometimes-uncomfortable review by Metzger [2].

In the turmoil of the social changes in the middle decades of the twentieth century, the use of cannabis and amphetamines grew steadily. The greatly improved knowledge of chemistry and biochemistry along with a greater understanding of the chemistry of natural products, permitted the targeted synthesis of 'designer' recreational drugs [3] and pointed the way to a raft of others. Along with cocaine, opium derivatives and heroin, these reached all levels of society in most of the world by the last few decades of the century. Their use is continuing its evolution today in spite of the well-documented harm that all these substances can cause to the users, their families and to society in general.

The level of abuse, particularly amongst the young is a cause for concern and is associated with other social problems both as a cause and effect of the drug taking. The figures are somewhat confusing since hard data come only from people who present themselves for treatment, whereas the numbers taking the drugs without referring themselves is undoubtedly much greater than that. Recent data from the North West of England [4] indicate that heroin, methadone and cocaine result in the most referrals for treatment, followed by amphetamines. The hallucinogens including LSD, psilocybin and ketamine account for only a couple of percent of referrals. A recent report from Germany [5] however reported that abuse of natural products was frequently noticed among young patients in one clinic, who used *Psilocybin* (see below), *Amanita* (fungus contains muscimol, 5-aminoethyl-3-(2H)-isoxazolone) and *Datura* (plant contains atropine and scopolamine amongst other tropane alkoloids) species.

In the amphetamine category, Ecstasy (3,4-methylenedioxy-*N*-methylamphetamine, MDMA) users exceed amphetamine sulfate users by a factor of 20–40 [4]. It is probable however that many users will be unaware of exactly what drug or mixture they are taking. Seizures of locally manufactured amphetamines in clandestine laboratories in the UK still indicate amphetamine sulfate as the most commonly synthesised material [6] and that was true also in Western Europe up to the nineteen-eighties and possibly now [7]. This somewhat fuzzy picture of the current scene serves to illustrate the hazards associated with the uncontrolled use of these psychotropic drugs, often taken in sublime ignorance by the user. A large number of texts and internet web-sites set up by state authorities and concerned groups give a wide range of advice to the recreational drugs users and their acolytes. A good example is the quite non-partisan compilation of facts and comment by Holland [8] on Ecstasy and there are similar texts for many other currently fashionable drugs.

The legislation that was brought in to control or prohibit the use of recreational drugs throughout modern history has proved at best able to slow rather than stop its prevalence. Legislation and health warnings seem unable to quell the market desire for these products, however misguided that is. What prohibition does inevitably, is to replace any possible legitimate trade by illegal traffic, as the profits to be made are huge. The main problem with that illegal trade is it being beyond legal control of the product quality, its availability or its market, particularly the target age cohort.

Some of the illegally produced drugs are of acceptable purity, even though intrinsically harmful, and have been manufactured to a high standard by professional organisations. On the periphery, however, there are small-scale clandestine producers often working with neither purity safeguards nor quality control, producing material of questionable composition. Middlemen create arbitrary mixtures of drugs and dilute them with other physiologically harmful materials in order to maximise profit, sometimes with fatal consequences.

Further down the chain of producers, are the scientifically naive experimenters, sometimes working from home or college [9], trying to synthesise recreational drugs from common precursors or proprietary medicines. The internet has provided these latter groups of producers and also the recreational drug users with a forum for education, advice, encouragement and warning from each other and concerned observers. There is now an extensive database available to these groups with synthetic routes and methodology referred to the scientific literature. It must be emphasised that some of the science is of questionable basis and some of the methodology positively hazardous, witnessed by hair-raising reports on the websites. Product quality is likewise probably not always guaranteed.

This review addresses some of the synthetic methods reported on the internet and in the literature of the recreational drug culture for the phenethylamine or amphetamine, and the indolethylamine or tryptamine families [10–15]. Documentation from the international law enforcement agencies has been consulted [16] and the scientific literature has been addressed also to validate or refute some of the claims made. The aim is to demonstrate the wide variety of psychotropic materials that can be synthesised and the complexity, although sometimes simplicity of the processes involved. In only

a few instances, can one hazard a guess as to the possible by-products of reaction or what will be the overall physiological effect of a poorly purified product.

2. Pharmacology

2.1. Neurochemistry of the psychotropic phenethylamines and tryptamines [17]

Psychotropic agents alter perception, mood and behaviour in man by interference with the pre-synaptic and post-synaptic processes or to influence the physiological activity of the neurons. There is evidence that they interfere with a number of processes including the catecholamine norepinephrine neurons, dopamine transport and on 5-HT (5-hydroxytryptamine, serotonin) receptor sites. The amphetamine family of drugs has psychomotor stimulating properties, increasing a range of physiological activities and extending periods of attention and wakefulness, in some cases for days. Amphetamines have been widely used for this property and fashions in western youth culture of the 1980s and 1990s particularly, encouraged their use to this end. Some psychotropic tryptamines have been used as plant extracts since ancient times. Although also influencing a range of neural processes, the natural and synthetic tryptamines have been used more for their psychedelic, hallucinogenic and mood-enhancing properties, comparable with the fashionable use of LSD in the 1960s and 1970s.

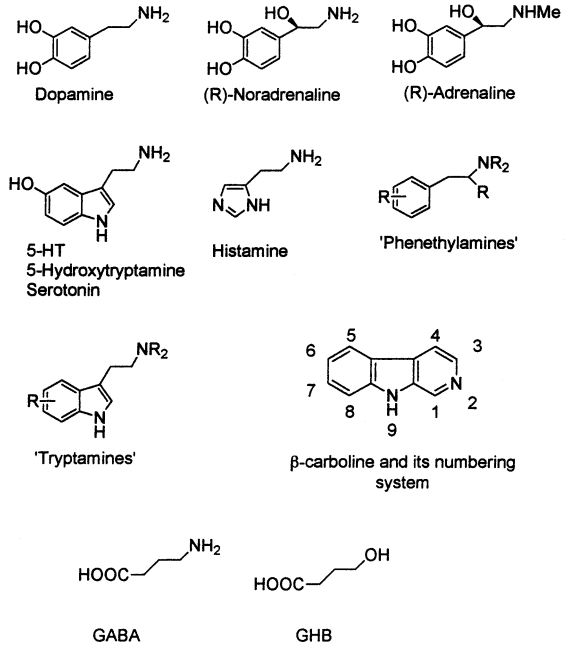


Fig. 1.

