Pharmacologic Studies on the Structure-Activity Relationship of Hydroxyindole Alkylamines

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Introduction

The active ingredients of various Mexican hallucinogenic mushrooms (especially *Psilocybe*, e.g., *Psilocybe mexicana* Heim) are simple derivatives of tryptamine (Hofmann *et al.*, 1958a,b; Hofmann and Troxler, 1959); psilocine has been identified as 4-hydroxy-*N*,*N*-dimethyltryptamine, and psilocybine as its phosphoric acid derivative, 4-phosphoryloxy-*N*,*N*-dimethyltryptamine. Both of these 4-substituted tryptamine derivatives—the first to be found in nature—are therefore chemically closely related to a number of other psychotropic or psychotomimetic agents with indole structure (Cerletti, 1960), for instance, to lysergic acid diethylamide (LSD), the most potent psychotomimetic agent known at this time, which possesses a 4-substituted tryptamine element as part of its molecular structure (see Fig. 1).

With this in mind, we considered it worthwhile to investigate the relationship between structure and activity of some simple tryptamine derivatives synthesized by Troxler *et al.* (1959) after the model of psilocine and psilocybine. However, before describing our present findings, we wish to review briefly the main pharmacologic properties of psilocine and psilocybine (hereafter referred to simply as 'Ps'), as reported by Weidmann *et al.* (1958) and Cerletti (1959a,b) some time ago (see Table I).

Tests on various isolated organs with smooth muscle structure have shown that Ps possesses no direct action on these, nor does it antagonize E, acetylcholine, or histamine. Nevertheless, an anti-5-HT effect could be demonstrated in the rat uterus which may indicate that Ps acts as a 5-HT antagonist rather than a cogener, as its structure might suggest (Weidmann *et al.*, 1958; Woolley and Campbell, 1962). The important pharmacologic effects of Ps (as in the case of LSD) all pertain to autonomic functions, showing a marked stimulation of sympathetic activity. The syndrome produced is of central origin and comprises mydriasis, piloerection, tachycardia, rise of blood pressure and body temperature, hyperglycemia, and contraction of the nictitating membrane (Buñag and Walaszek, 1961; Gessner *et al.*, 1960; Jacob and Lafille, 1963; Jacob *et al.*, 1962; Maxwell *et al.*, 1962; Steiner and Sulman, 1963; Weidmann *et al.*, 1958). Sympathetic activation is also shown

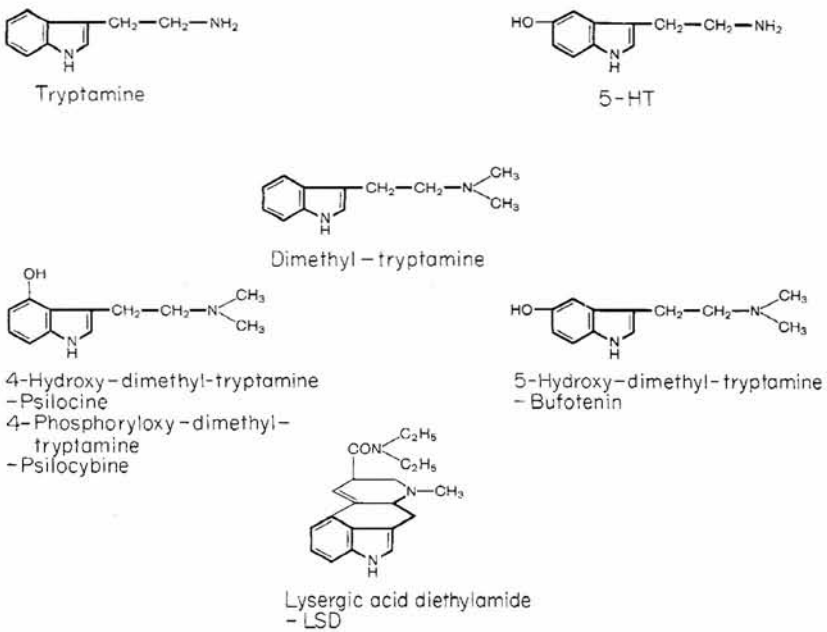


FIG. 1. Structural relationships between tryptamine and naturally occurring indole derivatives.

