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THE CENTRAL STIMULANT PROPERTIES OF SOME SUBSTITUTED INDOLYLALKYLAMINES AND β-CARBOLINES AND THEIR ACTIVITIES AS INHIBITORS OF MONOAMINE OXIDASE AND THE UPTAKE OF 5-HYDROXYTRYPTAMINE

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Some central stimulant properties of α-methyltryptamine and related compounds have been explained as due to an increased effectiveness of brain amines by a combination of interference with their storage and inhibition of their destruction by monoamine oxidase (Lessin, Long & Parkes, 1965a). A number of related indolylalkylamines and some β-carbolines related to harmaline have been examined for these two properties and this paper considers how far the results may account for the distribution of stimulant activities in the two series.

Some properties of a few of the indolylalkylamine derivatives studied here were previously reported by other workers (Greig, Walk & Gibbons, 1959 ; Tedeschi, Tedeschi, Fowler, Green & Fellows, 1962 ; Whittle & Young, 1963 ; Hester, Greig, Anthony, Heinzelman & Szmuszkovicz, 1964). The monoamine oxidase inhibitory properties of some of the β-carbolines have been reported by Udenfriend, Witkop, Redfield & Weissbach (1958) and Pletscher, Besendorf, Bächtold & Gey (1959).

METHODS

Stimulant activity in mice

This was assessed by measuring body tremors, using the method described by Lessin (Lessin, 1959 ; Parkes & Lessin, 1961).

"Latent" stimulant activity was assessed in mice pretreated with the irreversible monoamine oxidase inhibitor, pargyline hydrochloride (75 mg/kg), intraperitoneally, three times at intervals of 1.5 hr, the last dose being given 1.5 hr before the test compound.

Monoamine oxidase inhibitory activity in vitro

The enzyme preparation consisted of the mitochondrial fraction of guinea-pig liver homogenate, washed three times with water and resuspended in M/15 phosphate buffer, pH 7.2. The substrate used was 5-hydroxytryptamine, 2×10^{-3}M, and enzyme activity was measured manometrically.

Monoamine oxidase inhibitory activity in vivo

(a) Monoamine oxidase activity was measured, as described above, in brain homogenates prepared from mice treated with test compounds. Tissue concentrations of 400 mg wet wt/ml. buffer were used.

(b) The potentiation of tremors produced by 5-hydroxytryptophan in mice pretreated with test compounds was measured by the method described by Lessin (1959). Results are expressed relative to the activity of a standard inhibitor, such as harmaline.

Estimations of drug levels in brain

Indolylalkylamines were estimated by the methods referred to in an earlier paper (Lessin, Long & Parkes, 1966); harmaline was extracted by the method described by Udenfriend *et al.* (1958) and estimated fluorimetrically by comparison with standards after thin-layer chromatography.

Inhibition of the uptake of 5-hydroxytryptamine

The methods used for ox platelets *in vitro*, and for rat and mouse platelets *in vivo* are described in a previous paper (Lessin, Long & Parkes, 1965b). In addition, some values were obtained on mouse platelets *in vitro* by the method described by Stacey (1961) using 5-hydroxytryptamine labelled with ^{14}C. For *in vivo* studies in mice using labelled 5-hydroxytryptamine, blood withdrawn by heart puncture from several mice was pooled, platelets isolated and counted, as in the method quoted above.

The compounds studied were synthesized by Heath-Brown and Philpott. Details concerning some of these have appeared (Heath-Brown & Philpott, 1965) and others are yet to be published.

RESULTS

Activity in producing tremors was assessed in mice treated with the test compound, in doses up to 100 mg/kg, intraperitoneally. Active compounds are placed in Class A of Tables 1 and 2, in which is found the reference compound, α-methyltryptamine (Ro 3-0926). Compounds causing tremors only in mice pretreated with pargyline ("Latent" stimulation) are placed in Class B of Tables 1 and 2, in which are found the reference compounds, α,α-dimethyltryptamine (Ro 3-1638) and harmaline. Compounds causing no tremors under these conditions in doses up to 20 mg/kg intraperitoneally are classed as inactive (Class O). Activities causing tremors after intraperitoneal injection in mice are quoted relative to that of Ro 3-0926, which is active at doses of 10 to 25 mg/kg. Similarly, values for activity in causing tremors in mice repeatedly pretreated with pargyline are also given; in such mice, Ro 3-0926 was active in doses of 0.5 to 1.5 mg/kg.

