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Biological Activities of Some 5-Substituted N,N-Dimethyltryptamines, α-Methyltryptamines, and Gramines*

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Summary. Three series of derivatives of N,N-dimethyltryptamine, α-methyltryptamine and gramine bearing substituents of varying electronic nature on the C-5 position were tested for acute toxicity, effect on barbiturate sleeping time, antireserpine effect, swim maze, variable interval conditioned behavior, and inhibition of monoamine oxidase. No correlation could be made between the electronic effects and their pharmacological activities. It was thus suggested that there exist different pharmacological receptors for the tryptamines and gramines.

Key-Words: 5-Substituted N,N-Dimethyltryptamines, α-Methyltryptamine, and Gramines — Monoamine Oxidase Inhibitors — Psychopharmacology.

Introduction

The antiserotonin activities of some substituted N,N-dimethyltryptamines, α-methyltryptamines, and gramines have been investigated (Erspamer, 1953; Quadbeck and Röhm, 1954; Gaddum *et al.*, 1955; Ehrhart and Henning, 1961). N,N-Dimethyltryptamine and its 5-methoxy and 5-hydroxy (Bufotenine) derivatives were found to cause behavior changes in animals (McIsaac, 1961; Gessner and Page, 1962; Gallagher *et al.*, 1965; Gessner *et al.*, 1968). Moreover, the inhibitory activities towards monoamine oxidase of N,N-dimethyltryptamine, α-methyltryptamine, their 5-hydroxy and 5-methoxy analogs, and gramine have been reviewed (Zirkle and Kaiser, 1964). Curious as to the versatile activities of these compounds, we collected and synthesized a number of derivatives of N,N-dimethyltryptamine and gramines bearing C-5 substituents and

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studied the influence of their electron with-drawing or electron donating properties on pharmacological activity and monoamine oxidase inhibitory activity.

Method

Compounds

Compounds listed in Table 1 were obtained commercially, except nitrogramine(VIII) and cyanogramine (IX) which were synthesized in our laboratory.

5-Cyanogramine (IX). To a solution of 4.3 g (0.03 mole) of 5-cyanoindole in 15 ml of glacial acetic acid were added successively 6.0 g (0.033 mole) of 25% aqueous dimethylamine, 2.8 g (0.03 mole) of 33% aqueous formaldehyde, and 5 ml of glacial acetic acid. The mixture was stirred at 50°C for 3 hr, cooled, made distinctively alkaline with 10% aqueous potassium hydroxide, and first extracted with 500 ml of ether then 200 ml of benzene. The combined extracts were dried with anhydrous sodium sulfate and evaporated under reduced pressure leaving 5.2 g (86.6%) of product, m.p. 138—141°. Recrystallization of this product with benzene gave 4.3 g (71%) of solid, m.p. 144—145° (corrected).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.3; H, 6.57; N, 21.1. Found: C, 72.3; H, 6.39; N, 20.9.

5-Nitrogramine (VIII). 5-Nitroindole (5.0 g, 0.031 mole) was treated with dimethylamine and formaldehyde in a similar manner as described in the preparation of IX. The product was extracted into 500 ml of ether. After the removal of ether, the crude solid was recrystallized from benzene yielding 5.0 g (74.7%) of yellow needles, m.p. 154—156° (corrected) (lit. Cavallini and Ravenna, 1958, m.p. 169—170°).

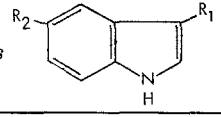
Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.97; N, 19.2. Found: C, 60.4; H, 6.04; N, 19.3.

Pharmacology

a) Acute Toxicity. All compounds in 30% propylene glycol (10 ml/kg mouse) were administered intraperitoneally at an average of 5 to 6 doses to groups of 10 male albino Yale-Swiss mice weighing 17—23 g. The LD_{50} within a 24-hr period was determined graphically according to the method of Miller and Tainter (1944).

b) Effect on Barbiturate Sleeping Time. Mice in groups of 10 were injected intraperitoneally with 5 μmoles/kg of compounds in 30% propylene glycol. After 5 min, sodium pentobarbital (40 mg/kg) in saline was given *via* the same route. Controls were treated first with 30% propylene glycol then with pentobarbital in saline. The pre-sleeping time and sleeping time (loss of the righting reflex) were recorded and treated statistically.