That the amphetamines and tryptamines affect the chemistry of neural processes comes as no surprise when one considers how closely their structures resemble those of the neurotransmitters. The detailed structure–psychotropic activity relationships are however much less obvious, due at least in part to the fact that one agent will affect a range of receptors and processes, and those effects are highly structure dependent [18] (Fig. 1).

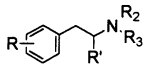
The simple statement of mechanistic pathways of the effect of these drugs belies the great complexity and unpredictability of their effects. Since the similar receptor types control different body functions, the drugs may influence a range of psychological and physiological processes as agonists, antagonists and/or modulators. That behaviour is moderated by the body's natural monoamineoxidase (MAO), the main agent of detoxification against these compounds. Drugs synthesised without proper care or quality control contaminated by MAO inhibitors (MAOI) and other by-products could have serious consequences to the eventual drug user. Change in potency due to MAOI or other agents added purposely to enhance the psychotropic effect, could and occasionally do result in overdose or unexpected side-reactions [12].

3. Phenethylamines or amphetamines

The psychoactive phenethylamine analogues given in Table 1 have been identified as being of potential interest to the clandestine synthetic chemist [10–14,16]. The compounds vary in both the substitution pattern of the aromatic ring and the substituents on the ethylamine side chain. These different substitution patterns are known to alter the effect of the drug. *N*-Methyl substitution on the amine and on the α-carbon increase the effect of the drug, at least in part due to both increased lipophilicity and resistance to MAO deactivation. Substitution by groups on the ring, particularly methoxy, is known to increase the hallucinogenic properties of the drug. In addition, the stereochemistry of the phenethylamine analogue is important, with the enantiomers showing different hallucinogenic effects.

The phenethylamine most commonly synthesised in clandestine laboratories in Europe is amphetamine sulfate **1** [6,7]. Methamphetamine **2**, the *N*-methyl analogue of amphetamine, is one of the most widely used recreational drugs in North America [13,14,16,19,20]. Of the 3,4-methylenedioxyphenylethylamine analogues **6**–**13**, MDMA **6** (Ecstasy) is the most widely used in Europe. The chain extended analogue, MBDB **9** and its demethylated metabolite BDB **8**, have also been detected in samples from drug users in Sweden [21]. Recreational drugs do not always contain just a single compound. A recent study [22] analysed Ecstasy

Table 1
Psychoactive phenethylamine analogues



	R	R^1	R^2	R^3	Names
1	H	Me	H	H	amphetanmine
2	H	Me	Me	H	*N*-methylamphetamine, methamphetamine, α, *N*-dimethylphenethylamine
3	H	Me	Et	H	*N*-ethylamphetamine, etilamfetamine
4	H	Me	Me	Me	*N*, *N*-dimethylphenethylamine
5	H	H	Me	Me	*N*, *N*-dimethylphenethylamine
6	3,4-$CH_2(O)_2$	Me	Me	H	3,4-methylenedioxy-*N*-methylamphetamine, **MDMA**, **ecstasy**
7	3,4-$CH_2(O)_2$	Me	Me	Me	3,4-methylenedioxy-*N*,*N*-dimethylamphetamine, **MDMMA,** 1-(3,4-methylenedioxyphenyl)-2-butanamine
8	3,4-$CH_2(O)_2$	Et	H	H	1-(1,3-benzidioxol-5-yl)-2-butanamine, **BDB**
9	3,4-CH2(O)2	Et	Me	H	*N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine, **EDEN**, *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine, **MBDB**
10	3,4-$CH_2(O)_2$	Me	OH	Me	*N*-hydroxy-*N*-methyl-3,4-methylenedioxyamphetamine, **FLEA**
11	3,4-$CH_2(O)_2$	Me	Et	H	3,4-methylenedioxy-*N*-ethylamphetamine, *N*-ethyltenamfetamine, **MDEA, MDE, EVE**
12	3,4-$CH_2(O)_2$	Me	H	H	3,4-methylenedioxyamphetamine, tenamfetamine, **MDA**
13	3,4-$CH_2(O)_2$	Me	OH	H	*N*-hydroxy-3,4-methylenedioxyamphetamine, **MDOH**
14	4-MeO	Me	H	H	4-methoxyamphetamine, para-methoxyamphetamine, **PMA, 4-MA**
15	4-MeS	Me	H	H	4-methylthioamphetamine, **4-MTA**
16	4-MeO	Me	H	H	para-methoxy-*N*-methylamphetamine, **PMMA**
17	2,5-$(MeO)_2$	Me	H	H	2,5-dimethoxyamphetamine, **DMA**
18	2,5-$(MeO)_2$	Me	Me	H	2,5-dimethoxymethamphetamine, **DMMA**
19	4-Br-2,5-$(MeO)_2$	Me	H	H	4-bromo-2,5-dimethoxyamphetamine, **DOB, BDMA**
20	4-Cl-2,5-$(MeO)_2$	Me	H	H	4-chloro-2,5-dimethoxyamphetamine, **DOC**
21	4-Et-2,5-$(MeO)_2$	Me	H	H	4-ethyl-2,5-dimethoxyamphetamine, **DOET**
22	2,5-$(MeO)_2$-4-Me	Me	H	H	2,5-dimethoxy-4-methylamphetamine, **DOM, STP**
23	2,4,5-$(MeO)_2$-4-Me	Me	H	H	2,4,5-trimethoxyamphetamine, **TMA-2**
24	4-EtS-2,5-$(MeO)_2$	H	H	H	2,5-dimethoxy-4-ethylthiophenethylamine, **2CT-2**
25	2,5-$(MeO)_2$-4-PrS	H	H	H	2,5-dimethoxy-4-(*n*)-propylthiophenethylamine, **2CT-7**
26	4-Br-2,5-$(MeO)_2$	H	H	H	4-bromo-2,5-dimethoxyphenethylamine, **2C-B**
27	3,4,5-$(MeO)_3$	H	H	H	3,4,5-trimethoxyphenethylamine, **mescaline**
28	3,4,5-$(MeO)_3$	Me	H	H	3,4,5-trimethoxyamphetamine, **TMA**
29	4-MAl-3,5-$(MeO)_2$	H	H	H	4-allyloxy-3,5-dimethoxyphenylamine, **AL**
30	4-MAl-3,5-$(MeO)_2$	H	H	H	4-methallyloxy-3,5-dimethoxyphenethylamine, **MAL**
31	3-MeO-4-Me	Me	H	H	3-methoxy-4-methylamphetamine, **MMA**
32	5-MeO-3,4-$CH_2(O)_2$	H	H	H	5-methoxy-3,4-methylenedioxyamphetamine, **MMDA**

samples from various European countries that revealed the presence of MBDB **9**, MDEA **11** and/or MDA **12**. 4-Bromo-2,5-dimethoxyphenethylamine **26** (2C–B) [16] has been sold as Ecstasy in Switzerland [23].

