CHAPTER 1

Chemistry of Psychotomimetics

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A. Introduction

A presentation and discussion of the psychotomimetic drugs in a handbook concerned with psychotropic agents must, at the onset, emphasize the several properties that make this class of materials unique.

Most psychotropic drugs are intended to be either curative or cosmetic. They may be used to reverse a pathologic mental state, or they may be intended to alleviate a persistent symptom which, in turn, might then allow some normal repair process to take effect. In either case, treatment is provided a patient who shows some psychological inadequacy with the intent of normalization. The psychotomimetics, on the other hand, are generally studied in subjects who have good psychological balance. To the extent that the effects are considered disruptive, the rationale of research is the generation of an intoxication that bears some superficial resemblance to a psychosis. When such a transient and reversible "model psychosis" is produced, biochemical and psychological changes can both be observed. But to the extent that the effects are considered constructive, there are benefits to be found in the areas of insight, changes of motivation, self-analysis, entertainment, and even simply escape. These results may be effected through a process of disorganization and reorganization, by a sensory elaboration such as visual or auditory enhancement, or by intense reverie or fantasy. There has been only limited experimentation with these drugs in the treatment of pathologic states, and so there has been little recognition of any potential medical utility. This limitation, along with a generalized abuse potential inherent in such drugs, has led to severe legal classifications which have, paradoxically, further restricted human experimentation. This latter point is exacerbated by another unique property. The effects that are observed such as changes in interpretation, in insight, and in communicability, can be assayed only in man. At the present time, no assays or behavioral tests in animals exist that allow satisfactory prediction of the qualitative nature of a new and unexplored psychotomimetic drug.

Thus, this group of drugs stands apart from the remainder of the psychotropic drugs and must be discussed in terms other than those of neuropathy, pathology, and related clinical presentations. Rather, a generalized chemical subdivision will be made predicated upon structure and grouped with reference to the principal neurotransmitters. Functional relationships with these endogenous factors are still controversial.

I. Terminology

A number of names are currently in use to identify this group of drugs. "Psychotomimetic," the adjective used in this chapter, literally means psychosis-imitating. In the

early work with these materials, it was believed that they led to an authentic psychotic state and might be of value in the search for endogenous psychotoxins or in biochemical unbalances that might he correlated with such mental states. To a clinician who interacts with mentally ill patients, these experiences might increase both understanding and compassion if he were to experience within himself the "psychotomimetic" syndrome. This concept fell into complete disrepute a decade ago, but today it has a balanced acceptability. The name remains neutral and medically unbiased and will be used in this chapter. The term "hallucinogen" is widely used, but it implies that the generation of hallucinations is a general property and, in fact, synthetic imagery of undocumentable origins is a rare property of these drugs. A third term, also widely used, is "psychedelic", which was coined in the mid-1960s to indicate mind-manifesting or mind-expanding properties. The term, however, has become associated with the broad and occasionally irresponsible popular use of these drugs. It is rarely seen in the medical and scientific literature due to the connotation of both condoning and encouraging paramedical use. The term "psychodysleptic" has been routinely employed in Europe for drugs of this classification to emphasize similarities to the psycholeptics (mood depressants) and psychoanaleptics (mood stimulators). A host of other terms proposed over the years (e.g., phantastica, delirients, schizogens, eidetikas, etc.) have historic interest but have never found wide acceptance.

II. Methods of Assay

Three broad areas of scientific discipline have been employed to rank and to attempt to explain the quantitative nature of the psychotomimetic drugs. The molecular structures of the active drugs themselves have been dissected and interpreted in completely physical terms; the materials have been titrated in animal models in a search for behavioral correlates that might relate to human activity; and most precisely, they have been studied in clinical experiments using humans.

The physical approach to explanations of biologic activity has been exclusively concerned with the geometry and measurable properties of the chemicals themselves. Intramolecular hydrogen bonding is a measurable property that can explain stabilization of unusual conformations (SMYTHIES et al., 1970), and it is widely felt that in the case of bifunctional molecules, the establishment of parameters, such as the separation of charged sites, might allow some definition of sites of action (KELLEY and ADAMSON, 1973). The natural molecular configuration of psychotomimetics can be determined using X-ray crystallography (BAKER et al., 1973), but these data are obtained from solid samples, whereas these drugs are, by definition, only active in solution. Computer calculations of orbital charge densities and charge distributions (SNYDER and MERRIL, 1965) have been correlated with potency, as have empirical measurements such as partition coefficients (BARFKNECHT et al., 1975) and strengths of charge transfer complexes (SUNG and PARKER, 1972). Such properties are, in general, simple to measure or calculate precisely, but successful generalizations have been restricted to studies of small classes of closely related drugs. There has been no successful extrapolation to new chemicals.

Biologic titration in animal models has given a wider correlation, but one which still lacks behavioral logic. In vitro experiments have concentrated largely on interactions of selected psychotomimetics with neurotransmitters. Their agonist or antag-

onist action on serotoninergic, dopaminergic, or cholinergic preparations often correlates closely with their relative potency in man, but a causal explanation for their action is not yet satisfactory. A number of in vivo tests have been developed, such as field behavior (BRIMBLECOMBE, 1963) and interference with conditioned responses in rats (SMYTHIES et al., 1969; TILSON and SPARBER, 1973), head twitching (CORNE and PICKERING, 1967) and interference with nest-building behavior of mice (SCHNEIDER and CHENOWETH, 1970), and the development of bizarre action patterns in cats (BENINGTON et al., 1958; JACOBS et al., 1977). None of these behavior patterns can be reasonably associated with the subtle effects of these drugs in man. An instructive example is the measure of psychotomimetic drugs on the body temperature of rabbits. In rectal hyperthermia measurements, a positive correlation between body temperature and psychotomimetic potency has been found to encompass drugs varying widely in chemical type, from the least potent (mescaline) to the most potent (LSD) (ALDOUS et al., 1974). Two recent critical analyses of these several behavioral systems (SILVA and CALIL, 1975; KUHN et al., 1977) have discussed their limited value.

A final weakness of many of these in vivo studies is that the level of drug used is often near a lethal dose for the species in question, and the responses observed may well be compounded by changes in the vital processes themselves.

The most reliable measure of the psychotomimetic character of a drug, but the most difficult to obtain, comes from clinical studies on human subjects. These are both ethically and legally difficult to perform. The ethical considerations involve the necessity of enlisting normal volunteers in good mental health, who must consent to a study wherein there will certainly be some disruption of this "normal" status. The classic requirements of a double-blind study, i.e., that the capsule with the active drug and the subject to whom it is given should be unknown to both the subject and the experimenter, are inapplicable. When the expected actions are those that embrace subtleties such as insight and interpretation of sensory integrity, it is obligatory to advise the subject of these possibilities, and the concept of "double-conscious" has gained acceptance (ALLES, 1959; SHULGIN et al., 1969). This implies a knowledge on the part of both the experimenter and the subject of the nature and the extent of psychological changes that might be expected. The legal complications result from the passage of statutes (at least in the United States) that effectively prohibit research with scheduled drugs (i.e., those with no recognized medical utility) in human subjects, without extensive approval and permission. New psychotomimetic drugs, those that are not legally recognized, can be studied with fewer restrictions, but the therapeutic potential of the better known materials will remain unexploited within the present structure.