Table 1. *Biological activities of 5-substituted indolealkylamines*



	R_1	R_2	LD_{50} (mg/kg, i.p.)	Pentobarbital sleeping time (min)	p[a]	Effect	Change in rectal temperature[b]	Antireserpine activity: Mean points ptosis[c]	Mean points motor activity[d]	Effect on hypothermia[e]	MAO Inhibition I_{50}[f] (mM)
I[g]	$CH_2CH_2N(CH_3)_2$	H	110 ± 7.2	55.8 ± 3.2	< 0.001	↑	No	2.0	1.7	No	1.0
II	$CH_2CH_2N(CH_3)_2$	OCH_3	115 ± 6.3	57.6 ± 3.1	< 0.001	↑	No	1.4	2.0	PA	3.4
III	$CH_2CH_2N(CH_3)_2$	OH	290 ± 19.5	42.6 ± 5.6	< 0.05	↑	No	1.7	2.0	A	4.9
IV	$CH_2CH_2N(CH_3)_2$	CH_3	110 ± 7.9	37.9 ± 3.7	N.S.	No	No	2.0	1.7	F(?)	1.8
V	$CH_2N(CH_3)_2$	H	122 ± 9.8	77.0 ± 8.0	< 0.001	↑	No	2.0	1.9	F(?)	3.6
VI	$CH_2N(CH_3)_2$	OCH_3	130 ± 4.2	46.6 ± 1.1	< 0.001	↑	↓(?)	1.8	1.5	No	5.0
VII	$CH_2N(CH_3)_2$	Br	75 ± 3.6	50.1 ± 5.1	< 0.02	↑	No	1.6	1.6	PA	0.72
VIII	$CH_2N(CH_3)_2$	NO_2	3.7 ± 0.4	47.8 ± 2.8	< 0.001	↑	↑	2.0	2.0	R	3.6
IX	$CH_2N(CH_3)_2$	CN	14.3 ± 0.8	34.5 ± 1.8	N.S.	No	↓(?)	2.0	2.0	No	20.8[h]
X	$CH_2N(CH_3)_2$	CH_3	87 ± 10.6	71.9 ± 6.6	< 0.001	↑	No	1.7	1.6	F	1.5
XI	$CH_2N(CH_3)_2$	F	82 ± 4.8	33.6 ± 0.8	N.S.	No	↑	2.0	1.9	R	2.3
XII[i]	$CH_2CH(CH_3)NH_2$	H	20 ± 6.6	32.3 ± 3.1	N.S.	↓(?)	↑(?)	1.4	1.4	A	2.6
XIII	$CH_2CH(CH_3)NH_2$	F	32 ± 4.9	23.4 ± 2.8	< 0.01	↓	↑	2.0	0.6	A	2.4
	Control			34.8 ± 2.1				2.0	2.0		

[a] p Value larger than 0.05 was considered to be not significant (N.S.). — [b] Read at 2 hr after administration of compound. — [c] Degree of ptosis is expressed as: 2 points for positive, 1 point for slight ptosis, and 0 point for negative. — [d] Decrease in motor activity is expressed as: reduced, 2 points; slightly reduced, 1 point; not reduced, 0 point. — [e] A, antagonism (minimization of the reserpine-induced hypothermia); PA, partial antagonism (minimization of hypothermia to a lesser extent); R, reversal (reversing the hypothermia by raising rectal temperatures); F. facilitation; No, no effect. — [f] Concentration of an inhibitor giving 50% inhibition of the enzyme. — [g] Hydrogen oxalate salt. — [h] Extrapolated. Due to the insolubility of this compound, the maximum concentration test was 1.0×10^{-2} M. — [i] Methanesulfonate salt.

c) Anti-Reserpine Effect. Male albino Sprague-Dawley rats in groups of five and with an average body weight of 240 g were used. Reserpine (5 mg/kg) in 10% propylene glycol containing 1% acetic acid was administered intraperitoneally. For controls and drug control groups only 10% propylene glycol was given. In approximately three hours after the injection of reserpine, when the reserpine-induced hyperthermia changed to hypothermia, the compounds (5 μmoles/kg) in 30% propylene glycol were administered to the drug control group and experimental group. Accordingly, the same volume of 30% propylene glycol (1 ml/kg) was administered to the control group and reserpine control group.

Rectal temperatures before the injection of reserpine as well as for 2 to 3 hr following the injection of compounds were read from a Yellowspring telethermometer, model 43TF. The mean temperature and its S.E. were calculated. The incidence of ptosis and the changes in motor activity were observed as well during the experiment.

d) Swim Maze Test. The H-shaped swim maze (Kosman, 1964; Buehler *et al.*, 1968), constructed of galvanized metal sheet, has an over-all dimension of 80×60×15 cm, three swim channels of 6 cm in width, and a landing strip of 30×6 cm with 10 cm projection and 40° angle. An 8 cm level of water was maintained at 37° by several straps of heating tape placed underneath the tank.