According to Shulgin and Shulgin [14], 4-methoxyamphetamine **14** (4-MA) was widely distributed in USA and Canada and several deaths were attributed to this compound. The thio- analogue **15**, was found in illicit tablets sold in the Netherlands and Switzerland in 1997–1998 [24]. Mescaline **27** (3,4,5-trimethoxyphenethylamine) was isolated in 1896 from the peyote cactus [25] and has been widely used as a recreational and ritual drug. Its α-methyl analogue 3,4,5-trimethoxyamphetamine (MMA) **21** has been found more recently for sale on the streets of Italy [26].

3.1. Synthetic routes to the phenethylamines

This review focuses on the most direct synthetic routes to the phenethylamines that are likely to be adopted by clandestine chemists [14,19,21,27–30]. As seems often to be the case in clandestine manufacture, it is the availability of the precursors that is the most important factor in the choice of synthetic route. There are five key aromatic precursors: the substituted allylbenzene, vinylbenzene (styrene), benzaldehyde or phenylpropan-2-one and the over-the-counter drug (pseudo)ephedrine. In the following discussion, chemistry utilising these precursors will be described, which provide the main routes for the synthesis of phenethylamines.

3.1.1. From allylbenzene analogues

The allyl-substituted benzene analogues are often key constituents of the essential oils that may be available in health food stores. The unsubstituted allylbenzene is required for the synthesis of (meth)amphetamine **1**, **2**. For Ecstasy **6** and the related 3,4-methylene-

dioxyphenethylamine analogues, this precursor is safrole, which supply is regulated in many countries. Safrole can be isolated by distillation of the natural oil obtained from the root bark of the native North American sassafras tree *Sassafras albidum* (*Lauraceae*), and also from the indigenous Brazilian tree *Ocotea pretiosa* [31,32]. Myristicin (3-methoxy-4,5-methylenedioxyallylbenzene) found in parsley leaf oil [33] is utilised for the synthesis of analogue **32** and 2,5-dimethoxyallylbenzene for the synthesis of analogues **17**–**20**.

Fig. 2 shows the route described in the original Merck patent for amphetamine synthesis [34], that is still utilised in illicit manufacture [16,35,36]. Hydrobromic or hydriodic acid [37] adds to the double bond of the allylbenzene analogue to give the 1-phenyl-2-halopropane derivative, which reacts with an amine nucleophile [38]. The route can be adapted to make any of the phenethylamine analogues by utilising different nucleophiles (e.g. ammonia, methylamine, dimethylamine or hydroxylamine) and different allylbenzenes.

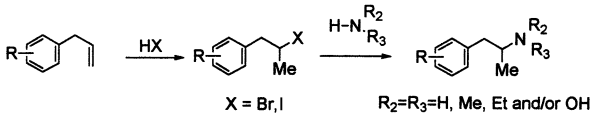


Fig. 2.

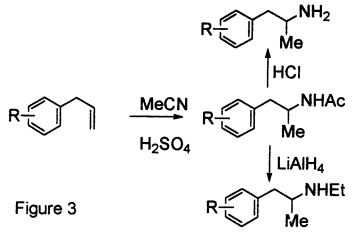


Fig. 3.

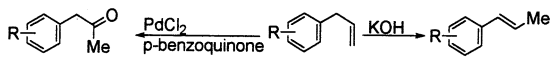


Fig. 4.

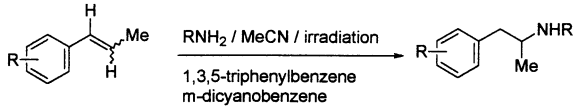


Fig. 5.

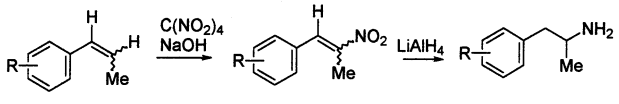


Fig. 6.

3.1.2. From allylbenzene analogues

The primary amine and *N*-ethyl (but not *N*-methyl) amphetamine analogues can be made from the allyl benzene (e.g. allylbenzene, safrole) and acetonitrile in two short steps with simple reagents, using the Ritter reaction (Fig. 3) [39], although with electron donating substituents on the aromatic ring, the yields are likely to be low. The allylbenzene analogue is often a precursor to the vinylbenzene (e.g. isosafrole, anethole, isomyristicin, asarone (2,4,5-trimethoxyphenyl-prop-1-ene), calamus oil) by isomerisation and conjugation of the double bond (Fig. 4), the routes to the amphetamines from which are discussed in the Section 3.1.3. In addition, the allylbenzene can be converted to the phenyl-2-alkanones (e.g. 3,4-methylenedioxyphenyl-2-propanone (MD-P2P), 1-(4-methoxyphenyl)-2-propanone) [14,16,40,41] by the Wacker oxidation using $PdCl_2$ and *p*-benzoquinone, and appears to be a preferred route for the clandestine chemist (Fig. 4, see Section 3.1.6) [42].

3.1.3. From vinylbenzene analogues

The vinylbenzene [e.g. isosafrole, anethole (anise oil, 1-methoxy-4-propenylbenzene)] can be used in a direct amination reaction, by irradiation in the presence of ammonia and *m*-dicyanobenzene (Fig. 5) [43,44]. The nitrostyrene can also be prepared by direct nitration of the appropriate vinyl benzene [e.g. isosafrole, anethole, isomyristicin, asarone (2,4,5-trimethoxyphenyl-prop-1-ene)] (Fig. 6) [14,30]. The intermediate [1-(4-methylthiophenyl)-2-nitropropene] has been found in a clandestine laboratory in the Netherlands [24].

