Enzyme Inhibitory Activity of 3-(2-Aminobutyl)indole Derivatives

J. B. HESTER, M. E. GREIG, W. C. ANTHONY, R. V. HEINZELMAN, AND J. SZMUSZKOVICZ

Research Laboratories of The Upjohn Co., Kalamazoo, Michigan

Received November 13, 1963

Several analogs of 3-(2-aminobutyl)indole were prepared and tested for monoamine oxidase and 5-hydroxytryptophan decarboxylase inhibitory activity. A rational for the superior *in vivo* and *in vitro* activity of 3-(2-aminobutyl)-7-methylindole is discussed.

3-(2-Aminobutyl)indole[1,2] (etryptamine, XIII) has been shown to be a clinically efficacious drug for treating some types of depression.[3] It was, therefore, of interest to study the relative pharmacology of several analogous compounds. Early pharmacologic studies clearly demonstrated that etryptamine was a reversible inhibitor of monoamine oxidase *in vitro*, with about the same potency as iproniazid; and that it had no effect on 5-hydroxytryptophan decarboxylase activity at a concentration of 10^{-2} *M*.[4] At low doses (<2 mg./kg.) etryptamine inhibited both rat brain and rat liver monoamine oxidase activity[5]; it caused a significant increase of endogenous brain serotonin and greatly enhanced 5-hydroxytryptophan potentiation of rat brain serotonin.[5,6] At high doses (<2–10 mg./kg.) in chronic experiments, etryptamine was found to depress brain serotonin levels below those observed with lower doses of the drug.[7,8] This result indicated that, although etryptamine inhibits serotonin metabolism, at high doses it also interferes with serotonin formation. Since the absence of appreciable 5-hydroxytryptophan decarboxylase inhibition had already been demonstrated, the effect of etryptamine on tryptophan-5-hydroxylation was investigated. The results of these experiments, which have been reported by Greig, *et al.*,[7,8] and are summarized in Fig. 1, strongly support the view that etryptamine *does* inhibit tryptophan-5-hydroxylation. Since the antidepressant effects of etryptamine have usually been ascribed to its activity as a monoamine oxidase inhibitor[9] we sought to prepare an analog that would not interfere with serotonin synthesis but would still inhibit serotonin metabolism by monoamine oxidase.

Recently Hall and co-workers[10] were able to show that both 7-methyltryptophan and 7-chlorotryptophan were poorly adsorbed on *Escherichia coli* tryptophanase,

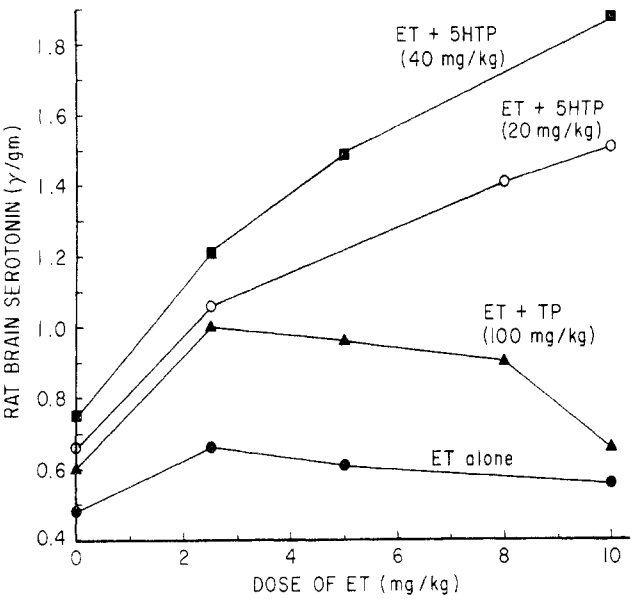


Fig. 1.—Effect of etryptamine on rat brain serotonin.

an enzyme that converts L-tryptophan to indole. This phenomenon was attributed to the fact that 7-substituents on the indole nucleus would sterically inhibit adsorption of the indole nitrogen to an enzyme surface. These workers proposed that three-point attachment, required for stereospecific enzyme adsorption, in this case involved the side-chain carboxyl and amino groups as well as the indole nitrogen, a conclusion that was supported by the work of Gooder and Happold.[11] Since tryptophan-5-hydroxylase is specific for the L-amino acid[12a] it appeared to us that three-point attachment would be required for enzyme interaction and that a likely point of attachment would be the indole nitrogen. Since enzyme inhibition usually involves adsorption of the inhibitor on the active site of the enzyme we speculated that indole substituents which would block the approach of the indole nitrogen of etryptamine to the enzyme surface would prevent the inhibition of tryptophan-5-hydroxylase by the resulting compound. These substituents were not expected to affect the monoamine oxidase inhibitory characteristics of the compound since we had already found that both

(1) (a) H. R. Snyder and L. Katz, *J. Am. Chem. Soc.*, **69**, 3140 (1947); (b) Monase®.

