Synthesis and Pharmacology of Some Hydroxylated Tryptamines[1]

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Studies on several classes of hydroxylated tryptamines were carried out to determine structure–activity relationships. Effects on the rat's behavior, blood pressure, and myotropic properties were investigated. β-Hydroxylation of 5-substituted tryptamines caused deactivation in all three pharmacological systems. An increase in potency occurred in some instances for unsubstituted tryptamines. Changes in the position of the hydroxyl group between 4, 5, 6, and 7 in N,N-dimethyltryptamines caused marked changes in behavioral effects with the 4-hydroxy compound being most potent. Attachment of groups larger than methyl (ethyl, *n*-butyl, benzyl) at the 1 position of serotonin did not increase pharmacological potency or caused diminution of effects.

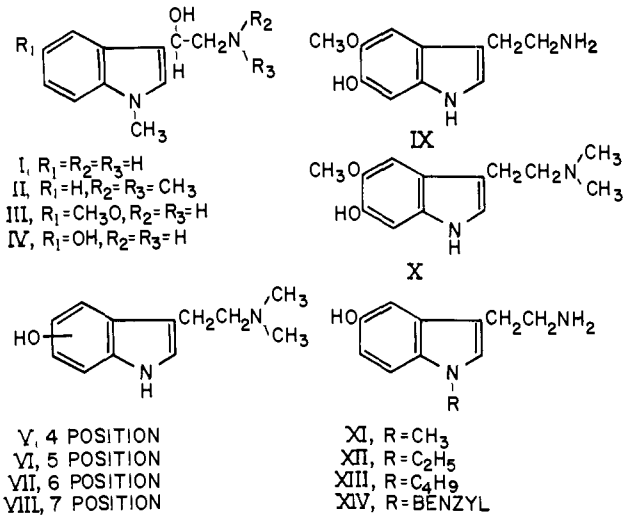
A biochemical basis for some kinds of chronic acute mental disease such as schizophrenia has been suggested as early as 1892 by Kraepelin.[3] This hypothesis has been given considerable impetus in recent times by the discovery and study of hallucinogenic drugs such as lysergic acid diethylamide. Evidence has been presented that schizophrenia is a genetic morphism including the fact that monozygotic twin pairs show a concordance rate of 76–91%, whereas in dizygotic pairs the rate is only 10–17%[4] of the disease. Occurrence of schizophrenia appears to be at a fixed rate of 1% transcending ethnic, racial, and cultural parameters.[4] Such considerations have given rise to the "metabolite theory of psychosis," stating that some individuals possess a unique genetic moiety which is responsible for an abnormal metabolizing enzyme functioning, possibly in the lung or liver, to produce psychotogenic compounds.

Efforts in our laboratory have been directed toward examining systematically known or potential metabolites related to physiological indoles and making correlations between structure and disruptive activity on behavior of trained rats. In addition, their effects on blood pressure and smooth muscle were examined. Hydroxylation can confer activity on phenethylamines resulting in potent physiological substances such as epinephrine and norepinephrine. Conversely, removal of a hydroxyl group from the latter by O-methylation reduces activity of this series.[5] Hydroxylation of tryptamine to serotonin (5-hydroxytryptamine) produces a potent physiologically active substance exhibiting many cardiovascular and central effects not seen in the precursor.[6] It has been postulated that the behavioral effects of N,N-dimethyltryptamine in rats are due to a metabolite because a substance having high potency was isolated from urine of rats receiving N,N-dimethyltryptamine. The investigators suggested, on the basis of chromatography, that the 6-hydroxy metabolite was the active form.[7]

In the present investigation several classes of hydroxylated indoles were examined (Table I) and are illustrated in Chart I. The synthesis and pharmacology of some 6-hydroxylated tryptamines have been reported previously.[8,9] The effect of the position of the hydroxyl group in the 4-, 5-, 6-, and 7-substituted N,N-dimethyltryptamines was of interest. Enzymes β-hydroxylating 3,4-dihydroxyphenethylamine are known,[10] and the β-hydroxyl group is an essential moiety in epinephrine and norepinephrine for their actions. Therefore, a synthesis of several β-hydroxylated tryptamines was carried out. Additionally, several serotonin analogs where the ring nitrogen is substituted were made. The rationale was based on the fact that 1-methylserotonin exhibited somewhat greater potency in behavioral studies than did serotonin, without appreciable changes on blood pressure or oxytocic effects.[11] It was considered this might be due to the fact that 1-methylserotonin may cross the blood–brain barrier in rats more readily than serotonin, probably because of greater lipid solubility.