TABLE I

PHARMACOLOGIC PROPERTIES OF PSILOCINE AND PSILOCYBINE

Effect on	Response
Isolated organs	No significant effect, except 5-HT antagonism in rat uterus
Blood pressure	Increase
Heart rate	Increase
Respiration	Increase
Pupil size	Increase (Mydriasis)
Nictitating membrane	Contraction
Body temperature	Increase
Blood sugar	Increase
EEG	Activation
Reaction time	Decrease
Spinal reflexes	Increase
Motor activity	Decrease
Isolation-induced fighting behavior	Decrease
Hexobarbital sleeping time	Increase (potentiation)

by the disappearance of slow-wave activity in the EEG of the rabbit (Adey *et al.*, 1962; Brodey *et al.*, 1963; Monnier, 1959; Steiner and Sulman, 1963; Weidmann *et al.*, 1958). Intensification of spinal reflexes in the cat, and shortening of the reaction time to nociceptive stimuli in the rat are also caused by Ps and may be regarded as signs of a generalized increase in reflex activity (Jacob *et al.*, 1962; Weidmann and Cerletti, 1960; Weidmann *et al.*, 1958). The effect of Ps on psychomotor behavior in animals is not striking. In contrast to its stimulating action on autonomic functions and spinal

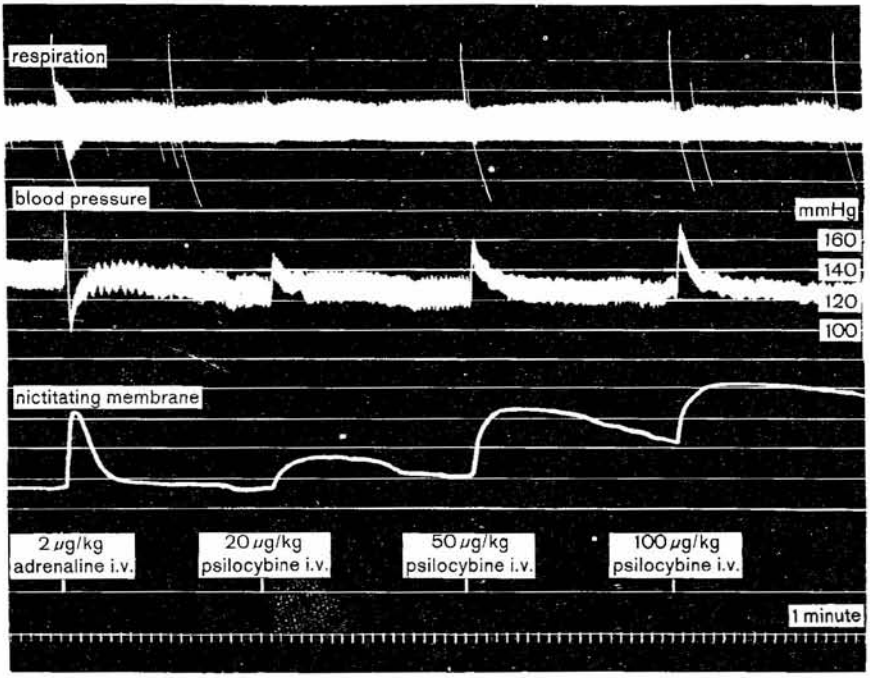


FIG. 2. Effect of psilocybine on respiration, blood pressure, and nictitating membrane in the cat (urethane-chloralose). Psilocybine 20 to 100 µg/kg i.v. produces dose-dependent pressor reaction and contraction of the nictitating membrane.

reflexes, Ps in larger doses has a calming effect on motor activity in mice, rabbits, and monkeys, and inhibits isolation-induced attack behavior in mice (Collins *et al.*, 1966; Uyeno, 1966; Weidmann *et al.*, 1958). Moreover, hexobarbital sleep in the mouse is significantly prolonged by Ps (Gessner *et al.*, 1960).

