1

AMPHETAMINES: STRUCTURE–ACTIVITY RELATIONSHIPS

J. H. Biel† and B. A. Bopp

1. INTRODUCTION

Amphetamine is a unique drug with respect to the simplicity of its structure and the multiplicity of its biological effects. Pharmacologically, amphetamine possesses central stimulant, anorexic, vasoconstrictor, and hyperthermic properties. Biochemically, amphetamine releases catecholamines from the neurons and inhibits the uptake of norepinephrine and dopamine but does not affect brain serotonin levels. It also is a moderately active inhibitor of monoamine oxidase. Clinically, amphetamine has been used as a stimulant, antidepressant, and appetite suppressant, but with repeated administration tolerance frequently develops to many of its effects. On chronic administration of increasingly higher doses, amphetamine may precipitate paranoid psychosis.

Chemically, the important structural features of amphetamine include (1) the unsubstituted phenyl ring, (2) the two-carbon side chain between the phenyl ring and the nitrogen, (3) the α-methyl group, and (4) the primary amino group (Fig. 1). All these factors appear to be critical for amphetamine's characteristic spectrum of pharmacological and biochemical activities. Amphetamine has become a favorite target for extensive molecular modifications since most structural changes will accentuate some of its effects, attenuate others, or even introduce new activities not found in the parent molecule.

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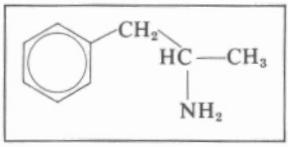


FIG. 1. Amphetamine.

2. EFFECTS ON BIOGENIC AMINES

2.1. Norepinephrine

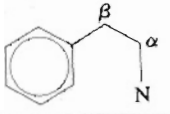
The mechanism of action of amphetamine, like that of other indirectly acting sympathomimetic amines, involves the inhibition of norepinephrine uptake and the release of the neurotransmitter. The structure–activity relationships of various sympathomimetic and related amines, including the phenethylamines and phenylisopropylamines, have been extensively investigated using the uptake of [^{14}C]norepinephrine by the isolated rat heart (Burgen and Iversen, 1965) and the *in vivo* release of [^{3}H]norepinephrine from the mouse heart (Daly *et al.,* 1966). The β-phenethylamine skeleton is a critical feature of the molecule since either increasing or decreasing the number of carbons between the phenyl ring and the nitrogen reduced or abolished the activity. Both the γ-phenylpropylamines (e.g., 1-phenyl-3-aminobutane, γ-phenylpropylamine, γ-phenyl-*N*-*N*-dimethylpropylamine) and the benzylamines (e.g., α-methylbenzylamine, *N*,*N*-diethylbenzylamine, benzylamine) were found to be inactive as releasers of norepinephrine (Daly *et al.,* 1966).

Since amphetamine is considerably more potent than phenethylamine (Table 1), the α-methyl group must at least be partially responsible for the high affinity for the norepinephrine neuronal membrane systems. The importance of the configuration of the α-methyl group can be seen in the marked difference in the activity of *d*- and *l*-amphetamine. Further methylation in the α-position to form phentermine or mephentermine greatly reduced the effects on norepinephrine uptake and release, while shifting the methyl group to the β-position abolished the ability of the compound to release norepinephrine. *N*-methylation progressively decreased the characteristic actions of the phenethylamines on the norepinephrine neuronal membrane systems. *d*-Methamphetamine was considerably less potent than *d*-amphetamine as an inhibitor of norepinephrine uptake. In the phenethylamine series, the secondary amine was less active than the primary amine as a norepinephrine releaser, while the tertiary amine was inactive.

Hydroxylation had variable effects depending on the placement of the group. Generally, side chain hydroxylation diminished the activity on norepinephrine uptake and release while hydroxylation of the phenyl ring enhanced it. The effects of β-hydroxylation are illustrated in Table 2. Phen-

TABLE I

Effects of Methylation on the Inhibition of Norepinephrine Uptake and the Release of Norepinephrine by Phenethylamines

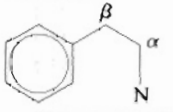


Compound	α	β	N	Uptake of NE by rat heart[a] ID_{50} (*M*)	Uptake of NE by rat heart[a] Relative affinity	Release of NE from mouse heart,[b] % control NE
Phenethylamine	—	—	—	1.1×10^{-6}	100	65
dl-Amphetamine	CH_3	—	—	4.6×10^{-7}	240	—
d-Amphetamine	CH_3	—	—	1.8×10^{-7}	610	58
l-Amphetamine	CH_3	—	—	3.7×10^{-6}	30	86
Phentermine	$(CH_3)_2$	—	—	—	—	95
d-Methamphetamine	CH_3	—	CH_3	6.7×10^{-7}	165	62
Mephentermine	$(CH_3)_2$	—	CH_3	1.0×10^{-6}	110	100
—	—	CH_3	CH_3	—	—	104
N-Methylphenethylamine	—	—	CH_3	—	—	80
N,N-Dimethylphenethylamine	—	—	$(CH_3)_2$	—	—	102

[a] Burgen and Iversen (1965).
[b] Daly *et al.* (1966) (10 mg/kg, s.c.).

TABLE 2

Effects of Side Chain Hydroxylation on the Inhibition of Norepinephrine Uptake and the Release of Norepinephrine by Phenethylamines



Compound	α	β	N	Uptake of NE by rat heart[a]		Release of NE from mouse heart,[b] % control NE
				ID_{50} (*M*)	Relative affinity	
Phenethylamine	—	—	—	1.1×10^{-6}	100	65
β-Phenethanolamine	—	OH	—	4.8×10^{-6}	23	91
dl-Amphetamine	CH_3	—	—	4.6×10^{-7}	240	58 (*d*); 86 (*l*)
dl-Phenylpropanolamine	CH_3	OH	—	2.0×10^{-6}	55	68
d-Methamphetamine	CH_3	—	CH_3	6.7×10^{-7}	165	62
Ephedrine	CH_3	OH	CH_3	2.2×10^{-6}	50	91
Pseudoephedrine	CH_3	OH	CH_3	—	—	84

[a] Burgen and Iversen (1965).
[b] Daly *et al.* (1966) (10 mg/kg, s c)

ethylamine, amphetamine, and methamphetamine were all considerably more active than the corresponding hydroxylated derivatives, β-phenethanolamine, phenylpropanolamine, and ephedrine. In contrast, ring hydroxylation imparted a greater affinity to the compounds (Table 3). Tyramine, *m*-tyramine, and especially dopamine were considerably more potent than phenethylamine. Likewise, *p*- and *m*-hydroxyamphetamine and α-methyldopamine were more active than amphetamine. Metaraminol with hydroxy groups in both the ring and β-position had the highest affinity for the norepinephrine neuronal uptake system among all the derivatives tested.

In contrast to the effects of ring hydroxylation, methoxylation of the phenyl ring markedly decreased both norepinephrine release and the inhibition of the reuptake of norepinephrine (Table 4). As was evident in the phenethylamine series, increasing the number of methoxy substituents progressively decreased the activity of the compounds. Mescaline, 3,4,5-trimethoxyphenethylamine, was the least active, having an affinity for the uptake site of 14,000 times less than that of phenethylamine.

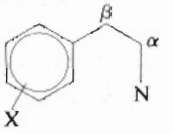
Iversen (1963, 1965) has identified two uptake systems by which norepinephrine can be accumulated in the rat heart. The first system, uptake 1, operates at a lower norepinephrine concentration than the second (uptake 2). As previously described, affinity for the first system was decreased by β-hydroxylation, *N*-methylation, or ring methoxylation but was increased by hydroxylation in the phenyl ring and α-methylation. The structural specificity required for high affinity in uptake 2 was generally opposite to that in uptake 1. α-Methylation and ring hydroxylation decreased affinity while *N*-substitution, β-hydroxylation, and especially ring methoxylation increased it. Thus, amphetamine was considerably less active as an inhibitor of the second uptake system ($ID_{50} = 1.1 \times 10^{-4}\ M$) than the first ($ID_{50} = 4.6 \times 10^{-7}\ M$) (Burgen and Iversen, 1965).