The synthesis of 1-methyl-β-hydroxytryptamines was carried out by reduction of the corresponding 1-methylindole-3-glyoxylamides. During preliminary investigations it was found difficult to stop the reduction of indole-3-glyoxylamides without much of it proceeding

CHART I



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(2) Research Fellow supported by Training Grant 5126-08 from the National Institutes of Health, U. S. Public Health Service.

(3) E. Kraepelin, "Uber die Beeinflussung einfacher psychischer Vorgaenge durch einige Arzneimittel," Gustave Fischer, Jena, 1892.

(4) J. Huxley, E. Mayer, H. Osmond, and A. Hoffer, *Nature*, **204**, 220 (1964).

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(6) I. H. Page, *ibid.*, **38**, 277 (1958).

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(9) R. G. Taborsky, P. Delvigs, and I. H. Page, *Science*, **153**, 1018 (1966).

(10) M. Goldstein, E. Lauber, and M. R. McKereghan, *J. Biol. Chem.*, **240**, 2066 (1965).

(11) R. G. Taborsky, P. Delvigs, I. H. Page, and N. Crawford, *J. Med. Chem.*, **8**, 460 (1965).

Table I

Hydroxylated Indoles and Intermediates

Compound	Yield, %	Mp, °C[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
1-Benzyl-5-methoxyindole	83	74–75[b]	$C_{16}H_{15}NO$	80.98	80.77	6.37	6.09	5.90	6.12
5-(Benzyloxy)-1-methylindole	96	127[c]							
5-(Benzyloxy)-1-ethylindole	68	68.5–70	$C_{17}H_{17}NO$	81.24	81.05	6.82	6.96	5.57	5.54
5-(Benzyloxy)-1-(*n*-butyl)indole	93	52.5–53	$C_{19}H_{21}NO$	81.68	81.42	7.58	7.45	5.01	5.00
5-(Benzyloxy)-1-benzylindole	54	108–109[d]	$C_{22}H_{19}NO$	84.58	84.39	6.13	6.15	4.48	4.32
5-(Benzyloxy)-3-(dimethylaminomethyl)-1-ethylindole hydrochloride	82	179–180	$C_{20}H_{23}ClN_2O$	69.58	69.30	7.31	7.37	8.12	7.92
5-(Benzyloxy)-3-(dimethylaminomethyl)-1-ethylindole methosulfate	70	151.5–153	$C_{22}H_{30}N_2O_5S$	60.80	60.68	6.96	7.29	6.45	6.54
5-(Benzyloxy)-1-ethylindole-3-acetonitrile	84	85–87	$C_{19}H_{18}N_2O$	78.59	78.57	6.25	6.28	9.65	9.86
3-(2-Aminoethyl)-5-(benzyloxy)-1-ethylindole oxalate	76	180–180.5	$C_{21}H_{24}N_2O_5$	65.61	65.66	6.29	6.25	7.29	7.48
3-(2-Aminoethyl)-1-ethyl-5-hydroxyindole (1-ethylserotonin) picrate	70	200–201 dec	$C_{18}H_{18}N_5O_8$	49.88	49.76	4.49	4.42	16.16	15.90
5-(Benzyloxy)-1-*n*-butyl-3-(dimethylaminomethyl)indole hydrochloride	94	154–155	$C_{22}H_{29}ClN_2O$	70.85	70.67	7.84	7.80	9.51[b]	9.52[b]