Figure 2 shows the distinctive circulatory effects of Ps in the cat, viz., a short dose-dependent pressor reaction and a prolonged contraction of the nictitating membrane, the duration and intensity of which also increase with dosage. Figure 3 shows the effect on the patellar reflex in the cat which is

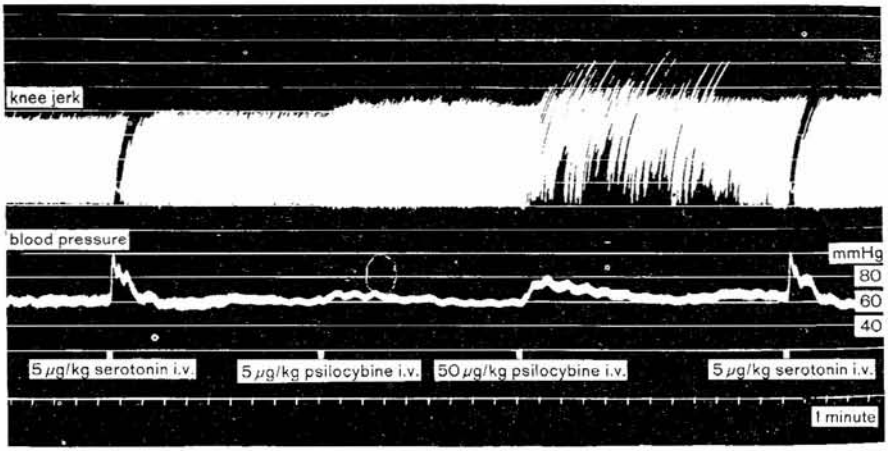


FIG. 3. Effect of psilocybine and 5-HT on the patellar reflex in the spinal cat. Serotonin 5 µg/kg i.v. temporarily inhibits reflex action, whereas psilocybine in doses of 5 and 50 µg/kg i.v. produces an increase of reflex activity.

enhanced by Ps over a considerable period of time. This steady action on monosynaptic reflexes is, in fact, a distinctive property of all tested 4-hydroxyindole derivatives and distinguishes these from such agents as 5-HT, bufotenin, etc. Our structure-activity studies of the hydroxyindole alkylamines were therefore based in the first place on the investigation of this property, but the following characteristic effects were also considered:

The *in vitro* 5-HT antagonism in the rat uterus.

The pyrogenic activity in the rabbit as a characteristic property of psilocine. The Pyrogenic Index, i.e., the quotient LD_{50}: $ED_{+0.5°C}$, is 555 for this substance.

The pressor effect in the spinal cat.

The reserpine antagonism in the mouse.

The *in vitro* MAO inhibition.

The results of our studies have revealed that within the class of indolealkylamines two groups of agents can be discerned according to their structure-activity properties. The one group comprises agents of the *N*,*N*-dimethyltryptamine type with a spectrum of activity similar to Ps. The other group consists of 2-aminopropyl indole derivatives which antagonize reserpine and inhibit MAO.

Methods

KNEE JERK AND BLOOD PRESSURE

Spinal cat. Knee jerk elicited by mechanical stimulation with an automatic hammer, every 2 seconds. Registration of hind limb reflex extension with a

semiisometric lever on a smoked drum. Carotid blood pressure continuously measured with a mercury manometer. Intravenous injections through an indwelling cannula into one of the jugular veins. Determination of the minimal i.v. dose of the test substance which produces a distinct and clearly visible stimulation or inhibition.

Serotonin Antagonism

Isolated rat uterus preparation according to Gaddum and Hameed (1954), and Lanz *et al.* (1955). Calculation, according to the probit method, of the dose necessary to produce a 50% reduction in the 5-HT response. Determination of the relative activity of the test substance in comparison with psilocine.

Pyrogenic Activity

Rabbits. Procedure according to USP XVII 1965. Determination of the i.v. dose of the test substance which raises the body temperature of the rabbits by 0.5°C. Establishment of the relative activity of the test substance by comparing it with the corresponding effect of psilocine.

Reserpine Antagonism

Mice. Use of the facilitating influence of reserpine on tonic extensor seizures by pentylenetetrazole as a quantitative measurement of its activity (Chen and Bohner, 1961). Subcutaneous injection of 2.5 mg/kg reserpine 1 hour after s.c. treatment with the test substance. After a further 3 hours the amount of pentylenetetrazole required to induce a terminal tonic extensor seizure in the hind limbs is determined by slow intravenous infusion. Determination of the dose of the test substance which raises the amount of pentylenetetrazole by at least 50% above the amount required for animals treated with reserpine alone.

Monoamine Oxidase Inhibition

Manometric determination of the oxygen uptake of guinea pig liver homogenate with 5-HT as a substrate according to the method of Alles and Heegard (1943). Activity expressed as the initial velocity of the reaction. Determination of I_{50} (= inhibitor concentration in mols/liter) by plotting the concentrations against the respective percentual inhibition.