It will be seen that stimulant activity was frequently found among the substituted indolylalkylamines (Table 1). Few of the β-carbolines, however, were stimulant and then only after pargyline pretreatment (Table 2). It should be mentioned that harmaline and other β-carbolines do cause a type of tremor after injection in mice. This, however, is a recognizably different, coarser tremor than that caused by indolylalkylamines, or 5-hydroxytryptophan following monoamine oxidase inhibition, and, in particular, is characterized by not occurring in the confined space in which the mice were placed for measurement of tremor.

Inhibition of monoamine oxidase

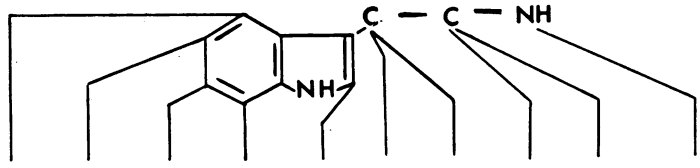
In vitro

Table 1 gives the activities, relative to that of harmaline, of substituted indolylalkylamines, calculated from the concentrations required to cause 50% inhibition. This value

TABLE 1

STRUCTURES AND ACTIVITIES IN A SERIES OF INDOLYLALKYLAMINE DERIVATIVES

Formula



Ro 3—											Stimulant class*
Harmaline	See Table 2										B++
0926	H	H	H	H	H	H	H	H	CH_3	H	A+++
1638	H	H	H	H	H	H	H	CH_3	CH_3	H	B+++
1674	H	H	CH_3O	H	H	H	H	CH_3	CH_3	H	B++
1691	H	H	H	H	H	H	CH_3	CH_3	CH_3	H	B+
1698	3-α-(Isopropylamino)ethyl indole										O
1701	3-(3-Aminobutyl)indole										B++
1703	H	H	H	H	H	CH_3	CH_3	H	H	H	A+
1715	H	H	H	H	H	H	H	H	CH_3	CH_3	A+++
1719	1-Amino-1-(3-indolylmethyl)cyclohexane										O
1720	3-(3-Amino-2-methylbutyl)indole										O
1723	H	H	H	H	H	H	H	H	CH_3	$CH(CH_3)_2$	B++
1727	H	H	H	H	H	H	H	H	CH_3	$CH_2CH_2CH_3$	B+
1729	H	H	H	H	H	H	H	H	CH_3	$(CH_2)_3CH_3$	O
1733	1-Amino-2-(3-indolylmethyl)cyclopentane										B++
1736	H	H	H	H	H	H	H	H	CH_3	CH_2CH_3	A+
1737	H	H	H	H	H	H	H	H	CH_3	CH_2Ph	O
1746	H	H	H	H	CH_3	H	H	H	CH_3	H	O
1791	1-Amino-2(-3-γ-indole)cyclohexane										O
1839	H	H	H	H	H	H	CH_3	CH_3	H	H	B+
1878	H	H	Cl	H	H	H	H	H	CH_3	H	B++
1880	H	H	Cl	H	H	H	H	CH_3	CH_3	H	B+
1883	H	H	Cl	H	H	H	H	H	CH_3	CH_3	B+
1890	H	H	CH_3O	H	H	H	H	H	CH_3	H	A++
1902	H	H	Cl	H	H	H	H	CH_3	CH_3	CH_3	B+
1908	H	CH_3O	H	H	H	H	H	H	CH_3	H	A+
1909	H	H	H	H	H	H	H	CH_3	CH_3	CH_3	B+++
1913	H	H	CH_3O	H	H	H	H	H	CH_3	CH_3	A+
1914	H	CH_3O	H	H	H	H	H	H	CH_3	CH_3	A+
1916	H	H	H	CH_3	H	H	H	CH_3	CH_3	H	B+++
1917	H	H	H	CH_3	H	H	H	H	CH_3	H	A++
1932	H	H	H	H	H	H	H	H	CH_2CH_3	H	A++
1950	H	H	CH_3O	H	H	H	H	H	CH_2CH_3	H	B++
1960	CH_3	H	H	H	H	H	H	CH_3	CH_3	H	B+
1985	H	Cl	H	H	H	H	H	H	CH_3	H	A++
1989	H	Cl	H	H	H	H	H	H	CH_3	CH_3	A+
2014	CH_3	H	H	H	H	H	H	H	CH_3	H	B+++
2015	CH_3	H	H	H	H	H	H	H	CH_3	CH_3	B+++
2024	H	Cl	H	Cl	H	H	H	H	CH_3	H	B+
2026	H	H	CH_3	H	H	H	H	H	CH_3	H	B+++
2027	H	H	CH_2	H	H	H	H	H	CH_3	CH_3	B+++
2048	H	H	CH_3	H	H	H	H	CH_3	CH_3	H	B+