3.1.4. From the 1-phenyl-2-nitroalk-1-ene intermediates

Reduction of these with $LiAlH_4$ or sodium borohydride–nickel chloride gives the primary phenethylamines directly [14,16,45–52], and this route has been commonly utilised (Fig. 6). Myristicin aldehyde (5-methoxypiperonal, 3-methoxy-4,5-methylenedioxybenzaldehyde) prepared from 3,4-dihydroxybenzaldehyde [14] or vanillin (4-hydroxy-3-methoxybenzaldehyde) [53] can be converted into MMDA by reacting first with nitroethane (Fig. 7), and subsequent reduction of the 2-nitropropene analogue [14,54].

3.1.5. From benzaldehyde analogues

The intermediate ketone can be prepared by reaction of the appropriate substituted benzaldehyde, e.g. piperonal (4-methoxybenzaldehyde), 4-(methylthio)benzaldehyde, 2,5-dimethoxybenzaldehyde, 4-bromo-2,5-dimethoxybenzaldehyde [55], 2,4,5-trimethoxybenzaldehyde (asaronaldehyde), 3,4,5-trimethoxybenzaldehyde (from gallic acid) or syringaldehyde (3-methoxy-4-methylbenzaldehyde), all with a nitroalkane (e.g. nitromethane, nitroethane or nitropropane) in the

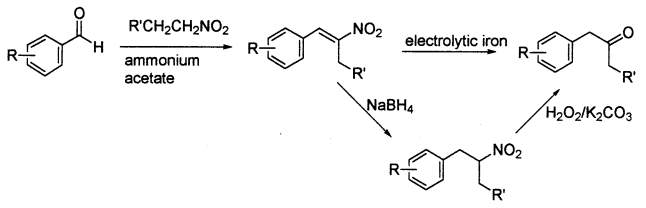


Fig. 7.

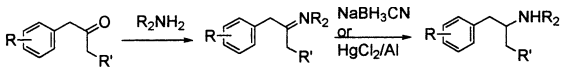


Fig. 8.

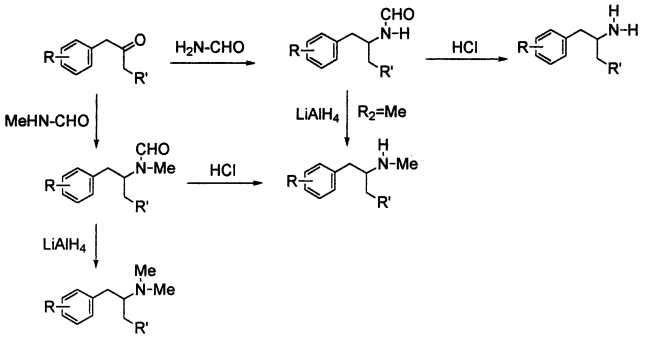


Fig. 9.

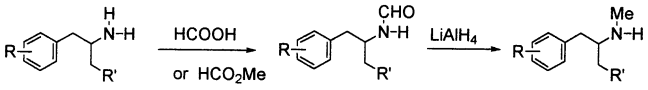


Fig. 10.

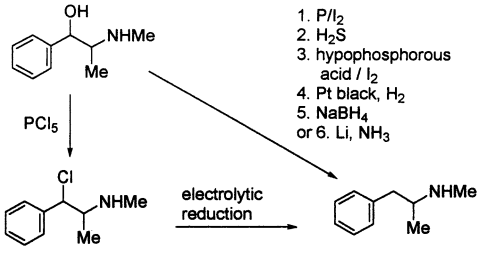


Fig. 11.

presence of ammonium acetate [14,16,56–60]. The phenyl-2-nitroalk-1-ene product (a nitrostyrene) is then reduced to the ketone by treatment with electrolytic iron (Fig. 7) [52,61]. Alternatively, the nitrostyrene product is reduced in a one-pot synthesis, first to 1-phenyl-2-nitropropane using sodium borohydride in methanol. The 1-phenyl-2-nitropropane is then hydrolysed to phenylacetone with hydrogen peroxide–potassium carbonate [62].

3.1.6. From phenylpropan-2-one analogues

The intermediate ketones [e.g. MD-P2P, 1-(4-methoxyphenyl)-2-propanone, 2,5-dimethoxyphenylacetone] can undergo reductive amination reactions with a range of nucleophiles to give amphetamine analogues (Fig. 8) [14,46]. This appears to be a popular route for the synthesis of Ecstasy **6** by the clandestine chemist [45,63]. Hydroxylamines can be utilisied as the nucleophile to prepare analogues **10** and **13** of Table 1.

The intermediate ketones [e.g. phenylacetone, MD-P2P, 1-(4-methoxyphenyl)-2-propanone, 1-(3-methoxy-4-methylphenyl)-2-propanone] can also be used to prepare amphetamine analogues by the Leuckart–Wallach reaction [64], the first step involving treatment with formamide or *N*-methylformamide (Fig. 9). The resulting formamides can either be hydrolysed or reduced [65]. It is reported that these routes are commonly used in illicit MDMA synthesis laboratories [36], and in recent years has been the most commonly used method in clandestine laboratories in Western Europe [7]. The primary amine amphetamine analogues are typically converted to the *N*-methyl derivatives by formylation followed by reduction (Fig. 10) [14,66].

3.1.7. From ephedrine and pseudoephedrine

A recurring feature of clandestine manufacture has been the conversion of proprietary medicines, or the diversion of precursors and products of common commercial products to drug synthesis. (1R, 2S)-Ephedrine and (1S, 2S)-pseudoephedrine (2-methylamino-1-phenylpropan-1-ol) are employed as starting materials for methamphetamine principally because they are present in proprietary medicines from which they are extracted for clandestine synthesis. In a two step approach, ephedrine is converted first to a β-haloephedrine using, for example phosphorus pentachloride or -tribromide, or thionyl chloride. The β-haloephedrine is then reduced to methamphetamine using platinum black on carbon, palladium black on barium sulfate or by electrolytic reduction on a platinum, lead, mercury or amalgamated copper electrode (Fig. 11). The yields of methamphetamine are reported to be 70–80% [67]. The reduction steps involve only the 1-chiral centre and so both starting materials yield the same (2S)-methamphetamine, the most potent psychotropic enantiomer. Purification of the product from residues of copper, lead and mercury is an important consideration using this route.