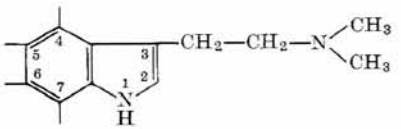
Results

We first tried to find out what importance could be attached to the position of the hydroxy group introduced into the benzene ring of *N*,*N*-dimethyltryptamine. At the same time the corresponding phosphoryloxy

derivatives were investigated. As can be seen from Table II only the unsubstituted *N,N*-dimethyltryptamine and its position 4 and 5 derivatives show activity in the knee jerk test, whereas the corresponding 6- and 7-substituted compounds are without any effect up to a dose of 200 μg/kg. With both of the 4-substituted compounds a stimulant effect on the knee jerk is seen

TABLE II

INFLUENCE OF THE POSITION OF THE OXY-SUBSTITUTION IN THE BENZENE RING OF DIMETHYLTRYPTAMINE



Substituent	Position	Knee jerk[a]	Serotonin[b] antagonism	Pyrogenic[b] activity	Pressure[c] activity
—	—	↑ 20–50	20	2	39
OH	4	↑ 5–10	100	100	50
OH	5	↓ 20–50	S[d]	1	40
OH	6	ø	1	<1	22
OH	7	ø	3	—	20
OPO_3H_2	4	↑ 5–10	18	3	25
OPO_3H_2	5	↓ > 50	20	—	53
OPO_3H_2	6	ø	<1	—	18
OPO_3H_2	7	ø	<1	—	ø

[a] In this and the subsequent tables, the signs and figures have the following meaning: The upward arrow means augmentation of the reflex response and the downward arrow reflex inhibition. The numbers indicate the minimal intravenous doses in μg/kg which were necessary to produce alteration of the knee jerk. ø indicates that there is no activity up to 200 μg/kg i.v.

[b] Relative activity based on psilocine = 100.

[c] Average rise in mm Hg after 50 μg/kg i.v.

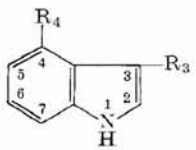
[d] Serotoninlike activity.

which is already visible after doses of 5–10 μg/kg and is rather long-lasting. It is interesting to note that phosphorylation does not modify the action, either quantitatively or qualitatively. In contrast to this stimulation, a clear-cut but short-lasting inhibition of the knee jerk is produced by 5-hydroxy-*N,N*-dimethyltryptamine (bufotenin). This effect is the same as that obtained after 5-HT, except that 4 to 5 times higher doses of bufotenin are required. Introduction of the phosphoryloxy radical diminishes the activity of bufotenin, without, however, producing a qualitative change. Apart from

this reflex activating effect, *N*,*N*-dimethyltryptamine and the 4- and 5-substituted compounds show measurable 5-HT antagonistic and pressor activity, whereas the 6- and 7-substituted products are practically inactive. Concerning the pyrogenic effect, it is noteworthy that this activity becomes visible mainly in the 4-substituted derivative with a free hydroxy group, but not in the corresponding phosphorylated compound and even less so in the other substances shown in Table II.

TABLE III

INFLUENCE OF SUBSTITUTION IN POSITION 3 OF INDOLE AND 4-HYDROXYINDOLE

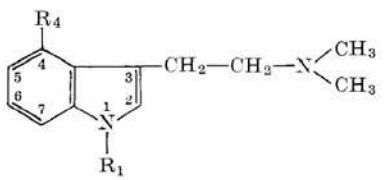


Substituent		Knee jerk	Serotonin antagonism	Pressure activity
R_3	R_4			
$CH_2—CH_2—NH_2$	—	↓ > 50	S	61
$CH_2—CH_2—N(H)(CH_3)$	—	ø	S	40
$CH_2—CH_2—N(CH_3)_2$	—	↑ 20–50	20	39
$CH_2—CH_2—NH_2$	OH	↓ 20–50	S	64
$CH_2—CH_2—N(H)(CH_3)$	OH	↓ 20–50	14	35
$CH_2—CH_2—N(CH_3)_2$	OH	↑ 5–10	100	50
$CH_2—CH_2—N(H)(C_2H_5)$	OH	↑ 20–50	11	50
$CH_2—CH_2—N(C_2H_5)_2$	OH	↑ 20–50	11	42
$CH_2—CH(CH_3)—N(CH_3)_2$	OH	↑ > 50	78	20
$CH(CH_3)—CH_2—N(CH_3)_2$	OH	ø	49	5
$CH(OH)—CH_2—N(CH_3)_2$	OH	↑ > 50	1	19