(2) (a) R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuszkovicz, *J. Org. Chem.*, **25**, 1548 (1960); (b) J. Szmuszkovicz and R. C. Thomas, *ibid.*, **26**, 960 (1961).

(3) For an early clinical evaluation see L. J. Meduna, *J. Neuropsychiat. Suppl.*, **2** (1961).

(4) M. E. Greig, R. A. Walk, and A. J. Gibbons, *J. Pharmacol. Exptl. Therap.*, **127**, 110 (1959).

(5) M. E. Greig, P. H. Seay, and W. A. Freyburger, *J. Neuropsychiat. Suppl.*, **2**, 131 (1961).

(6) K. F. Gey and A. Pletscher, *Brit. J. Pharmacol.*, **19**, 161 (1962).

(7) M. E. Greig, R. J. Matthews, and W. A. Freyburger, "Psychosomatic Medicine," J. H. Nodine and J. H. Moyer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, p. 643.

(8) M. E. Greig and A. J. Gibbons, *Arch. Intern. Pharmacodyn.*, **136**, 147 (1962).

(9) Dissenting opinions have recently been expressed by Gey and Pletscher (see ref. 6) and by J. R. Vane, H. O. J. Collier, S. J. Corne, E. Marley, and P. B. Bradley, *Nature*, **191**, 1068 (1961).

(10) A. N. Hall, J. A. Leeson, H. N. Rydon, and J. C. Tweddle, *Biochem. J.*, **74**, 209 (1960).

(11) H. Gooder and F. C. Happold, *ibid.*, **55**, xxxii (1953).

(12) (a) F. A. Freedland, I. M. Wadzinski, and H. A. Waisman, *Biochem. and Biophys. Res. Commun.*, **6**, 227 (1961). (b) Since the writing of this manuscript, B. A. Whittle and E. H. P. Young, *J. Med. Chem.*, **6**, 378 (1963), have published the chemistry and pharmacology of the 4-, 5-, 6-, and 7-chloro derivatives of 3-(2-aminopropyl)indole and 3-(2-aminobutyl) indole. 3-(2-Aminobutyl)-7-chloroindole was a potent inhibitor of both monoamine oxidase and 5-hydroxytryptophan decarboxylase activity *in vitro;* it was, however, a relatively weak inhibitor of monoamine oxidase *in vivo* as measured by its reversal of reserpine-induced ptosis in mice.

optical enantiomers of etryptamine (Table II) had similar activity as monoamine oxidase inhibitors, indicating that a three-point attachment of the inhibitor to this enzyme was evidently not required.

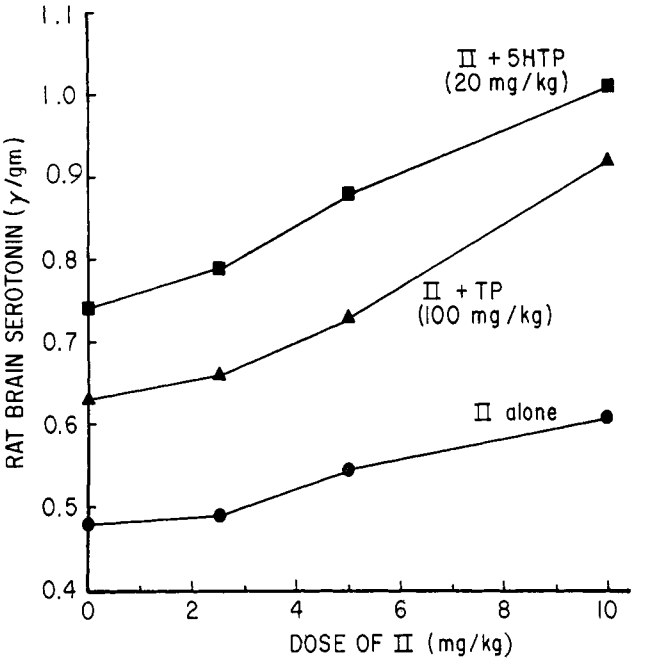


Fig. 2.—Effect of 3-(2-aminobutyl)-2,7-dimethylindole (II) on rat brain serotonin.