There is a number of methods that can convert pseudoephedrine to methamphetamine directly in one step. Red phosphorus with iodine generates hydriodic acid that can reduce pseudoephedrine to methamphetamine. This method was popular in North America, in spite of the necessity for careful purification of the product. Recent controls on iodine and phosphorus have, however, forced a change in tactics. A modification is to use a 50% aqueous solution of hypophospho-

rous acid and iodine [67] to form the requisite hydriodic acid. Direct reduction of ephedrine can also be carried out by hydrogenation with a metal catalyst (e.g. palladium black) [19]. The lithium–ammonia or sodium–ammonia reduction of ephedrine to methamphetamine is useful, especially if a ready supply of anhydrous ammonia is available, as is sometimes the case in agricultural areas where it is used for direct-injection fertilisation. Lithium is reportedly obtained for small-scale synthesis by re-cycling lithium batteries [19,68,69].

3.1.8. Synthesis of single enantiomers

The majority of the phenethylamine analogues have a chiral center and, therefore, exist as two enantiomers. The (*S*)-(+)-isomers of MDMA and MBDB are more potent psychotropic agents than the (*R*)-(−)-isomers [70]. At present the clandestine chemist is satisfied with synthesis of the racemates, however, this may change. In addition, for toxicological, metabolism, pharmacological and analytical studies it is important to be able to prepare both enantiomers of the amphetamine analogues. The above conversion of the 'chiral pool' material, (pseudo)ephedrine, into (2*S*)-methamphetamine provides an approach for the synthesis of a single enantiomer. There is, however, no equivalent precursor available for the substituted-phenyl ring amphetamine exemplified by Ecstasy.

In a more general approach, the synthesis of single enantiomers of amphetamine analogues can be prepared by asymmetric synthesis utilising the chiral auxiliary, (*R*)- or (*S*)-α-methylbenzylamine in both good yield and enantiomeric purity (Fig. 12) [71,72]. Reaction with the ketone (e.g. 1-(2,5-dimethoxy-4-ethyl-phenyl)propan-2-one, 3,4,5-trimethoxyphenylprop-2-one) gives the imine, which undergoes a stereoselective reduction. Subsequent cleavage of the *N*-α-methylbenzyl group and N-alkylation (if required) has been used for the syntheses of single enantiomers of several amphetamine analogues [14,51,73].

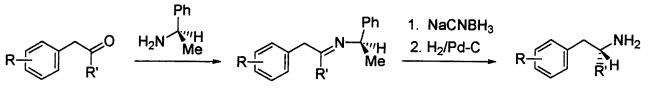


Fig. 12.

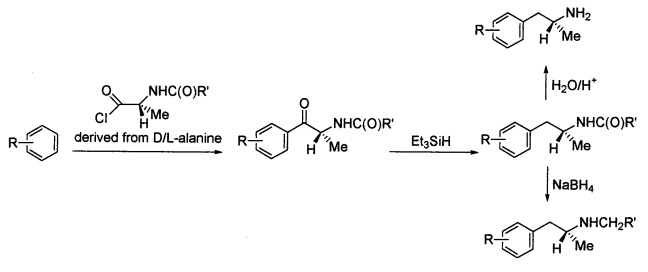


Fig. 13.

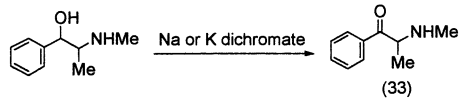


Fig. 14.

Another useful route for the synthesis of single enantiomers utilises the chiral pool precursors, D or L-alanine. The key step is a Friedel Crafts acylation reaction between the substituted benzene substrate (e.g. 1,2-methylenedioxybenzene) and (*R*)- or (*S*)-2-*N*-trifluoroacetylaminopropanoyl chloride (Fig. 13) [74].

4. Derivatives of ephedrine and norephedrine: methcathinone, 4-methylaminorex and pemoline

Methcathinone **33** (1-phenyl-2-*N*-methylaminopropan-1-one) [16] appeared in the 1980s in the former Soviet Union and rapidly gained popularity throughout Europe and the USA [75]. It is a central nervous system stimulant and its psychotropic effects are reportedly similar to methamphetamine. Clandestine manufacture focuses on the conversion of ephedrine, mainly obtained from pharmaceutical preparations, by oxidation with permanganate or more usually by dichromate–sulfuric acid (Fig. 14).

Given the similarity of effects, and the two routes from ephedrine to either methcathinone or methamphetamine, the final choice is going to be influenced by the availability of the respective reagents for either. At present, the user discussions on the internet sites indicate that most are recovering the ephedrine and pseudoephedrine from tablets and converting it for personal consumption. That small-scale operation seems to be best served by the simple oxidation to methcathinone rather than the more elaborate reductions to methamphetamine. For the larger scale operations where there is an abundant supply of ephedrine, methamphetamine appears to be the more favoured product, possibly because of customer preference [76].

4-Methylaminorex **34** (2-amino-4-methyl-5-phenyl-2-oxazoline) [16] has two chiral centres and unusually all four stereoisomers are reported to be active [77]. The starting material is phenylpropanolamine (2-amino-1-phenylpropan-1-ol, norephedrine, norpseudoephedrine) which can be extracted from over-the-counter medicines [78]. Phenylpropanolamine is converted into 4-methylaminorex by reaction with cyanogen chloride [79] or more commonly, cyanogen bromide [80] (Fig. 15). For the small-scale clandestine chemist, the biggest problem seems to be the separation of the active components from the excipients and bulking agents in the commercial products, into a concentrated form suitable for synthesis [12].

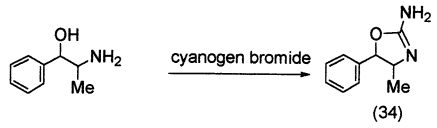


Fig. 15.

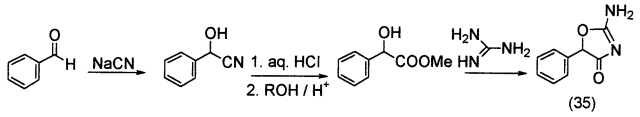


Fig. 16.

Pemoline **35** (2-amino-5-phenyl-4(5H)-oxazalone) [16] synthesis utilises benzaldehyde that reacts with sodium cyanide to give mandelonitrile (Fig. 16). Acid catalysed hydrolysis yields racemic mandelic acid [81]. Esterification of the acid with either methanol or ethanol gives methyl or ethyl mandelate that reacts with guanidine to give pemoline [82]. Cyanamide–sodium methoxide can be substituted for guanidine in that reaction [16,82]; methyl mandelate is commercially available and is, therefore, an important precursor to pemoline.