* Class: A=Stimulant when given alone to mice; B=stimulant only in mice pretreated with irreversible monoamine oxidase inhibitors; O=not stimulant in either situation.

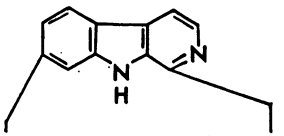
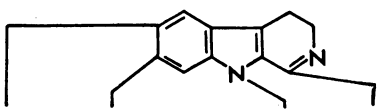
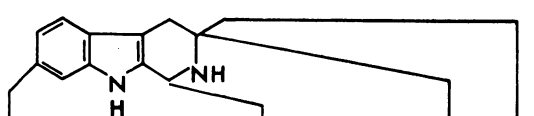
+, ++, +++=Approximate degree of activity within class.

Table 1 (Cont.)

Activities						
Relative stimulant activity		Relative MAO inhibitory activity		Rel. act. v. 5-hydroxy-tryptamine uptake platelets *in vitro* (Trypt.=1)	Min. dose reducing 5-hydroxy-tryptamine uptake *in vivo* (mg/kg)	
Alone	After pargyline	*in vitro*	5-Hydroxy-tryptophan potentiation *in vivo*		Rat	Mouse
0	35(15–75)	*100*	*100*	10	>10	
100	*100*	1	50(30–80)	2		2·5
7	60	0·2	17·5(14–21·5)	0·8	2·5	5
<1	6	1·5	<5	1·4	⩽10	
<1	25	0·02	<5	0·6	10	20
		0·02	<5	0·6		
10	33	0·8	5	2·5		
		0·005				
100	100	1·3	48(28–84)	1·5	10	
		<0·005	<5	0·4		
<1	10	0·1	<5			
		0·2				
		0·5	<5	2		
		0·1	<5	1·5	⩽10	
<1	16	0·14	<5	1·2		
10		1·2	<5	1·2	>10	
		0·05	<5	4	>10	
		0·14	<5	1	>25	
		<0·01	<5	1·6	>10	
		0·06	<5	1·5		
12	25	0·06	<5	10	⩽10	
<1	16	0·1	<5	6	25	100
<1	16	0·3	<5	3·3	⩽10	
30	16	0·4	22(13–37)		⩽10	
<1	20	0·4	<5		>10	
		0·08	<5	1		
<1	40	0·4	<5	0·3	>10	20
12	12	0·6	10(6–16)	1	>10	
1	6	0·07	<5	<0·5	>10	
<1	40	0·25	10	1·5		⩽20
		1·2	16(7–37)	1·6		
66	55	0·75	5			
		0·06	<5			
<1	15	0·3	<5	0		
		0·14	<5	1·5		
		0·14	<5			
		0·3	10			
		0·3	10			
		0·6	10			
		0·3	10			
		0·14	10			
		0·14	<5			