Inhibition of monoamine oxidase by 3-(2-aminobutyl)-2,7-dimethylindole (II), the first compound in this series to be investigated, was inferior to that of etryptamine both *in vitro* and *in vivo*. It did, however, potentiate the effects of *both* tryptophan and 5-hydroxytryptophan on rat brain serotonin levels (Fig. 2). Further investigation showed that 3-(2-aminobutyl)-2-methylindole (IX) had little effect on monoamine oxidase *in vitro* and did not potentiate the effect of either tryptophan or 5-hydroxytryptophan on rat brain serotonin (Fig. 3). Thus the 2-methyl substituent on these compounds markedly inhibits formation of the enzyme-inhibitor complex, an effect which may be rationalized by a consideration of steric factors. On the other hand, the inhibition of monoamine oxidase by 3-(2-aminobutyl)-7-methylindole (X) was striking. Its *in vitro* activity was 10 times that of etryptamine, and it was 2–4 times as effective as etryptamine in increasing endogenous rat brain serotonin *in vivo*. It also caused a marked increase of rat brain serotonin when followed by either tryptophan or 5-hydroxytryptophan. In both cases there was a direct relationship between dose and response (Fig. 4).[12b] It is interesting to note that there was little selective inhibition of monoamine oxidase by either of the optical enantiomers of X as compared with X itself. Both the *in vitro* (Table II) and the *in vivo* inhibition of monoamine oxidase by these isomers closely approximated that of the racemic mixture. These data offer support for the view that tryptophan-5-hydroxylase, like tryptophanase, requires unhindered approach to the indole nitrogen for substrate–complex formation.

It has been found that etryptamine, like many other indole derivatives, is metabolized primarily by 6-

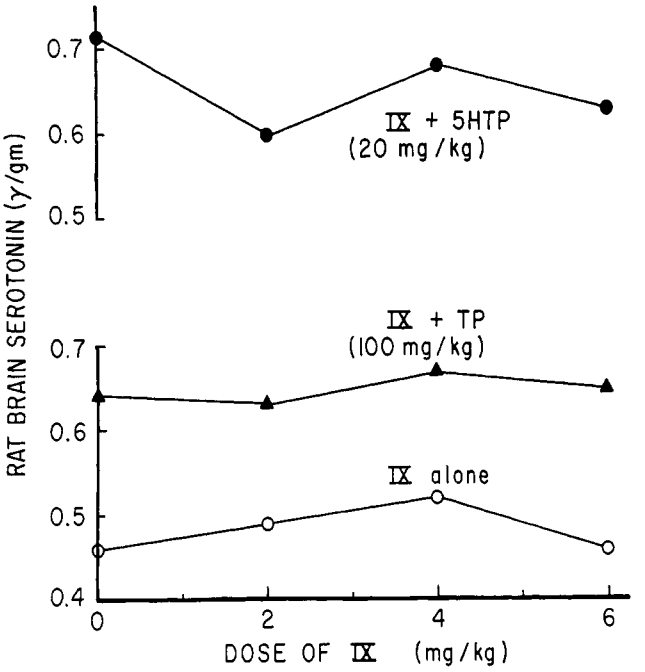


Fig. 3.—Effect of 3-(2-aminobutyl)-2-methylindole (IX) on rat brain serotonin.

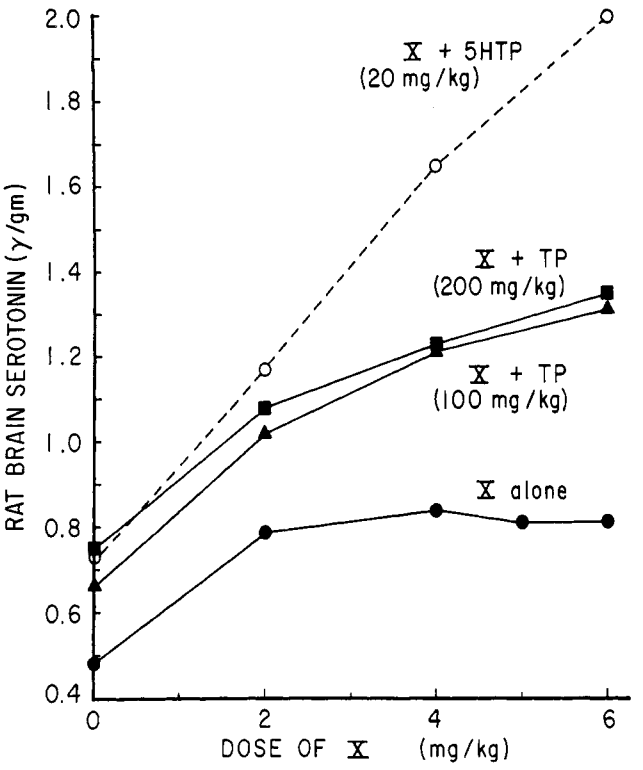


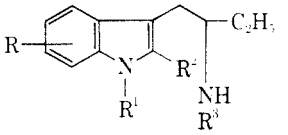
Fig. 4.—Effect of 3-(2-aminobutyl)-7-methylindole (X) on rat brain serotonin.