III. Classification

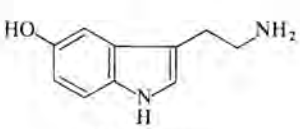
The central action of the psychotomimetic drugs requires, by definition, that they express their effects by interference with the several neurotransmitters known to be of primary importance in the regulation and function of the central nervous system. There are a number of major neurotransmitters, directly or indirectly involved in the sensory, affective, and cognitive processes, any and all of which can be shown to be interfered with during the action of a psychotomimetic drug. The highest concentrations of serotonin are found in the brain stem and the hypothalamus. Destruction

of the raphe system (rich in serotoninergic fibers) leads to sleeplessness in experimental animals, whereas the pharmacologic depletion of serotonin in the hypothalamus leads to sedation. This neurotransmitter, in these areas, appears to integrate the mechanisms that are associated with reactivity to external stimuli and that are reflected in the parasympathetic branch of the autonomic nervous system. The catecholamines, specifically dopamine and norepinephrine and to a lesser extent epinephrine, are also widely distributed in the brain, dopamine being most concentrated in the basic ganglia and norepinephrine, again largely in the hypothalamus. It is still unclear if any of these bases actually plays a primary role in neurotransmission in the brain, but certainly they act as regulators of synaptic transmission. The role of acetylcholine in the activation of cholinergic neurons is well established in brain neurochemistry, and it may well be these synaptic junctions that are modulated by the catecholamines and serotonin. GABA (γ-aminobutyric acid) has recently been accepted as a neurotransmitter playing an inhibitory role within the CNS. It, too, has agonists that will be discussed here.

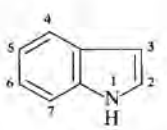
It is convenient to arrange most of the known psychotomimetics into groups that appear to be chemically related to each of these neurotransmitters. It is appealing to think that each psychotomimetic drug might have some particular selectivity for the transmitter that it resembles (i.e., LSD for serotonin, both indoles; and mescaline for dopamine, both phenethylamines), but research has not allowed any such simple explanation of activity. Total brain biochemistry is an intricate interbalance of many neuronal amines working in concert, and it is this homeostasis that is disrupted by the administration of a psychotomimetic drug. In this chapter, the various psychotomimetics will be grouped on the basis of a resemblance of their structures to those of the neurotransmitters, but there should be no inference that these natural hormones are specifically or uniquely involved in the mechanism of action. These mechanisms, in the present state of pharmacology, are still largely unknown.

B. Psychotomimetics Structurally Related to Serotonin

Serotonin (1) contains an indole nucleus (2), which is substituted on the 3-position with a β-aminoethyl side chain, and on the 5-position with a hydroxyl group. The parent base of serotonin is tryptamine [(3-β-aminoethyl)indole] (3), and this structural moiety is found in a large number of psychotomimetic drugs. These will be presented



(1) Serotonin

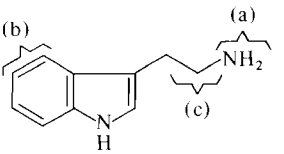


(2) Indole

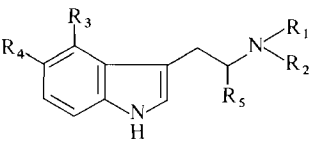
in three subgroups: those that are indoles with chemical modifications on the chain nitrogen and/or on the aromatic ring; those that have the β-aminoethyl group brought into the form of a third ring system; and those that contain yet additional rings and structural complexity.

I. Indoles

All of the psychotomimetic indoles are substituted derivatives of tryptamine (3) with substituents located at one or more of the following locations: the aliphatic nitrogen, the aromatic ring, or the aliphatic chain α-position. These are indicated as areas (a), (b), and (c) in (3). Several drugs are known to be substituted in more than one location.



(3) Tryptamine



(4) Substituted tryptamine

1. Nitrogen-Substituted Tryptamine Derivatives

The *N*-substituted tryptamines that are known to be psychotomimetic are listed in Table 1. All are symmetrically disubstituted with aliphatic groups, and all are of approximately the same potency, active in man at between 60 and 100 mg. The simplest member, *N*,*N*-dimethyltryptamine (DMT, 4a) is known in nature, being a major alkaloid in a number of New World snuffs. It is rapidly deaminated in vivo following oral administration and so must be used parenterally or in admixture with an effective deaminase enzyme inhibitor. It has an unusually rapid onset of action (apparent within a minute or two following smoking or injection), and the effects are largely dissipated within an hour of administration. The diethyl homologue (DET, 4b) is slightly longer lived in action, and the higher homologues (4c, 4d, 4e) are separate in that they are active orally. DPT (4c) is of potential clinical use due to its rather abrupt termination of effect (Grof et al., 1973).

2. Ring-Substituted Tryptamine Derivatives

Psychotomimetic tryptamine derivatives are known in which there are oxygen substituents at either position 4 or position 5 of the indole nucleus, and in most cases the basic amine function is dialkylated.

The tryptamine analogues with an oxygen function in the 4-position of the indole ring (4f–4k) are all orally active and appreciably more potent than the parent refer-

Table 1. Nitrogen-substituted tryptamines (4) R_3, R_4, R_5 = H

Compound	R_1	R_2	Potency relative to DMT = 1	Reference
4a DMT	CH_3	CH_3	1	Szara (1956)
4b DET	CH_2CH_3	CH_2CH_3	1	Szara (1957)
4c DPT	*n*-C_3H_7	*n*-C_3H_7	1	Faillace et al. (1967) Soskin et al. (1973)
4d DIPT	*i*-C_3H_7	*i*-C_3H_7	1.5	Shulgin (1976)
4e	$CH_2CH=CH_2$	$CH_2CH=CH_2$	1	Szara and Hearst (1962)

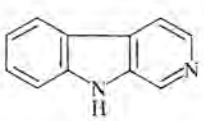
ence compound DMT (4a). The simplest of these, psilocin (4f) is a naturally occurring hallucinogenic component of the many "magic" mushrooms of the western hemisphere (HEIM and WASSON, 1962) where it is found to a large measure as the phosphate ester, psilocybin (4g). The two bases are approximately equivalent, both stoichiometrically and qualitatively in man, implying that dephosphorylation occurs metabolically. The demethylated homologues of psilocybin (*N*-monodemethyl, baeocystin; *N*-didemethyl, norbaeocystin) are reported congeners of psilocybin in several hallucinogenic species of mushroon (LEUNG and PAUL, 1967, 1968), but they are unexplored pharmacologically.