5-(Benzyloxy)-1-*n*-butyl-3-(dimethylaminomethyl)indole methosulfate	87	104.5–106	$C_{24}H_{34}N_2O_5S$	62.31	62.10	7.41	7.50	6.06	6.23
3-(2-Aminoethyl)-5-(benzyloxy)-1-*n*-butylindole oxalate	73	160.5–161.5	$C_{23}H_{28}N_2O_5$	66.97	67.70	6.84	6.94	6.79	7.16
3-(2-Aminoethyl)-1-*n*-butyl-5-hydroxyindole (1-butylserotonin) picrate	74	135–136	$C_{20}H_{23}N_5O_8$	52.06	51.99	5.02	5.03	15.18	14.99
1-Benzyl-5-(benzyloxy)-3-(dimethylaminomethyl)indole hydrochloride		162.5–164	$C_{25}H_{27}ClN_2O$	73.78	73.70	6.69	6.85	6.89	6.88
1-Benzyl-5-(benzyloxy)-3-(dimethylaminomethyl)indole methosulfate	70	161.5–162.5	$C_{27}H_{32}N_2O_5S$	65.30	65.99	6.50	6.77	5.64	5.46
3-(2-Aminoethyl)-1-benzyl-5-(benzyloxy)indole oxalate	89	177–178	$C_{25}H_{26}N_2O_5$	69.93	69.81	5.87	5.82	6.28	6.41
3-(2-Aminoethyl)-1-benzyl-5-(benzyloxy)indole picrate	89	188–190	$C_{30}H_{27}N_5O_8$	61.53	61.62	4.65	4.69	11.96	12.12
3-(2-Aminoethyl)-1-benzyl-5-hydroxyindole (1-benzylserotonin) monohydrate picrate	..	165	$C_{24}H_{23}N_5O_9$	53.80	53.89	4.52	4.38	13.64	13.68
1-Methylindole-3-glyoxyloyl chloride	73	112–114[e]							
3-(1-Methylindolyl)ethanediol	42	102.5–103.5	$C_{11}H_{13}NO_2$	69.09	68.95	6.85	6.90	7.33	7.61
1-Methylindole-3-glyoxylamide	96	189.5–190.5[f]							
1-Methylindole-3-glyoxyl-N,N-dimethylamide picrate	92	136.5–137[g]	$C_{19}H_{17}N_5O_9$	49.68	49.63	3.73	3.72	15.25	15.30
α-(Aminomethyl)-1-methylindole-3-methanol hydrochloride	23	209[g]	$C_{11}H_{15}ClN_2O$	58.27	58.14	6.67	6.48	15.64[b]	15.86[b]
α-(Dimethylaminomethyl)-1-methylindole-3-methanol picrate	44	125–125.5[g]	$C_{19}H_{21}N_5O_9$	51.00	51.05	4.73	4.80	15.65	15.57
5-Methoxy-1-methylindole-3-glyoxyloyl chloride	85	134.5–135[h]							
5-Methoxy-1-methylindole-3-glyoxylamide	95	173–174.5	$C_{12}H_{12}N_2O_3$	62.06	61.76	5.21	5.24	12.06	11.80
α-(Aminomethyl)-5-methoxy-1-methylindole-3-methanol	60	121–122	$C_{12}H_{16}N_2O_2$	65.43	65.16	7.32	7.62	12.72	12.56
5-(Benzyloxy)-1-methylindole-3-glyoxyloyl chloride	79	109.5–111[b]							
5-(Benzyloxy)-1-methylindole-3-glyoxylamide	92	169–169.5	$C_{18}H_{16}N_2O_3$	70.12	70.30	5.23	5.34	9.09	9.02
α-(Aminomethyl)-5-(benzyloxy)-1-methylindole-3-methanol	70	113.5–114.5	$C_{19}H_{20}N_2O_2$	72.95	73.01	6.80	7.01	9.45	9.20
α-(Aminomethyl)-5-hydroxy-1-methylindole-3-methanol (indole-3-acetic acid salt)	80	160 dec	$C_{21}H_{23}N_3O_4$	66.13	66.01	6.08	6.37		

TABLE I (*Continued*)