TABLE 2

STRUCTURES AND ACTIVITIES IN A SERIES OF β-CARBOLINE DERIVATIVES

Ro 3—	Formula					Activities				
						Relative stimulant activity after pargyline	Relative MAO inhibitory activity: *in vitro*	Relative MAO inhibitory activity: 5-Hydroxytryptophan potentiation *in vivo*	Rel. act. v. 5-hydroxytryptamine uptake Platelets *in vitro* (Trypt.=1)	Min. dose reducing 5-hydroxytryptamine uptake *in vivo* (mg/kg) Mouse
Harmine		CH_3O		CH_3		<10	75	33(26–42)	5	
Harmol		HO		CH_3		<10	10	<1		
1666		CH_3CH_2O		CH_3			150	150(80–280)		
1697		$CH_3CH_2CH_2O$		CH_3		10(4·5–24)	200	265(222–317)		
1699		$CH_3CH_2CH_2CH_2O$		CH_3		25	35	92(74–115)		
										
Harmaline	H	CH_3O	H	CH_3		35(15–75)	*100*	*100*	10	>10
Harmalol	H	HO	H	CH_3		<10	15	<1		
1564 (Harmalan)	H	H	H	CH_3		<10	15	31(24–40)	1·9	
1565	H	CH_3O	CH_3	CH_3			60	145(89–250)	4	>5
1587	H	$C_9H_{19}O$	H	CH_3		<10	1·5	8		
1590	H	$C_{10}H_{21}O$	H	CH_3		<10	1·5	2		
1594	CH_3O	H	H	CH_3			0·6	25	1·5	
1605	CH_3O	H	CH_3	CH_3		<10	1·5	5		
1620	H	CH_3CH_2O	H	CH_3		30(15–70)	300	680(540–900)	5	>20
1651	H	$(CH_3)_2CHO$	H	CH_3		10	50	58(44–76)	6	>20
1675	H	$CH_3CH_2CH_2O$	H	CH_3		25	300	650(570–750)		
1676	H	$CH_3CH_2CH_2CH_2O$	H	CH_3			60	320(270–280)		
1764	H	CH_3O	H	CH_2CH_3		<10	7·5	<2	1·2	
1768	H	CH_3O	H	$CH_2CH_2CH_3$		<10	0·05	<2	1·8	
1774	H	CH_3O	H	$CH_2CH_2CH_2CH_3$		<10	0·04	<2		
										
Tetrahydroharmine		CH_3O		CH_3	H H		3	25(20–32)		
1728		H		CH_3	CH_3 H	<10	0·1	<2	0·8	>10
1777		H		CH_3	CH_3 CH_3	<10	<0·01	<2	1·5	>20
0926	See Table 1					*100*	1	50(30–80)	2	2·5

for harmaline is 3×10^{-7}M. It will be seen that the values vary over approximately a twentyfold range, and show some degree of correlation with stimulant activity. By assigning arbitrary ranking values to the stimulant categories in which the compounds are placed, a significant correlation was found with the *in vitro* log I_{50} values ($r = 0.36$; $P < 0.01$ for 39 values). Relative inhibitory activities are given for a number of β-carbolines in Table 2. Many of these, although possessing only "latent" stimulant activity, showed enzyme inhibitory activities several orders greater than those of the indolylalkylamines.

In vivo

Tables 1 and 2 show the activities of the indolylalkylamines and β-carbolines in causing tremors in mice treated with 5-hydroxytryptophan; harmaline was active at doses of 0.5 to 1.5 mg/kg intraperitoneally.

The β-carbolines as a group are more active than the indolylalkylamines but the latter show higher relative activities *in vivo*.

