Elution with benzene yielded a yellow oily solid which was recrystallized from acetone–hexane to give the phthalide (XXI) (24.8 g), mp 132–133°. Recrystallization from the same solvent system afforded the analytical sample, mp 133–134°, λ_{max} 5.67 (vs) μ.

Anal. Calcd for $C_{21}H_{16}ClNO_2$: Cl, 10.14; N, 4.01. Found: Cl, 10.06; N, 4.01.

Further elution with 1:1 $CHCl_3$–benzene followed by $CHCl_3$ afforded additional XX: 21.0 g, mp 140–143°. Total yield of the benzamide (XX) was 42% and that of the phthalide (XXI) was 20%.

2-Benzoyl-N-(4-chloro-2-nitrophenyl)-N-methylbenzamide (XIX).—Concentrated HNO_3 (10.0 g) was added dropwise to a stirred suspension of XX (10.0 g) in acetic anhydride (100 ml) at 5–10°. The reaction mixture was cautiously heated to reflux and maintained in that state for 4 hr. Most of the solvent was evaporated and the residual oil poured into 10% Na_2CO_3 (*ca.* 400 ml). After 3 days the crude solid product was filtered off and recrystallized from 1:1 methanol–acetone affording a yellow crystalline solid (7.6 g), mp 138–141°. Further recrystallization from the same solvent system raised the melting point to 140–141°.

Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.88; H, 3.83; N, 7.10. Found: C, 63.83; H, 3.88; N, 7.02.

Hydrolysis of XIX.—Compound XIX (0.6 g) was added to 70% H_2SO_4 (12 ml) heated to 105°, and the resultant solution was heated to 145° in 8 min and then poured over ice (55 g). The orange gummy solid which formed was extracted with $CHCl_3$ (two 50-ml portions) and the $CHCl_3$ extracts were extracted with 5% NaOH (two 25-ml portions) and then washed with water (two 10-ml portions) and dried (Na_2SO_4). The dried $CHCl_3$ solution was concentrated to a very low volume, diluted with petroleum ether, and chilled. An orange crystalline solid formed which was filtered off and dried: 0.18 g, mp 104–105°, shown by mixture melting point determination and infrared spectra comparison with an authentic sample[7] to be 4-chloro-*N*-methyl-2-nitroaniline. The alkali extracts were acidified with 10% HCl and chilled. A tan solid was filtered off, washed with water, and dried, 0.30 g, mp 92–95°. Recrystallization from $CHCl_3$–petroleum ether gave 0.2 g of solid, mp 125–127°, shown to be identical with an authentic sample of *o*-benzoylbenzoic acid by mixture melting point determination and comparison of infrared spectra.

2-Chloro-5,6-dihydro-5-methyl-6-oxo-11-phenyldibenzo[*b*,*f*][1,4]diazocine (IV).—From XIX (2.0 g), NH_4Cl (1.6 g), and iron filings (1.6 g) following essentially the procedure described for the preparation of III, there was obtained an oily crude product (1.8 g). This was dissolved in benzene (15 ml) and chromatographed on a column of alumina (30 g). Elution with benzene gave a yellow oil (0.7 g) which after long standing afforded yellow crystals (0.25 g), mp 131–152°. Recrystallization from CH_2Cl_2–hexane furnished 0.12 g, mp 154–155°. Further recrystallization from the same solvent system gave the analytical sample: mp 157–158°; λ_{max} 6.00 (vs), 6.14 (s) μ; nmr ($CDCl_3$), δ = 3.18 (NCH_3, 3 H, sharp band) ppm.

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.72; H, 4.36; Cl, 10.22. Found: C, 72.66; H, 4.36; Cl, 10.25.

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(7) J. J. Blanksma, *Rec. Trav. Chim.*, **21**, 273 (1902).

Synthesis and Biological Activity of Some Ring-Substituted Tryptamines

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The synthesis of tryptamines having a hydroxy, methoxy, or benzyloxy substituent in the 5, 6, or 7 positions is reported. Eight of the nine compounds examined showed activity in modifying the open-field behavior of rats. With two exceptions all of the compounds evoked a hyperthermia in rabbits; the more active compounds in this respect were also lethal to rabbits. The tentative conclusion is made that substitution in the 5 position of the indole nucleus conferred higher biological activity than did substitution by the same group in either the 6 or 7 positions.

The tryptamine nucleus is present in many naturally occurring and synthetic compounds which show psychotomimetic activity. Brimblecombe and coworkers[2] have reported the synthesis and pharmacological properties of a number of tryptamines which were unsubstituted in the benzene ring of the indole nucleus. The present paper describes the effect on biological activity of the introduction of selected substituents in the 5, 6, and 7 positions of the benzene ring.