Compound	Yield, %	Mp, °C[a]	Formula	—Carbon, %— Calcd	Found	—Hydrogen, %— Calcd	Found	—Nitrogen, %— Calcd	Found
3-(2-Dimethylaminoethyl)-6-hydroxyindole picrate	51	205–206 dec[i]	$C_{18}H_{19}N_5O_8$	49.88	50.02	4.42	4.41	16.16	16.04
3-(2-(Dimethylaminoethyl)-7-hydroxyindole picrate	60	188.5–189 dec[i]	$C_{18}H_{19}N_5O_8$	49.88	49.97	4.42	4.48	16.16	16.33

[a] Carried out in a Mel-Temp apparatus corrected with standards. [b] Product obtained by a different procedure (G. Ehrhart and I. Henning, *Arch. Pharm.*, **294**, 550 (1961)) had mp 79–80. [c] Mixture melting point with a compound prepared according to R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuskowicz, *J. Org. Chem.*, **25**, 1548 (1960), with mp 131–131.5°, produced no depression. [d] Product obtained by different procedure[2] had mp 108–109°. [e] A. Buzas, C. Hoffmann, and J. L. Regnier, *Bull. Soc. Chim. France*, 643 (1960). [f] M. E. Speeter (U. S. Patent 2,825,734 (1958)) reported mp 185–187°. [g] Compounds prepared according to footnote *e*, and the picrates and hydrochlorides were made. [h] Acid chlorides were unstable and difficult to purify and were used directly in further reactions. [i] Procedure used by F. Troxler, F. Seeman, and A. Hofmann, *Helv. Chim. Acta*, **42**, 2073 (1959), to prepare the base was applied and the picrate was prepared as a convenient derivative. [j] H. Morimoto and H. Oshio (*Ann.*, **676**, 168 (1964)) report for the picrate mp 183°. [k] Chlorine analysis.

to the nonhydroxylated tryptamine even when the amide was kept in excess of the reducing agent. However, when 1-methylindole-3-glyoxyloyl chloride was reduced with lithium aluminum hydride, the glycol, 3-(1-methylindolyl)ethanediol, was formed (Table I) without the β-hydroxyl group being reduced further, though the compound proved to be unstable during several weeks of storage. Reduction of 1-methylindole-3-glyoxylamides with excess hydride also gave predominantly the β-hydroxylated tryptamines as had been previously demonstrated for other members of this series.[12] Since it was shown previously[11] that 1-methylation does not usually modify the actions of tryptamines and other indoles, the presence of a methyl group in the 1 position of the molecule was not considered to be a handicap in assessing effects of the β-hydroxyl group on the pharmacological actions of tryptamines.

The substituted 1-methylindole-3-glyoxylamides used were prepared in the usual manner[12] from 1-methylindole-3-glyoxyloyl chlorides and ammonia or amines. Indole-3-glyoxyloyl chlorides were made by allowing the corresponding indoles to react with oxalyl chloride.[12] These products could not be readily purified for analysis and were used to form amides without purification. Four representatives of β-hydroxylated tryptamines were prepared.

Preparation of ring 1-alkylated serotonin compounds required the corresponding alkylated indoles as intermediates. 1-Alkylation of indoles has been performed previously through the preparation of the sodioindole in liquid ammonia followed by interaction with an alkyl halide.[13] Another procedure useful only for methylation consists of refluxing the indole in xylene with anhydrous potassium carbonate and methyl *p*-toluenesulfonate for several days.[14] Each of these procedures had limitations to prepare a series of methylated indoles.[11] Ammonia caused degradation of some indoles sensitive to base, whereas heat-labile indoles did not survive the treatment in refluxing xylene. Previous mention has been made of 1-methylation of indoles with methyl iodide by use of sodium hydride.[15,16] The generality of that reaction was more fully explored here.

Sodium hydride has been used previously for alkylation of amides,[17] urethans,[18] and an imide,[19] but generally not for that of the nitrogen atom in heterocyclic compounds. Because of the resonance in the indole ring the nitrogen forms a unique secondary amine which is neutral. Alkylations were done by dissolving the indole in anhydrous dimethylformamide and adding an equivalent amount of sodium hydride slowly. Alkylating agents which were employed successfully were methyl, ethyl, and *n*-butyl iodides, dimethyl sulfate, and benzyl chloride. 1-Ethyl-, 1-*n*-butyl-, and 1-benzylserotonin were prepared from the alkylated indoles *via* the gramine salts and nitriles according to a procedure used to make 1-methylserotonin.[11]

Pharmacological Activity.—The hydroxylated tryptamines were examined for three types of activity: effects on behavior, which were judged to be results of gross effects on the central nervous system; effects on rat blood pressure; and action on the isolated estrus rat uterus.