5. Tryptamines

The principal structural feature of the tryptamine family that gives rise to the desired hallucinogenic and other psychotropic effects is the 3-(2-ethylamine)indole nucleus. The effect is maximal with 2-aminoethyl and 2-aminopropyl as the side-chain. The hallucinogenic property of the drug is enhanced by *o*- and *p*-directors (e.g. MeO) in the 4- and 5-positions of the indole ring. Substitution on the 2-carbon of the indole nucleus with methyl-also affects the activity of the molecule, possibly through steric hindrance. An α-methyl group enhances the molecule lipophilicity and consequently the transport of the drug across the blood brain barrier. Amine substitution with *N*-methyl, *N*-ethyl and *N*-propyl modifies the effect of the drug, particularly with regard to its oral activity. Unsubstituted primary amine analogues tend not to be orally active because they are metabolised by MAO. Substituted amines and those where there is steric hindrance (e.g. Me- on the α-carbon of a tryptamine) are not substrates by MAO, and are orally active [83].

There is, therefore, an important balance with tryptamines, as indeed with the amphetamines, between the rate of absorption of the drug into the blood, the rate of its deactivation by MAO and the rate of transfer from blood to brain. This feature is particularly relevant in the domain of the tryptamines where a MAO inhibitor may be employed by the drug user as a potentiator to render active those tryptamines that are otherwise orally inactive. This is exemplified in some ancient traditions where plant infusions containing β-carbolines are ingested along with others containing the otherwise orally inactive *N*,*N*-dimethyltryptamine. The picture is further complicated because the potentiators themselves may be neurologically active, as is the case with at least some of the β-carbolines. Furthermore, tryptophan, serotonin, (5-hydroxytryptamine), and other tryptamines are all known to be converted to substituted β-carbolines or tetrahydro-β-carbolines in the body [84] and are also present in foodstuffs [85]. 1-Methyl-1,2,3,4-tetrahydro-β-carboline (Fig. 1) and 1,2,3,4-tetrahydro-β-carboline are present in beers and wines, but not in distilled spirits such as whisky, brandy and gin [86]. Harman (1-methyl-β-carboline) is a natural inhibitor of monoamine oxidase Type A (MAOI-A) [87] while norharman (β-carboline) probably acts by stimulation of a specific β-carboline receptor [88].

Harmaline (5-methoxy-1-methyl-3H, 4H-β-carboline) and harmalol (5-hydroxy-1-methyl-3H, 4H-β-carboline) both found in *Peganum harmala* (*Syrian Rue*), *Passiflora* and other species, are known to bind to the muscarinic acetylcholine receptors [89] and thus are active agents in their own right. Whereas the effects cited are known, it is probable that other β-carboline and tryptamine derivatives act also on the complex neural processes and alter the effect of the principal drug being taken. The Ayahuasca psychoactive plant mixture infusion known since ancient times in the Amazon region is typically composed of *Banisteriopsis caapi*, and *Psychotria viridis*, which latter contains DMT amongst other alkaloids. Harmine (7-methoxy-1-methyl-β-carboline) is the principal β-carboline component and thought to be the main active agent in *B. Caapi* [90]. The situation is, therefore, complex with the often impure psychotropic agents being administered by the recreational user into a complex equilibrium of other drugs, inhibitors and potentiators within the body, that can change on each occasion depending upon the dietary and natural history of the individual.

As with the phenylethylamines, choices of synthetic routes chosen by clandestine chemists are often conditioned by precursor availability through unwatched or unwatchable channels. The ubiquitous occurrence of tryptamine and indole species in nature leaves great scope for preparation and concentration of the key precursors en route to the psychotropic drugs. Tryptophan is an essential amino acid and was widely available as a dietary supplement. A major health scare involving 39 fatalities in the 1980s, later attributed to impurities produced by a flawed tryptophan manufacturing process, resulted in some legislative authorities banning its use for humans. The current replacement material 5-hydroxytryptophan is widely available in the arena of health preparations and dietary supplements [91].

Indole-3-acetic acid IAA, is an important plant hormone and both it and indole-3-butyric acid are available widely in this role, particularly to enhance root growth. Gramine, 3-(methylene-(*N*, *N*-dimethylamine))indole is found extensively in nature, e.g. *Lupinus* and *Arundo* species and can be readily converted into tryptamines. Indole and skatole (3-methylindole), two of the end products of tryptophan metabolism are two dominant malodorous agents in faeces of humans and other animals. The substituted indoles and tryptamines are also to be found extensively. Noteworthy are serotonin and melatonin (5-methoxy-*N*-acetyltryptamine) found in the human body and brain, and in many plants, insects etc. Bufotenine (5-hydroxy-*N*, *N*-dimethyltryptamine) is found in the skin of the toad *Bufo marinus*, psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine), and psilocybin (4-phosphate-*N*,*N*-dimethyltryptamine) found in fungi particularly of the *Psilocybe* and *Stropharia* species. *N*,*N*-Dimethyltryptamine is found in a number of plants, particularly *Mimosa hostilis* and in a wide variety of others also [89]. An important related source is indigo containing two indoline (2,3-dihydroindole) nuclei in a fused structure; it is synthesised for the dyeing industry (indigo blue, indigotin). The precursor compound, indican (indole-3-glucoside) is found in the indigo bush *Indigofera tinctoria*, native to India and China [92]. In Europe indican has been obtained from Woad *Isatis tinctoria* since ancient times. Extraction of the dye product from the plant source is still practised on a large scale [93].

The many possible sites for substitution around the tryptamine molecule and the effect substituents may have on the psychotropic activity of the product results in a plethora of potential drugs. Predicting the effect of a particular compound, toxicity, oral activity, duration of effect etc., is by no means straightforward. The picture is further complicated by their natural presence and the role that some of the simpler tryptamines play in the human body. Serotonin, melatonin, tryptophan, tryptamine and *N*,*N*-dimethyltryptamine **36** (DMT) at least, are involved in normal human metabolism and brain activity. Cooper et al. report [17] that the hallucinogenic DMT can be formed in human plasma from tryptamine. There is some evidence that schizophrenic

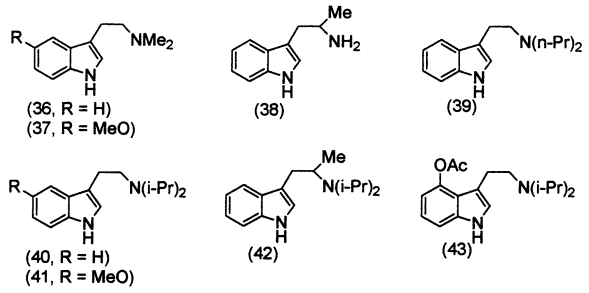


Fig. 17.

patients have abnormally low platelet MAO levels, which could permit the build-up of abnormal amounts of plasma tryptamine and hence DMT.