2.2. Dopamine

In contrast to the marked difference in the affinity of *d*- and *l*-amphetamine for norepinephrine neuronal uptake systems, such stereospecificity at the α-carbon does not appear to exist in dopaminergic neurons. Snyder and his colleagues (1970*b*; Taylor and Snyder, 1970; Coyle and Snyder, 1969) have compared the effects of the two amphetamine isomers on norepinephrine and dopamine uptake by synaptosomes from the rat hypothalamus and corpus striatum, respectively. The dextro isomer was ten times more potent than the levo isomer in inhibiting norepinephrine uptake but the two isomers were equipotent in inhibiting dopamine uptake. The marked difference in the potency (tenfold) of the two isomers in increasing locomotor activity contrasted with a relatively small (twofold) difference in potency in eliciting stereotyped behavior. This observation led to the suggestion that norepinephrine might be primarily involved with central

TABLE 3

Effects of Ring Hydroxylation on the Inhibition of Norepinephrine Uptake and the Release of Norepinephrine by Phenethylamines



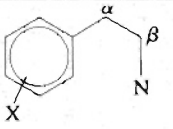
Compound	X	α	β	N	Uptake of NE by rat heart[a]		Release of NE from mouse heart,[b] % control NE
					ID_{50} (*M*)	Relative affinity	
dl-Amphetamine	—	CH_3	—	—	4.6×10^{-7}	240	58 (*d*);86 (*l*)
4-Hydroxy-*dl*-amphetamine	4-OH	CH_3	—	—	1.8×10^{-7}	610	38
3-Hydroxy-*dl*-amphetamine	3-OH	CH_3	—	—	—	—	34
α-Methyldopamine	3,4-diOH	CH_3	—	—	1.8×10^{-7}	610	39*
l-Metaraminol	3-OH	CH_3	OH	—	7.6×10^{-8}	1440	22*
Phenethylamine	—	—	—	—	1.1×10^{-6}	100	65
Tyramine	4-OH	—	—	—	4.5×10^{-7}	245	48*
m-Tyramine	3-OH	—	—	—	5.1×10^{-7}	215	46
Dopamine	3,4-diOH	—	—	—	1.7×10^{-7}	650	50*

[a] Burgen and Iversen (1965).

[b] Daly *et al.* (1966) (10 mg/kg, s.c. or *5 mg/kg, s.c.).

TABLE 4

Effects of Ring Methoxylation on the Inhibition of Norepinephrine Uptake and the Release of Norepinephrine by Phenethylamines



Compound	X	α	β	N	Uptake of NE by rat heart[a]		Release of NE from mouse heart,[b] % control NE
					ID_{50} (*M*)	Relative affinity	
Phenethylamine	—	—	—	—	1.1×10^{-6}	100	65
—	4-OCH_3	—	—	—	1.0×10^{-5}	11	102
—	3,4-di-OCH_3	—	—	—	2.0×10^{-4}	0.55	96
Mescaline	3,4,5-tri-OCH_3	—	—	—	1.5×10^{-2}	0.007	99
Phenylpropanolamine	—	CH_3	OH	—	2.0×10^{-6}	55	68
Methoxamine	2,5-di-OCH_3	CH_3	OH	—	1.0×10^{-5}	0.11	101
Methamphetamine	-	CH_3	—	CH_3	6.7×10^{-7}	165	62
Methoxyphenamine	2-OCH_3	CH_3	—	CH_3	1.1×10^{-5}	10	66
dl-Amphetamine	—	CH_3	—	—	4.6×10^{-7}	240	58 (*d*); 86 (*l*)
—	3,4-di-OCH_3	CH_3	—	—	—	—	109

[a] Burgen and Iversen (1965).
[b] Daly *et al.* (1966) (10 mg/kg s.c.).

stimulatory effects while dopamine was implicated in causing stereotyped behavior patterns.

2.3. Serotonin

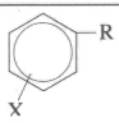
In contrast to its effects on dopaminergic and noradrenergic neurons, amphetamine has little, if any, influence on serotonergic neurons. However, certain amphetamine derivatives, especially those with electron-withdrawing substituents on the phenyl ring, do have marked effects on serotonin neurons. Pletscher *et al.* (1964) initially reported that *p*-chloro-*N*-methylamphetamine decreased the brain serotonin and 5-hydroxyindoleacetic acid levels but did not diminish either dopamine or norepinephrine concentrations.

The mechanism of action by which the *p*-chlorinated amphetamine derivatives decrease 5-hydroxyindole levels has not been completely elucidated as yet. It is known that these analogues inhibit the uptake of serotonin (Carlsson, 1970; Wong *et al.*, 1973), release serotonin (Bartholini and Pletscher, 1964; Pletscher *et al.*, 1965; Wong *et al.*, 1973; Gallager and Sanders-Bush, 1973), inhibit monoamine oxidase (Pletscher *et al.*, 1965; Fuller, 1966; Fuller and Hines, 1970), and may inhibit brain tryptophan hydroxylase and thus serotonin biosynthesis (Sanders-Bush and Sulser, 1970; Sanders-Bush *et al.*, 1972*a*,*b*). Some or all of these actions may be responsible for the characteristic effects of the chlorinated amphetamines. Inhibition of serotonin synthesis or release of serotonin might account for the reduction in brain serotonin levels while MAO inhibition might also contribute to the decreased levels of the acidic metabolite. Moreover, recently Sanders-Bush *et al.* (1972*b*; 1975) and others (Fuller and Molloy, 1974) have demonstrated that the serotonin and 5-hydroxyindoleacetic acid levels as well as the turnover of serotonin were still diminished for several weeks after the administration of *p*-chloroamphetamine. These long-lasting effects might imply either a prolonged retention of the compounds in the serotonergic neurons or, more likely, destruction of the neurons similar to that caused by 5,6-dihydroxytryptamine or 6-hydroxydopamine (Harvey *et al.*, 1975).

Certain structure–activity correlations have been made with respect to serotonin depletion. Neither amphetamine nor methamphetamine was active but both their 4-chlorinated derivatives were quite potent. The effect of *p*-chloro-*N*-methylphenethylamine was approximately equivalent to that of *p*-chloromethamphetamine (Pletscher *et al.*, 1964), but *p*-chloro-α-methylbenzylamine had no effect on serotonin levels (Fuller and Molloy, 1974) (Table 5). Thus, it appears that at least a two-carbon chain between the nitrogen and phenyl ring may be necessary for activity, but the presence of an α-methyl group may not be a structural requirement. However, the addition of a second methyl group to form chlorphentermine practically abolished the serotonin-depleting properties (Møller-Nielsen and Dubnick, 1970). In con-

TABLE 5

Effects of Alterations in the Side Chain on the Serotonin-Depleting Activity of Chlorinated Amphetamine Derivatives



R	X	Serotonin, % of control	5-HIAA, % of control
$CH_2CH(CH_3)NH_2$	—	95[a]	105[a]
$CH_2CH(CH_3)NH_2$	4-Cl	34[b]	55[b]
$CH_2CH(CH_3)NHCH_3$	—	103[a]	91[a]
$CH_2CH(CH_3)NHCH_3$	4-Cl	32[a]	40[a]
$CH_2CH_2NHCH_3$	4-Cl	39[a]	50[a]
$CH(CH_3)NH_2$	4-Cl	104[b]	—
$CH_2C(CH_3)_2NH_2$	4-Cl	91[c]	—

[a] Pletscher *et al.* (1964); serotonin and 5-hydroxyindoleacetic acid (5-HIAA) in rat brain 16 hr after intraperitoneal administration of dose equivalent to 25 mg/kg (0.11 mmole/kg) of *p*-chloro-*N*-methylamphetamine.

[b] Fuller *et al.* (1973), Fuller and Molloy (1974); serotonin and 5-HIAA in rat brain 6 hr after intraperitoneal administration of 0.1 mmol/kg.

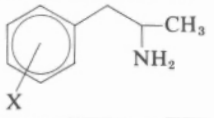
[c] Møller-Nielsen and Dubnick (1970); serotonin in rat brain 4 hr after intraperitoneal administration of 32 mg/kg.

trast to the relative activities of the optical isomers of amphetamine as releasers of norepinephrine, the characteristic effects of *p*-chloroamphetamine and *p*-chloromethamphetamine on serotonin appear largely to reside in the *l*-isomers rather than the *d*-isomers (Møller-Nielsen and Dubnick, 1970).

The position of the chloro substituent also markedly affects the activity of the compounds (Table 6). The effect of the meta derivative was approximately equivalent to that of the para derivative but only after inhibition of para-hydroxylation, while the ortho-substituted compound actually slightly raised rather than lowered the serotonin levels (Fuller and Molloy, 1974). The effects of dichloro substitution also varied with the position. 2,4-Dichloroamphetamine was considerably less active as a serotonin depletor than the 4-chloro derivative, but their effects on 5-hydroxyindoleacetic acid were similar due to the potent MAO inhibitor activity of the dichlorinated compound (Fuller and Molloy, 1974). However, the activity of 3,4-dichloroamphetamine was generally comparable to that of *p*-chloroamphetamine (Pletscher *et al.*, 1964). These observations are consistent with the finding that ortho substitution is detrimental to the serotonin-depleting activity of chlorinated amphetamines.