Effect on Behavior (Table II).—Compounds were compared by measuring their interference with rats performing a positively reinforced task (bar pressing) for food reward in a Skinner box.[20] Each β-hydroxylated tryptamine was paired with the nonhydroxylated form and comparisons were made. 1-Methylserotonin exhibited considerably more potency than its β-hydroxylated analog. At equivalent dosage β-hydroxylation deactivated the effects of 5-methoxy-1-methyltryptamine, as it did for N,N,1-trimethyltryptamine which, however, was only weakly active. Only with 1-methyltryptamine did β-hydroxylation increase moderately effects on work rates.

Comparison of the four hydroxylated isomers (4, 5, 6, and 7) of N,N-dimethyltryptamine showed that psilocin (4-hydroxy isomer) caused almost complete extinction (over 90% decrease in rates).[1] The 6- and 7-hydroxy derivatives did not exhibit any effects at 33 μmoles/kg. Deactivation effects of 6-hydroxylation on tryptamines has been reported by us previously and some of the results obtained are restated in Table II[8,9] for comparison. Two 1-alkylated and a 1-benzylserotonin derivative were compared to serotonin and 1-methylserotonin. 1-Methylserotonin was somewhat more active than serotonin; 1-ethyl- and 1-benzylserotonin were equivalent to the latter while 1-*n*-butylserotonin was inactive at the dosage used.

(12) M. E. Speeter, U. S. Patent 2,825,734 (1958).
(13) K. T. Potts and E. J. Saxton, *J. Chem. Soc.*, 2641 (1954).
(14) D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).
(15) A. P. Gray, *ibid.*, **75**, 1253 (1953).
(16) J. B. Hester, *J. Org. Chem.*, **29**, 1158 (1964).
(17) W. S. Fones, *ibid.*, **14**, 1099 (1949).
(18) R. L. Dannley and M. Lukin, *ibid.*, **22**, 268 (1957).
(19) R. G. Taborsky and R. J. Starkey, *J. Med. Pharm. Chem.*, **5**, 775 (1962).
(20) B. F. Skinner, "The Behavior of Organisms: An Experimental Analysis," The MacMillan Co., New York, N. Y., 1938.

Table II

Pharmacological Characteristics of Selected Hydroxyindoles

Compound[a]	Effect on behavior[b] Response	Dose, μmoles/kg	Effect on rat blood pressure[c] Response	Dose, μmole/kg	Serotonin act.[d] on estrus rat uterus
α-(Aminomethyl)-1-methylindole-3-methanol (I)	S−	33	M+	0.1	>1000
3-(2-Aminoethyl)-1-methylindole	M−	33	0	0.1	1000
α-(Dimethylaminomethyl)-1-methylindole-3-methanol (II)	0	75	W±	0.1	100
3-(2-Dimethylaminoethyl)-1-methylindole	M−	56	0	0.1	>10,000
α-(Aminomethyl)-5-methoxy-1-methylindole-3-methanol (III)	0	33	0	0.1	10
3-(2-Aminoethyl)-5-methoxy-1-methylindole	S−	33	S+	0.1	1
α-(Aminomethyl)-5-hydroxy-1-methylindole-3-methanol (IV)	M−	66	W±	0.1	100–1000
3-(2-Aminoethyl)-5-hydroxy-1-methylindole (XI)	S−	8	S±	0.1	1
Psilocin (V)	S−	16	W+	1.0	10
Bufotenine (VI)	M−	16	S+	1.0	10
3-(2-Dimethylaminoethyl)-6-hydroxyindole (VII)	0	33	W+	1.0	100
3-(2-Dimethylaminoethyl)-7-hydroxyindole (VIII)	0	33	W+	1.0	S1 >100
3-(2-Aminoethyl)-6-hydroxy-5-methoxyindole (IX)	0	33	W±	0.1	100
3-(2-Aminoethyl)-5-methoxyindole	S−	15	S±	0.1	1
3-(2-Dimethylaminoethyl)-6-hydroxy-5-methoxyindole (X)	0	17	W+	1.0	100
3-(2-Dimethylaminoethyl)-5-methoxyindole	S−	17	S±	1.0	10
3-(2-Aminoethyl)-5-hydroxyindole (serotonin)	S−	17	S±	0.1	1
3-(2-Aminoethyl)-5-hydroxy-1-methylindole (XI)	S−	8	S±	0.1	1
3-(2-Aminoethyl)-5-hydroxy-1-ethylindole (XII)	S−	17	W±	0.1	10
3-(2-Aminoethyl)-5-hydroxy-1-butylindole (XIII)	0	17	W±	0.1	S1 >100
3-2(Aminoethyl)-5-hydroxy-1-benzylindole (XIV)	S−	17	...	...	...