Chemistry.—3-(2-Dimethylaminoethyl)-5-hydroxyindole bioxalate (bufotenin dioxalate, I) was purchased from Koch-Light Laboratories Ltd. 3-(2-Diethylaminoethyl)-5-benzyloxyindole oxalate (II), 3-(2-pyrrolidinoethylindole hydrochloride (IV), 3-(2-pyrrolidinoethyl)-5-benzyloxyindole hydrochloride (V), 3-(2-pyrrolidinoethyl)-5-methoxyindole hydrochloride (VII), 3-(2-pyrrolidinoethyl)-6-methoxyindole (VIII), and 3-(2-pyrrolidinoethyl)-7-methoxyindole (IX) were all prepared from the appropriate indole by reduction of the corresponding intermediate glyoxylamides (Table I) with $LiAlH_4$ in dioxane according to the method of Speeter and Anthony.[3] 3-(2-Diethylaminoethyl)-5-hydroxyindole (III) and 3-(2-pyrrolidinoethyl)-5-hydroxyindole (VI) were obtained from the respective benzyloxytryptamines (II and V) by catalytic debenzylation with hydrogen over 10% Pd–C in methanol. The physical properties of these tryptamines are recorded in Table II.

Experimental Section

Pharmacology. Methods. (a) Toxicity.—Using a suitable solvent, see Table III, the compounds were injected subcutaneously into male 190–210-g albino rats. The animals were observed over a period of 7 days for overt changes in behavior, signs of poisoning, or deaths and, in addition, were tested for their ability to climb a pair of inclined rods. Two animals were used at each dose level, the highest dose being 50 mg/kg; progressively smaller doses were administered to additional pairs of rats until a dose was reached which had no effect. Control animals were injected with the solvent alone to confirm that no toxic effects followed solvent administration.

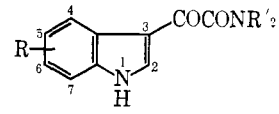
(1) To whom inquiries should be addressed.

(2) R. W. Brimblecombe, D. F. Downing, D. M. Green, and R. R. Hunt, *Brit. J. Pharmacol.*, **23**, 43 (1964).

(3) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

TABLE I

INDOLE GLYOXYLAMIDES



R	NR'2	Mp, °C[a] (lit.)	Yield, %	Crystn solvent	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
5-$C_6H_5CH_2O$	NEt_2	180–181 (176–177[b])	70	Ethyl acetate	$C_{21}H_{22}N_2O_3$	71.98	6.33	8.00	71.86	6.47	8.04
H	Pyrrolidinyl	224–225 (220–222[c])	93	Benzene–ethanol	$C_{14}H_{14}N_2O_2$	69.41	5.82	11.56	69.66	5.79	11.44
5-$C_6H_5CH_2O$	Pyrrolidinyl	196–197 (194–196[c])	90	Methanol	$C_{21}H_{20}N_2O_3$	72.40	5.79	8.04	72.66	6.02	7.95
5-MeO	Pyrrolidinyl	213–214 (212–214[c])	73	Methanol	$C_{15}H_{16}N_2O_3$	66.16	5.92	10.29	66.43	5.79	10.34
6-MeO	Pyrrolidinyl	188–189 (222[b])	78	Methanol	$C_{15}H_{16}N_2O_3$	66.16	5.92	10.29	65.97	6.17	10.44
7-MeO	Pyrrolidinyl	199–200	78	Methanol	$C_{15}H_{16}N_2O_3$	66.16	5.92	10.29	66.60	6.22	10.54

[a] Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. [b] H. Kondo, H. Kataoka, Y. Hayashi, and T. Dodo, *Itsuu Kenkyusho Nempo*, **10**, 1 (1959). [c] S. Miztal, *Dissertationes Pharm.*, **14**, 305 (1962).

(b) **Hall's Open Field Test.**[2,4]—All of the compounds were tested for effects on rat behavior in this situation. The initial dose used was the maximum dose found in the toxicity tests to produce no overt effects. Serially decreasing doses were used until an approximate minimal effective dose for change in open-field behavior was reached.

(c) **Rabbit Hyperthermia.**—The method used has been described previously.[2] The approximate minimal effective dose for a significant change in mean rectal temperature of a group of four rabbits was obtained. A change was considered to be significant when it was greater than 0.5°.