When the indolic oxygen function is located at the 5-position, the drugs become subject to the loss of the dimethylamino group by deamination (as with the simpler tryptamines) and thus are only active parenterally. 5-Methoxy-*N*,*N*-dimethyltryptamine (4l) is found as a component of several snuff mixtures used by Indians in the New World. It has a remarkably rapid onset of action and a short duration (the entire intoxication cycle lasts perhaps 15 min). The analogue of 4l without the methyl group on the 5-position oxygen is a natural alkaloid known as bufotenine (4, R_1,R_2 = CH_3; R_3,R_5 = H; R_4 = OH). This drug has been claimed to be psychotomimetic (FABING and HAWKINS, 1956), but it is now known to be a cardiovascular stimulant involving serotonin release (TURNER and MERLIS, 1959; ISBELL, 1967; FISCHER, 1968). The increase of bulk of the substituents on the terminal nitrogen seen in 4m again allows oral activity, as seen in the tryptamine counterparts in Table 2.

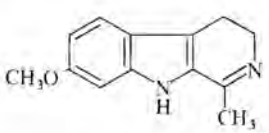
A second structural manipulation can be employed to protect the basic nitrogen from enzymatic deamination: the introduction of a methyl group alpha. This device is examined in more detail in Sect. C in the comparison of the phenethylamine and amphetamine structures. Within the tryptamines, α-methylation allows oral activity with the two psychotomimetics 4n and 4o.

II. Beta-Carbolines

The β-carboline ring system (5) has a great potential significance in brain biochemistry, as it can be synthesized in vitro under physiologic conditions from various natural tryptamines.



(5) β Carboline



(6) Harmaline

Cyclization of biologic tryptamines can occur with formaldehyde or acetaldehyde to form tetrahydro-β-carbolines (called tryptalines), which are potent serotonin uptake inhibitors (KELLER et al., 1976) and monoamine oxidase inhibitors (MELLER et al., 1977). These products can be formed simply by the incubation of mammalian tissue (e.g., from the brain) with 5-methyl tetrahydrofolic acid as the source of formaldehyde (HSU and MANDELL, 1975; WYATT et al., 1975). Also, melatonin (5-methoxy-*N*-acetyltryptamine, a serotonin-derived natural hormone found in the pineal body) can be cyclized under physiologic conditions to form the biologically active carboline 6-methoxyharmalan (MCISAAC, 1961). A number of these "in vivo"-generated bases are

Table 2. Ring-substituted tryptamines (4)

Compound	R_1	R_2	R_3	R_4	R_5	Potency relative to DMT = 1	Reference
4f Psilocin	$-CH_3$	$-CH_3$	$-OH$	H	H	8	WOLBACH et al. (1962)
4g Psilocybin	$-CH_3$	$-CH_3$	$-OPO_3H_2$	H	H	6	DELAY et al. (1959) RINKEL et al. (1960)
4h CZ-74	$-C_2H_5$	$-C_2H_5$	$-OH$	H	H	8	LEUNER and BAER (1965)
4i CEY-19	$-C_2H_5$	$-C_2H_5$	$-OPO_3H_2$	H	H	6	LEUNER and BAER (1965)
4j	$-CH_3$	*i*-C_3H-	$-OH$	H	H	8	REPKE and SHULGIN (1979)
4k 4-OH-DIPT	*i*-C_3H-	*i*-C_3H-	$-OH$	H	H	4	REPKE and SHULGIN (1979)
4l 5-MeO-DMT	$-CH_3$	$-CH_3$	H	$-OCH_3$	H	10	SHULGIN and NICHOLS (1978)
4m 5-OCH_3-DIPT	*i*-C_3H-	*i*-C_3H-	H	$-OCH_3$	H	10	SHULGIN and CARTER (1977)
4n Monase-M	H	H	H	H	$-CH_3$	3	HOLLISTER et al. (1960) MURPHREE et al. (1960)
4o DMS	H	H	H	$-OCH_3$	$-CH_3$	20	SHULGIN and NICHOLS (1978)

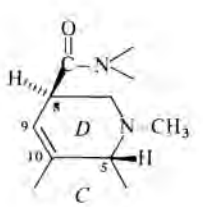
believed to be psychotomimetic agents, but efforts to document them as being endogenous factors in mental illness have failed.

The only β-carboline that has been extensively studies in man as a psychotomimetic agent is harmaline (6). It is the major active alkaloid found in the intoxicating South American drink *ayahuasca*, made from plants of the genus *Banisteriopsis*. As a pure chemical, harmaline is active in man at the 300–400 mg level, leading in many subjects to elaborate visual synthesis (NARANJO, 1973a), although in others there is little more than a generalized sedation. A second pharmacologic property of harmaline is that it is an effective inhibitor of the monoamine oxidase enzyme system (UDENFRIEND et al., 1968). Dimethyltryptamine (4a), which is normally inactive when given orally in man, is frequently found in *Banisteriopsis* extracts (POISSEN, 1965; AGURELL et al., 1968; DER MARDEROSIAN et al., 1968). Thus, the biologic activity of the native plant decoction may be due in large part to DMT that is protected from metabolic destruction by the presence of a relatively small amount of harmaline, itself without activity.

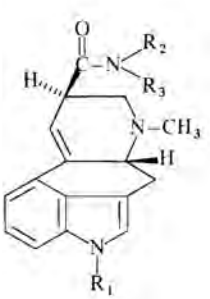
Several other substituted β-carbolines have been studied in man. Harmine [the completely aromatic counterpart of (6)] is inactive orally at levels of 1 g (PENNES and HOCH, 1957), but upon intravenous administration there are effects observed with doses of less than 50 mg (SLOTKIN et al., 1970). Limited studies (NARANJO, 1967) have been reported concerning the dihydroderivative of (6) (tetrahydroharmine) and the positional isomer of (6) in which the methoxyl is relocated into the position analogous to that found with serotonin (6-methoxy-harmalan); the former appears to be less active and the latter more active than harmaline itself.

III. Ergot-Related Drugs

All of the known psychotomimetic drugs that contain the alkaloid nucleus ergoline have a consistent structural feature of a carboxamide function at the 8-position and dehydration at the 9,10 position (see partial structure 7). The activity of this class of compounds is extremely sensitive to minor structural variations in this ring. Inversion of the hydrogen at the 5-position (to yield the isolysergic acid family), at the 8-position (to yield the L-lysergic acid family), and saturation of the 9,10-double bond (with hydrogen or solvent) all effectively eradicate the psychotomimetic properties of the product. Hydrogenation of the indolic double bond (to give 2,3-dihydro-LSD) reduces the potency by an order of magnitude (GORODETZKY and ISBELL, 1964). Although most of the better studied drugs are synthetic, they depend upon the use of lysergic acid as a starting material, and it must be obtained from natural sources.