[a] Roman numerals after compounds correspond to structures in Chart I. [b] M, moderate effect where work rates have been changed over 30 to 75% from control values; S, strong effect with changes greater than 75% from controls; −, decrease of work rates. [c] W, weak representing changes less than 10 mm in blood pressure; M, medium representing changes of 10–20 mm pressure; S, strong responses of over 20 mm; −, lowering of pressure; +, elevation of pressure; ± amphibaric response where both an elevation and lowering occur, one following the other or else a pressor response is seen in one experiment and depressor response in another. Rats were whole Sprague–Dawley rats weighing 300 g. [d] Values represent molar ratios of test compound to serotonin creatinine sulfate, to the nearest multiple of 10, required to produce a contraction equal to the latter at concentrations of 10^{-6} to 10^{-8} *M*.

Blood Pressure Effects (Table II).—At 0.1 μmole/kg β-hydroxylation decreased the pressor response of 1-methyl-5-methoxytryptamine in the pentobarbital anesthetized whole rat. β-Hydroxylation conferred pressor activity on 1,N,N-trimethyltryptamine and 1-methyltryptamine at 0.1 μmole/kg. At ten times the dosage used for the above compounds 4-, 5-, 6-, and 7-hydroxylated N,N-dimethyltryptamines had weak pressor activity with the 5-hydroxy isomer being the most potent. 6-Hydroxylation decreased the pressor effects of 5-methoxy-1-methyltryptamine and 5-methoxy-N,N-dimethyltryptamine. Substitution on the ring nitrogen with ethyl or *n*-butyl in serotonin decreased pressor responses but was not affected appreciably by 1-methylation, as shown before.[11]

Effect on Rat Uterus (Table II). Molar ratios of the test compound to serotonin creatinine sulfate to the nearest multiple of 10 required to produce a contraction equal to the latter at concentrations of 10^{-6} to 10^{-8} *M* were determined. β-Hydroxylation reduced activity of 1-methylserotonin and 1-methyl-5-methoxytryptamine and slightly for 1-methyltryptamine but increased it for N,N,1-trimethyltryptamine. Among the hydroxylated N,N-dimethyltryptamines, the 4- and 5-substituted compounds were more active than the 6 and 7 derivatives. 6-Hydroxylation decreased oxytocic activity for the two tryptamines examined. 1-Substitution of serotonin did not change the oxytocic effects for the 1-methyl derivative but reduced it for the 1-ethyl and 1-*n*-butyl compound.

General Comments.—Among 5-substituted tryptamines, β-hydroxylation decreased behavioral, pressor, and oxytocic activities. For the unsubstituted tryptamine, however, β-hydroxylation increased potency in some instances. In the case of N,N-dimethyl-1-methyltryptamine, reduction in behavioral activity was seen with β-hydroxylation while pressor and oxytocic potencies were increased. 6-Hydroxylation of the tryptamines employed produced deactivation in behavioral effects as already shown and, in addition, diminished pressor and oxytocic effects. The position of the hydroxyl group in N,N-dimethyltryptamines produced changes in pharmacological potency, the greatest differences occurring on behavioral activity. Thus the 4-hydroxy compound was more active than the 5 isomer and both were more active than 6 and 7 isomers. However, the 5 isomer had the most potent pressor actions.