Table 3 shows the degree of inhibition of the brain enzyme measured by the disappearance of 5-hydroxytryptamine incubated with brain homogenates prepared from animals treated with inhibitors, expressed as percentage of that disappearing from control homogenates. It also shows the concentrations of each compound which would be required to produce the inhibition observed, if added *in vitro*. It may be seen that these concentrations agree with the brain levels of compound actually found in animals

TABLE 3

INHIBITION OF MONOAMINE OXIDASE ACTIVITY IN BRAIN HOMOGENATES FROM MICE TREATED WITH HARMALINE AND INDOLYLALKYLAMINE DERIVATIVES

Inhibition is measured by the 5-hydroxytryptamine disappearing in 45 min, expressed as % that disappearing in homogenates from untreated mice. The effective concentration of the compound is that required to produce the observed degree of inhibition when added to homogenate *in vitro*

		Mice killed 40 min later			Mice killed 90 min later		
Ro 3–	Dose (mg/kg I.P.)	5-hydroxy-tryptamine disappear-ing (%)	Brain level of compound (μg/g)	Effective concn. (μg/ml.)	5-hydroxy-tryptamine disappear-ing (%)	Brain level of compound (μg/g)	Effective concn. (μg/ml.)
Harmaline	2	10	0·5	0·2	52	0·1	0·4
	5	4	1·0	at least 0·4	25	0·3	0·08
	20	2	3	at least 0·4	3	1·0	at least 0·4
0926	10	80	3·2	0·9			
	25	45	6·8	2·6	36		3·0
	50	20	14·4	6·8	14		8·0
1638	25	95	5·4	3·8	82		7·4
	50	80	13·6	7·6	64		9·5
1674	10	63		1·4			
	25	48		2·0			
1745	25	84		1·8			
	50	70		3·2			
1715	10	85	2·9	0·95			
	25	48	6·2	3·8	42		4·0
	50	30	14·8	7·6	18		8·6

treated with the stated doses, which may suggest that the compounds are exerting *in vivo* the inhibitory activities that they show *in vitro*.

Inhibition of 5-hydroxytryptamine uptake by blood platelets

Activities, relative to tryptamine, of various indolylalkylamines and β-carbolines in inhibiting 5-hydroxytryptamine uptake by suspensions of ox blood platelets *in vitro* are shown in Tables 1 and 2. In these experiments tryptamine caused 50% inhibition at 9.5×10^{-5}M. It will be seen that all compounds of both series show a very similar order of activity. The Tables also show that treatment of rats or mice with several indolylalkylamines prevented the blood platelets from taking up as much 5-hydroxytryptamine as those of control animals. Harmaline and other β-carbolines showed no detectable *in vivo* reduction of 5-hydroxytryptamine uptake in the largest dose that could be given. On the contrary, they caused a significant increase in uptake (Table 4).

TABLE 4

EFFECT ON 5-HYDROXYTRYPTAMINE UPTAKE BY BLOOD PLATELETS FROM MICE TREATED WITH INDOLYLALKYLAMINES AND β-CARBOLINES

Compound	Dose (mg/kg I.P.)	5-Hydroxytryptamine uptake as % controls
Ro 3–0926, (α-methyltryptamine)	10	44
	20	52
Ro 3–1638, (α,α-dimethyltryptamine)	20	44
Harmaline	10	190
Ro 3–1620, (7-ethoxyharmalan)	10	180
	20	200

DISCUSSION

Two series of compounds, indolylalkylamine derivatives related to α-methyltryptamine and β-carboline derivatives related to harmaline, have been studied for stimulant properties; as inhibitors of monoamine oxidase; and for interference with uptake of 5-hydroxytryptamine by blood platelets. Stimulant properties were more marked in the indolylalkylamines, while the β-carbolines were the more powerful inhibitors of monoamine oxidase. The property of inhibiting 5-hydroxytryptamine uptake *in vitro* was of a similar, moderate order throughout the two series, although the carbolines showed no activity *in vivo*.