(7)
Ring D of the ergot alkaloids



(8)

1. Synthetic Lysergic Acid Derivatives

The best studied of the synthetic ergot derivatives, and one of the most potent psychotomimetics yet reported, is the diethylamide, LSD (8, $R_1 = H$; $R_2 = R_3 = C_2H_5$). It was originally prepared and studied in 1938 (STOLL and HOFMANN, 1943) as an ergot-related analogue of the medullary stimulant nikethamide (*N,N*-diethylnicotinamide). Its intense psychological effectiveness was discovered 5 years later. Its extremely high potency (50–250 μg, given orally) and the complexity and richness of the evoked response have prompted widespread experimentation. In the scientific community, its initial description as producing a model psychosis commanded the attention of researchers in the area of mental health. In the lay community, its fast-spreading reputation as a hallucinogenic drug quite literally ushered in the psychedelic era. There is a greater volume of literature – scientific, philosophic, and fictional – on this one material than on any other psychotomimetic drug.

The destructive effects of structural modification within the "D" ring mentioned above apply to LSD itself as well. However, substitution on the indolic nitrogen (1-position) or modifications of the identities of the amide nitrogen substituents can result in the maintenance of psychotomimetic activity albeit with some attenuation of potency. Table 3 lists these variations and their approximate potencies relative to LSD. Most of the homologues are less active than LSD, several are of similar potency, and none are of higher potency. Two of the listed compounds are pharmaceutical drugs: ergonovine (8k, ergometrine) is used clinically as a uterine contractant, and methysergide (Sansert, 8l) is popular as a prophylactic against migraine. The latter drug has shown side effects in clinical use similar to those seen with LSD, and the material has been employed as an LSD substitute in psychotherapeutic LSD therapy. The 2-bromo analogue of LSD (BOL-148) is of considerable pharmacologic interest, having served as a continuing challenge to proposed mechanisms of action in this family of drugs. It is even more potent than LSD as a serotonin antagonist (CERLETTI and ROTHLIN, 1955), but it is practically devoid of psychotomimetic activity (HOFMANN, 1959).

2. Natural Lysergic Acid Derivatives

A number of higher plants, largely of the family Convolvulaceae, are also sources of alkaloids of the lysergic acid family and have been employed as intoxicants. Three morning glory species are especially rich in centrally active bases and have proven active orally in man as psychotomimetics. The Aztec drug ololiuqui has been established botanically as *Rivea corymbosa* (SCHULTES, 1941). The Zapotecs employ, in addition to ololiuqui, a similar plant known as *badoh negro* which is the closely related morning glory *Ipomoea violacea* (MADDOUGALL, 1960); most of the many *Ipomoea* subspecies are, however, devoid of alkaloids (DER MARDEROSIAN and YOUNGKEN, 1966). The third plant of this group, and the richest yet known in alkaloid content, is the Hawaiian baby wood rose, *Argyeia nervosa*. Of the large number of alkaloids present in these species, the ones believed to account for the plants' activities are lysergamide (Ergine, 8r) and the epimer with opposite configuration at the 8-position, isolysergamide. As a pure compound, isolysergamide produces a depressed and sedative effect at dosages of 2 mg (HOFMANN, 1963). The labile hydroxyethyl amides of these two bases are also present and might give rise by hydrolysis to the free amides. Ergonovine (8k) is also present in small amounts and may contribute to the activity as well. The

Table 3. Lysergic acid amide derivatives (8)

Compound	R_1	R_2	R_3	Potency relative to LSD = + + + +[a]	Reference
8a LSD-25	H	$-CH_2CH_3$	$-CH_2CH_3$	+ + + +	
8b ALD-52	$-COCH_3$	$-CH_2CH_3$	$-CH_2CH_3$	+ + + +	Abramson (1959)
8c OML-632	$-CH_2OH$	$-CH_2CH_3$	$-CH_2CH_3$	+ + +	Abramson (1959) Cerletti (1959)
8d MLD-41	$-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	+ + +	Abramson (1959)
8e LAE-32	H	$-CH_2CH_3$	H	+ +	Rothlin (1957)
8f ALA-10	$-COCH_3$	$-CH_2CH_3$	H	+	Usdin and Efron (1972a)
8g MLA-74	$-CH_3$	$-CH_2CH_3$	H	+	Usdin and Efron (1972b)
8h LPD-824	H	$-CH_2CH_2CH_2CH_2-$		+ +	Murphree et al. (1958) Cerletti (1959)
8i MPD-75	$-CH_3$	$-CH_2CH_2CH_2CH_2-$		+	Usdin and Efron (1972c)
8j LSM-775	H	$-CH_2CH_2OCH_2CH_2-$		+ + +	Gogerty and Dille (1957)
8k	H	$-CH(CH_2OH)CH_3$	H	+	Bigwood et al. (1979)
8l UML-491	$-CH_3$	$-CH(CH_2OH)CH_2CH_3$	H	+	Abramson and Rolo (1967)
8m	H	$n-C_3H_7$	$n-C_3H_7$	+ +	Hofmann (1959)
8n LEP	H	$n-C_3H_7$	$-CH_2CH_3$	+ + +	Abramson and Rolo (1967)
8o LMP	H	$n-C_3H_7$	$-CH_3$	+	Abramson and Rolo (1967)
8p LME	H	$-CH_2CH_3$	$-CH_3$	+	Abramson and Rolo (1967)
8q DAM-57	H	$-CH_3$	$-CH_3$	+ +	Abramson (1959) Cerletti (1959)
8r LA-111	H	H	H	+	Hofmann (1963)

[a] Each loss of a + indicates the loss of a half order of magnitude of potency

Table 4. Components of the psychotomimetic convolvulaceae[a]

Compound	*Rivea corymbosa* %	*Ipomoea violacea* %	*Argyrea nervosa* %
Lysergamide (8r)	48 (a) 54 (b)	5–50 (a)[b] 58 (b) 10–16 (c)[b]	23 (d) 25 (c)
1-Hydroxyethyl lysergamide	[c]	[c]	6 (d)
Isolysergamide	17 (b) 35 (a)	9–17 (a) 18–26 (c) 8 (b)	18 (c) 31 (d)
1-Hydroxyethyl isolysergamide	[c]	[c]	4 (d)
Ergonovine (8k)		8 (b)	8 (d)
Total alkaloid content (wet weight)	0.012 (b)	0.06 (a, b)	0.3 (c)

[a] Reference: (a) GENEST (1965); (b) HOFMANN (1971); (c) HYLIN and WATSON (1965); (d) CHAO and DER MARDEROSIAN (1973)

[b] Range covering several varieties of *I. violacea*

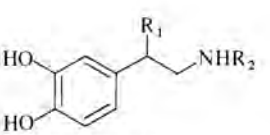
[c] Possibly hydrolysed to lysergamide or isolysergamide during analysis. See HOFMANN (1971)

alkaloid composition of these three morning glories, insofar as these potentially contributing components are concerned, is given in Table 4. Most of the remaining alkaloids lack the 8-position carboxyl group, or even an intact piperidine ring, and have not been evaluated as psychotomimetic agents.