Many mammalian species possess a blood brain barrier to serotonin.[21] However, evidence has been presented that the rat may be an exception, with exogenous administration of the amine raising brain levels.[22] Our data would lend support to this latter view since serotonin exhibits marked effects on the trained rat's behavior similar to that seen with known psychotropic tryptamines (Table II). 1-Methylserotonin exhibited an increase in potency over serotonin; however, further alkylation did not increase potency, with diminution occurring eventually. 1-Benzylation did not increase potency on behavior. In general, increased alkylation and supposedly greater lipid solubility did not confer greater potency on the serotonin

(21) S. Garattini and L. Valzelli, "Serotonin," Elsevier Publishing Co., New York, N. Y., 1965, p 203.

(22) W. T. Karki and M. K. Paasonen, *Acta Pharmacol. Toxicol.*, **16**, 20 (1959).

molecule. This suggests, as had been noted before for antimicrobials and other pharmacological agents,[23-25] that increased lipid solubility or a more favorable organic–water distribution reaches an optimal value. Further increase of partitioning into the lipid over the aqueous phase results in trapping of the molecule in the lipoidal areas of the organism and of its cell membranes, thus reducing its effects.[25]

Experimental Section

Reagents and Other Compounds.—Psilocin was obtained from the Sandoz Pharmaceutical Co., Hanover, N. J. Bufotenine was purchased from the California Biochemical Corp., Los Angeles, Calif. Other substituted indoles used as intermediates were purchased from the Regis Chemical Co., North Chicago, Ill. The synthesis of 1-substituted indoles in this study (Table I) is exemplified by the procedure given below.

5-(Benzyloxy)-1-*n*-butylindole.—Sodium hydride (1.1 g, 4.0 × 10^{-2} mole, 54% mineral oil mull) was suspended in 30 ml of dimethylformamide (DMF) and 5-(benzyloxy)indole (5.0 g, 2.2 × 10^{-2} mole) in 60 ml of redistilled DMF was added over 15 min with stirring. Evolution of hydrogen occurred together with slight warming of the contents of the flask, and the mixture was stirred for 1 hr at room temperature. 1-Iodobutane (4.3 g, 2.5 ml, 2.3 × 10^{-2} mole) was added dropwise to the mixture with some ice cooling since heat was generated. Addition required less than 10 min. The mixture was stirred at room temperature for 1 hr and slowly added to 150 ml of water. The water solution was extracted with four 75-ml portions of chloroform and the combined extracts were dried (Na_2SO_4) and filtered. Evaporation of the solutions under vacuum (50°) yielded 5.8 g of product, mp 52–53°. Further crystallization sharpened the melting point (Table I). Indoles alkylated included 5-methoxyindole, 5-(benzyloxy)indole, and indole with yields obtained as high as 96% (Table I). Some of these compounds were converted to stable equimolar picrate complexes as indoles where the pyrrole N–H is not substituted. 5-(Benzyloxy)-1-*n*-butylindole-3-acetonitrile and 5-(benzyloxy)-1-benzylindole-3-acetonitrile were used without purification. The substituted serotonins were unstable as is 5-hydroxytryptamine, but formed stable picrates. Compounds prepared and intermediates used to make them are reported in Table I.

The synthesis of β-hydroxylated 1-methyltryptamines followed the example procedure described below.

5-(Benzyloxy)-1-methylindole-3-glyoxyloyl Chloride.—A solution of oxalyl chloride (6.45 g, 4.32 ml, 5.08 × 10^{-2} mole) in anhydrous ether (30 ml) was added dropwise to a stirred suspension of 5-(benzyloxy)-1-methylindole (6.00 g, 2.53 × 10^{-2} mole) in anhydrous ether (200 ml), cooled to 0°. The reaction mixture was stirred for another 30 min in the cold. The orange crystalline product was filtered and washed with ether to give 6.62 g of product which was used in the next step without purification.