hydroxylation.[13] Since Szara and Hearst[14] had shown that 6-hydroxy-N,N-diethyltryptamine, the major metabolite of N,N-diethyltryptamine, was a potent psychotomimetic agent and probably accounted for the observed activity of its precursor, we were surprised to find that 3-(2-aminobutyl)-6-hydroxyindole (V), the major metabolite of etryptamine, had little activity on the central nervous system of intact animals and

(13) F. S. Eberts, Jr., and E. G. Daniels, *Federation Proc.*, **21**, 180 (1962).
(14) S. Szara and E. Hearst, *Ann. N. Y. Acad. Sci.*, **96**, 134 (1962).

TABLE I

3-(2-AMINOBUTYL)INDOLES



No.	R	R^1	R^2	R^3	Yield, %	Method	M.p., °C., (solvent)
I	H	H	H	C_2H_5	75[a]		141.5–142.5 (MeOH–EtOAc)
II	7-CH_3	H	CH_3	H	24.9	B	167–168 (EtOAc)
III[d]	5-OCH_3	H	H	H	70	B[e]	143–144
IV[e]	6-OCH_3	H	H	H	41	A[f]	144–145 (EtOAc)
V	6-OH	H	H	H	78.5[a]		87–90
VI[h]	6-F	H	H	H	60.2	A	211–212.5 (EtOH–EtOAc)
VII	H	CH_3	H	H	74	C	225–226 (MeOH–Et_2O)
VIII	H	CH_3	CH_3	H	55	C	274.5–276 (MeOH–Et_2O)
IX[l]	H	H	CH_3	H	58[k]	A[f]	141.5–142.5 (EtOH–Et_2O)
X[m]	7-CH_3	H	H	H	63.8[n]	B[o]	206.5–208 (MeOH–EtOAc)
XI	6-NH_2	H	H	H	34.7[q]	B[p]	261–262 dec. (MeOH–EtOAc)
XII	6-$OCH_2C_6H_5$	H	H	H	66.9[q]	A[a]	214.5–215 (EtOH–EtOAc)
XIII[r]	H	H	H	H			

[a] The procedure is described in the experimental section. [b] Acetic acid salt. [c] Palladium-on-carbon catalyst was used for this reduction. Preliminary purification of the product was effected by acid–base extraction rather than by distillation. [d] 5-Methoxygramine was prepared according to the method of J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951). [e] 6-Methoxyindole was prepared by the method of R. B. Woodward, *et al.*, *Tetrahedron*, **2**, 1 (1958); 6-methoxygramine was reported by E. Leete, *J. Am. Chem. Soc.*, **82**, 6338 (1960). [f] The reduction was carried out by adding a benzene solution of the nitrobutylindole to an ethereal solution of lithium aluminum hydride and refluxing the mixture for 18–21 hr. [g] Creatinine sulfate salt. Calcd. for S: 7.40. Found:

TABLE II

OPTICAL ISOMERS OF COMPOUNDS X AND XIII

Compound	Monoamine oxidase, % inhibition/ *M* drug concentration
d-3-(2-Aminobutyl)-7-methylindole hydrochloride	$50/2.6 \times 10^{-5}$
l-3-(2-Aminobutyl)-7-methylindole hydrochloride	$50/2.1 \times 10^{-5}$
d-3-(2-Aminobutyl)indole acetate salt	$79/10^{-3}$
l-3-(2-Aminobutyl)indole acetate salt	$50/1.5 \times 10^{-4}$

did not inhibit monoamine oxidase *in vitro*.[15] Recently Kalir and Szara[16] reported results similar to ours for 3-(2-aminopropyl)-6-hydroxyindole, the major metabolite of 3-(2-aminopropyl)indole.