(d) **Operant Conditioning in Cats.**—The most active compound VII and the corresponding tryptamine having no substituent in the benzene ring IV were tested for their effect on an operant conditioning procedure in cats. This method has been described previously[2] and consisted essentially of an investigation into the effects of the drugs on cats which had been trained to press a pedal to obtain a food reward.

(e) **Operant Conditioning in Monkeys.**—The same two compounds as in (d) were studied in this test, where monkeys (*Papio cynocephalus* and *Erythrocebus patas*) were trained to select a white lever from a bank of six levers. When the correct lever was pulled a lid opened and the monkey was confronted with a row of six cups. Five of the cups had black lids and the sixth had a white lid and contained a food reward. Each animal was confronted with the apparatus on six successive occasions and the number of correct selections of both levers and cups was recorded. The general behavior of the animal was also carefully noted.

(f) Compounds were administered in the form as indicated in Table II.

Results and Discussion

The results of the toxicity screening, of the open-field tests, and of the tests on rabbit rectal temperature are summarized in Table III.

Toxic effects were noted following administration of five (I, III, IV, VI, and VII) of the nine compounds. The most lethal was VII with an LD_{50} of about 6 mg/kg sc to rats. The rats which died following compounds VI and VII did so in the period between 3 and 24 hr after injection.

With one exception (IX) all of the compounds produced changes in the open-field behavior of rats. Compound VII was also the most active in this respect, with an approximate MED of 0.1 mg/kg.

There is some evidence, that among indole-containing compounds, the production of hyperthermia in rabbits tends to parallel psychotomimetic activity in man. That this is so among derivatives of lysergic acid has been shown by Hofmann[5] and the suggestion has been made[2] that this may also be the case of some simple tryptamines. Seven of the nine compounds examined here produced hyperthermia in rabbits and all of these were also effective in changing the pattern of behavior of rats in the open-field situation. On the other hand compound IV was active at 5 mg/kg in the open-field test but was without effect on rabbit rectal temperature. However, this compound was so lethal to rabbits that it was only possible to administer low doses in the hyperthermia test. All of the rabbits which died did so in the 4-hr period after injection.

Some 5- and 6-methoxytryptamines were studied by Julia and Manoury.[6] These authors reported that VII had an ED_{50} for increase in rabbit rectal temperature of 0.03 mg/kg. This is not greatly at variance with the MED reported here of 0.1 mg/kg. Julia and Manoury also reported that the corresponding 6-methoxy compound VIII was much less active in producing hyperthermia. This is in agreement with the present finding that the MED for this compound was 5 mg/kg.

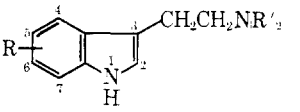
The above results indicate that high activity in this group of compounds tends to be associated with high toxicity. This impression was supported by the results of the tests on conditioned behavior of pairs of cats and monkeys. Compound IV at 0.1 mg/kg sc (30 min before testing) was without effect on the performance of cats. Compound VII at a dose of 0.05 mg/kg resulted in the animals becoming slightly incoordinate and 0.025 mg/kg was without effect on performance though the animals became somewhat hyperactive. In the tests on monkeys the compounds were administered by intramuscular injection 30 min before the test. After 1 mg/kg of IV the animals were drowsy and neither completed the task; after 0.5 mg/kg both completed the task but in a much longer time than normal; 0.2 mg/kg was without effect. Following 0.1 mg/kg of VII both animals were subdued and slightly incoordinated and made no attempt at the task; after

(4) C. S. Hall, *J. Comp. Psychol.*, **18**, 385 (1934).

(5) A. Hofmann, *Svensk Kem. Tidskr.*, **72**, 723 (1960).

(6) M. Julia and P. Manoury, *Bull. Soc. Chim. France*, 1411 (1965).

