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SOME PHARMACOLOGICAL EFFECTS OF A SERIES OF TRYPTAMINE DERIVATIVES

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The methods of synthesis and some pharmacological properties of a number of *N*-substituted tryptamines are described. Peripheral vasopressor activity decreased with increase in complexity of the substituent and was not related to toxicity or to behavioural activity. Activity in increasing the rectal temperature of rabbits appeared to parallel modifications in the open-field behaviour of rats. Some compounds were investigated for their ability to block a conditioned avoidance-response in rats and to affect operant conditioning in cats. Evidence is presented which suggests that the tryptamine derivatives are metabolized *in vivo* to more active forms.

Some *N*-substituted tryptamines have been reported by Szara (1961) and others to produce autonomic symptoms with disturbances in thought and perception when administered to man in doses of about 1mg/kg. A series of these compounds has been prepared and tested for pharmacological activity, mainly on behaviour. An attempt has been made to elucidate structure/activity relationships within the group.

METHODS

Synthesis of compounds

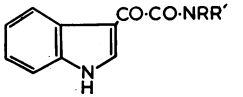
The tryptamine derivatives were prepared from indole through an intermediate glyoxylamide by methods similar to those used by Speeter & Anthony (1954). Most of the glyoxylamides (Table 1) and some of the tryptamines (Table 2) have not been reported previously, but, when they have, references are given in the Tables. Most of these earlier preparations were by methods other than the present one.

The tryptamines were usually isolated as their hydrochlorides and, with the exception of 3-(2-isoindol-2′-ylethyl)indole, the preparation of which is given in (*b*) below, they were all prepared in the same way as *NN*-dipropyltryptamine. Melting-points are uncorrected.

(*a*) *Indol-3-yl*-NN-*dipropylglyoxylamide.* This compound was prepared by adding a solution of oxalyl chloride (11 g) in dry ether (150 ml.) drop-by-drop to a solution of indole (10 g) in dry ether (150 ml.). The addition took about 30 min and was accompanied by constant stirring, which was continued for a further 15 min. The solid indol-3-ylglyoxalyl chloride which separated was collected by filtration and was added carefully, with stirring, to anyhydrous dipropylamine (20 ml.). An excess of 2 N-hydrochloric acid was added, and the mixture cooled and filtered. The indol-3-yl-*NN*-dipropylglyoxylamide was collected and recrystallized from aqueous ethanol. Yield: 13.2 g (57%), melting point 96° C. Found: C 70.9, H 7.2; N 10.4; $C_{16}H_{20}N_2O_2$ requires: C 70.6, H 7.4, N 10.3%.

TABLE 1

PREPARATION OF INDOL-3-YLGLYOXYLAMIDES



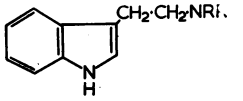
*Boiling point, 60–80° C.