There are many hundred substituted tryptamines listed in Shulgin and Shulgin [15] of which about 50 are known to be psychotropically active. DMT **36**, 5MeO–DMT **37** (5-methoxy-*N*,*N*-dimethyltryptamine), AMT **38** (α-methyltryptamine), DPT **39** (*N*,*N*-di-*n*-propyltryptamine), DIPT **40** (*N*,*N*-diisopropyltryptamine), 5-MeO–DIPT **41** (5-methoxy-*N*,*N*-diisopropyltryptamine), AMDIPT **42** (α-methyl-*N*,*N*-diisopropyltryptamine) and recently 4-AcO–DIPT **43** (4-acetoxy-*N*,*N*-diisopropyltryptamine) (Fig. 17), as well as natural plant extracts are used by the recreational drug community. The situation is by no means static: Xu et al. [94] comment that reported 5-HT_{1D} receptor agonists have at least one heteroatom (N, O, S) at the indole 5-position. In their work, however, they demonstrated that *N*-methyl-5-*tert*-butyltryptamine is a potent 5-HT_{1D} receptor agonist, and that 5-alkyltryptamines all exhibit binding affinities for that receptor. This opens a new group of compounds that alone or in mixtures may demonstrate psychotropic properties. Others will undoubtedly arise from different substitution patterns in the indole nucleus and at the terminal amine.

Synthetic routes to the tryptamines have been reviewed by Sundberg [95]. The key to many of these is exploitation of the aromaticity of the indole ring structure. Synthetic routes generally start either with the indole nucleus intact or with a ready-substituted benzene ring. Formation of the pyrrole ring and the associated stabilisation energy of the aromatic indole is usually the driving force to completion of the reaction. The best known and most widely used method is the Fischer indole synthesis starting from materials such as 2-ethylaniline to form the indole. The properties of the indole nucleus then point the way to the next stages of substitution. The aromaticity gives rise to electron excess at the indole-2 and -3 positions. Protonation and electrophilic substitution occur preferentially at the 3-carbon. Nucleophilic attack would favour the 1-nitrogen and selective N1 substitution generally involves a base catalysed process [95]. The 3-substituted indoles however still retain the electron rich character at C-2 that can then exhibit nucleophilic activity. This is particularly important in tryptamines through an intramolecular nucleophilic attack on the N-substituted 3-(2-ethylamine)indole leading to the formation of a β-carboline in a Pictet–Spengler cyclisation.

The 3-carbon in 3-substituted indoles retains also some of its electron-rich character and is subject to photosensitised electron transfer, particularly with oxygen producing initially the 3-hydroperoxy-3H-indole. The indoles, therefore, tend to be light sensitive and syntheses are generally carried out in inert atmospheres

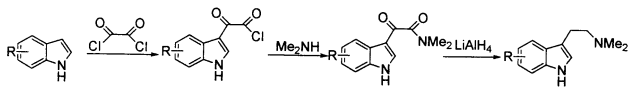


Fig. 18.

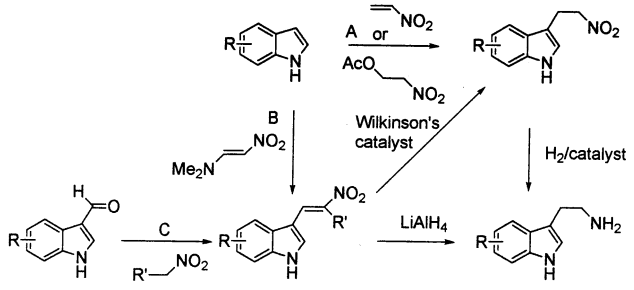


Fig. 19.

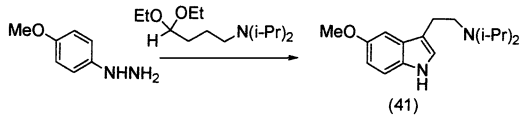


Fig. 20.

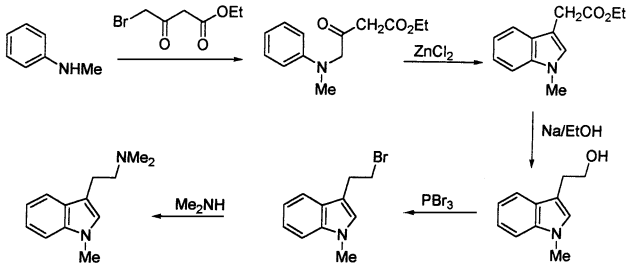


Fig. 21.

and dark conditions. Tar formation is also a problem in some reactions possibly due to photo-catalysed oxidation intermediates giving polymeric products. These problems are reduced, as might be expected, if the 3-substituent is electron-withdrawing.

Substitution in the carbocyclic ring imparts important psychotropic property alterations in the tryptamines. The introduction of these substituents during synthesis is complicated by the lack of regioselectivity in the six-membered ring of the indole nucleus. It is normal, therefore, to have the appropriate substitution in the benzene ring of the starting material, rather than introducing the group after formation of the indole.

The benzylic- or α-carbon of 2- or 3-substituted indoles can show enhanced susceptibility to radical reactions, characteristic of many aromatic compounds. Stabilisation of the radical intermediate by its participation in the overall aromatic structure is enhanced in the indoles by participation of the ring nitrogen, an effect enhanced by *N*-deprotonation. This facilitates a group of synthetic methods where an α-substituent is displaced in an elimination-substitution reaction by a nucleophile. Even a poor leaving group such as alkoxy- and dialkylamino can be treated this way. These and other key properties less relevant to psychotropic tryptamine synthesis, are discussed in detail by Sundberg [95].