Our investigations were, furthermore, concerned with the significance of the side chain structure in position 3 of the indole ring. For this purpose only unsubstituted and 4-hydroxylated compounds were selected (Table III). Tryptamine itself has a weak inhibitory action and its monomethylated derivative is practically without effect on the knee jerk, whereas *N,N*-dimethyltryptamine produces a moderate increase of reflex action. All three of these compounds have marked hypertensive actions, while only the dimethylated substance has anti-5-HT properties. Of the 4-hydroxylated derivatives, 4-hydroxytryptamine and 4-hydroxymonomethyltryptamine

TABLE IV

INFLUENCE OF SUBSTITUTION IN POSITION 1 OF DIMETHYLTRYPTAMINE AND ITS 4-SUBSTITUTED-DERIVATIVES



Substituent		Knee jerk	Serotonin antagonism	Pressure activity
R_1	R_4			
CH_3	—	o	71	37
CH_3	OH	↑ 20–50	340	25
CH_3	OPO_3H_2	ø	44	15
$COCH_3$	OH	o	50	10
$CH_2C_6H_5$	OH	o	19	17

inhibit the knee jerk moderately, while all other compounds derived from 4-hydroxytryptamine produce a more or less pronounced excitatory effect. The most active compound in this series is 4-hydroxy-*N,N*-dimethyltryptamine or psilocine. In comparison, any alteration in the Ps side chain is followed by a decrease of activity. Of the compounds not substituted in position 4, only *N,N*-dimethyltryptamine antagonizes 5-HT while all show moderate to marked pressor activity. All 4-substituted compounds with the exception of 4-hydroxytryptamine inhibit 5-HT, and all except the α- or β-substituted derivatives lead to a marked blood pressure rise.

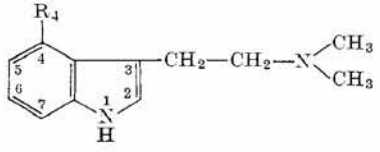
In Table IV we have summarized the results obtained with 4-hydroxylated indoles substituted in position 1, i.e., on the indole nitrogen. Quite obviously the 1-substitution leads to a marked decrease of action on the knee jerk.

However, it also leads to an increase of anti-5-HT activity of some Ps derivatives, as exemplified by 1-methylpsilocine, 1-methylpsilocybine, 1-acetylpsilocine, and 1-benzylpsilocine. The pressor activity of the 1-substituted derivatives is weaker than that of the corresponding substances without *N*-substitutions.

From all the results reported up to now, it becomes evident that the stimulatory effect of Ps on the knee jerk is a property observed only with derivatives of 4-hydroxyindoles. It remained to be investigated to what extent other types of substituents in position 4 will influence this characteristic activity. As illustrated in Table V, an effect similar to that produced by

TABLE V

INFLUENCE OF SUBSTITUTION IN POSITION 4 OF THE INDOLE RING OF DIMETHYLTRYPTAMINE



Substituent R_4	Knee jerk	Serotonin antagonism	Pressure activity
OH	↑ 5–10	100	50
Br	↑ > 50	155	50
CH_3	↑ 20–50	131	44
OCH_3	↑ 20–50	28	30
$OCH_2C_6H_5$	↑ 20–50	131	40
$OCOC_6H_5$	↑ 5–10	318	40
OSO_3H	o	< 1	ø

4-hydroxy or 4-phosphoryloxy substitution can also be obtained with other substituents. From a quantitative point of view the replacement of the hydroxy group in position 4 by bromine or methyl, methoxy, benzyloxy, etc., diminishes the activity in most instances quite markedly, but the quality of the effect is preserved. The full effect as observed with Ps is only present in the case of the benzoic acid ester. However, if 4-hydroxy-*N*,*N*-dimethyltryptamine is esterified with sulfuric acid, the activity is lost completely. With the exception of this last example, the anti-5-HT activity remains practically unchanged regardless of the type of 4-substitution. The same is the case with regard to the pressor activity of these compounds.