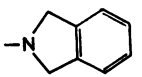
R	R′	Reference	Melting Point (°C)	Formula	Required			Found			Solvent of Recrystallization	Yield (%)
					C	H	N	C	H	N		
H	CH_3		223–224	$C_{11}H_{10}N_2O_2$	65·3	5·0	13·9	65·3	5·1	13·8	Isopropanol	68
CH_3	CH_3	Speeter (1958)	159–161	$C_{12}H_{12}N_2O_2$							Ethyl acetate	79
H	C_2H_5		208–210	$C_{12}H_{12}N_2O_2$	66·7	5·6	12·9	66·8	5·9	12·9	Benzene	67
C_2H_5	C_2H_5	Nógrádi (1957)	175–177	$C_{14}H_{16}N_2O_2$							Methanol	93
H	n-C_3H_7		179–181	$C_{13}H_{14}N_2O_2$	67·8	6·1	12·2	67·6	6·5	12·3	Benzene	75
n-C_3H_7	n-C_3H_7		96	$C_{16}H_{20}N_2O_2$	70·6	7·4	10·3	70·9	7·2	10·4	Aqueous ethanol	57
H	i-C_3H_7		199–200	$C_{13}H_{14}N_2O_2$	67·8	6·1	12·2	67·6	6·2	12·0	Methanol	98
i-C_3H_7	i-C_3H_7		200–202	$C_{16}H_{20}N_2O_2$	70·6	7·4	10·3	70·6	7·8	10·5	Methanol	49
H	n-C_4H_9		167–169	$C_{14}H_{16}N_2O_2$	68·8	6·6	11·5	69·2	6·9	11·8	Benzene	81
n-C_4H_9	n-C_4H_9		131–132	$C_{18}H_{24}N_2O_2$	72·0	8·1	9·3	71·7	8·3	9·6	Aqueous ethanol	77
H	i-C_4H_9		172–174	$C_{14}H_{16}N_2O_2$	68·8	6·6	11·5	68·8	6·6	11·6	Benzene	92
i-C_4H_9	i-C_4H_9		167–168	$C_{18}H_{24}N_2O_2$	72·0	8·1	9·3	72·2	7·9	9·6	Light petroleum*/ ethyl acetate	64
H	s-C_4H_9		172–174	$C_{14}H_{16}N_2O_2$	68·8	6·6	11·5	68·9	6·9	11·6	Cyclohexane	94
H	$CH_2.C_6H_5$	British Patent (1957)	178–179	$C_{17}H_{14}N_2O_2$	73·4	5·1	10·1	73·5	5·3	10·3	Acetone	59
$CH_2.C_6H_5$	$CH_2.C_6H_5$	Nógrádi (1957)	171–171·5	$C_{24}H_{20}N_2O_2$							Acetone	49
H	$CH_2.C_6H_4.Cl(p)$		208–210	$C_{17}H_{13}N_2O_2Cl$	64·9	4·2	9·1	65·3	4·2	9·0	Methanol	60
H	$CH_2.C_6H_4.OCH_3(p)$		161–162	$C_{18}H_{16}N_2O_3$	70·1	5·2	9·1	69·9	5·3	9·5	Benzene	82
H	$CH_2.CH_2.C_6H_5$		209–210	$C_{18}H_{16}N_2O_2$	74·0	5·5	9·6	74·1	5·5	9·6	Methanol	51
H	$CH(CH_3).C_6H_5$		195–196	$C_{18}H_{16}N_2O_2$	74·0	5·5	9·6	73·9	5·5	9·8	Methanol	54

TABLE 2

PREPARATION OF TRYPTAMINES

*Melting points refer to the hydrochlorides, except for Compound 11 which is the maleate, and Compound 20 which is the free base. † Boiling point 80–100° C.



Compound No.	R	R′	Reference	Melting Point* (°C.)	Formula	Required C	Required H	Required N	Found C	Found H	Found N	Solvent of Recrystallization	Yield (%)
1	H	CH_3	Fish *et al.* (1956)	175–177	$C_{11}H_{15}N_2Cl$							Ethanol	75
2	CH_3	CH_3	Vitali & Mossini (1959)	165–167	$C_{12}H_{17}N_2Cl$							Benzene	92
3	H	C_2H_5		188–190	$C_{12}H_{17}N_2Cl$	64·1	7·6	12·5	64·4	7·7	12·7	Benzene/methanol	35
4	C_2H_5	C_2H_5	Nógrádi (1957)	170–171	$C_{13}H_{19}N_2Cl$							Benzene/methanol	75
5	H	n-C_3H_7	Barlow & Khan (1959)	187–187·5	$C_{13}H_{19}N_2Cl$							Benzene/methanol	33
6	n-C_3H_7	n-C_3H_7	Vitali & Mossini (1959)	178–179	$C_{16}H_{25}N_2Cl$							Benzene/methanol	89
7	H	i-C_3H_7		245–246	$C_{13}H_{19}N_2Cl$	65·4	8·0	11·7	65·7	8·0	11·8	Benzene/methanol	60
8	i-C_3H_7	i-C_3H_7	Barlow & Khan (1959)	198–199	$C_{16}H_{25}N_2Cl$							Benzene/methanol	40
9	H	n-C_4H_9		203–205	$C_{14}H_{21}N_2Cl$	66·5	8·4	11·1	66·4	8·4	11·2	Benzene/methanol	13
10	n-C_4H_9	n-C_4H_9	Barlow & Khan (1959)	186–188	$C_{18}H_{29}N_2Cl$							Benzene/methanol	65
11	H	i-C_4H_9		150–151	$C_{18}H_{24}N_2O_4$	65·1	7·3	8·4	65·4	7·2	8·8	Ethyl acetate	65
12	i-C_4H_9	i-C_4H_9		202–204	$C_{18}H_{29}N_2Cl$	70·0	9·5	9·1	70·2	9·9	9·4	Benzene/methanol	86
13	H	s-C_4H_9		175–177	$C_{14}H_{21}N_2Cl$			11·1			11·1	Benzene/methanol	39
14	H	$CH_2.C_6H_5$	British patent (1957)	241–243	$C_{17}H_{19}N_2Cl$							Ethanol	89
15	$CH_2.C_6H_5$	$CH_2.C_6H_5$	Nógrádi (1957)	218–220	$C_{24}H_{25}N_2Cl$							Ethanol	40
16	H	$CH_2.C_6H_4.Cl(p)$		250–252	$C_{17}H_{18}N_2Cl_2$	63·5	5·7	8·7	64·0	5·9	8·9	Benzene/methanol	86
17	H	$CH_2.C_6H_4.OCH_3(p)$		219–220	$C_{18}H_{21}N_2OCl$	68·2	6·7	8·8	68·5	6·8	9·1	Benzene/methanol	60
18	H	$CH_2.CH_2.C_6H_5$	Protiva *et al.* (1959)	215–216	$C_{18}H_{21}N_2Cl$							Benzene/methanol	20
19	H	$CH(CH_3).C_6H_5$		262–263	$C_{18}H_{21}N_2Cl$	71·9	7·0	9·3	72·3	7·5	9·5	Benzene/methanol	25
20	NRR′			144–145	$C_{18}H_{18}N_2$	82·4	6·9	10·7	82·5	6·8	11·0	Light petroleum†	72