Since etryptamine is metabolized rapidly *in vivo* it was of interest to prepare a 3-(2-aminobutyl)indole that was substituted at the 6-position in the hope that such a compound would retain the activity of etryptamine and resist metabolism by the 6-hydroxylation mechanism. 3-(2-Aminobutyl)-6-fluorotryptamine (VI) was therefore prepared. This compound was, however, a poor monoamine oxidase inhibitor in both *in vivo* and *in vitro* assays.

The 3-(2-aminobutyl)indoles prepared for this study are listed in Table I along with their physical constants and *in vitro* monoamine oxidase and 5-hydroxytryptophan decarboxylase inhibitory activities.

Chemistry.—Most of the amines listed in Table I were prepared by reducing the corresponding nitro-

(15) M. E. Greig, H. H. Keasling, and R. J. Matthews, unpublished results.

(16) A. Kalir and S. Szara, *Federation Proc.*, **21**, 337 (1962).

Formula	% Calcd. / % Found C	H	N	Cl	λ_{max}, mμ (ε)	Inflection, mμ (ε)	Monoamine oxidase, % inhibition/*M* drug concentration	5-Hydroxytryptophan-decarboxylase, % inhibition at 10^{-2} *M*
$C_{14}H_{20}N_2 \cdot C_2H_4O_2$[b]	69.53	8.75	10.14		220 (37,650)		$50/7 \times 10^{-4}$	0
	69.50	8.52	10.05		274 (5,800)			
					280 (6,250)			
					289 (5,450)			
$C_{14}H_{20}N_2 \cdot C_2H_4O_2$[b]	69.53	8.75	10.14		222 (37,650)	274 (7450)	$54/10^{-3}$	6
	68.89	8.22	10.11		279 (7,650)	288 (6100)		
$C_{13}H_{18}N_2O \cdot C_2H_4O_2$[b]	64.72	7.97	10.06		221 (25,750)	306 (3600)	$10/10^{-3}$	7
	64.47	8.15	10.09		275 (6,200)			
					295 (4,950)			
$C_{13}H_{18}N_2O \cdot C_2H_4O_2$[b]	64.72	7.97	10.07		223 (34,750)	263 (3750)	$48/10^{-3}$	58
	64.80	7.93	10.03		293 (5,350)	273 (4400)		
						302 (3850)		
$C_{16}H_{27}O_7N_5S$[g]	44.32	6.27	16.15		222 (33,150)	264 (3600)	$0/10^{-3}$	58
	44.38	5.96	15.88		273 (4,050)	300 (3350)		
					295 (4,600)			
$C_{12}H_{15}N_2F \cdot HCl$[i]	59.38	6.65	11.54	14.61	218 (30,050)	271 (4900)	$44/10^{-3}$	0
	59.24	6.72	11.46	14.55	278 (4,150)	288 (5150)		
					283 (5,550)			
$C_{13}H_{18}N_2 \cdot HCl$	65.39	8.02	11.74	14.85	223 (36,250)	276 (5350)	$35/10^{-3}$	0
	65.27	8.22	11.58	14.36	286 (5,900)	296 (4750)		
$C_{14}H_{20}N_2 \cdot HCl$	66.51	8.37	11.08	14.03	227 (36,900)	280 (6700)	$0/10^{-3}$	14
	66.26	8.23	11.05	13.88	285 (5,200)			
					294 (6,850)			
$C_{13}H_{18}N_2 \cdot C_4H_4O_4$[j]	64.13	6.97	8.80		221 (44,800)	289 (7000)	$22/10^{-3}$	13
	63.84	7.06	9.32		298 (7,350)			
					304 (6,400)			
$C_{13}H_{18}N_2 \cdot HCl$	65.39	8.02	11.74	14.85	218 (43,700)		$50/3 \times 10^{-5}$	0
	65.46	8.10	11.40	14.72	271 (6,900)			
					279 (6,900)			
					289 (5,150)			
$C_{12}H_{17}N_3 \cdot 2HCl$	52.18	6.93			225 (32,700)	304 (3050)	$18/10^{-3}$	100
	52.27	6.83			276 (4,550)			
					291 (4,150)			
$C_{19}H_{22}ON_2 \cdot HCl$	68.97	7.01	8.47	10.72	223 (40,550)	258 (3850)	...	...
	69.18	6.83	8.22	10.77	273 (4,650)	264 (4400)		
					292 (5,450)	302 (3750)		
							$50/2.6 \times 10^{-4}$	0