Prior to the administration of drugs, mice were trained to swim the maze for two consecutive days (at intervals of 2 hr). They were placed in the water at one end of the tank and the swimming time was recorded as the time from placement in the tank until exit at the landing strip. The trained animals were able to complete the two-right-turn swimming task in an average of 5 sec and with an average of less than one error. During the training period, those that did not show good performance were excluded from the study. The animals in groups of 10 were injected i.p. with 25 μmoles/kg of compounds in 30% aqueous propylene glycol with the exception of VIII, IX, X, and XI, in which 10 μmoles/kg dose were used. The control group was given only propylene glycol. The swim tests were performed at both 10 and 30 min after the injection. The results were expressed as: (a) the completion time for swimming, X, and (b) number of errors during that time, Y. With the emphasis on Y, the disruption of mouse behavior was evaluated at $X + 2Y$.

e) Conditioned Behavior (vi). Conditioned behavior was studied in Skinner chambers in which rats were trained to press a lever for 0.45 mg Noyes food pellets delivered on a variable interval 90 sec (vi 90 sec) reinforcement schedule. Five female albino Holtzman rats of approximately 10 months of age (230 to 270 g) were trained daily in sessions which ranged between one and four hours for a period of three months and then placed on the drug regimen. Each animal received various dosages of

the drugs. Five training sessions and seven days intervened between each injection. Injections were made intraperitoneally 15 min prior to testing sessions. The drugs were dissolved in 50% propylene glycol in 0.3 ml of solvent, which proved to have no effect on learning behavior in control sessions.

Inhibition of Monoamine Oxidase

Mitochondrial monoamine oxidase (MAO) from beef liver was isolated and purified as previously described (Ho *et al.*, 1968). Due to insolubility of V and VII they were converted to their ethanesulfonate salts. All the stock solutions of the sulfonate salts (Table 1) of compounds and I-hydrogen oxalate were prepared in water. Compounds II, IV, VIII, and XIII were dissolved in 0.05 N HCl, compounds IX and XI in dimethyl sulfoxide, and III, VI, and X in 50% aqueous dimethyl sulfoxide. Incubation was carried out with tryptamine-2-C^{14}-hydrochloride according to the previously described procedure (Ho *et al.*, 1968).

Results and Discussion

Compounds chosen for the study (Table 1) were indolealkylamines substituted on C-5 position with an electron-withdrawing group (CN, NO_2, or Br) electrondonating group (OCH_3, OH or CH_3) or nearly neutral group (F).

Pharmacology

a) Acute Toxicity. Of the four N,N-dimethyltryptamine derivatives (I—IV) tested, all except bufotenine (III) had a similar LD_{50} in mice (Table 1). The lower toxicity of III could be due to the 5-hydroxyl group, which either impeded its transport to the site of action or increased the rate of metabolism of III by conjugation with glucuronic acid. Substituted gramines in general are slightly more toxic than the corresponding 5-substituted N,N-dimethyltryptamines. Compounds VIII and IX bearing electron-withdrawing groups on C-5 position were especially toxic. The LD_{50} values of the two α-methyltryptamines XII and XIII were unusually low. After the administration of compounds, death usually occurred with 30 min. Those surviving after 2 hr exhibited no delayed toxicity with the exception of XI, XII, and XIII. Jumping action, clonic and tonic convulsions among each group of animals were seen before the death. Tremor was also common to all mice treated with tryptamine derivatives, but was *not* typical for gramine derivatives. Animals receiving II assumed abnormal positions and movements such as walking backwards, which could possibly be indicative of hallucinogenic activity. A similar effect was observed in animals receiving dimethyltryptamine I. During the course of tremor and/or convulsion, rectal temperatures in most cases were highly elevated.

b) Effect on Barbiturate Sleeping Time. At the dosage of 5 μmoles/kg i.p. to mice, gramine (V) and 5-methylgramine (X) showed the most profound effect on the potentiation of barbiturate sleeping time, whereas 5-fluoro-α-methyltryptamine (XIII) was the only compound which significantly decreased the sleeping time (Table 1). No effect was observed with 5-cyanogramine (IX), 5-fluorogramine (XI) and α-methyltryptamine (XII). In the dimethyltryptamine series, the potentiation effect increased on the order of CH_3 (IV), OH (III), H (I), and OCH_3 (II), while in the gramine series a reverse order of activity was observed with OCH_3 (VI) less than H (V) and CH_3 (X). Thus no correlation could be found between electron properties of 5-substituents and the potentiation of the sleeping time. None of the compounds had a significant effect on the induction of sleep, i.e. the pre-sleeping time.