TABLE II: TRYPTAMINES



No.	R	NR′₂	Mp, °C[a] (lit.)	Yield, %	Crystn solvent	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
II	5-$C_6H_5CH_2O$	NEt_2	158–159[b] (162[d])	53	Acetone	$C_{23}H_{28}N_2O_5$	66.97	6.84	6.79	67.13	6.77	6.91
III	5-OH	NEt_2	150–151 (147–149[d])	85	Benzene	$C_{14}H_{20}N_2O$	72.38	8.68	12.06	72.14	8.73	11.97
IV	H	Pyrrolidinyl	193–194[c] (183–184[e])	81	Benzene–methanol	$C_{14}H_{19}ClN_2$	67.06	7.64	11.17	67.01	7.55	11.02
V	5-$C_6H_5CH_2O$	Pyrrolidinyl	198–199[c]	73	Benzene–methanol	$C_{21}H_{25}ClN_2O$	70.67	7.06	7.85	70.45	7.30	7.97
VI	5-OH	Pyrrolidinyl	204–206 (204–208[f])	70	Methanol	$C_{14}H_{18}N_2O$	73.01	7.88	12.16	72.89	7.69	12.14
VII	5-MeO	Pyrrolidinyl	164–167[c] (167[a])	75	Benzene–methanol	$C_{15}H_{21}ClN_2O$	64.16	7.54	9.98	64.31	7.61	10.03
VIII	6-MeO	Pyrrolidinyl	90–91	83	Petr ether (bp 40–60°)	$C_{15}H_{20}N_2O$	73.74	8.25	11.47	74.15	8.41	11.76
IX	7-MeO	Pyrrolidinyl	87–88	97	Cyclohexane	$C_{15}H_{20}N_2O$	73.74	8.25	11.47	73.71	8.72	11.13

[a] See footnote *a*, Table I. [b] Oxalate. [c] Hydrochloride. [d] A. Stoll, F. T. Troxler, J. Peyer, and A. Hofmann, *Helv. Chim. Acta*, **38**, 1452 (1955). [e] T. Vitali and F. Mossini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **17**, 84 (1959). [f] Footnote *c*, Table I.

TABLE III: PHARMACOLOGICAL RESULTS

No.	Testing solvent	Toxicity test Dose, mg/kg, and effect	Hall's open-field test MED,[b] mg/kg, and effect	Rabbit rectal temp Dose, mg/kg, and effect
I	50% EtOH	50, hypoactivity, +IRT[a] 25, no effect	15, ↓ in rearings, no. of defecation, and no. of fecal boluses	5, 3/4 animals died, ↑ in temp 1.58, 2/3 animals died, no effect on temp
II	N-Methylacetamide	50, no effect	5, ↓ in no. of defecations	5, ↑ in temp 1.58, no effect on temp
III	Propylene glycol	50 and 25, tremors, cyanosis, +IRT 12.5, no effect	5, ↓ in no. of defecations	0.5, 2/4 animals died, ↑ in temp 0.16, no effect on temp (lethal at higher doses)
IV	Propylene glycol	50, 25, 12.5, and 6.25, tremors and muscular rigidity, +IRT 3.1, no effect	5, ↑ in no. of squares traversed	0.16, no effect on temp (lethal at higher doses)
V	N-Methylacetamide	50, no effect	10, ↓ in no. of defecations and no. of fecal boluses; ↑ in no. of squares traversed	5, 3/4 animals died, ↓ in temp 1.58, no effect on temp
VI	N-Methylacetamide	50, 2/2 died 25, tremors, +IRT 12.5, no effect	0.25, ↑ in no. of squares traversed	1.58, 3/4 animals died, ↑ in temp 0.5, no effect on temp
VII	Saline	50, 25, 12.5, 2/2 died 6.25, 1/2 died 3.1, 1.6, 0.8, tremors, +IRT 0.4, no effect	0.1, ↓ in no. of defecations and fecal boluses; ↑ in no. of squares traversed	0.1, 1/4 animals died, ↓ in temp 0.05, no effect on temp (lethal at higher doses)
VIII	Propylene glycol	50, no effect	50, ↓ in no. of times rearing; ↑ in no. of defecations, fecal boluses, and squares traversed	5, ↑ in temp 1.58, no effect on temp
IX	Propylene glycol	50, no effect	50, no effect	15.8, 1/4 died, no effect on temp

[a] +IRT denotes inability of the rats to maintain their balance on the inclined rods. [b] MED = minimal effective dose.

0.05 mg/kg the animals became tremulous with only one of the pair completing the task (in a longer time than normal).

These results, indicating that speed rather than accuracy of performance is affected, taken in conjunction with the results showing apparent physical effects of the compounds, suggest strongly that the inability of the animals to perform was not due to any specific effects on the central nervous system leading to disorientation in behavior, but rather to a generalized depressant action.

It appears therefore that although these compounds affect behavior this is likely to be masked in many situations by other toxic effects.

It can be stated tentatively that a methoxy substituent in the 5 position of the benzene ring appears to confer higher activity than substitution by the same group in either the 6 or 7 positions (*cf.* VII–IX). Similarly it appears that indoles having a pyrrolidinoethyl side chain in position 3 (V and VI) have higher activities than those having a dialkylaminoethyl side chain in the same position (I–III).