7.38. [h] 6-Fluorogramine was prepared by the method of A. Allais and J. Meier, U. S. Patent 3,042,685 (July 3, 1962). [i] *Anal.* Calcd.: F, 7.83. Found: F, 7.69. [j] Maleate salt. [k] Initial purification of the base was effected by distillation, b.p. 165–170° (0.3 mm.). [l] 2-Methylgramine was prepared according to the procedure of J. E. Pretka and H. G. Lindwall, *J. Org. Chem.*, **19**, 1080 (1954). [m] 7-Methylgramine was prepared by the method of H. N. Rydon, *J. Chem. Soc.*, 705 (1948). [n] Yield based on 7-methylindole. [o] Acid–base extraction rather than distillation was used for the initial purification. [p] The hydrogenation required 1.5 hr.; the product was isolated and purified by crystallizing its hydrochloride. [q] Yield based on 3-(2-nitrobutyl)indole. [r] See ref. 1, 2.

butyl indoles which, in turn, were prepared by allowing the requisite gramine to react with 1-nitropropane under the conditions described by Snyder and Katz.[1] In most cases the nitrobutyl indoles were not crystalline. Satisfactory results were obtained when the crude oils were reduced either catalytically with Raney nickel or palladium-on-carbon, or chemically with lithium aluminum hydride. 3-(2-Ethylaminobutyl)indole (I) was prepared by lithium aluminum hydride reduction of the corresponding N-acetate (XIV) which was prepared by the reaction of etryptamine with acetic anhydride. Alkylation of the indole nitrogen to obtain VII and VIII was achieved with sodamide and methyl iodide in liquid ammonia. 6-Amino-3-(2-aminobutyl)indole (XI) was obtained by catalytic reduction of 3-(2-nitrobutyl)-6-nitroindole which was prepared in the usual manner from 6-nitrogramine. 3-(2-Aminobutyl)-6-hydroxyindole (V) was prepared by palladium-catalyzed hydrogenolysis of the corresponding benzyloxy derivative (XII). A facile condensation of V with acetone will be the subject of a future communication.

Resolution of *d,l*-3-(2-aminobutyl)-7-methylindole (X) was effected by fractional crystallization of the dibenzoyl-*d*-tartrate salts from ethanol. Resolution of etryptamine was accomplished by fractional crystallization of the *d*-camphor-10-sulfonate salts from isopropyl alcohol.

Experimental

Pharmacology.—Monoamine oxidase activity was determined manometrically by the method of Bhagvat, *et al.*[17] The source of enzyme was guinea pig liver. The substrate used was serotonin in a concentration of 6×10^{-3} *M*. Compounds tested for in-

(17) K. Bhagvat, H. Blaschko, and D. Richter, *Biochem. J.*, **33**, 1338 (1939).

hibitory activity were added to the manometer vessel for initial testing in concentrations to give a final molarity of 10^{-3}. For compounds inhibiting more than 50% at this concentration, $[I]_{50}$ determinations were carried out. It is obvious that for monoamine oxidase inhibitors, such as etryptamine, which compete with the substrate the $[I]_{50}$ values are valid only with the substrate concentration used.

5-Hydroxytryptophan (5-HTP) decarboxylase activity was measured manometrically by the method of Clark, *et al.*[18]

In vivo enzyme inhibiting activity was assessed by determining brain serotonin as follows: 4 to 10 rats were dosed i.p. with the tryptamine derivative either alone or followed in 10 min. by tryptophan (TP) (100 mg./kg.) or 5-hydroxytryptophan (20 or 40 mg./kg.). One hour later they were decapitated and brain tissue serotonin was determined by the method of Bogdanski, *et al.*[19] using the Aminco Bowman spectrophotofluorometer.

Chemistry.—Melting points were taken in a capillary tube and are corrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol using a Cary Model 14 spectrophotometer. Infrared spectra (recorded in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer Model 421 recording infrared spectrophotometer. Skellysolve B is commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo. Florisil is a synthetic magnesia–silica gel manufactured by the Floridin Co., Tallahassee, Fla. Celite is a filter-aid manufactured by Johns-Manville, New York 16, N.Y.