The effects of substitution with other groups in the para position have also been investigated (Fuller *et al.*, 1973). *p*-Trifluoromethylamphetamine caused a small decrease in the serotonin concentration but a somewhat greater reduction in 5-hydroxyindoleacetic acid (Table 7). The *p*-phenoxy

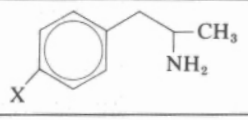
TABLE 6
Effects of the Position of the Chlorine on the Serotonin-Depleting Activity of Chlorinated Amphetamine Derivatives



X	Serotonin, % of control
4-Cl	36[a]
3-Cl*	34[a]
2-Cl*	124[a]
2,4-di-Cl	68[a]
3,4-di-Cl	43[b]

[a] Fuller and Molloy (1974); serotonin in rat brain 6 hr after intraperitoneal administration of 0.1 mmol/kg; *, in desmethylimipramine treated rats to prevent para hydroxylation.
[b] Pletscher *et al.* (1964); serotonin in rat brain 16 hr after intraperitoneal administration of dose equivalent to 25 mg/kg of 4-chloro-*N*-methylamphetamine.

TABLE 7
Effects of Ring Substitution on Serotonin-Depleting Activity of Chlorinated Amphetamine Derivatives



X	Serotonin, % of control[a]	5-HIAA, % of control[a]
4-Cl	34	55
4-CF_3	80	55
4-O- 	80	113
4-CH_3	94	94
4-OCH_3	96	87

[a] Fuller *et al.* (1973); serotonin and 5-hydroxyindoleacetic acid (5-HIAA) in rat brain 6 hr after intraperitoneal administration of 0.1 mmol/kg.

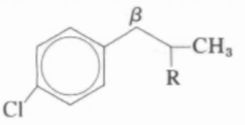
substituted compound had only a slight effect on both the 5-hydroxyindole levels, while the *p*-methoxy and *p*-methyl derivatives were inactive.

Substitution on the side chain did not enhance activity and frequently had an adverse effect (Table 8). The depletion of serotonin produced by the β-hydroxy derivative was considerably less than that caused by comparable brain levels of *p*-chloroamphetamine (Fuller *et al.*, 1973). The β-difluoro analog decreased serotonin but was less potent and much shorter acting than *p*-chloroamphetamine (Fuller and Molloy, 1974).

Most substitution on the amino group also appeared to have a detrimental effect (Table 8). The exception was, of course, *p*-chloromethamphetamine, which was as potent a serotonin depletor as *p*-chloroamphetamine. The *N*-cyclopropyl derivative did not decrease serotonin but was a potent, irreversible MAO inhibitor and therefore decreased 5-hydroxyindoleacetic acid (Fuller and Molloy, 1974). The effects of two possible metabolites of *p*-chloroamphetamine, the oxime and the hydroxylamine, have also been investigated (Fuller *et al.*, 1974*a*). The former had only a slight effect, while the latter caused a reduction in serotonin similar to that produced by *p*-chloroamphetamine but appeared to be reduced *in vivo* to the amine. The introduction of large groups on the amino group appeared to change the characteristics of the serotonin depletion. Pletscher *et al.* (1965, 1970) found that bis(3,4-dichlorophenethyl)-amine decreased dopamine as well as serotonin and increased homovanillic acid and 5-hydroxyindoleacetic acid. Deriv-

TABLE 8

Effects of Substitution on the Side Chain or Amino Group on the Serotonin-Depleting Activity of Chlorinated Amphetamine Derivatives



β	R	Serotonin, % of control[a]
—	NH_2	36
OH	NH_2	80
diF	NH_2	28 *
—	NH◁	127
—	NHOH	33
—	=NOH	80

[a] Fuller and Molloy (1974) and Fuller *et al.* (1973, 1974*a*); serotonin in rat brain 6 hr after intraperitoneal administration of 0.1 or 0.4 (*) mmol/kg.

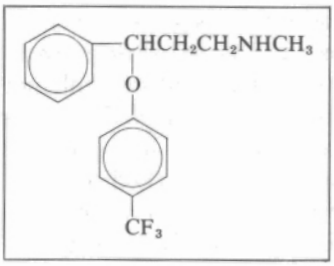


FIG. 2. Lilly-110140.

atives with other large complex substituents on the nitrogen as well as para nitro-substituted compounds had similar effects. Like reserpine, these derivatives may interfere with the intracellular accumulation of amines in storage granules.

Lilly-110140 [3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine] (Fig. 2), which represents a more radical departure from the structure of amphetamine, was found to be a very selective inhibitor of serotonin uptake in brain both *in vitro* and *in vivo*. Its selectivity for serotonergic neurons has been demonstrated by its ability to prevent the depletion of serotonin induced by *p*-chloroamphetamine without affecting the depletion of norepinephrine induced by 6-hydroxydopamine (Fuller *et al.*, 1974*b*). Lilly-110140 decreased the 5-hydroxyindoleacetic acid levels without affecting the serotonin concentration but did reduce the turnover of the indoleamine (Fuller *et al.*, 1974*c*). These effects presumably result from the enhanced activity at serotonergic neurons due to the inhibition of reuptake of neurotransmitter. The selectivity of Lilly-110140 for serotonin neurons makes it a unique agent among the many compounds that inhibit the uptake of biogenic amines and offers an opportunity for possibly separating the functions of the catecholamines and the indoleamines. This compound is now being investigated clinically as an antidepressant.

3. CENTRAL STIMULATORY EFFECTS

3.1. Phenethylamine Derivatives

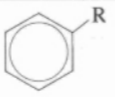
Perhaps the most outstanding pharmacologic characteristic of amphetamine is its central stimulatory activity. A prerequisite for the CNS activity of amphetamine and its congeners appears to be moderate to high affinity for the norepinephrine neuronal uptake. The converse, however, is not true, since some of the compounds with the highest affinity for the norepinephrine uptake systems do not have stimulatory effects (e.g., metaraminol). These compounds may be too polar to pass through the blood–brain barrier,

may be metabolized too rapidly, or may be sufficiently similar in structure to norepinephrine so that they serve either as substitute transmitters or stimulants of the negative feedback mechanisms of norepinephrine synthesis, thereby interfering with adrenergic neurotransmission, which may be necessary for eliciting the stimulant effects (Biel, 1970).

Although the central stimulatory properties of amphetamine and its derivatives have been extensively investigated, the multiplicity of experimental procedures and techniques used to evaluate the stimulant effects makes comparison of the results obtained in different studies difficult. Van der

TABLE 9

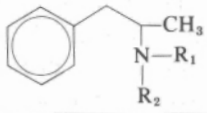
Effects of Alterations in the Side Chain on Stimulant Activity of Phenylisopropylamine Derivatives in Mice

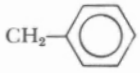
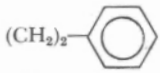


R	Stimulant activity[a]
CH_2NH_2	Inactive
CH_3 | $CHNH_2$	Inactive
$CH_2CH_2NH_2$	<3
CH_3 | CH_2CHNH_2	100
CH_3 | $CH_2—C—NH_2$ | CH_3	49
$CH_2CH_2CH_2NH_2$	Inactive
CH_3 | $CH_2CH_2CH—NH_2$	Inactive
CH_3 | $CH_2—C—NH_2$ | CH_2CH_3	Inactive

[a] Van der Schoot *et al.* (1961); effect on spontaneous locomotor activity of mice relative to the effect of amphetamine (100). All compounds administered intraperitoneally.

TABLE 10
Effects of Substitution on the Amino Group on Stimulant Activity of Phenylisopropylamine Derivatives in Mice



R_1	R_2	Stimulant activity[a]
H	H	100
H	CH_3	168
H	CH_2CH_3	60
H	$CH_2CH_2CH_3$	51
H	$(CH_2)_3CH_3$	15
H	$(CH_2)_5CH_3$	Inactive
H		8
H		6
CH_3	CH_3	19

[a] Van der Schoot *et al* (1961); effect on spontaneous locomotor activity of mice relative to the effect of amphetamine (100). All compounds administered intraperitoneally.

Schoot *et al.* (1961) have examined the stimulant effects of a large number of phenylisopropylamines on the spontaneous motor activity of mice. A two-carbon chain between the phenyl ring and the nitrogen was necessary for activity, since neither compounds with one carbon nor three or more carbons possessed central stimulant effects (Table 9). The α-methyl group was also a significant feature of the amphetamine molecule with respect to central stimulation. β-Phenethylamine had only minimal activity compared to amphetamine, while phentermine was only half as active. Thus, binding of the amino group to a secondary carbon atom appears to be necessary for maximal activity.