NN-*Dipropyltryptamine hydrochloride.* Indol-3-yl-*NN*-dipropylglyoxylamide (13 g) in dry dioxan (350 ml.) was added slowly to lithium aluminium hydride (19 g) in stirred refluxing dioxan (350 ml.). After the addition was complete the mixture was refluxed for a further 16 hr and was decomposed by the addition of wet dioxan. The inorganic precipitate was filtered off and thoroughly washed with hot dioxan. The washings were combined with the filtrate, dried with anhydrous magnesium sulphate, and the dioxan was removed under reduced pressure to leave a brown oil, which was dissolved in dry ether and treated with dry hydrogen chloride. *NN*-Dipropyltryptamine hydrochloride was precipitated, collected and recrystallized from a benzene methanol mixture. Yield: 11.9 g (80%), melting point 178 to 179° C; Vitali & Mossini (1959) give melting point 174.5 to 176° C.

(*b*) *3-(2-Phthalimidoethyl)indole.* A mixture of tryptamine (11 g), phthalic anhydride (13.2 g) and dry toluene (500 ml.) was heated for 2 hr in an oil bath at 160 to 170° C. The toluene was evaporated under reduced pressure, the residual solid dissolved in ethanol (100 ml.) and ethyl acetate (1 l.), and the resulting solution washed first with a cold 5% solution of sodium bicarbonate and then with cold water. The organic layer was dried with anhydrous magnesium sulphate, the solvent removed by distillation and the residue crystallized from ethanol to give 3-(2-phthalimidoethyl)indole. Yield: 15.3 g (77%), melting point 160 to 162° C. Further recrystallization from ethanol raised the melting point to 164.5 to 165.5° C; Manske (1929) gives melting point 164 to 165° C.

3-(2-Isoindol-2'-ylethyl)indole. 3-(2-Phthalimidoethyl)indole (4.8 g) in dry dioxan (150 ml.) was added slowly to a stirred refluxing suspension of lithium aluminium hydride (3.5 g) in dry dioxan (100 ml.) and the mixture refluxed for 17 hr. The excess of lithium aluminium hydride was decomposed by careful addition of wet dioxan, the precipitated inorganic salts were removed by filtration and the filtrate was distilled under reduced pressure, leaving an oily residue, which was crystallized from light petroleum (boiling point 80 to 100° C) to give colourless crystals. Yield. 3 g (72%), melting point 144 to 145° C. Found: C 82.5, H 6.8, N 11.0; $C_{18}H_{18}N_2$ requires: C 82.4, H 6.9, N 10.7%.