Structure-activity relations

The structures of the indolylalkylamine derivatives, shown in Table 1, permit some conclusions to be drawn as to the effect of chemical constitution upon stimulant and monoamine oxidase inhibitory activities. Methylation of the amino-N causes little change in activities (compare Ro 3-1715 with Ro 3-0926; Ro 3-1883 with Ro 3-1878; Ro 3-1909 with Ro 3-1638; Ro 3-1913 with Ro 3-1890; Ro 3-1989 with Ro 3-1985; Ro 3-2015 with Ro 3-2014; Ro 3-2027 with Ro 3-2026). Substitution by other alkyl groups, however, reduces all activities. Monoamine oxidase inhibitory activity *in vitro* decreases

with increasing chain length (compare Ro 3-0926 and Ro 3-1715 with Ro 3-1736, Ro 3-1727, Ro 3-1729, Ro 3-1723 and Ro 3-1737).

Replacement of the α-methyl group by α-ethyl reduces activities somewhat, particularly the potentiation of 5-hydroxytryptophan tremors (compare Ro 3-1932 (etryptamine) with Ro 3-0926; Ro 3-1950 with Ro 3-1890). The presence of a second α-methyl group reduces activities, particularly stimulant activity (compare Ro 3-1638 with Ro 3-0926; Ro 3-1909 with Ro 3-1715), though this effect is not so clear where ring substituents are present. These consistently reduce activity, a methyl substituent having the greatest effect when in position 2- (Ro 3-1746 vs. Ro 3-0926) and least when in position 7- (Ro 3-1917 vs. Ro 3-0926; Ro 3-1916 vs. Ro 3-1638).

The β-carbolines may be considered in three groups differing in the degree of saturation of the pyridine ring. In general, compounds in the dihydro series, to which harmaline belong are more active monamine oxidase inhibitors than corresponding compounds in either the aromatic or the tetrahydro series (compare harmaline, harmine and tetrayhdro-harmine; harmalol and harmol) (cf. Udenfriend *et al.*, 1958; Pletscher *et al.*, 1959); Ro 3-1620 and Ro 3-1666; Ro 3-1675, Ro 3-1697 and Ro 3-1699. Alkylation of the 7-hydroxy group increases activity over the parent phenol. This effect increases with chain length to a maximum which is reached for monoamine oxidase inhibition with ethyl or propyl (compare the series: harmalol, harmaline, Ro 3-1620, Ro 3-1675, Ro 3-1676, Ro 3-1651, Ro 3-1587 and Ro 3-1590; harmol, harmine, Ro 3-1666, Ro 3-1697 and Ro 3-1699). The alkoxy group is less effective for activity in the 6-position than in the 7-, and 6-alkoxy compounds are inferior to those lacking any substituent in this position. (Compare Ro 3-1594 with harmaline and Ro 3-1564 (harmalan)). Replacement of the 1-methyl group by longer alkyl chains reduces activities. (Compare the series: harmaline, Ro 3-1764, Ro 3-1768 and Ro 3-1774).

Significance of activities

In an earlier paper (Lessin *et al.*, 1965a) it was argued that, whereas inhibition of monoamine oxidase alone could result in the accumulation of tissue amines sufficient to cause central stimulation, this was unlikely to be responsible for the stimulant properties of compounds like α-methyltryptamine, since drugs far more potent as inhibitors of the enzyme lacked these stimulant properties. The distribution of stimulant activities among the substituted indolylalkylamines reported here, and the degree of correlation found with their activities in inhibiting monoamine oxidase, suggest, however, that these two properties are related to some extent, since only the more active inhibitors exert frank stimulation, the less active inhibitors causing stimulation only after prior irreversible enzyme inhibition.