Some substitution on the amino group was allowable (Table 10). Methamphetamine was the only derivative tested that was more potent than amphetamine (Van der Schoot *et al.,* 1961). Larger substituents appeared to decrease activity as observed in the progressive reduction in stimulant effects as the alkyl chain length was increased. Even larger alkyl or aralkyl substituents led to compounds that were inactive or at best had minimal activity. *N*-Dimethylation also caused a marked reduction in the psychostimulant properties.

Substitution on the side chain also had detrimental effects (Van der Schoot *et al.,* 1961). The β-hydroxy derivatives had only minimal activity,

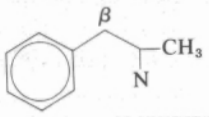
while the β-keto derivatives retained stimulant properties but their potency was considerably reduced (Table 11). Ring hydroxylation essentially abolished the activity (Van der Schoot *et al.,* 1961). Other ring substituents, such as methyl and methoxy groups, also markedly diminished or abolished the stimulant properties (Table 12).

In summary, both the β-phenethylamine skeleton and the α-methyl group appeared to be critical features of the molecule for potent stimulant activity. *N*-Methylation was allowable and even slightly enhanced the potency. However, most other structural modifications, including the introduction of larger alkyl or aralkyl substituents on the amino group, *N*-dialkylation, side chain oxidation, and ring substitution, resulted in a decrease or even a loss of the characteristic stimulant effects of amphetamine.

The configuration of the α-methyl group is also an important determinant of the stimulant activity. The dextro isomers of both amphetamine and methamphetamine are considerably more potent as stimulants than the levo isomers. Depending on the parameter measured, the potency difference may range from two- to tenfold (Taylor and Snyder, 1970; Snyder *et al.,* 1970*b*; Svensson, 1971; Roth *et al.,* 1954; Van Rossum, 1970; Moore, 1963). The anorexic activity of the dextro isomers also exceeds that of the levo isomers (Lawlor *et al.,* 1969). However, the two isomers are approximately equipotent in eliciting certain peripheral effects, such as the vasoconstriction, vasopressor, and other cardiovascular effects (Roth *et al.,* 1954; Swanson *et al.,* 1943).

TABLE 11

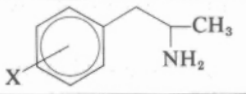
Effects of Substitution on the Side Chain on Stimulant Activity of Phenylisopropylamine Derivatives in Mice



β	N	Stimulant activity[a]
H	H	100
H	CH_3	168
=O	H	51
=O	CH_3	68
OH	H	4
OH	CH_3	8
	H	18

[a] Van der Schoot *et al.* (1961); effect on spontaneous locomotor activity of mice relative to the effect of amphetamine (100). All compounds administered intraperitoneally.

TABLE 12
Effects of Ring Substitution on Stimulant Activity of Phenylisopropylamine Derivatives in Mice



X	Stimulant activity[a]
3-OH	Inactive
4-OH	Inactive
3-CH_3	14
4-CH_3	9
3-OCH_3	10
4-OCH_3	5
2-OCH_3	<3
3,4-di-CH_3	<3
3,4-di-OCH_3	Inactive

[a] Van der Schoot *et al.* (1961); effect on spontaneous locomotor activity of mice relative to the effect of amphetamine (100). All compounds administered intraperitoneally.

3.2. Structurally Modified Phenethylamine Derivatives

The incorporation of the aminoalkyl side chain into a ring structure represents another important structural modification that has been made in the amphetamine molecule. Two well-known stimulants, methylphenidate and pipradrol (Fig. 3), both contain a piperidine ring and can be considered as cyclized amphetamine derivatives. Some structural features that are associated with the stimulant activity of these piperidine derivatives have been reviewed by Krueger and McGrath (1964).

Methyl-α-phenyl-3-piperidine acetate was considerably less potent than methylphenidate (methyl-α-phenyl-2-piperdine acetate) (Scholz and Panizzon, 1954), suggesting that once again increasing the number of carbons between the phenyl ring and nitrogen to three reduced the stimulant activity. Variations have also been made in the ester group of methylphenidate

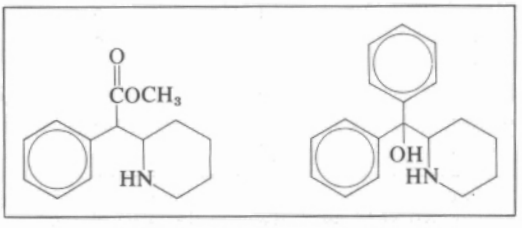


FIG. 3. Methylphenidate and pipradrol.

(Portoghese and Malspeis, 1961). None of the derivatives was as potent as the methyl ester, and increasing the size of the group appeared to progressively decrease the activity. However, the free acid has also been found to be inactive (Sheppard *et al.,* 1960).

Since methylphenidate contains two centers of asymmetry, two diastereoisomers exist. The threo form of methylphenidate was found to possess all the central stimulant properties while the erythro form was inactive (Krueger and McGrath, 1964; Shafi'ee *et al.,* 1967; Shafi'ee and Hite, 1969). Resolution of the active racemate into its optically active forms indicated a fivefold difference in activity (Krueger and McGrath, 1964).

As with methylphenidate, alterations in the structure of pipradrol that increased the number of carbons between the phenyl ring and nitrogen markedly reduced or abolished the stimulant activity (Krueger and McGrath, 1964). Neither α,α-diphenyl-4-piperidinemethanol (Fabing, 1955) nor α,α-diphenyl-2-piperidine ethanol (Tilford and Van Campen, 1954) was active as a stimulant. Several compounds in which the phenyl rings of pipradrol were substituted or replaced with a heterocyclic ring have been synthesized and evaluated for CNS activity (McCarty *et al.,* 1957). Generally, stimulant effects were retained in derivatives containing a phenyl ring substituted with an alkyl, alkoxy, hydroxy, fluoro, chloro, or dimethylamino group in the para position. Para substitution in both rings or ortho or meta substitution in either ring caused a reduction in potency. Stimulant activity was also reduced when a phenyl ring was replaced with a 2-piperidyl, 2-furyl, 2-tetrahydrofuryl, benzyl, or 2-thienyl group. Also, the piperidine group of pipradrol may be replaced by other heterocyclic rings (e.g., 2-pyrrolidyl, 3-morpholinyl, 3-tetrohydroisoquinolinyl, and 3-thiomorpholinyl) without a loss of stimulant activity (Winthrop and Humber, 1961; Belleau, 1960).

The two enantiomers of pipradrol have been prepared, and the levorotary isomer was found to be a potent CNS stimulant while the dextrorotary isomer was inactive (Portoghese *et al.,* 1968). However, the configuration of the active form was not superimposable on the more active (dextro) isomer of amphetamine, suggesting a different mechanism of action for the two stimulants.

3.3. Pemoline

Pemoline (Fig. 4) differs from the structurally modified amphetamines in having a carbonyl function at the α-position of the side chain, which in turn is incorporated into a heterocyclic ring system (oxazolidinone). Pemoline possesses mild central stimulant properties but has minimal sympathomimetic properties. It has recently been approved for use in the treatment of hyperkinesis or minimal brain dysfunction in children.

One of the greatest limitations to the therapeutic use of amphetamine and related stimulants has been the development of tolerance and drug

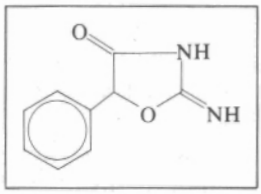


FIG. 4. Pemoline.

dependence. Self-administration techniques have been widely used to study the abuse liability of various classes of CNS active compounds. A number of phenethylamine derivatives, including amphetamine (Deneau *et al.*, 1964, 1969; Schuster *et al.*, 1969; Yanagita *et al.*, 1969; Balster and Schuster, 1973; Hoffmeister and Goldberg, 1973; Wilson and Schuster, 1973; Yokel and Pickens, 1973), methamphetamine (Deneau *et al.*, 1969; Yanagita *et al.*, 1970; Schuster *et al.*, 1969; Dren *et al.*, 1971, 1972; Balster and Schuster, 1973; Yokel and Pickens, 1973), methylphenidate (Wilson *et al.*, 1969, 1971; Schuster *et al.*, 1969; Dren *et al.*, 1971, 1972), phenmetrazine (Wilson *et al.*, 1969, 1971; Wilson and Schuster, 1973; Schuster *et al.*, 1969; Yanagita, *et al.*, 1970), and pipradrol (Wilson *et al.*, 1969, 1971; Schuster *et al.*, 1969; Yanagita *et al.*, 1970) have been found, like cocaine, to be reinforcers of self-administration in rhesus monkeys.