Recrystallization of this material from cyclohexane gave another crystalline form, melting point 133 to 134° C, which reverts to the higher-melting form (melting point 144 to 144.5° C) on recrystallization from light petroleum (boiling point 80 to 100° C). Found: C 81.9, H 7.2, N 11.0%.

Pharmacological tests

Toxicity. An indication of the subcutaneous toxicity of each compound to 200 g male albino rats was determined by injecting two animals with a dose of 50 mg/kg in a volume of 1 ml./kg, or with the highest possible dose where lack of solubility in a suitable solvent did not allow this to be given in a suitable volume.

The LD50 was then determined using 20 to 30 g male albino mice. Four groups of five mice were used in each test and the compounds were injected into the tail vein. LD50s were calculated using Thompson's (1947) method of moving averages employing the tables calculated by Weil (1952).

Preliminary behavioural studies. The rats used in the initial toxicity tests were observed carefully for any behavioural abnormalities and in addition were tested at 30 min intervals after injection for their ability to maintain their balance on a pair of steel rods, 0.35 in. diameter, set 1 in. apart and inclined at an angle of 25° to the horizontal.

Hall's open-field test. This test was used to investigate the effects of the compounds on the behaviour of naive rats in a novel environment. Under these test conditions, as first shown by Hall (1934), the rat urinates, defaecates, walks round its new surroundings, rears and preens. The apparatus consisted of a circular drum, 6 ft in diameter with 2 ft high walls. The floor and walls were painted grey and the floor was divided into numbered 1 ft squares. A 100 W lamp hanging 6 ft above the centre of the field provided the only illumination. At each dose-level groups of eight rats were injected subcutaneously with the compound being tested and the animals were placed individually for 3 min in the field 1.5 or 3 hr after

injection. The number of times each rat preened, reared and defaecated, the number of faecal boluses passed, the total number of squares crossed and the number of central squares (that is those away from the periphery of the field) entered were recorded on a bank of manually operated counters. The number of central squares entered was expressed as a percentage of the total squares traversed. The mean value for each type of behaviour was tested for significant difference from the corresponding control value using Students *t*-test.

The initial dose of each compound used in these experiments was the highest dose that had been given without causing any acute toxic, or overt behavioural effects and that did not affect performance in the inclined rods test. Successively lower doses were used in the open-field to obtain an approximate minimal effective dose ; a control group was always tested after injection with the solvent being used.

Conditioned avoidance-response test. The apparatus consisted of a Perspex box, 12 in. square and 10 in. high, with a metal grid floor. A hinged Perspex shelf was fitted to one wall, 4 in. above the floor. Rats were conditioned to respond to a light stimulus by jumping onto the shelf, which was raised simultaneously with the light being switched on. Failure to respond within 7 sec resulted in the light being switched off and a current applied to the grid for a further 7 sec. In each run, groups of five rats were tested. Five groups treated with logarithmically spaced doses of the compound and a control group were used. Using Weil's (1952) tables, ED50s were calculated for block of conditioned response and unconditioned response.

2-Diethylaminoethyl diphenylpropylacetate (SKF 525A) is a compound which blocks the liver metabolism of various drugs by inhibiting the enzymes concerned in this process. To investigate whether metabolism of the tryptamine derivatives to a more active form occurred in the liver, rats were treated with this compound previous to some experiments. An intraperitoneal dose of 50 mg/kg, given 40 min before injection of the tryptamine, was used.

Operant conditioning. Cats were trained, under a schedule of continuous reinforcement, to press a pedal in order to obtain a reward of a cube of boiled pig-liver. The apparatus consisted of a Perspex box, 2×2×2.5 ft. When pressed, the pedal, situated in one corner of the box, brought into action a synchronous motor which operated a moving belt delivering a cube of liver down a chute into a small Perspex box with a hinged lid. The cats opened this to obtain the liver.

Twelve pieces of liver were delivered and eaten in succession. The time of each press of the pedal was noted and general observations made of the behaviour of the cats. The interval between pedal presses was used as an index of performance. An analysis of variance was carried out on the results for each cat for the 6-day period before drug treatment. Providing there was no significant difference between days, performance on the day of the test was then compared, using Students *t*-test, with the mean performance for the 6 days.