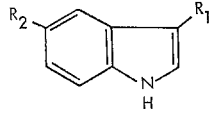
c) Effect on Rectal Temperatures. When XI was administered alone to rats, a rise in rectal temperature took place after 3 hr, exceeding the pre-injection level by 1.1°C. After pretreatment with reserpine the drug demonstrated faster increase in temperature. Compounds VIII andXIII alone also caused hyperthermia in rats. For nitrogramine (VIII) the dose which produced hyperthermia was too near to the toxic convulsive dose for proper evaluation.

d) Effect on Reserpine Action. At a dosage of 5 μmoles/kg, VIII and XI caused a reversal of reserpine-induced hypothermia. In addition, II, III, VII, XII and XIII seemed to prevent the reserpine hypothermia, whereas IV, V and X slight potentiated the reserpine effect at the same dose.

α-Methyltryptamine (XII) and especially its 5-fluoro derivative (XIII) were most effective in antagonizing the decrease in motor activity after reserpine. A lesser effect was observed in the gramine series VI, VII, X, and XI. Compounds XII and II were most active in reversing the reserpine-induced ptosis. Compound XII, already known to exhibit antidepressive effect, was the only compound of the series showing consistent antireserpine action with all three parameters measured. However, some of the compounds tested showed apparent antireserpine effects only in one or two of the parameters, suggesting possible different mechanisms of action.

e) Behavioral Activity. Behavioral activity of the 5-substituted indolealkylamines was evaluated on the swim test and the conditioned behavior. Compounds which were active in the disruption of animal behavior in both tests were 5-methoxy-N,N-dimethyltryptamine (II) and 5-nitrogramine (VIII) (Table 2). Compound II has previously been demonstrated to disrupt conditioned avoidance behavior of rats (McIsaac, 1961; Gessner and Page, 1962; Gessner *et al.*, 1968). It is possible that the methoxy group increased the lipid solubility of II, thus facilitating

Table 2. *Behavioral activity of 5-substituted indolealkylamines*



Compound	R_1	R_2	Swim test									Conditioned response[b] (mg/kg)
			10 min					30 min				
			Completion Time		Error		$X + 2Y$	Completion Time		Error		$X + 2Y$
			sec[a]	X	e	Y		sec[a]	X	e	Y	
I	$CH_2CH_2N(CH_3)_2$	H	24.7	+	3.8	+++	7+	28.4	+	3.9	+++	7+	2.5
II	$CH_2CH_2N(CH_3)_2$	OCH_3	62.3	+++	5.1	++++	11+	62.8	+++	4.6	++++	11+	0.5
III	$CH_2CH_2N(CH_3)_2$	OH	15.5	—	2.5	++	3+	13.3	—	2.0	++	3+	1.5
IV	$CH_2CH_2N(CH_3)_2$	CH_3	7.0	——	1.9	+	0	20.6	+	3.6	+++	7+	5.0
V	$CH_2N(CH_3)_2$	H	16.4	—	2.9	++	3+	34.7	++	3.9	+++	8+	7.0
VI	$CH_2N(CH_3)_2$	OCH_3	1.2	——	1.5	+	0	26.4	+	3.5	+++	7+	9.0
VII	$CH_2N(CH_3)_2$	Br	7.2	——	1.9	+	0	20.4	+	3.2	+++	7+	12.4
VIII	$CH_2N(CH_3)_2$	NO_2	28.8	+	3.9	+++	7+	38.0	++	4.0	++++	10+	0.4
IX	$CH_2N(CH_3)_2$	CN	13.3	—	2.5	++	3+	16.8	—	3.0	+++	5+	0.3
X	$CH_2N(CH_3)_2$	CH_3	11.3	—	3.5	+++	5+	33.6	++	4.6	++++	10+	8.0
XI	$CH_2N(CH_3)_2$	F	−0.7	———	1.0	+	1—	9.9	—	2.3	++	3+	9.0
XII	$CH_2CH(CH_3)NH_2$	H	21.4	+	3.3	+++	7+	37.4	++	3.3	+++	8+	3.0
XIII	$CH_2CH(CH_3)NH_2$	F	11.2	—	2.6	++	3+	24.4	+	3.3	+++	7+	—[c]

$e = \bar{x}^{1/2} + (\bar{x} + 1)^{1/2}$, where $\bar{x}$ is the mean number of errors. — X Above 40, +++; 30—39, ++; 20—29, +; 10—19, —; 0—9, ——; —1 and below, ———. Y Above 4.0, ++++; 3.0—3.9, +++; 2.0—2.9, ++; 1.0—1.9, +.