In contrast, the psychostimulant, pemoline did not have the capacity to reinforce self-administration behavior in rhesus monkeys (Dren *et al.*, 1971, 1972; Wilson *et al.*, 1969; Schuster *et al.*, 1969). Dren *et al.*(1971, 1972) trained rhesus monkeys with chronic in-dwelling jugular catheters to self-administer cocaine. When pemoline was substituted for cocaine, the animals did not continue to self-administer the drug. However, when either methamphetamine or methylphenidate was substituted for cocaine, self-administration behavior was maintained. Also, drug-naive monkeys failed to initiate self-administration behavior when given access to pemoline but did start to self-administer cocaine or methylphenidate.

4. ANOREXIC EFFECTS

Another prominent pharmacologic action of amphetamine is anorexia. For therapeutic use as an appetite suppressant, stimulant activity represents an important and frequently a limiting side effect. Therefore, much effort has been directed toward achieving a separation of the two activities. It will be recalled that the addition of a second α-methyl group, the introduction of an oxygen function at the β-position, and substitution of the terminal amino group with bulky groups attenuated the central stimulant effects. Derivatives containing these structural modifications, e.g., phentermine, diethylproprion,

and benzphetamine, still retain anorexic properties and have been used clinically as appetite suppressants. Other anorexic agents have resulted from the incorporation of the amphetamine side chain into ring structures, such as the morpholine derivatives phenmetrazine and phendimetrazine or the oxazoline derivative aminoxaphen (aminorex). However, the most important structural modification for achieving good separation of the stimulant and anorexic properties of amphetamine has been the introduction of a trifluoromethyl group into the phenyl ring.

Cox and Maickel (1972) have compared the anorexic and stimulant potencies of selected phenethylamine derivatives in rats. Anorexic effects were assessed by the depression of hunger-induced food intake while the behavioral effects were measured using the response rate in a continuous avoidance situation. Only five compounds tested—fenfluramine, *p*-chloroamphetamine, aminoxaphen, *p*-chloromethamphetamine, and methamphetamine—had more potent appetite suppressant effects than amphetamine (Table 13). However, the separation between the anorexic ED_{50} and stimulant ED_{50} is even more important than anorexic potency *per se*. Obviously, best in this respect were the three compounds, fenfluramine, *p*-methylamphetamine, and *p*-chlorobenzphetamine, that possessed depressant rather than stimulant properties. Also, three other derivatives, chlorphentermine, benzphetamine, and *p*-hydroxyamphetamine, failed to cause stimulation at

TABLE 13

Comparison of the Anorexic and Behavioral Effects of Selected Phenylisopropylamine Derivatives in Rats

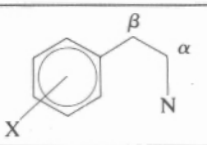
Compound	Anorexia ED_{50},[a,b] μmol/kg	Behavior ED_{50} μmol/kg[a,c]	
		Stimulant	Depressant
Fenfluramine	8.7		17.3
p-Chloroamphetamine	8.8	4.7	
Aminoxaphen	9.9	9.3	
p-Chloromethamphetamine	11.4	20.5	
Methamphetamine	12.1	2.0	
Amphetamine	14.1	5.9	
Phentermine	31.5	47.7	
Chlorphentermine	31.5	>87.0	
Diethylpropion	40.0	13.7	
Benzphetamine	52.3	>133.9	
p-Methylamphetamine	59.1		16.1
p-Chlorobenzphetamine	71.6		91.3
Phenmetrazine	73.4	24.3	
Phendimetrazine	178.5	52.9	
p-Hydroxyamphetamine	249.7	>397.4	

[a] Cox and Maickel (1972).
[b] Dose required to cause 50% decrease in hunger-induced food intake by rats.
[c] Dose required to cause 50% increase or decrease in response rate of rats in a continuous avoidance situation.

the highest doses tested. The only other compounds with anorexic ED_{50}'s at levels below the stimulant ED_{50} were *p*-chloromethamphetamine and phentermine. Several derivatives that have frequently been used as anorexic agents, such as aminorex, diethylproprion, phenmetrazine, and phendimetrazine, failed to show significant anorexia at doses below the stimulant level in this test procedure. Thus, although the stimulant potency of these derivatives may have been reduced, it appears that the anorexic activity may also have been diminished by these structral modifications. The most selective anorexic agents appear to have resulted from (1) ring substitution with electron-withdrawing groups such as chloro or especially the trifluoromethyl group present in fenfluramine, (2) substitution on the terminal amino group with large bulky groups such as in benzphetamine and *p*-chlorobenzphetamine, and (3) dimethylation in the α-position as in phentermine and chlorphentermine.

Holm *et al.* (1960) have compared the anorexic and stimulant properties of a series of nuclear-substituted phenyl-tertiary-butylamines (Table 14). The desired combination of a marked reduction in food consumption and a lack of stimulant activity was achieved in compounds with chloro or bromo substituents in the aromatic ring, whereas methyl, methoxy, or hydroxy substitution gave compounds without anorexic activity. Only chloro substitution in the para or meta positions produced the desired effects; the ortho-substituted derivative lacked potent appetite suppressant properties. Likewise, the meta- and para-, but not the ortho-, substituted trifluoromethyl

TABLE 14
Anorexic and Stimulant Effects of Selected Phentermine Derivatives

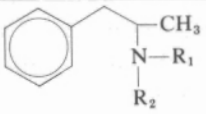


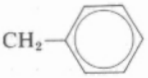
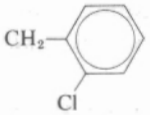
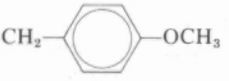
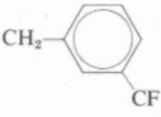
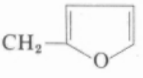
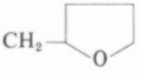
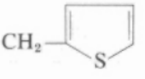
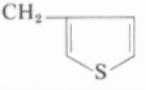
X	α	Anorexia in rats[a]		Stimulant activity in mice,[a]
		% in Diet	Weight change (g)	DMI[b] 100 (mg/kg)
—	CH_3	0.025	−38	3
—	$(CH_3)_2$	0.05	−38	10
4-Cl	$(CH_3)_2$	0.05	−29	>50
3-Cl	$(CH_3)_2$	0.05	−33	20
2-Cl	$(CH_3)_2$	0.05	+27	>50
4-Br	$(CH_3)_2$	0.05	−34	>50
4-CH_3	$(CH_3)_2$	0.05	+23	>60
4-OCH_3	$(CH_3)_2$	0.05	+ 7	>30
4-OH	$(CH_3)_2$	0.05	+22	>50

[a] Holm *et al.* (1960).
[b] DMI 100 defined as dose necessary to cause 100% increase in spontaneous motor activity of mice.

TABLE 15

Effects of N-Substitution on the Anorexic Activity of Phenylisopropylamine Derivatives in Rats



R_1	R_2	Dose, mg/kg	% Inhibition of food intake[a]
H	H	5	26
	CH_3	50	47
	H	50	38
	CH_3	50	42
	H	50	19
	CH_3	50	50
	H	50	20
	CH_3	50	0
	H	50	0
	CH_3	50	6
	H	50	7
	CH_3	100	15
	H	50	0
	CH_3	100	12
	H	50	48
	CH_3	50	61
	H	100	17
	CH_3	100	55
	H	50	0
	CH_3	100	0
	H	50	16
	CH_3	10	33
	H	100	16
	CH_3	100	34

[a] Boisser *et al.* (1966).

phentermine derivatives retained appetite suppressant activity but were not superior to the *p*-chloro derivative (Beregi *et al.*, 1970).

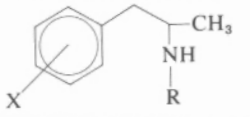
Boissier *et al.* (1966, 1970) have compared the anorexic activities of various *N*-substituted phenylisopropylamines (Table 15). The introduction of benzyl, substituted benzyl, and furfuryl groups gave compounds that possessed appetite suppressant effects but were somewhat less potent than amphetamine. In this series, the tertiary amines were generally as active or more active than the secondary amines.

Fenfluramine and other trifluoromethyl-substituted derivatives are outstanding among the phenethylamine anorexic agents in possessing potent appetite suppressant effects but minimal central stimulant and vasopressor effects. A detailed investigation of the structure–activity relationships of the trifluoromethylphenylisopropylamines has been conducted by Beregi *et al.* (1970).