Rectal temperature. Rabbit rectal temperatures were recorded by copper/constantan thermocouples embedded in ebonite rods with the contact surfaces flush with the domed ends of the rods. The rabbits were minimally restrained and the thermocouples were inserted about 4 cm. Reference thermocouples were insulated and placed in glass tubes containing liquid paraffin. The glass tubes were immersed in a constant temperature water bath at 36° C and room temperature was kept as near as possible to 20° C. Recording was continuous for 4 hr, with the temperature for each rabbit and the mean temperature for each group of animals being printed out on a Honeywell Brown recorder.

Each compound was tested on four rabbits ; 5 mg/kg was injected into an ear vein in 0.5 ml./kg of a suitable solvent. Four control animals were given solvent alone. Rises in rectal temperature were expressed as the total area under the curve (in ° C min) when the mean increases in temperature over the controls at 0.5, 1, 2, 3 and 4 hr after injection were plotted and the points joined by straight lines. This is an arbitrary method of expressing the results and is complicated by the fact that in a few experiments animals died. When this occurred the mean temperature of the survivors was used for subsequent points on the graph.

Spinal cat blood pressure. A spinal preparation was made using cats anaesthetized with pentobarbitone sodium (40 mg/kg, intraperitoneally). A carotid artery was cannulated and

blood pressure recorded by a mercury manometer. Compounds were injected into a femoral vein in a volume of 0.1 ml./kg and washed in with 2 ml. of 0.9% saline. The pressor response after 100 μg/kg of each tryptamine derivative was compared with that from 100 μg/kg of tryptamine hydrochloride.

RESULTS

Glyoxylamides

Only three of these intermediate compounds (indol-3-yl-*NN*-diethylglyoxylamide, indol-3-yl-*N*-*p*-chlorobenzylglyoxylamide and indol-3-yl-*N*-*p*-methoxylbenzylglyoxylamide) were tested. None produced any signs of poisoning in rats at 50 mg/kg, none had any effect on rabbit rectal temperature at 5 mg/kg, and changes in open-field behaviour of rats occurred only after high doses (50 mg/kg) of the last two compounds. No other tests were carried out.

Tryptamine derivatives

Toxicity. None of the compounds was toxic to rats at 50 mg/kg, subcutaneously, or at the highest dose used when 50 mg/kg could not be given for reasons of solubility. Performance on the inclined rods was adversely affected by three of the compounds: *N*-ethyltryptamine and *NN*-dipropyltryptamine at the relatively high doses of 25 and 33 mg/kg respectively and *NN*-diethyltryptamine at 3 mg/kg. With the latter compound the rats showed tremors at doses as low as 6 mg/kg.

The results of the toxicity tests on mice are given in Table 3. All the compounds were more toxic than tryptamine, having LD50s of between 20 and 78 mg/kg compared with 109 mg/kg for tryptamine. Dialkyl-substituted tryptamines were always more toxic than their monosubstituted analogues.

TABLE 3

INTRAVENOUS TOXICITY OF TRYPTAMINE DERIVATIVES TO MALE ALBINO MICE

The mice weighed 20 to 30 g. All compounds were hydrochlorides unless marked *, when they were free bases.

Compound No.	Solvent	LD50 (mg/kg)	95% Fiducial Limits
Tryptamine	Water	109	96–124
1	Saline	78	74–83
2*	Ethanol (50%)	43	39–47
3	Water	41	35–48
4	Saline	28	24–32
5	Saline	33	30–35
6	Saline	20	16–24
7	Ethanol (50%)	53	47–60
8	Water	26	22–30
9	Water	41	36–45
10	Ethanol (50%)	20	18–23
11	Water	57	48–68
12	Propylene glycol	29	26–33
14	Propylene glycol	49	42–55
15	*N*-Methylacetamide (95%)	61	52–72
16	Propylene glycol	36	33–40
17	Propylene glycol	51	47–56
18	Water	29	26–33
19	*N*-Methylacetamide	54	49–59
20*	*N*-Methylacetamide	37	32–43

Hall's open-field test. Of the twenty substituted tryptamines tested, eight were active in changing open-field behaviour at doses of 5 mg/kg or less. Compounds showing activity at higher doses were considered to be less specific in their action, the activity appearing to be determined to a large extent by the orginal tryptamine nucleus, tryptamine itself being active at 20 mg/kg.