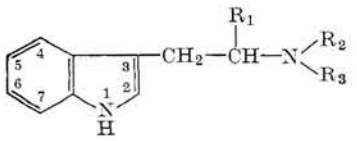
A further interesting property of the simple tryptamine derivatives is their

ability to inhibit MAO. Noteworthy in this respect are especially the α-alkylated tryptamine derivatives (Gey and Pletscher, 1962; Greig and Gibbons, 1962; Greig *et al.*, 1959, 1962). Possibly the enzyme-inactivating effect may contribute to central stimulation of sympathetic functions—an effect very characteristic of this whole class of substances. Upon thorough pharmacologic investigation of α-methyltryptamine, our attention was drawn to the antireserpine action of this compound. We decided, therefore, to follow up this lead by investigating the structure-activity relationship of a number of preparations in this respect. As a test we used the facilitating influence of reserpine on tonic extensor seizures by pentylenetetrazole (Chen *et al.*, 1954; Jenney, 1954). This reserpine effect is inhibited or abolished, for instance, by MAO inhibitors (Chen and Bohner, 1961; Hertting, 1958; Kobinger, 1958; Lessin and Parkes, 1959; Weiss *et al.*, 1960).

The results in Table VI show that α-alkylation distinctly enhances the antireserpine activity, e.g., α-methyltryptamine is 20 times more active than

TABLE VI

INFLUENCE OF α-ALKYLATION OF TRYPTAMINE OR DIMETHYLTRYPTAMINE



Substituent			Reserpine[a] antagonism	Monoamine oxidase[b] inhibition in vitro
R_1	R_2	R_3		
H	H	H	15.0	—
CH_3	H	H	0.75	5.8×10^{-5}
C_2H_5	H	H	0.75	1.3×10^{-4}
H	CH_3	CH_3	100.0	—
CH_3	CH_3	CH_3	3.5	—

In this and the subsequent tables the figures have the following meaning:

[a] Dose of the antagonist in mg/kg s.c. which raises the amount of pentylenetetrazole by at least 50% above the control value obtained in reserpine-treated animals only.

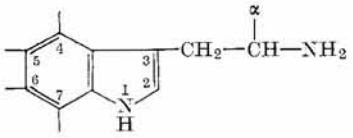
[b] Concentration of test substance (mols/l) inhibiting monoamine-oxidase by 50% ($= I_{50}$).

tryptamine, and α-methyl-*N*,*N*-dimethyltryptamine 28 times more active than *N*,*N*-dimethyltryptamine. Furthermore, it appears that the primary amines are distinctly more active than the corresponding tertiary amines.

In order to get some information about the influence of ring substitution, derivatives of α-methyltryptamine and α-ethyltryptamine with a hydroxy or a methyl group in various positions of the benzene ring were investigated (see Table VII). It was found that hydroxylation reduces the antireserpine activity, especially with the hydroxy group in position 6 and 7. Methylation, on the other hand, enhances the antireserpine activity, as compared with the corresponding hydroxy derivatives. The 7-methyl derivative is even more active than the unsubstituted α-methyltryptamine. However, no rule could be established with respect to the methylation effect.

TABLE VII

INFLUENCE OF THE POSITION OF SUBSTITUTION IN THE BENZENE RING OF α-ALKYLATED TRYPTAMINES

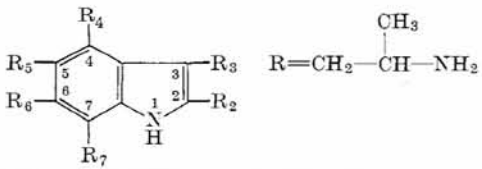


α-substituent	Ring-substituent	Reserpine-antagonism	Monoamine oxidase inhibition in vitro
CH_3	4-OH	3.50	8.3×10^{-4}
C_2H_5	4-OH	> 10.0	$> 10^{-3}$
CH_3	4-CH_3	0.75	5.9×10^{-4}
C_2H_5	4-CH_3	1.50	$> 10^{-3}$
CH_3	5-OH	3.50	—
CH_3	5-CH_3	2.00	4.0×10^{-4}
CH_3	6-OH	10.0	—
CH_3	6-CH_3	2.00	2.0×10^{-4}
CH_3	7-OH	5.00	—
CH_3	7-CH_3	0.35	8.3×10^{-6}

In this context it seemed to us of importance also to examine the activity changes produced by shifting the 2-aminopropyl side chain from its 3-position present in α-methyltryptamine to the other possible positions in the indole ring system, viz., to positions 2, 4, 5, 6, and 7 (see Table VIII). Our results have revealed the rather interesting fact that activity is not bound to the "classical" 3-position. Thus, we found that the 6-(2-aminopropyl)indole by far outstrips its analogs with respect to antireserpine activity and inhibition of MAO. The 5- and 3-substituted indoles were found to be somewhat less active. In contrast to this, the 2-, 4-, and 7-substituted compounds showed a distinct loss of activity.