The higher order of monoamine oxidase inhibitory activities found both *in vitro* and *in vivo* for the β-carboline derivatives is clearly not correlated in the same manner with stimulant properties in mice, since none of these compounds is even moderately stimulant except in animals pretreated with an irreversible inhibitor. In attempting to find a reason for this difference between the β-carbolines and the indolylalkylamines, we may consider the other property that was suggested in an earlier paper as contributing to the stimulant actions of the latter class—namely, inhibition of amine uptake. But all

the indolylalkylamines show very similar activities in reducing the uptake of 5-hydroxytryptamine by ox platelets *in vitro*, although they differ in stimulant potency. Moreover, the β-carbolines are also active in inhibiting the 5-hydroxytryptamine uptake *in vitro*, and their activities are of the same order as those of the indolylalkylamines. When activities *in vivo* are considered, however, the β-carbolines do not reduce the uptake of 5-hydroxytryptamine. Indeed, they are found to increase the amount taken up, as might be expected, from their inhibition of monoamine oxidase. These results were obtained using blood platelets as a model system and the reservation must be made that the activities found may not reflect those operating in the central nervous system.

We may thus conclude that stimulant activity (tremors) in the indolylalkylamine and β-carboline derivatives depends both on inhibition of monoamine oxidase and interference with tissue amine distribution. Where both actions are exerted *in vivo*, as in the indolylalkylamines, the degree of stimulant activity appears to depend on the degree of enzyme inhibitory activity. Where activity in interfering with amine distribution is weak, as in the β-carbolines, even higher activity as enzyme inhibitors does not result in stimulant properties.

Regarding the relative potency of indolylalkylamines and β-carbolines as inhibitors of monoamine oxidase *in vivo*, the evidence from brain homogenates suggests that compounds of both series may exert *in vivo* the same relative activities that are found *in vitro*. It must be remembered that determination of enzyme inhibition by reversible inhibitors given *in vivo* suffers from several objections. These result principally from the effects of the destruction of tissue organization, the inevitable dilution and the subsequent addition of substrate upon equilibrium between enzyme and inhibitor. The resulting situation in the homogenate resembles that following addition of inhibitor *in vitro*. The procedure may, in fact, amount to a method for estimating the quantity of inhibitor present by the inhibition of enzyme observed, and thus the results agree with those of determination by other methods (Table 4).

On the other hand, judged by potentiation of the stimulant effect of 5-hydroxytryptophan, the indolylalkylamines were considerably more active, relative to the β-carbolines, than would appear from their *in vitro* activities. Although potentiation of 5-hydroxytryptophan tremors has been taken as a measure of monoamine oxidase inhibition (Lessin, 1959), the assumption that this is the only operative factor may not be true in the case of compounds such as the indolylalkylamines. Their property of interfering with amine distribution could contribute to potentiation of the tremorigenic action of injected 5-hydroxytryptophan by rendering the resultant 5-hydroxytryptamine in the tissues more effective for stimulation. They would thus appear unduly active in comparison with other inhibitors which do not exert such an effect.

SUMMARY

1. A number of indolylalkylamine and β-carboline derivatives have been examined as inhibitors, both *in vitro* and *in vivo*, of monoamine oxidase and uptake of 5-hydroxytryptamine by blood platelets, and for activity in causing tremors in mice.

2. Stimulant activity in the indolylalkylamine series showed some correlation with monoamine oxidase inhibitory activity, the less active compounds causing tremors only after treatment of the mice with irreversible inhibitors of the enzyme.

3. Although more potent inhibitors of monoamine oxidase, the β-carboline derivatives showed no stimulant properties except in mice pretreated with irreversible inhibitors.

4. Similar activities in reducing the uptake of 5-hydroxytryptamine by blood platelets *in vitro* were found in both groups, but the β-carbolines did not show this activity *in vivo*.

5. It is suggested that the property of interfering with amine distribution permits the indolylalkylamine derivatives to exert stimulant activity, the degree of which may depend upon monoamine oxidase inhibitory activity, while the more potent enzyme inhibitors among the β-carboline derivatives are weaker stimulants because they do not reduce amine uptake *in vivo*.

6. It is further suggested that interference with amine distribution contributes to an unduly high apparent monoamine oxidase inhibitory activity for the indolylalkylamines, measured *in vivo* by the potentiation of the stimulant effects of 5-hydroxytryptophan, compared with the activity of β-carbolines such as harmaline.

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