The three compounds with reported psychotomimetic activity in man—*NN*-dimethyltryptamine, *NN*-diethyltryptamine and *NN*-dipropyltryptamine—were active in this test at 2 to 5 mg/kg. *NN*-Diethyltryptamine and *NN*-dipropyltryptamine decreased defaecation at the minimal effective dose, while *NN*-dimethyltryptamine increased the number of times rearing occurred. Other compounds with equal or greater activity than these were *N*-ethyltryptamine, *NN*-di-isopropyltryptamine, *N*-butyltryptamine, *NN*-dibutyltryptamine and *N*-benzyltryptamine; *NN*-dibutyltryptamine was of special interest in that it was not active at 50 mg/kg even though it had been found to be active at the much lower dose of 5 mg/kg. This is discussed later.

Conditioned avoidance-response test. Only four compounds were tested and the results are given in Table 4. The ED50s for block of conditioned response and unconditioned response are shown, the rats having been tested 1 hr after injection.

TABLE 4

THE EFFECT OF SOME TRYPTAMINE DERIVATIVES ON CONDITIONED-AVOIDANCE RESPONSE OF MALE ALBINO RATS WITH AND WITHOUT PREVIOUS TREATMENT WITH SKF 525A

The rats were tested 1 hr after injection of the tryptamine derivative. SKF 525A = 2-diethylaminoethyl diphenylpropylacetate, and was given in a dose of 50 mg/kg. ED50s are in mg/kg

	ED50s after previous treatment			
	None		SKF 525A	
Compound No.	Conditioned response	Unconditioned response	Conditioned response	Unconditioned response
2	9·3	>20	24·5	>40
3	3·0	12·0	6·1	18·6
4	6·8	>15	23·2	>30
14	9·3	>20	>40	>40

With all the compounds tested there was a selective block of conditioned response, that is the dose required to block the conditioned response was less than that required to block the unconditioned response. Previous treatment with 2-diethylaminoethyl diphenylpropylacetate always raised the dose required to block the response which suggests that metabolism to a more active compound had been prevented.

Operant conditioning. The results in Table 5 show the effects of intramuscular or subcutaneous injections of some of the tryptamine derivatives on cats in this test. The analysis of variance of performances during the six days before treatment established the fact that the cats had always achieved a stable level of performance, since there were no significant differences between the mean intervals on the different days, that is there was no steady change in performance over the period of study. In each experiment the cats were tested 1.5 hr after injection and their performance was compared with their mean performance for the previous 6 days.

TABLE 5

THE EFFECT OF SOME TRYPTAMINE DERIVATIVES ON OPERANT CONDITIONING IN NEUTERED MALE CATS

The cats were tested 1·5 hr after injection. Times between pedal presses are means and standard deviations. *P* was estimated from Students *t*-test. S.c.= subcutaneous ; i.m. = intramuscularly

Compound No.	Dose (mg/kg)	Solvent	Route of injection	Cat No.	Time (sec) between pedal presses		*P*	Remarks
					Control	After drug		
2	2·5	Propylene glycol	S.c.	1	11·5 ± 4·0	8·4 ± 1·7	>0·05	Cat appeared to be very anxious to carry out test run
				7	9·8 ± 2·9	21·4 ± 9·8	<0·01	Cat was uneasy and constantly walked round box
4	5	Saline	I.m.	1	10·9 ± 2·8	16·5 ± 2·9	<0·01	No unusual behaviour
				7	9·7 ± 3·1	14·4 ± 2·3	<0·01	No unusual behaviour
4	1	Saline	I.m.	5	15·8 ± 5·9	19·2 ± 8·7	>0·05	No unusual behaviour
				8	14·6 ± 5·6	25·5 ± 9·0	<0·01	Long delay before initial pedal press ; cat restless
6	1	Saline	I.m.	7	11·0 ± 3·5	18·6 ± 11·8	>0·01	Cat only completed nine presses then delivered final four pieces of liver but did not eat them. Persistent leg shaking
				17	12·4 ± 3·5	17·4 ± 5·6	<0·05	Persistent shaking of all four paws
3	5	Saline	I.m.	13	—	—		No run possible as both cats were very aggressive and mydriatic with some salivation
				19	—	—		
14	5	Propylene glycol	S.c.	13	11·9 ± 6·1	13·5 ± 3·8	>0·05	No unusual behaviour
				19	11·9 ± 3·3	17·8 ± 4·5	<0·01	Tendency to hold pedal down too long
14	1	Propylene glycol	S.c.	7	11·7 ± 3·9	10·5 ± 2·3	>0·05	No unusual behaviour
				17	13·4 ± 7·2	15·5 ± 6·7	>0·05	No unusual behaviour