The effects of ring substitution are summarized in Table 16. Compared to amphetamine, the fluoro- and trifluoromethyl-substituted derivatives generally retained potent anorexic activity in both rats and dogs but were significantly less toxic in mice. Substitution in the para or meta positions was more favorable than in the ortho position. However, the most notable

TABLE 16

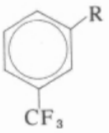
Effects of Fluoro and Trifluoromethyl Substitution on the Anorexic Activity of Phenylisopropylamines



X	R	Anorexia[a] Rat[b]	Anorexia[a] Dog[c]	Toxicity, mouse[a,d]
—	H	4.4	0.9	13
4-F	H	3.5	2	46
3-F	H	7.5	1.5	63
2-F	H	15	1	100
4-CF_3	H	3	8	153
3-CF_3	H	2	2	51
2-CF_3	H	>40	>20	171
4-CF_3	CH_2CH_2OCO–⬡	20	10	—
3-CF_3	CH_2CH_2OCO–⬡	5.4	7.5	108
2-CF_3	CH_2CH_2OCO–⬡	>20	>20	300

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Minimal oral dose that delayed food ingestion by dogs for 2 hr.
[d] Acute toxicity, mg/kg, i.p.

TABLE 17
Effects of Alterations of the Side Chain on the Anorexic Activity of Trifluoromethyl-Substituted Phenylisopropylamine Derivatives



R	Anorexia,[a,b] rat	Toxicity,[a,c] mouse
$CH_2CH_2NH_2$	>20	131.5
CH_2CHNH_2 $\vert$ CH_3	2	51
$CH_2CH_2CHNH_2$ $\vert$ CH_3	>20	152
CH_2CHNH_2 $\vert$ CH_2CH_3	>20	130
CH_2CNH_2 $\vert$ CH_3 $\vert$ CH_3	10	127.5

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Acute toxicity, mg/kg, i.p.

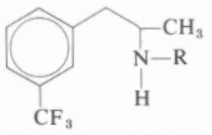
feature of the trifluoromethyl derivatives was the lack of central stimulant properties (Beregi *et al.*, 1970).

Most modifications of the basic phenylisopropylamine skeleton resulted in a marked decrease in the anorexic activity (Table 17). In the trifluoromethyl series, the separation of the phenyl ring and the nitrogen by no more than two carbons and the presence of an α-methyl group appeared to be essential for maximal anorexic activity. However, one allowable change was the introduction of a second methyl group in the α-position.

The effects of a variety of substituents on the amino group have also been determined (Beregi *et al.*, 1970). Many monoalkylated derivatives retained high potency as anorexic agents and, most significantly, exerted a considerably smaller vasopressor effect in rats (Table 18). For example, the rise in blood pressure with the methyl and ethyl derivatives was only one-quarter that produced by the unsubstituted analogue. Other compounds that possessed good anorexic activity with minimal vasopressor effects included

TABLE 18

Effects of N-Monoalkylation on the Anorexic and Vasopressor Activity of Trifluoromethyl-Substituted Phenylisopropylamine Derivatives



R	Anorexia,[a,b] rat	Vasopressor,[a,c] rat	Toxicity,[a,d] mouse
H	2	+100	51
CH_3	6.8	+24	130
CH_2CH_3 (Fenfluramine)	5.2	+27	71
$CH_2CH_2CH_3$	10.4	+21	87
$CH(CH_3)_2$	8.7	0	142
$(CH_2)_3CH_3$	10	0	94.6
CH_2CH_2Cl	10	+15	123.4
$CH_2CH{=}CH_2$	8.4	+17	109
$CH_2C{\equiv}CH$	7.6	+11	283
$CH_2CH{=}CHCH_3$	>20	—	78
$CH_2CH{=}C(CH_3)_2$	>20	—	79

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Increase in blood pressure (mm Hg) following intravenous dose of 5 mg/kg.
[d] Acute toxicity, mg/kg, i.p.

the propenyl and propargyl derivatives. However, somewhat larger substituents on the amino group resulted in a loss of the appetite-suppressant effects. *N*-Dialkylation generally led to a marked decrease in activity (Table 19).

Various other derivatives, including amides, carbinols, ethers, and esters, were also synthesized and tested (Beregi *et al.*, 1970). Only one of the amides, the propinyl derivative, possessed significant anorexic activity and had quite low toxicity (Table 20). In the series of carbinols, ethers, and esters, a two-carbon chain between the nitrogen and hydroxy group was found to be essential for good activity (Table 21). The ethers were generally more toxic and less active than the hydroxyethyl derivative while esterification of the hydroxylalkyl group was more beneficial. The anorexic activity of the alkyl esters was only slightly reduced and their toxicity was unchanged. In contrast, the toxicity of many aryl and aralkyl esters was substantially decreased while the activity was maintained, thus resulting in high therapeutic ratios. However, large differences frequently existed in the oral and intraperitoneal toxicity of these derivatives. No consistent effects were observed with substitutions in the phenyl ring of these esters. The final group of compounds tested by Beregi *et al.* (1970) was the amino acid

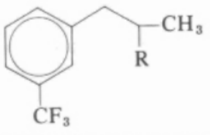
derivatives. Generally the presence of one carbon between the nitrogen and carboxy group was required for potent anorexic activity (Table 22).

The potencies of the optical isomers of certain trifluoromethyl derivatives have been compared by Beregi *et al.* (1970) (Table 23). The dextro isomer of fenfluramine was more active than the racemic mixture, which in turn was more active than the levo isomer. This relationship was valid for most of the derivatives tested but certain exceptions occurred. For example, the racemic mixture of S-992 was more potent as an appetite suppressant in rats than either isomer while in dogs the order of potency followed the general trend ($d > dl > l$).

Several conclusions can be drawn about the structure–activity relationships of the trifluoromethyl-substituted phenethylamines from this detailed

TABLE 19

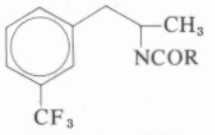
Effects of N-Dialkylation on the Anorexic and Vasopressor Activity of Trifluoromethyl-Substituted Phenylisopropylamines



R	Anorexia,[a,b] rat	Vasopressor,[a,c] rat	Toxicity,[a,d] mouse
NH_2	2	+100	51
$NHCH_3$	6.8	+ 24	130
$N(CH_3)_2$	20	—	144
$N(CH_2CH_3)_2$	20	+ 48	132
$N(CH_3)(CH_2)_3CH_3$	>20	+ 15	149
$N(CH_3)CH_2C{\equiv}CH$	15	—	263
$N(CH_3)CH_2C{\equiv}C$–C$_6$H$_5$	>20	+ 20	600
$N(CH_3)_3$	>20	+115	35

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Increase in blood pressure (mm Hg) following intravenous dose of 5 mg/kg.
[d] Acute toxicity, mg/kg, i.p.

TABLE 20
Effects of Acylation on the Anorexic Activity of Trifluoromethyl-Substituted Phenylisopropylamine Derivatives



R	Anorexia,[a,b] rat	Toxicity,[a,c] mouse
CH_3	>20	750
CH_2CH_3	4.3	2000
CH_2Cl	>20	>2000
	30	900
NH_2	>20	1500
CH_2CH_2—N 	>20	300

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Acute toxicity, mg/kg, i.p.

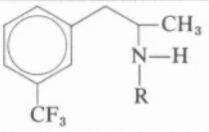
study. Most notably, trifluoromethyl substitution resulted in a loss of stimulant properties. Substitution in the meta position was most beneficial in retaining anorexic activity while ortho-substituted derivatives had only minimal activity. As was true in the unsubstituted phenylisopropylamine series, the distance between the amino group and the phenyl ring was restricted to a two-carbon chain and the binding of the amino group to a secondary carbon atom was necessary for maximal activity. Small substituents in the amino group were allowable and the formation of secondary amines led to a marked reduction in the vasopressor effects. In contrast to the amphetamine series, the introduction of large substituents and disubstitution on the amino group tended to decrease or abolish the anorexic activity. Hydroxyethyl substitution on the amino function was beneficial, and some of the aryl and aralkyl esters combined potent anorexic activity and low toxicity. However, there are indications that the *N*-hydroxyethyl group is cleaved metabolically, thereby yielding the primary amine.