2,7-Dimethylgramine.—Acetic acid (50.6 ml.) was added during 15 min. to 67 ml. of dimethylamine (25% aqueous solution) while cooling in ice. Formalin (25.4 ml. of 37% solution) was then added during 10 min. followed by 2,7-dimethylindole[20] (49.4 g., 0.34 mole) over a 15-min. period. The mixture was stirred in the cold for 1 hr. and then at room temperature overnight. Water (50 ml.) was added and the mixture was extracted with two 50-ml. portions of ether. The ether extracts were washed with two 50-ml. portions of water and the combined aqueous solution was extracted once more with ether. The resulting clear yellow aqueous layer was cooled in ice and made basic with 250 ml. of 10% sodium hydroxide solution. The resulting oil was extracted with three 100-ml. portions of ether. The ether extracts were washed with saturated salt solution, dried through sodium sulfate, and evaporated *in vacuo* at 30–40° to give 22 g. (32%) of crude 2,7-dimethylgramine. This product (0.202 g.) and picric acid (0.229 g.) were dissolved in benzene containing a little ethanol and the solution was allowed to stand overnight. The resulting product (m.p. 155–159°) was recrystallized twice from benzene–methanol to give small orange prisms, m.p. 158–159°. The ultraviolet spectrum had λ_{max} 219, 286.5, and 358 mμ (ε 59,100, 7750, and 15,900, respectively) with inflections at 264, 276, and 410 mμ (ε 11,600, 9950, and 9700, respectively).

Anal. Calcd. for $C_{19}H_{21}N_3O_7$: C, 52.89; H, 4.91; N, 16.24. Found: C, 53.18; H, 4.92; N, 16.06.

The original neutral extracts were washed with saturated salt solution and evaporated to dryness to give 32 g. of a brown oil which was distilled at 165–170° (0.3 mm.), leading to recovery of 12 g. of 2,7-dimethylindole.

3-(2-Nitrobutyl)-6-fluoroindole. General Procedure for the Preparation of 3-(2-Nitrobutyl)indoles.—Nitrogen was passed through a refluxing mixture of finely ground sodium hydroxide (2.7 g.), 6-fluorogramine (13.6 g., 0.0707 mole), and 1-nitropropane (100 ml.). After 10 hr. the evolution of dimethylamine had ceased; the mixture was cooled, diluted with ether, and extracted successively with dilute acetic acid, water, dilute ammonium hydroxide, and saturated sodium chloride. The ether solution was then filtered through anhydrous sodium sulfate and concentrated *in vacuo*. The excess nitropropane was removed by azeotropic distillation with toluene and benzene to yield the product as a light tan oil which was used in the next reaction without further purification. The infrared spectrum (liquid film) showed NH, 3426 $cm.^{-1}$ and NO_2, 1534 and 1327 $cm.^{-1}$.

3-(2-Aminobutyl)-6-fluoroindole (VI). General Procedure A for the Preparation of 3-(2-Aminobutyl)indoles.—A solution of the product from the previous reaction in 200 ml. of dry tetrahydrofuran was added slowly, under nitrogen, with stirring to a solution of 14 g. of lithium aluminum hydride in 200 ml. of dry tetrahydrofuran. The mixture refluxed gently during the addition and a gas was evolved (it is believed that the initial reaction is the abstraction of the hydrogen attached to the indole nitrogen). An additional 10 ml. of tetrahydrofuran was added to the reaction mixture which was allowed to reflux for 5.5 hr., cooled in an ice bath, and treated successively with water (14 ml., dropwise), 15% aqueous sodium hydroxide (14 ml.), and water (28 ml.). The resulting solid was collected by filtration and washed with ether. Concentration of the combined filtrates yielded an oil which was dissolved in ethyl acetate and acidified with ethanolic hydrogen chloride. Crystallization of the resulting hydrochloride from ethanol-ethyl acetate yielded 10.35 g. (60.2%), m.p. 210–211.5°. An analytical sample, m.p. 211–212.5°, was prepared by recrystallizing the hydrochloride from ethanol-ethyl acetate.

3-(2-Aminobutyl)-2,7-dimethylindole Acetate Salt (II). General Procedure B for the Preparation of 3-(2-Aminobutyl)-indole.—Crude 2,7-dimethyl-3-(2-nitrobutyl)-indole (22 g., 0.085 mole) was dissolved in 200 ml. of ethanol, a teaspoon of Raney nickel (washed 3 times with ethanol) was added, and the mixture was refluxed 15 min. It was then filtered, a fresh teaspoon of Raney nickel was added, and hydrogenation was carried out, in a Parr shaker, at initial pressure of 3.5 $kg./cm.^2$ After 22.5 hr. 93% of the theoretical amount of hydrogen was absorbed. The mixture was filtered and evaporated at 40–50° *in vacuo* to give 17 g. of a brown oil. Distillation of 15 g. of this oil in an oil-jacketed flask at 0.1 mm. afforded 8 g. of a yellow oil (bath temperature 180–190°). It was dissolved in 5 ml. of ethyl acetate, 2.3 ml. of acetic acid was added, and the solution was cooled. The resulting solid amounted to 7.5 g. and melted at 167–169°. A 0.3 g. sample was recrystallized from 20 ml. of ethyl acetate containing a drop of acetic acid to give colorless small prisms, m.p. 167–168°.