There was an increase in the interval between pedal presses in at least one of the cats after all except one of the compounds. The lowest doses at which this occurred were 5 mg/kg for *N*-benzyltryptamine, 2.5 mg/kg for *NN*-dimethyltryptamine, and 1 mg/kg for *NN*-diethyltryptamine, and *NN*-dipropyltryptamine. *N*-Ethyltryptamine (5 mg/kg) evoked a different effect as evidenced by aggressive behaviour and mydriasis. When these cats were tested 4 hr after the injection they completed only a few presses and these at long intervals apart.

TABLE 6

THE EFFECT OF TRYPTAMINE DERIVATIVES ON RABBIT RECTAL TEMPERATURE

Absolute increases in temperature are mean maximal changes, and occurred at the times after injection indicated. The negative value is a fall in temperature. Integrated increases in rectal temperature are means and are the integrals of the temperature increases (°C × min) recorded during 4 hr after intravenous injections of 5 mg/kg of the compounds. Compounds No. 1, 5, 9, 12, 13, 15, 16, 17, 18, 19, 20 and tryptamine had no effect

	Increase in rectal temperature		
	Absolute		Integrated
Compound No.	Magnitude (°C)	At time (hr.)	(°C. min)
2	1·6	1	255
3	4·5	1	570
4	2·0	2	305
6	4·5	2	725
7	0·7	1	115
8	1·7	2	325
10	0·6	1	95
11	−0·4	2	Small negative
14	3·6	2	550

Rectal temperature. Results are shown in Table 6, the active compounds falling into one of three categories:

(*a*) Compounds that caused maximum mean rises of over 3° C and had scores of of over 500° C min; these were *NN*-dipropyltryptamine, *N*-ethyltryptamine and *N*-benzyltryptamine.

(*b*) Compounds that caused mean rises of 1 to 3° C and had scores of between 250 and 500° C min; these were *NN*-diethyltryptamine, *NN*-dimethyltryptamine and *NN*-di-isopropyltryptamine.

(*c*) Compounds that caused mean rises of less than 1° C and had scores of less than 250° C min; these were *N*-isopropyltryptamine and *NN*-dibutyltryptamine.

Spinal cat blood pressure. Three of the compounds, *N*-methyltryptamine, *NN*-dimethyltryptamine and *N*-ethyltryptamine at doses of 100 μg/kg, gave sharp rises in blood pressure of the spinal cat, very similar to those produced by the same dose of tryptamine. The remaining compounds had little or no effect on blood pressure, any rises which did occur being slow. Some responses are illustrated in Fig. 1.

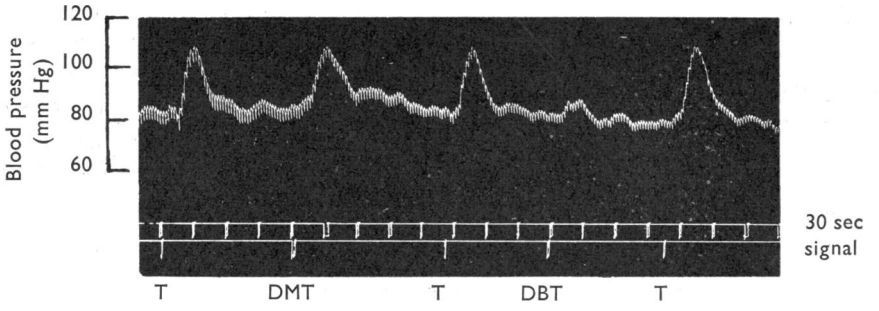


Fig. 1. Spinal cat. Arterial blood pressure responses to intravenous injections of 100 μg/kg of tryptamine hydrochloride (at T), *NN*-dimethyltryptamine at (DMT) and *NN*-dibutyltryptamine (at DBT). Time marks, 30 sec.