5. INHIBITION OF MONOAMINE OXIDASE

The presence of an α-methyl group protects amphetamine from rapid degradation by monoamine oxidase (MAO) but amphetamine still retains at least moderate MAO inhibitory properties. However, this MAO inhibitory

TABLE 21

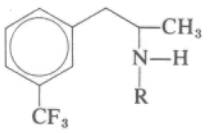
Anorexic Activity of Hydroxyalkyl Derivatives of Trifluoromethyl-Substituted Phenylisopropylamines



R	Anorexia,[a,b] rat	Toxicity,[a,c] mouse
CH_2CH_2OH	5.2	184 300*
$CH_2CH_2CH_2OH$	>20	207
$CH_2CH_2OCH_2CH_3$	10	118
CH_2CH_2O—C$_6$H$_5$	>20	100
$CH_2CH_2OCOCH_3$	10	125
$CH_2CH_2OCOCH_2CH_3$	10	178
CH_2CH_2OCO—C$_6$H$_5$	5.4	108 2300*
CH_2CH_2OCO—C$_6$H$_4$—F	7.5	1000*
CH_2CH_2OCO—C$_6$H$_4$—Cl	15	1000*
CH_2CH_2OCO—C$_6$H$_4$—CH_3	10	1000*
CH_2CH_2OCO—C$_6$H$_4$—NH_2	15	400*
CH_2CH_2OCO—C$_6$H$_4$—NO_2	20	1000*
CH_2CH_2OCO—C$_6$H$_4$—CF_3	5	750*
$CH_2CH_2OCOCH_2$—C$_6$H$_5$	10	150 1000*

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Acute toxicity, mg/kg, i.p. or p.o. (*).

TABLE 22
Anorexic Activity of Amino Acid Derivatives of Trifluoromethyl-Substituted Phenylisopropylamines



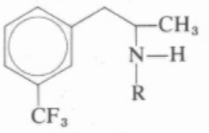
R	Anorexia,[a,b] rat	Toxicity,[a,c] mouse
CH_2COOH	4	125
		500*
CH_2CH_2COOH	35	300
CH_2CONH_2	7.5	350*
$CH_2CONHCH_3$	3.0	250
$CH_2CON(CH_3)_2$	7.5	150
$CH_2CONHNH_2$	4	250

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Acute toxicity, mg/kg, i.p. or p.o. (*).

effect can be markedly enhanced by certain structural modifications. Three potent, irreversible MAO inhibitors, tranylcypromine, pheniprazine, and deprenyl (Fig. 5), have been derived from relatively simple changes in the amphetamine molecule.

Incorporation of the α-methyl group into a cyclopropane ring led to tranylcypromine (Burger and Yost, 1948; Zirkle and Kaiser, 1964). When this group is "tied back" in such a fashion, it exposes the amino group, thereby facilitating receptor interaction and binding. Furthermore, the less stable cyclopropane ring could conceivably contribute to the increased binding with the receptor protein through a ring-opening reaction. Tranylcypromine is about 5000 times more potent as a MAO inhibitor than amphetamine, and judging by its duration of action it is probably an irreversible enzyme inhibitor. Recently it has been recognized that MAO exists as at least two isoenzymes with different substrate specificities and different affinities for inhibitors (Neff and Yang, 1974). While amphetamine has been found to be about 50 times more effective as an *in vitro* inhibitor of rat brain mitochondrial MAO when serotonin is the substrate than phenethylamine, tranylcypromine was about 15 times more potent in blocking phenethylamine oxidation than serotonin oxidation (Fuller, 1972). Tranylcypromine shares some of the other pharmacological properties of amphetamine. It also possesses CNS stimulant effects and has the ability to inhibit the uptake of norepinephrine and to release norepinephrine, but is considerably less potent than amphetamine in all these activities.

TABLE 23
Anorexic Activity of Isomers of Trifluoromethyl-Substituted Phenylisopropylamine Derivatives



R	Isomer	Anorexia[a] Rat[b]	Anorexia[a] Dog[c]	Toxicity,[a,d] mouse
CH_2CH_3	*dl*	5.2	6.5	71
(Fenfluramine)	*d*	2.8	4.0	60
	l	10.0	21.2	105.2
CH_2CH_2OCO– 	*dl*	5.4	7.5	2300
(S-992)	*d*	12.5	3.0	300
	l	>30	15.0	850

[a] Beregi *et al.* (1970).
[b] Oral dose (mg/kg) that inhibited food intake of rats by 50% for 2 hr.
[c] Minimal oral dose which delayed food ingestion by dogs for 2 hr.
[d] Acute toxicity, mg/kg, i.p.

A marked increase in the MAO inhibitory activity can also be achieved by substitution of the amino group of amphetamine with a hydrazine moiety, thus producing pheniprazine (Biel *et al.*, 1964). A similar change in the structure of phenethylamine leads to the formation of phenelzine. The highly reactive hydrazine group causes a pronounced, irreversible inhibition of the enzyme that lasts for several days. Pheniprazine demonstrates relatively little substrate specificity, being only slightly more potent in inhibiting serotonin oxidation than phenethylamine oxidation (Fuller, 1972). Like tranylcypromine, pheniprazine also retains moderate CNS stimulant activity, but it lacks any significant anorexic properties.

The introduction of a propargyl group on the terminal amino group of methamphetamine produced deprenyl, another potent, irreversible MAO inhibitor (Knoll and Magyar, 1972). Deprenyl is considerably more active in blocking the oxidation of benzylamine than serotonin. A marked stereospecificity was evident in the *in vitro* and *in vivo* MAO inhibitory effects of deprenyl with the levo isomer being considerably more potent in both brain

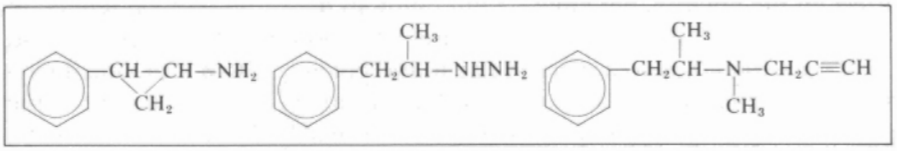


FIG. 5. Tranylcypromine, pheniprazine, and deprenyl.

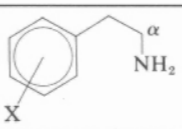
and liver. However, the *d*-isomer proved to be considerably more effective in blocking the uptake of norepinephrine in rat brain slices and had much greater CNS stimulant activity than the *l*-isomer. Deprenyl, especially the *l*-isomer, is unique among MAO inhibitors in that it blocked the tyramine-induced pressor effects on blood vessels and the contractile responses of the cat nictitating membrane. One of the greatest drawbacks to the therapeutic use of MAO inhibitors as antidepressants has been the occurrence of hypertensive crises precipitated by the ingestion of tyramine-rich foods, such as cheese. The lack of tyramine potentiation and possible antagonism of the effects of tyramine should minimize the risk of the so-called cheese reaction following the administration of deprenyl.

6. PSYCHOTOMIMETIC EFFECTS

Amphetamine administered chronically in increasing doses may produce severe symptoms of paranoid psychosis within as short a time interval as five days (Ellinwood, 1967, 1968; Griffith *et al.*, 1968). This inherent psychotogenic propensity of amphetamine was enhanced by polyalkoxylation of the phenyl ring. Several methoxyphenethylamine and methoxyphenylisopropylamine derivatives have been synthesized and tested as psychotomimetic agents in man (Shulgin *et al.*, 1969). The potency of each compound was compared to that of mescaline (3,4,5-trimethoxyphenethylamine), a well-known hallucinogen that occurs naturally in several cacti, including *Lophophora williamsii*. The addition of the α-methyl group appeared to enhance the activity as the methoxy analogs of amphetamine were generally considerably more potent than the corresponding phenethylamines (Table 24). Replacement of the α-methyl group with an ethyl decreased the psychotomimetic effects.

A total of three methoxy groups appeared to provide optimal activity in the phenylisopropylamine series (Shulgin *et al.*, 1969). The mono-, di-, and tetra-substituted derivatives were less potent than certain trimethoxyamphetamines (Table 25). However, the positions of the methoxy groups had a marked effect on activity (Table 26). For example, 3,4,5-trimethoxyamphetamine was approximately twice as potent as mescaline, while 2,4,5-trimethoxyamphetamine was 17 times as potent as mescaline. In general, para and ortho substitution enchanced activity, while meta substitution decreased it. Replacement of the para methoxy group with an ethoxy group had little effect on the potency, but ethoxy substitution in the ortho position tended to reduce activity (Table 27). However, the introduction of a methyl group in the para position led to a marked rise in the potency. DOM (2,5-dimethoxy-4-methylamphetamine), also known as STP, is one of the most potent of the psychotomimetic phenylisopropylamines, presumably due to reduced metabolic degradation in the para position (Snyder *et al.*, 1970*a*).

TABLE 24
Effects of α-Methylation on the Psychotomimetic Potency of Methoxyphenethylamine Derivatives in Man

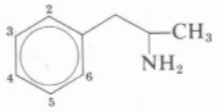


α	X	Relative potency[a]
H	4-OCH_3	<1
CH_3	4-OCH_3	5
H	3,4-di-OCH_3	<0.2
CH_3	3,4-di-OCH_3	<1
H	3,4,5-tri-OCH_3	1.0
CH_3	3,4,5-tri-OCH_3	2.2
H	2,4,5-tri-OCH_3	1
CH_3	2,4,5-tri-OCH_3	17

[a] Shulgin *et al.* (1969); potency relative to that of mescaline (1.0).