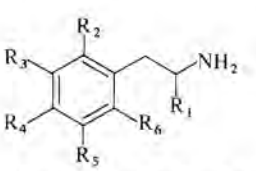
C. Psychotomimetics Structurally Related to Dopamine

I. Phenethylamines

Dopamine (9a) is the simplest of the catecholamine neurotransmitters and serves also as the metabolic precursor of the related compounds norepinephrine (noradrenalin, 9b) and epinephrine (adrenalin, 9c). These bases carry the carbon skeleton of phenethylamine (10) which is itself naturally present in human tissue (ASATOOR and DALGLEISH, 1959), including the brain (BORISON et al., 1977). The variability of its concentration in urine reflects clinical diagnosis (decreased in depression, FISCHER et al., 1973; increased in schizophrenics, POTKIN et al., 1979) and suggests that it may play a role as an endogenous stimulant. When administered exogenously, it is readily in-



(9a) $R_1 = R_2 = H$
Dopamine
(9b) $R_1 = OH$; $R_2 = H$
Norepinephrine
(9c) $R_1 = OH$; $R_2 = CH_3$
Epinephrine



(10) $R_1, R_2, R_3, R_4, R_5, R_6 = H$
Phenethylamine

activated by the ubiquitous monoamine oxidase (MAO), and it is only with extensive ring substitution that the phenethylamines become centrally active. The best-studied phenethylamine psychotomimetic is mescaline (10a, $R_1=R_2=R_6=H$; $R_3=R_4=R_5=OCH_3$), which is itself immune to deamination by the MAO system. It and related phenthylamines are listed in Table 5, with comparisons of their relative potencies in man. Most of these materials have had their origin in the established activity of the phenylisopropylamine counterparts, which will be discussed in the next section.

It is apparent that no compounds with less than trisubstitution are centrally active, presumably due to rapid deamination in vivo. The mono-methoxy analogue 4-methoxyphenethylamine is inactive (BROWN et al., 1968), and the dimethoxy analogue similar to dopamine appears to be a mild stimulant but only at the rather high dosage of 1,500 mg (VOJTECHOVSKY and KRUS, 1967). This latter compound, because of its close resemblance to dopamine and its possible appearance in the urine of schizophrenic subjects (FRIEDHOFF and VAN WINKLE, 1962), has been thoroughly studied in its possible role in mental health. There is as yet no consensus as to its origins or its significance in the body. Two positional isomers of mescaline have been studied, but they appear to be of limited activity. The 2,3,4-isomer, "reciprocal" or "iso" mescaline, has been reported to be inactive in normal subjects, but highly potent in schizophrenic patients (SLOTTA and MÜLLER, 1936). The 2,4,5-isomer, which bears the substitution pattern of the potent neurotoxin 6-hydroxydopamine, has been reported as being similar to mescaline (JANSEN, 1931), but recent work suggests that its only indication of central availability is the potentiation of the action of mescaline (DITTRICH, 1971).

II. Phenylisopropylamines

As discussed above, an appropriate ring-substitution pattern can protect a phenethylamine derivative from desctructive metabolism by MAO deamination. A second structural modification has been frequently employed to this same end, i.e., the placement of a sterically hindering methyl group on the carbon alpha to the primary amine. Thus, amphetamine (10; $R_1=CH_3$, $R_2,R_3,R_5,R_6=H$) is a long lived and little metabolized stimulant, whereas phenethylamine, of intrinsically similar potency, is relatively inactive when administered orally. A large family of psychotomimetic drugs is known which are ring-substituted derivatives of amphetamine. These are presented in Table 6, with their potency relative to mescaline, and with appropriate leading references. There are some generalities that are not apparent from the table. The mono- and disubstituted isomers show, in addition to psychotomimetic action, considerable central stimulation. PMA (10i), although active as a hallucinogen at 60–80 mg, has been implicated in fatal overdoses involving cardiovascular stimulation (CIMBURA, 1974). DMA (10l), upon intravenous administration, elicits extensive visual distortion complicated by gross body tremor (FAIRCHILD, 1963). Several of these substituted amphetamine analogs have been studied as their *N*-methyl homologues (in analogy with the relationship between amphetamine and methamphetamine). Although most show a striking drop in potency, MDMA (the *N*-methyl homologue of MDA, 10 m) retains full activity (SHULGIN and NICHOLS, 1978). Referring to Table 6, it is apparent by comparing compounds 10p, 10q, and from 10dd to 10nn, that the 2,4,5-trisubstitution pattern is needed for maximum potency, and that there is a great sensitivity to

Table 5. Substituted phenethylamines (10) (with $R_1 = H$)

Compound	R_2	R_3	R_4	R_5	R_6	Potency relative to mescaline (10a = 1)	Reference
10a Mescaline	H	OCH_3	OCH_3	OCH_3	H	1	BERINGER (1927)
10b Escaline	H	OCH_3	OCH_2CH_3	OCH_3	H	6	BRAUN et al. (1978)
10c Proscaline	H	OCH_3	$OCH_2CH_2CH_3$	OCH_3	H	6	BRAUN et al. (1978)
10d 2-CD	OCH_3	H	CH_3	OCH_3	H	20	SHULGIN and CARTER (1975)
10e 2-CB	OCH_3	H	Br	OCH_3	H	30	SHULGIN and CARTER (1975)
10f 2-CI	OCH_3	H	I	OCH_3	H	30	SHULGIN (1979)
10g 2-CE	OCH_3	H	CH_2CH_3	OCH_3	H	20	SHULGIN (1979)
10h 4-Thiomescaline	H	OCH_3	SCH_3	OCH_3	H	10	BRAUN et al. (1978)

Table 6. Substituted phenylisopropylamines (10) (with $R_1 = CH_3$)

Compound	R_2	R_3	R_4	R_5	R_6	Potency relative to mescaline (10a = 1)	Reference
10i PMA	H	H	OCH_3	H	H	6	SHULGIN et al. (1969)
10j 2,4-DMA	OCH_3	H	OCH_3	H	H	6	SHULGIN (1978)
10k 2,5-DMA	OCH_3	H	H	OCH_3	H	6	SHULGIN (1978)
10l DMA	H	OCH_3	OCH_3	H	H	1	FAIRCHILD (1963)
10m MDA	H	OCH_2O—		H	H	3	NARANJO et al. (1967) TUREK et al. (1974) YENSEN et al. (1976)
10n TMA	H	OCH_3	OCH_3	OCH_3	H	2	PERETZ et al. (1955) SHULGIN et al. (1961)
10o	H	OCH_3	$OCH_2\Phi$	OCH_3	H	2	SHULGIN (1978)
10p TMA-2	OCH_3	H	OCH_3	OCH_3	H	20	SHULGIN (1964a)