DISCUSSION

The potency of these tryptamines in increasing blood pressure by a peripheral action decreased with increasing complexity of the alkyl or aralkyl substituents and was independent of the behavioural potency. Only three of the compounds showed considerable activity: the mono- and dimethyltryptamines had the same activity as tryptamine itself, and the monoethyl analogue was only slightly less active. The diethyl and all higher homologues were at least ten-times less potent than the parent compound.

No clearcut structure/activity relationships were apparent in the toxicity figures, except that each dialkyltryptamine was significantly more toxic than the corresponding monoalkyltryptamine. Toxicity appeared to be independent of peripheral vasopressor activity and also of behavioural effects.

In general, compounds with simple alkyl substituents were most potent in raising rectal temperature. Hofmann (1960) reported for a series of lysergic acid derivatives a marked parallelism between pyrogenic effect in rabbits and psychotomimetic activity in man. At present insufficient evidence exists concerning the effects of the tryptamines on man to indicate a similar relationship. However, the three compounds, *NN*-dimethyltryptamine, *NN*-diethyltryptamine and *NN*-dipropyltryptamine, which were shown by Szara (1961) to produce mental disturbances in man, were effective in raising body temperature, and on this basis *N*-ethyltryptamine and *N*-benzyltryptamine might be expected to be effective at similar doses.

Brimblecombe (1963) described the effects of some known psychotomimetic drugs on open-field behaviour in the rat. In most instances a significant decrease in the amount or frequency of emotional defaecation occurred. This effect was observed after *NN*-diethyltryptamine and *NN*-dipropyltryptamine; with *NN*-dimethyltryptamine there was a decrease which was not statistically significant.

Four other tryptamines evoked behavioural changes at similar doses to the known psychotomimetic drugs. These were *N*-ethyltryptamine, which decreased emotional defaecation at a MED of 5 mg/kg, and *N*-benzyl-, *N*-butyl- and *NN*-dibutyltryptamines, which, although active at doses of from 0.5 to 5 mg/kg, decreased emotional defaecation only at higher doses or not at all; *NN*-dibutyltryptamine was tested

by Szara (1961) and shown to be only slightly active as a psychotomimetic. This compound, though active in the open-field test at 5 mg/kg, was without effect at 50 mg./kg. Szara (1961), in *in vitro* experiments, showed that a high concentration of *NN*-dialkyltryptamine as substrate self-inhibited 6-hydroxylation of the molecule which, he claims, is necessary to produce an active metabolite. This self-inhibiting effect is said by the same author to be more pronounced with higher homologues of the series. Our *in vivo* result with *NN*-dibutyltryptamine is, therefore, not inconsistent with Szara's *in vitro* experiment.

The results of the conditioned avoidance-response experiments indicated that active metabolites of these tryptamines were probably formed in the liver. Previous treatment with 2-diethylaminoethyl diphenylpropyl acetate led to a two- to fourfold increase in the ED50 for block of conditioned response. Szara (1961) stated that the 6-hydroxy derivative of *NN*-diethyltryptamine was five- to six-times more active psychotropically in man than *NN*-diethyltryptamine itself. On the assumption that 6-hydroxylation occurred in the liver these results, too, seem to be consistent.

All compounds tested for effects on operant conditioning in cats increased the interval between pedal presses, but the overt behaviour of the animals differed from drug to drug. *NN*-Dimethyltryptamine made the cats appear uneasy and this may perhaps be compared with the observations by Böszörményi, Dér & Nagy (1959) and by Sai-Halasz (1962) that anxiety was often present in *NN*-dimethyltryptamine-induced psychoses. Little change in behaviour was noted after administration of *NN*-diethyltryptamine to cats; Böszörményi *et al.* (1959) stated that in man the pyschosis produced was qualitatively different from that after *NN*-dimethyltryptamine, in that the former produced a meditative, pleasant, euphoric mood with the contact maintained. *NN*-Dipropyltryptamine produced an unusual effect in that both cats tested persistently shook all four paws, the significance of this is unknown. The effect of *N*-benzyltryptamine was similar to that of *NN*-diethyltryptamine, with few obvious behavioural changes. *N*-Ethyltryptamine had the most striking actions; cholinergic effects such as mydriasis and salivation were seen and whether the aggressive behaviour of the cats was secondary to these or a separate central phenomenon is not at present clear.

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