The main synthetic routes have been split into methods that start with indole and substituted indoles, those that create the indole nucleus by cyclisation, and those methods that modify a commonly available molecule which contains the indolethylamine moiety.

The method of Speeter and Anthony [96] (Fig. 18) was used by Shulgin and Shulgin [15] for many tryptamine analogues and is considered to be one of the most important methods. The procedure involves acylation of a (substituted) indole with oxalyl chloride followed by reaction with an amine to give an indol-3-ylglyoxamide. The glyoxamides are then reduced to tryptamines. The method is quite versatile with, for example, halo-, nitro-, alkoxy- and benzyloxy-substituents possible in the benzene ring. Mono-, di- and mixed alkylamines up to C-4 have been introduced at the α-carbon [15].

Tryptamines can also be synthesised from the reduction of nitroethyl and nitroethenyl indoles. 3-Alkylation of indole occurs in good yield with either nitroethene or 2-nitroethyl acetate to give the 3-[2-nitroethyl]indole (Fig. 19A). Reaction of an indole with 2-[dimethylamino]-1-nitroethene in TFA [97] yields a 3-[2-nitroethenyl]indole (Fig. 19B). Tryptamines can also be made by condensing indole-3-carboxaldehydes with nitroalkanes [98] (Fig. 19C). The nitroethenyl indoles can be reduced to the tryptamines with $LiAlH_4$ and AlH_3, or by first reducing them to the nitroalkane using Wilkinson's catalyst and then with hydrogen over Pd–C to the amine. Depending on available reagents, the routes given in Fig. 19 can be utilised to prepare a range of substituted tryptamines.

There are many cyclisation routes to (substituted) indoles, the most important being the Fischer indole synthesis, which is shown in Fig. 20 for the synthesis of 5-MeO–DIPT **41**. The cyclisation occurs with a wide range of substituted phenyl hydrazines and substituted/protected aldehydes or ketones (e.g. 4-aminobutyraldehyde or its diacetal, other 4-substituted butyraldehydes and 5-substituted-pentan-2-ones) [99]. Great versatility is possible in both substitution of the 3-ethylamine side chain and the indole nucleus to yield a range of substituted tryptamines.

In a related cyclisation Julia and Tchernoff [100] used *N*-methylaniline and ethyl 4-bromoacetoacetate to give ethyl 3-indoleacetate (Fig. 21). There is a number of routes from 3-indoleacetic acid (Fig. 21), either reduction with $NaBH_4$ via the Me- or Et-ester, or direct reduction and reduction with Na–EtOH to tryptophol

(indol-3-yl-2-ethanol). Conversion of tryptophol to *N*,*N*-disubstituted tryptamines is possible by conversion to the alkyl-α-Br derivative with PBr_3 then reaction with secondary amines. It is also reported that direct refluxing of tryptophols in benzene or xylene with secondary amines over a nickel catalyst gives high yields of the tertiary amines [101].

Conversion of tryptophan to tryptamine is achieved by heating at reflux in a high boiling solvent in the presence of a ketone (Fig. 22) [102]. A method had been proposed to convert tryptamine to *N*,*N*-dimethyltryptamine using methyl iodide in the presence of sodium hydroxide and a phase transfer catalyst [67]. This method appears to be flawed, at least for dimethylation. Recent discussions on the websites indicate the more likely product as being the tri-methylated quaternary ammonium salts. Work in our own laboratory supports that proposition [103]. Fig. 22 also shows an alternative *N*-methylation step using formalin solution, which the present authors have not yet attempted.

Indigo is a source of indole that has been identified by the clandestine drug community [104]. It is broken down by nitric acid or CrO_3 to isatin, indole-2, 3-dione [105] and there is a more recent report on isatin from indigo using oxygen and ozone in sodium hydroxide–DMF [106]. Isatin is susceptible to base catalysed addition of a ketone to the 3-position, which can lead to a series of ring and side chain substituted tryptamines [107] (Fig. 23). As a specific example, Franklin and White [108] reacted 5-methoxyisatin with acetone. Reaction of the ketone product with hydroxylamine gave the oxime that was reduced with lithium aluminium hydride to give 5-methoxy-α-methyltryptamine.

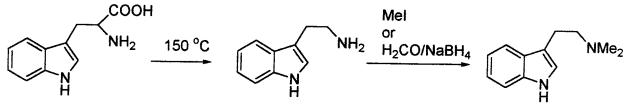


Fig. 22.

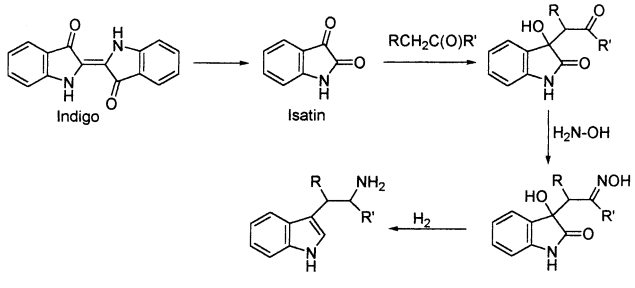


Fig. 23.

6. Possible future trends in recreational drug clandestine synthesis

Many of the references given in this review are to relatively old literature, reflecting the maturity of many synthetic methods for the amphetamines and tryptamine psychotropic agents. It also reflects the conservatism of the clandestine synthetic chemists and the dependence they have on certain precursor chemicals. That conservatism will undoubtedly evolve slowly, as is seen in the discussions on the web sites, with new ideas gradually being adopted. There is presently very extensive research in the general area of indole pharmaceutical chemistry. Many indole derivatives are biologically active and many natural products contain indole nuclei. One can expect, therefore, research in this area to unearth new psychotropic and psychotomimetic materials. Whether these will find themselves in the recreational drug community repertoire will depend at least in part upon the market forces that drive that scene. The current amphetamine products seem to hold favour with the illegal recreational drug community at present [109] due to their availability and familiar blend of psychomotor and hallucinogenic properties, whilst being relatively less harmful in the shorter term than heroin and cocaine. There is still active research in this area too, to develop new analytical methods for possible regioisomeric and homologous compounds of the amphetamine family [110–112].

The fact that all of these materials occasionally cause sudden death, and appear to cause longer term mental and physical damage to the user, seems not to be a particular concern to the generally younger cohort who choose to use them. What effect any further relaxation of laws governing the availability of cannabis will have on the consumption of these other psychotropic agents, remains to be seen.

Acknowledgements

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