Table 6 (continued)

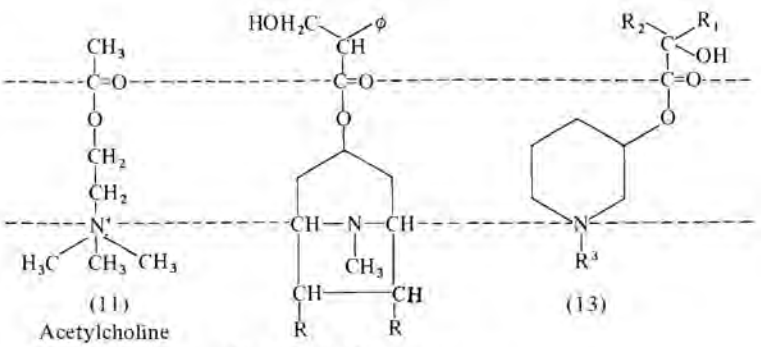
Compound		R_2	R_3	R_4	R_5	R_6	Potency relative to mescaline (10a = 1)	Reference
10q	MEM	OCH_3	H	OCH_2CH_3	OCH_3	H	20	SHULGIN (1978)
10r	TMA-3	OCH_3	OCH_3	OCH_3	H	H	< 2	SHULGIN (1964a)
10s	TMA-4	OCH_3	OCH_3	H	OCH_3	H	4	SHULGIN et al. (1969)
10t	TMA-5	OCH_3	OCH_3	H	H	OCH_3	10	SHULGIN et al. (1969)
10u	TMA-6	OCH_3	H	OCH_3	H	OCH_3	10	SHULGIN et al. (1969)
10v	MMDA	H	OCH_3	$-OCH_2O-$		H	3	SHULGIN (1964b) SHULGIN et al. (1973)
10w	MMDA-2	OCH_3	H	$-OCH_2O-$		H	10	SHULGIN (1964a)
10x	MMDA-3a	OCH_3	$-OCH_2O-$		H	H	10	SHULGIN (1964a)
10y	MMDA-3b	$-OCH_2O-$		OCH_3	H	H	3	SHULGIN (1964a)
10z	MMDA-5	$-OCH_2O-$		H	H	OCH_3	10	SHULGIN (1978)
10aa		OCH_3	OCH_3	OCH_3	OCH_3	H	6	SHULGIN et al. (1969)
10bb	DMMDA	OCH_3	$-OCH_2O-$		OCH_3	H	12	SHULGIN and SARGENT (1967)
10cc	DMMDA-2	OCH_3	OCH_3	$-OCH_2O-$		H	5	SHULGIN and SARGENT (1967)
10dd	p-DOT (Aleph-1)	OCH_3	H	SCH_3	OCH_3	H	40	SHULGIN and NICHOLS (1978)
10ee	Aleph-2	OCH_3	H	SCH_2CH_3	OCH_3	H	80	SHULGIN (1978)
10ff	Aleph-4	OCH_3	H	SPr (*i*)	OCH_3	H	40	SHULGIN (1980)
10gg	Aleph-7	OCH_3	H	SPr (*n*)	OCH_3	H	60	SHULGIN (1980)
10hh	DOM(STP)	OCH_3	H	CH_3	OCH_3	H	80	SNYDER et al. (1967)
10ii	DOET	OCH_3	H	CH_2CH_3	OCH_3	H	100	SNYDER et al. (1968)
10jj	DOPR	OCH_3	H	Pr (*n*)	OCH_3	H	80	SHULGIN and DYER (1975)
10kk	DOBU	OCH_3	H	Bu (*n*)	OCH_3	H	40	SHULGIN and DYER (1975)
10ll	DOAM	OCH_3	H	Am (*n*)	OCH_3	H	10	SHULGIN and DYER (1975)
10mm	DOB	OCH_3	H	Br	OCH_3	H	400	SHULGIN et al. (1971)
10nn	DOI	OCH_3	H	I	OCH_3	H	400	SHULGIN (1978)

the identity of the substituent on the 4-position. This consistency has suggested a mechanism of action involving in vivo oxidation to a quinonoid intermediate to, in turn, some subsequent indole metabolite (ZWEIG and CASTAGNOLI, 1974, 1975).

Several of these racemic bases have been studied as separated optical isomers. The observation that the "R" isomer of DOM (10hh) can account for most of the psychotomimetic activity (SHULGIN, 1973) is consistent with this same absolute configuration being required for the 5-carbon of LSD, whereas the active isomer of amphetamine (a stimulant rather than a psychotomimetic) is the "S" isomer. This generality applies to the other primary amines studied as separated isomers (10m, 10ii, and 10mm) (COOK and FELLOWS, 1961; SNYDER et al., 1974; ANDERSON et al., 1978). The only known active *N*-methyl derivative (MDMA; see above) has a reversal of activity, the "S" isomer being the more active (ANDERSON, 1978).

D. Psychotomimetics Structurally Related to Acetylcholine: Atropine-Related Drugs

The third major neurotransmitter in the human nervous system is acetylcholine (11), and a number of psychotomimetics are known that are closely related to this compound structurally.



(11)
Acetylcholine

(12a) R = H, H; Atropine
(12b) R = –O– ; Scopolamine

(13)

These compounds are based upon the structure of atropine (12a) and scopolamine (12b) (both potent inhibitors of acetylcholine) and, as shown in the diagram, they bear structural points in common with it (the distance of separation of the nitrogen atom from the ester carbonyl function). These two natural alkaloids have proven to be the active components of many plants from around the world renowned for centuries for their mystical powers. The belladonna plant, *Atropa belladonna*, was used in Europe in the Middle Ages as a witch's brew. Henbane, *Hyoscyamus niger*, was also widely cultivated in Europe (as was mandrake, *Mandragora officinarum*), and from this name come the alkaloidal names hyoscyamine and hyoscine (for 12a and 12b, respectively). Pituri, *Duboisia hopwoodii*, has been used broadly by the Australian aborigines, and many species of *Datura* have been used for centuries in the New World for religious purposes and as stupefacients.

The intoxication produced by these alkaloids, and the chemical relatives listed in Table 7, is distinctly different than that characteristic of the serotonin- and dopamine-related psychotomimetics already discussed. There are peripheral changes (dry mouth, nonreflexive pupillary dilation, urinary retention, tachycardia, muscular weakness) characteristic of parasympatholytic activity. Centrally, the hallucinations are usually clouded in amnesia, and there is intellectual impairment and confusion, often incoherence.