5-(Benzyloxy)-1-methylindole-3-glyoxylamide.—5-(Benzyloxy)-1-methylindole-3-glyoxyloyl chloride (6.56 g, 2.00 × 10^{-2} mole) was added in small portions to a stirred concentrated NH_4OH solution (70 ml), cooled to 0°. The mixture was stirred for 20 min more in the cold. The yellowish product was collected by filtration and washed with water to give 6.12 g of crude material, mp 167.5–168.5°. Crystallization from toluene gave colorless crystals (5.65 g).

α-(Aminomethyl)-5-(benzyloxy)-1-methylindole-3-methanol.—5-(Benzyloxy)-1-methylindole-3-glyoxylamide (5.10 g, 1.66 × 10^{-2} mole) was added in small portions to a vigorously stirred suspension of $LiAlH_4$ (5.0 g) in anhydrous tetrahydrofuran (THF) (200 ml) and the mixture refluxed for 16 hr. After cooling, excess hydride was destroyed by successive addition of 5 ml of water, 5 ml of 15% aqueous NaOH, and 15 ml of water. The mixture was filtered and the residue was leached thoroughly with hot chloroform. The combined filtrates were extracted ($CHCl_3$, 300 ml) and the organic layer was evaporated to dryness *in vacuo* to give the crude product, a yellow solid (4.23 g), mp 98–108°. Crystallization from ethyl acetate gave 3.46 g.

α-(Aminomethyl)-5-hydroxy-1-methylindole-3-methanol.—A solution of α-(aminomethyl)-5-(benzyloxy)-1-methylindole-3-methanol (500 mg, 1.69 mmoles) in 25 ml of methanol was hydrogenated over 200 mg 10% Pd–C at 2.8 kg/cm² for 18 hr. Filtration and evaporation to dryness *in vacuo* gave the crude product (295 mg, 85%), mp 85° (sinters at 75°). The amine was unstable in air, turning dark brown after several days. Thirty milligrams of crude amine was dissolved in a minimum volume of methanol and added to a solution of indole-3-acetic acid (25 mg) in 30 ml of ether. The precipitated salt gave on filtration 29 mg of yellowish fine crystals, mp 160° dec. The filtrate was cooled overnight to give a second crop (7 mg), mp 160° dec. The latter was chromatographically pure in 99:1 methanol–concentrated NH_4OH on silica thin layer, on glass. Crystallization of the first crop from ethyl acetate or 1-butanol failed to give a chromatographically pure sample.

Behavioral Pharmacology.—White, male rats weighing between 320–395 g were used (average age 8 months). They were fed a diet of 12–16 g of Rockland rat and mouse chow each evening and trained for a minimum of 8 weeks, 1 hr daily, in a Skinner box on a positive reinforcement variable interval schedule. Animals were not fed each day prior to their stay in the chamber. Intervals between opportunities for reward were variably spaced so that the rats were unable to remember their duration. For the rats to obtain maximum profit from the situation they continued to press the bar at a steady rate for the hour in the chamber. Their efforts as bar presses per hour were automatically recorded. Each animal had an individual work rate ranging from 26–68 presses/min. Normal performance of each animal served as its own control against work rates when under test. Compounds were administered on the test day by the intraperitoneal route. Statistical analyses were done to gauge the significance of the results.[9]

Effect on Smooth Muscle.—Estrus rat uterus suspended in a Tyrode–Ringer solution muscle bath was used.[26] The muscle was standardized to give consistent contractions to serotonin creatinine sulfate. Potency of oxytocic activity was expressed as the molar ratio of compound giving equal contraction to 10^{-6} to 10^{-8} *M* solutions of serotonin creatinine sulfate (Table II).

Blood Pressure.—Compounds were injected intravenously into pentobarbital-anesthetized, whole, male, Sprague–Dawley rats at 10-min intervals. Injections of serotonin creatinine sulfate were included among the test compounds to ensure that the response remained constant to 15% of initial injections. Each compound was examined at least three times in different animals. Blood pressure changes were measured by means of an arterial cannula attached to a mercury manometer which operated a lever attached to a pen on a kymograph. Responses and blood pressure changes were recorded in the usual manner.

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