TABLE VIII

INFLUENCE OF THE POSITION OF 2-AMINOPROPYL SUBSTITUTION IN THE INDOLE RING



Position of side chain	Reserpine antagonism	Monoamine oxidase inhibition *in vitro*
R_2	> 5.0	—
R_3	0.75	5.8×10^{-5}
R_4	7.50	3.7×10^{-5}
R_5	0.50	2.2×10^{-5}
R_6	0.15	4.6×10^{-6}
R_7	5.00	ca. 1×10^{-3}

A parallelism between the antireserpine activity and the MAO-inhibiting properties of the various α-alkyltryptamine derivatives does not seem to exist. This is not surprising, seeing that the doses necessary to produce a traceable inhibition of MAO activity *in vivo* are about 100 times greater than those required for inhibition of the seizure-enhancing effect of reserpine.

Summary and Conclusions

The structure-activity relationships of a number of hydroxylated, phosphorylated, and alkylated tryptamines and tryptamine analogs have been investigated. Within the limits of the tests applied it was found that 4- and 5-hydroxy, and 4- and 5-phosphoryloxy derivatives of *N*,*N*-dimethyltryptamine possess considerable activity while the corresponding 6- and 7-derivatives are practically inactive. Contrary to the short blocking action of the 5-hydroxyindole derivatives (bufotenin and 5-HT), the 4-hydroxyindoles (psilocine and psilocybine) exert a characteristically long-lasting activating effect on the patellar reflex. Within the rather large group of investigated compounds it was found that the reflex-activating property was associated with substitution in position 4 of the indole ring. The side chain structure is a determining factor insofar as only the tertiary amines possess reflex-stimulating activity. With respect to anti-5-HT and pyrogenic effects, it was found that the 4-hydroxylated *N*,*N*-dimethyltryptamines surpass their 5-substituted analogs in activity. Substitution in position 1 of the indole ring leads to an increase of anti-5-HT activity and reduction of reflex activation both with the 4-hydroxylated and 4-phosphorylated compounds.

The action pattern of the 4-substituted *N*,*N*-dimethyltryptamines is qualitatively remarkably similar to that of LSD, the characteristic effects of which also include reflex activation, 5-HT antagonism and pyrogenic activity (Cerletti, 1956; Little *et al.*, 1957; Rothlin, 1957; Rothlin *et al.*, 1956; Weidmann and Cerletti, 1957). More than chance would seem to be responsible for this parallelism of action, since LSD may also be regarded as a 4-substituted dimethyltryptamine derivative. Interestingly enough, a further structure-activity parallelism may be seen in the fact that substitution in position 1 of the lysergic acid ring system (1-methyl-LSD; 1-acetyl-LSD) also leads to a significant increase of anti-5-HT activity (Cerletti and Doepfner, 1958).

It is tempting to speculate whether the pronounced activation of spinal reflexes by small doses of 4-hydroxyindoles is in some way connected with the psychotropic activity of these compounds in man. This does not presuppose the identity of these two effects, but rather that a mechanism similar to that producing reflex sensitization could also be at work at higher levels in the central nervous system. In favor of such an idea is the fact that the psychic syndrome produced by psilocybine in man is also accompanied by an increased sensitivity of the knee jerk (Isbell, 1959). This is also the case in human experiments with LSD (Isbell *et al.*, 1956; Stoll, 1947). It must, however, be observed that in this kind of animal experiment psilocybine and LSD are active at the same dose level, whereas the human dose range for psychotropic effects differs greatly, LSD being at least 100 times more potent than psilocybine (Isbell, 1959).

In the group of indoles with varying 2-alkyl-2-aminoethyl substitution both the action pattern and structure-activity relationship are of a different kind. Antireserpine action and MAO inhibition are pronounced, whereas reflex activation and pyrogenic action are weak. The primary amine structure (though not its position) in the side chain is of decisive importance for the activity in these compounds. Nevertheless, linkage of the side chain to position 6 of the indole ring has yielded a remarkably active product.

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