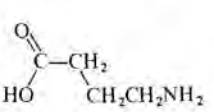
Table 1 lists several compounds that do not strictly follow the generalized formula (13). Atropine and scopolamine are with the structures drawn above. Benactyzine (13a) and Win-2299 (13j) are both open-chain compounds, esters of *N,N*-diethylaminoethanol with diphenylglycolic acid and thionyl cyclohexylglycolic acid, respectively. Ditran (JB-329, 13h) is actually a mixture of the listed piperidinyl compound and the ring-contracted pyrrolidinylmethyl analogue. And finally, the last-mentioned compound 13m, quinuclidinyl benzilate, has as the nitrogen substituent a two-carbon chain folded back to the 4-position of the piperidine to form the quinuclidine ring. This anticholinergic has been studied extensively in the chemical warfare research laboratories of several countries as an incapacitating agent. The potency given in the table is for a subcutaneous injection.

E. Miscellaneous Psychotomimetics

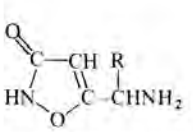
I. Ibotenic Acid

Another chemical implicated in normal neurologic function, in this case as an inhibitory transmitter, is the aliphatic amino acid γ-aminobutyric acid (GABA, 14) (see IVERSEN, 1978). The historic mushroom *Amanita muscaria* (fly agaric) contains a number of pharmacologically active alkaloids. Two of these, ibotenic acid (15a) and muscimol (15b), are potent GABA agonists and are believed to account for most of the psychopharmacologic action of the intact mushroom, including disorientation and deep sleep. Ibotenic acid, at lower dosages (up to 50 mg) leads only to facial flushing (WASER, 1967), a generalized weakness, and disequilibrium (CHILTON, 1975).

Moderately effective dosages appear to approach 100 mg (CHILTON, 1975), with considerable motor disturbance and the promotion of a deep sleep. Muscimol is some five times more potent in man (THEOBALD et al., 1968), producing, in the 10–15 mg range, dizziness, elevated mood, and sensory distortions in both vision and sound perception (WASER, 1967). Again, sedation and a generalized intoxication seem to characterize both the mushroom and the active components, rather than the more expected psychotomimetic responses seen with psilocybin or the ergot alkaloids (THEOBALD et al., 1968). The several analogues of muscimol that have been studied as effective GABA agonists have not yet been clinically assayed in man as either intoxicants or sedatives.



(14) GABA



(15a) R = COOH Ibotenic acid
(15b) R = H Muscimol

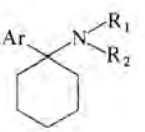
Table 7. Anticholinergic psychotomimetics (13)

Compound	R_1	R_2	R_3	Effective dose range (mg)	Reference
12a Atropine[a]				10 15	KETCHUM et al. (1973)
12b Scopolamine[a]				1 4	KETCHUM et al. (1973)
13a Benactyzine[a]	Phenyl	Phenyl	Ethyl	50 200	VOJTĚCHOVSKÝ et al. (1958)
13b JB-841	Phenyl	Phenyl	H	> 20	ABOOD et al. (1959a)
				> 100	ABOOD et al. (1959b)
13c JB-18	Phenyl	Phenyl	Allyl	> 20	ABOOD et al. (1959a)
13d JB-868	Phenyl	Phenyl	$(CH_2)_2NHNMe_2$	> 20	ABOOD et al. (1959a)
13e JB-344	Phenyl	Thionyl	CH_3	10 20	ABOOD et al. (1959b)
13f JB-318	Phenyl	Phenyl	Ethyl	10– 20	OSTFELD et al. (1958)
					ABOOD (1968)
13g JB-851	Phenyl	Phenyl	$(CH_2)_2NMe_2$	> 10	ABBOD et al. (1959b)
13h JB-329[a] (Ditran)	Phenyl	Cyclopentyl	Ethyl	10	ABOOD et al. (1959b)
13i JB-840	Phenyl	Cyclohexyl	CH_3	10	ABOOD et al. (1959b)
13j Win-2299[a]	Thionyl	Cyclohexyl	Ethyl	5- 10	PENNES and HOCH (1957)
13k JB-328	Phenyl	Cyclohexyl	Ethyl	5 - 10	ABOOD et al. (1959b)
13l JB-336	Phenyl	Phenyl	CH_3	5 10	ABOOD (1968)
13m QB, BZ[a]	Phenyl	Phenyl		0.2	SCHALLEK and SMITH (1952)

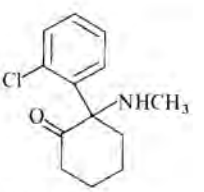
[a] Does not follow the generalized formula; see text

II. Dissociative Anesthetics

Two clinically useful anesthetics have recently come into popular acceptance as psychotomimetic drugs. Pharmacologically, phencyclidine (16a) and ketamine (17) are best classified as parasympatholytics akin to scopolamine and the related JB compounds. Structurally, they are distinct, being extremely lipophilic benzyl amines. Two properties of phencyclidine have contributed to its rapidly increasing popularity: its relatively high potency (5–10 mg), regardless of the route of administration (orally, smoking, injection), and the ease of its synthesis. The social problems associated with its abuse have prompted extensive federal action, both in research (PETERSEN and STILLMAN, 1978) and in legislation. Its original promise as a powerful anesthetic (CHEN et al., 1959) was compromised by bizarre symptoms of delusional and sensorially distorted interpretations upon postoperative recovery (GREIFENSTEIN et al., 1958; JOHNSTONE et al., 1959). It has been just these latter properties that have popularized the drug. The facile synthesis has prompted the exploratory synthesis of numerous analogues, partly to circumvent the law and partly to exploit more readily obtainable starting materials. The thiophene analogue (16b) is easily prepared (KALIR et al., 1969) and has appeared as an illegal drug in street usage. Similarly, the *N*-ethyl analogue (16c, PCE, SMIALEK et al., 1979) and the pyrrolidine analogue (16d, PHP, NAKAMURA et al., 1979) have both been involved in deaths.



Ar	R_1	R_2	
(16a) Phenyl	$-(CH_2)_5-$		Phencylidine (PCP)
(16b) Thiophene	$-(CH_2)_5-$		Thiophene analogue of phencyclidine (TCP)
(16c) Phenyl	ethyl	H	Cyclohexamine (PCE)
(16d) Phenyl	$-(CH_2)_4-$		Pyrrolidine analogue of phencyclidine (PHP)



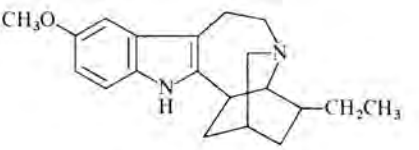
(17) Ketamine

Ketamine (17) is a structural analogue of phencyclidine that has been introduced to bypass some of the limitations of phencyclidine, and it appears clinically effective, although less potent (DOMINO et al., 1965). However, the recovery period was again flawed by bizarre hallucinatory experiences (FINE and FINESTONE, 1973; PEREL and DAVIDSON, 1976). The drug may have a dubious future in clinical practice, but it has appeared broadly in paramedical usage. Its complex synthesis will require that the supply come from diverted legitimate channels; analogues are not likely to appear soon.