[a] Time for completion of swimming task (after subtraction of 5 sec necessary for control animals to complete swim). — [b] Dose required for 40—60% decrease in conditioned response. — [c] Not tested.

its entry into the brain and exerting greater behavioral activity. 5-Cyanogramine (IX), the most active compound in our variable interval conditioned behavioral test, however, did not show corresponding activity in the swim test; a reverse effect was seen with 5-methylgramine (X). Bromine substitution on C-5 position of the gramine caused a marked decrease in behavioral activity (see VII in Table 2). These results seemed to indicate that in the case of disruption of behavior, compounds of the tryptamine series were in general more potent than those of the gramine series. However, in the swim test, almost all of the gramine derivatives showed increased activity after 30 min, indicating the onset of action in this series was slower than the tryptamine series.

Inhibition of Monoamine Oxidase

There was no definite indication that the inhibitor activities of the three classes of indolealkylamines had been affected by the electronic nature of the substituents (Table 1). Bromogramine (VII), however, was found to be five times more active than gramine (V). Obviously, the increased binding of VII with the enzyme could not be attributed to the electron-withdrawing property of the Br group, since other electron-withdrawing substituents such as NO_2 (VIII) and CN (IX) did not enhance the activity. The unexpected low activity of 5-cyanogramine (IX) was inexplicable.

Since inhibition of monoamine oxidase did not show a clear correlation with any of the biological activities measured, the observed effects of these compounds may be due to action on amine uptake (Lessin *et al.*, 1967) or direct action on receptor.

Conclusion

No correlation could be made between the electronic nature of 5-substituents and the biological activities of either the tryptamine or gramine derivatives (see rank-order potency of compounds on Table 3).

The two compounds in the α-methylseries showed higher toxicity in mice than the compounds in the N,N-dimethyltryptamine and gramine series. The nitro- and cyano-gramines were exceptionally toxic, probably because these nitro and cyano compounds are metabolized in specific ways (Williams, 1959).

When the three series of compounds bearing the same substituents on the C-5 position were compared, the gramine analogs in general potentiated the sleeping time, whereas the N,N-dimethyltryptamine analogs did not have a significant effect. The differences in antireserpine effects were also noted; 5-methoxygramine (VI) reduced the motor activity and 5-methylgramine (X) antagonized ptosis, yet 5-methoxydimethyltryptamine (II) and 5-methyldimethyltryptamine (IV) were devoid of these two effects.

Table 3. *Rank-order potency of activities*

	5-Substituent	LD_{50}	MAO inhibition	Swim test	Conditioned response
		Group I. Substitued dimethyltryptamines			
I	H	3.5	1	2	3
II	OCH_3	2	3	1	1
III	OH	1	4	3	2
IV	CH_3	3.5	2	4	4
	Coefficient of concordance[a] (W) = 0.27, not significant (p 0.05).				
		Group II. Substituted gramines			
V	H	2	4.5	3.5	3
VI	OCH_3	1	6	5.5	5.5
VII	Br	5	1	5.5	7
VIII	NO_2	7	4.5	1	2
IX	CN	6	7	3.5	1
X	CH_3	3	2	2	4
XI	F	4	3	7	5.5
	Coefficient of concordance[a] (W) = 0.14, not significant (p 0.05).				

[a] Siegel, S.: Nonparametric statistics for the behavioral sciences, pp. 229—239. New York: McGraw-Hill 1956.

The antireserpine activities of VI and X could not be explained in terms of the inhibition of the monoamine oxidase because the gramine analogs in general were weaker inhibitors of the enzyme than the N,N-dimethyltryptamine analogs. α-Methyltryptamine (XII) antagonized reserpine ptosis more than gramine (V) and N,N-dimethyltryptamine (I). Gramine (V), 5-methoxygramine (VI) and 5-methylgramine (X) were found to cause hypothermia, while the corresponding N,N-dimethyltryptamine (I, II, IV) and α-methyltryptamine (XII) showed slight hyperthermia. Regarding the disrupture of behavior, 5-methoxydimethyltryptamine (II) was much more active than 5-methoxygramine (VI).

With the assumption that N,N-dimethyltryptamine (I) and gramine (VII) both bind at a common site on monoamine oxidase, similar configurations for these two compounds can be proposed. The additional methylene group in I results in better accommodation of the side chain so that stronger binding through the amine nitrogen can be achieved. This would possibly account for the increased MAO inhibitory activity of the N,N-dimethyltryptamine derivatives compared to the gramine derivatives. However, the varying effects on pharmacological activities of corresponding C-5 substituents of these two classes of compounds seem to suggest the existence of different pharmacological receptors for the N,N-dimethyltryptamine derivatives and the gramine derivatives.

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