The incorporation of two adjacent methoxy groups into a methylenedioxy ring generally caused no loss of activity and frequently led to a distinct increase (Shulgin *et al.*, 1969). For example, the relative potency of 2-methoxy-4,5-methylenedioxyamphetamine (12) was generally comparable to that of its analog, 2,4,5-trimethoxyamphetamine (17), while 2-methoxy-3,4-methylenedioxyamphetamine (10) was considerably more potent than its corresponding trimethoxy analog (<2) (Table 28).

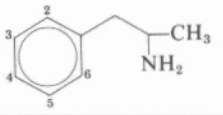
TABLE 25
Psychotomimetic Potency of Mono-, Di-, and Tetramethoxyamphetamine Derivatives in Man



Ring substituents					Relative potency[a]
2	3	4	5	6	
H	H	OCH_3	H	H	5
OCH_3	H	H	OCH_3	H	8
OCH_3	H	OCH_3	H	H	5
H	OCH_3	OCH_3	H	H	<1
OCH_3	OCH_3	OCH_3	OCH_3	H	6

[a] Shulgin *et al.* (1969); potency relative to that of mescaline (1.0).

TABLE 26
Psychotomimetic Potency of Trimethoxyamphetamine Derivatives in Man

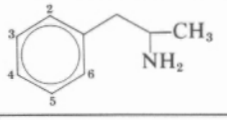


Ring substituents					Relative potency[a]
2	3	4	5	6	
OCH_3	H	OCH_3	OCH_3	H	17
OCH_3	OCH_3	H	H	OCH_3	13
OCH_3	H	OCH_3	H	OCH_3	10
OCH_3	OCH_3	H	OCH_3	H	4
H	OCH_3	OCH_3	OCH_3	H	2.2
OCH_3	OCH_3	OCH_3	H	H	<2

[a] Shulgin *et al.* (1969); potency relative to that of mescaline (1.0).

The psychotomimetic activity of the phenethylamine derivatives has been correlated with the ability of the structures to form a ring system that would closely resemble the C ring of LSD (Snyder *et al.*, 1970*a*). An ortho methoxy group that could assume a relatively rigid spatial conformation would be necessary for the formation of such a ring system. The presence of a second methoxy group in the meta position and therefore adjacent to the ortho methoxy group would sterically hinder the ability of the latter to fulfill this requirement. Thus, compounds with methoxy groups at both C_2 and C_3 or C_6 and C_5 would be relatively weak psychotomimetics, while compounds

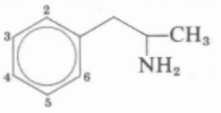
TABLE 27
Effects of Ethoxy and Methyl Substitution of Trimethoxyamphetamine Derivatives in Man



Ring substituents					Relative potency[a]
2	3	4	5	6	
OCH_3	H	OCH_3	OCH_3	H	17
OC_2H_5	H	OCH_3	OCH_3	H	<7
OCH_3	H	OC_2H_5	OCH_3	H	15
OCH_3	H	OCH_3	OC_2H_5	H	<7
OCH_3	H	CH_3	OCH_3	H	80

[a] Shulgin *et al.* (1969); potency relative to that of mescaline (1.0).

TABLE 28
Psychotomimetic Potency of Methylenedioxy-Substituted Amphetamine Derivatives in Man



Ring substituents					Relative potency[a]
2	3	4	5	6	
H	O—CH_2—O		H	H	3
OCH_3	H	O—CH_2—O		H	12
OCH_3	O—CH_2—O		H	H	10
O—CH_2—O		OCH_3	H	H	3
H	OCH_3	O—CH_2—O		H	2.7
OCH_3	O—CH_2—O		OCH_3	H	12
OCH_3	OCH_3	O—CH_2—O		H	5
H	OCH_3	O—CH_2—O		H	<1

[a] Shulgin *et al.* (1969); potency relative to that of mescaline (1.0).

with unhindered ortho-substituents should be among the most potent derivatives. In the methylenedioxy series, incorporation of the methoxy groups at the 3 and 4 positions into a ring lessens the steric hindrance of the methoxy group at C_2 and thus might enhance the potency of such compounds.

Thus, the addition of methoxy groups changes the activity spectrum of the amphetamine derivatives rather drastically. As well as enchancing the psychotogenic propensity of the compounds, progressive methoxylation of the phenyl ring practically abolishes the ability of the compounds to inhibit the neuronal uptake of norepinephrine (uptake 1) and to release norepinephrine from its binding sites (Burgen and Iversen, 1965; Daly *et al.*, 1966). Therefore, unlike amphetamine, these drugs presumably do not exert their characteristic effects through norepinephrine as an intermediate neurotransmitter, but perhaps rather through a direct interaction with the receptor. Although methoxy substitution in the phenyl ring abolished the affinity of the compounds for uptake 1, it appeared to increase the ability of the phenethylamines to inhibit the accumulation of norepinephrine by the so-called second uptake system (Burgen and Iversen, 1965). Norepinephrine and normetanephrine are also taken up extraneuronally in sympathetically innervated tissues by a process thought to be similar to uptake 2. The potency of the trimethoxyamphetamine derivatives as inhibitors of normetanephrine uptake by this system was found to correlate with their hallucinogenic potency (Hendley and Snyder, 1971). For example, 2,4,5,-trimethoxy-

amphetamine, 2,4,6-trimethoxyamphetamine, and DOM were highly active as uptake inhibitors and were among the most potent psychotogenic compounds in man. Conversely, 3,4,5-, 2,3,5-, and 2,3,4-trimethoxyamphetamines were all quite weak both as psychotomimetics and inhibitors of normetanephrine uptake. This finding led to the suggestion that the site of action of these drugs may be related to the site of normetanephrine uptake, which may possible involve the postsynaptic norepinehprine receptor.

7. SUMMARY

Amphetamine remains the medicinal chemist's "Cinderella" molecule. No other compound has displayed such a plethora of pharmacological, biochemical, and physiological effects, which have endowed this drug with a variety of therapeutic applications and made it a highly effective tool for the pharmacologist and biochemist in the study of the role of neurotransmitter amines in the control of the emotional state and the chemical etiology of certain mental disorders. Nor have many other molecules served as so versatile a starting base for the synthetic elaboration of a host of novel therapeutic agents.

Pharmacologically, amphetamine *per se* is a potent central stimulant, vasoconstrictor, anorexigenic agent, uptake inhibitor, and releaser of dopamine and norepinephrine at the neuronal level. Therapeutically, these pharmacological and biochemical properties of amphetamine translate into drugs for the treatment of mild depressions, fatigue states, hyperkinesis, nasal congestion, and obesity.

From the standpoint of human toxicity, the chronic abuse of amphetamine has lead to severe drug addiction, paranoid psychosis, and ultimately death, when high intravenous doses of the drug are self-administered. Its biochemical properties of releasing dopamine and inhibiting the cellular uptake of dopamine coupled with its ability to produce stereotypical behavior in animals have given rise to the plausible hypothesis that the neutransmitter dopamine may be implicated in the chemical genesis of psychoses. Further credence in support of this hypothesis is lent by the major antipsychotic drugs, all of which are potent antagonists of dopamine and the fact that increasing doses of amphetamine can precipitate a model psychotic state in humans within a period of five days.

Even more fascinating has been the impressive array of drugs that have resulted from the diverse molecular modification of the amphetamine molecule: nonaddicting antiobesity drugs, antihyperkinetic agents, potential antidepressants (selective inhibitors of serotonin uptake) devoid of the anticholinergic properties of the tricyclics, irreversible MAO inhibitors in the treatment of hypertension and mental depression, long-acting nasal decongestants, and powerful psychotomimetic agents. More recently, cyclization of

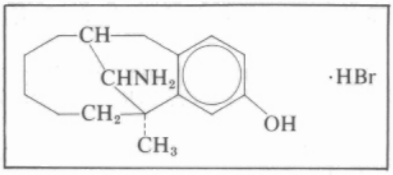


FIG. 6. Wy-16225.

the amphetamine side chain has yielded a potent, nonaddicting analgetic agent (Figure 6).

Thus amphetamine remains a valuable laboratory tool for the biochemist and pharmacologist, a seemingly inexhaustible starting base for the synthetic medicinal chemist in the design and development of novel medicinals, and the wellspring of a continuous flow of novel therapeutic agents for the practicing physician.

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