III. Ibogaine

Ibogaine (18) is one of the principal alkaloids isolated from the root and bark of the African plant *Tabernanthe iboga*. It has cholinesterase inhibitory properties (VINCENT

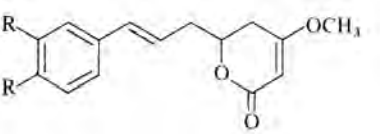
and SERO, 1942) reminiscent of those mentioned for a similarly complex plant alkaloid harmaline, and its hallucinatory actions, with anxiety and apprehensions (SCHNEIDER and SIGG, 1958), seem to be parallel. A recent report of extensive clinical studies on ibogaine (NARANJO 1973b) has supported its psychotomimetic potential, at dosages of 300 mg.



(18) Ibogaine

IV. Kavakava

Another botanical binomial known in psychotropic pharmacology is *Piper methysticum*, the source of the drug kavakava. This plant contains nonnitrogenous components, principally kawain (19a) and the methylenedioxy analogue methysticin (19b). Kavakava is used widely throughout the South Pacific as a social intoxicant. These and related isolated lactones have been studied pharmacologically as anticonvulsants (KRETZSCHMAR and MEYER, 1969) and analgetics (BRÜGGEMANN and MEYER, 1963), and there has been extensive synthetic exploration in the preparation and study

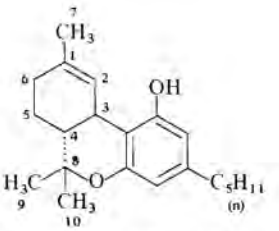


(19a) R = H, H Kawain
(19b) R = $-OCH_2-$ Methysticin

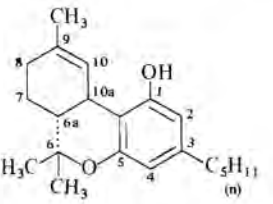
of potentially useful analogues. The results have been largely disappointing. It has been observed that the narcotic action of the native plant preparation requires emulsification of the root material (STEINMETZ, 1960), and the natural preparations employ chewing to produce an effective drink. The intrinsic activity of the plant may not be observable in the purified isolated components.

V. Marijuana

The most important and the most extensively studied of the nonnitrogenous psychotomimetics are the terpenic components of the intoxicating plant *Cannabis sativa*. This material has been known since antiquity, and although it may be misleading to classify it as a psychotomimetic drug, it has been widely employed in many forms as an intoxicant, as a therapeutic agent, and as a subtle disinhibitor of sensory stimuli. The active principles are fusion products of a 10-carbon terpene unit and (usually) 5-(*n*)-amylresorcinol. The main active component is Δ^1 (or Δ^9)-tetrahydrocannabinol (THC, 20a), which is shown in the illustration with its two frequently encountered numbering systems. The first system (terpene-based numbering) reflects the biosynthetic origin, with the numbering of the aliphatic half done in accord with classic ter-



(terpene – based numbering)



(dibenzopyran – based numbering)

(20a)

Δ^1 (Δ^9)-Tetrahydrocannabinol (THC)

pene nomenclature. It has the advantage of being applicable (and allowing easy cross-reference) to natural components wherein the pyran ring is opened, but the aromatic moiety must be numbered separately. The second system (dibenzopyran-based numbering) is based upon the intact dibenzopyran nucleus, and although it allows exact assignment in written names (in abstracting), it becomes useless when the pyran ring does not exist. Neither is satisfactory and both are (unfortunately) widely used.

Table 8. Cannabinoids (20a)

Compound	Double-bond position	Aromatic side chain	Effective dosage range in mg (route)	Reference
20a Δ^1-THC	1,2	n-C_5H_{11}	20 (o)	HOLLISTER (1973) HOLLISTER and TINKLENBERG (1973)
			5 (p)	HOLLISTER (1973) ISBELL et al. (1967)
20b Δ^6-THC	6,1	n-C_5H_{11}	20 (o)	HOLLISTER (1973)
20c CBN	Aromatic	n-C_5H_{11}	>400 (o) 15 (p)	HOLLISTER (1973) PEREZ-REYES et al. (1973)
20d Δ^3-THC	3,4	n-C_5H_{11}	120 (o) 15 (p)	ADAMS (1942) HOLLISTER (1970)
20e Pyrahexyl	3,4	n-C_6H_{13}	60 (o)	ADAMS (1942) WILLIAMS et al. (1946)
20f DMHP	3,4	$-CH(CH_3)CH(CH_3)C_5H_{11}$	5 (o)	ISBELL (1968) SIM (1970)
20g Nabilone	3,4 (carbonyl at C_1)	$-C(CH_3)_2C_6H_{13}$	5 (o)	LEMBERGER and ROWE (1975)
20h 7-OH-Δ^1-THC	1,2 (hydroxy at C_7)	n-C_5H_{11}	3 (p)	PEREZ-REYES et al. (1972)
20i 6(β)OH-Δ^1-THC	1,2 (hydroxy at C_6)	n-C_5H_{11}	4 (p)	WALL et al. (1976)

Although several dozen cannabinoid compounds are now known to be components of the intoxicating resinous extracts of the marijuana plant, only four have been seriously considered as contributors to the overall pharmacologic syndrome of intoxications. Besides Δ^1-THC there is the positional isomer Δ^6-THC (20b), the aromatic counterpart cannabinol (CBN, 20c), and the open-ring counterpart of Δ^1-THC, cannabidiol (CBD). The first three are centrally active, but cannabidiol is not, regardless of the route of administration, either oral (HOLLISTER, 1973; KARNOLL et al., 1975), smoking (ISBELL et al., 1967), or intravenous (PEREZ-REYES et al., 1973).

The published data concerning potency in humans of these natural, as well as synthetic analogues of marijuana, and on human metabilites, are gathered in Table 8. The terpene-based numbering system is employed.

In the earliest synthetic approaches to the THC molecule, the double bond in the terpene ring usually remained at the conjugated position 3,4 (6a, 10a in the dibenzopyran-based system). Three of these synthetic materials (20d, e, f) are orally active in man, the last of these carrying the dimethylheptyl side chain found to be of the greatest animal potency in the seminal studies of ADAMS. A recently proposed pharmaceutical lacks the methyl group at position C 1, possessing a carbonyl in its place. This drug, nabilone, is currently in clinical trials as a sedative. Studies on the metabolic fate of THC have shown that hydroxylation is a major pathway. This can occur on the amyl side chain, or in several locations within the terpene moiety. Two of the known human metabolites themselves have intrinsic central action (compounds 20h, i) and have been implicated in the mechanism of action of THC itself.

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