3-(2-Nitrobutyl)-6-benzyloxyindole.—Nitrogen was passed through a refluxing mixture of 20 ml. of 1-nitropropane, 1.02 g. (3.82 mmoles) of 6-benzyloxygramine[21] and 200 mg. of powdered sodium hydroxide. After 7 hr. the dimethylamine evolution had stopped; the mixture was cooled and diluted with ether. The ether solution was washed successively with 10% acetic acid, saturated sodium chloride, dilute ammonium hydroxide, and saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The excess nitropropane was removed by azeotropic distillation with toluene and benzene and the product was dissolved in ethyl acetate and decolorized with activated carbon. Crystallization of the product from benzene–Skellysolve B yielded 1.09 g. (88%), m.p. 100–103°. An analytical sample, m.p. 101–103°, was prepared by recrystallizing this material from benzene–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 222 and 292 mμ (ε 41,850 and 5800, respectively) with inflections at 264 and 274 mμ (ε 4600 and 4950, respectively). The infrared spectrum (Nujol) showed NH, 3400 $cm.^{-1}$ and NO_2, 1550 and 1340 $cm.^{-1}$.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.62; H, 6.17; N, 8.81.

3-(2-Aminobutyl)-6-benzyloxyindole Sulfate and Hydrochloride (XII).—To an ice-cold solution of 4.0 g. of lithium aluminum hydride in 200 ml. of dry tetrahydrofuran, under nitrogen, was added a solution of 3.77 g. (11.7 mmoles) of the nitro compound in tetrahydrofuran. The resulting mixture was refluxed for 4.5 hr., cooled in an ice bath, and treated successively with water (4 ml.), 15% aqueous sodium hydroxide (4 ml.), and water (12 ml.). Filtration of this mixture removed the inorganic salts which were washed well with chloroform. The combined filtrate was concentrated *in vacuo* and the residue was dissolved in ether and extracted with dilute acetic acid. The acetic acid extract was washed with ether, made ammoniacal, and extracted with ether. This ether extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated to yield 2.75 g. of an oil. This was treated with 12.9 ml. of 0.72 *N* ethanolic sulfuric acid (it is probable that on standing some of the acid was converted to ethyl hydrogen sulfate) and the resulting sulfate salt was crystallized from ethanol–ethyl acetate to yield 1.46 g. (35.6%), m.p. 175–179° (softening at 168°). An analytical sample, m.p. 179–183°, was prepared by recrystallization from ethanol–ethyl acetate. The ultraviolet spectrum (ethanol)

(18) C. T. Clark, H. Weissbach, and S. Udenfriend, *J. Biol. Chem.*, **210**, 139 (1954).

(19) D. F. Bogdanski, A. Pletscher, B. B. Brodie, and S. Udenfriend, *J. Pharmacol. Exptl. Therap.*, **117**, 82 (1956).

(20) 2,7-Dimethylindole was obtained from Aldrich Chemical Co.

(21) Regis Chemical Co.

had λ_{max} 223, 274, and 292 mμ (ε 77,500, 9260, and 10,800, respectively) with inflections at 258 and 265 mμ (ε 7500 and 8750, respectively).

Anal. Calcd. for $C_{28}H_{46}N_4O_6S \cdot H_2O$: C, 64.75; H, 6.86; N, 7.95; S, 4.55. Found: C, 64.78; H, 6.62; N, 7.92; S, 4.84.

The residue from the sulfate crystallization was converted to the free base and then to the hydrochloride salt with ethanolic hydrogen chloride to yield 1.21 g. (31.3%), m.p. 212–212.5°.

3-(2-Aminobutyl)-6-hydroxyindole Creatinine Sulfate Hydrate (V).—A solution of 154.3 mg. (0.45 mmole) of the sulfate salt, m.p. 175–179°, in 95% ethanol was treated with 97.9 mg. of 10% palladium-on-carbon and hydrogenated at atmospheric pressure. The reaction proceeded rapidly. After 1.5 hr. the catalyst was removed from the mixture by filtration through Celite and the filtrate was concentrated *in vacuo*, under nitrogen, at 30–40°. To a solution of the product in a small amount of water was added 74.0 mg. (0.223 mmole) of creatinine sulfate and the resulting salt was crystallized from acetone–water to yield 153.5 mg. (78.5%) of the creatinine sulfate salt, m.p. 87–90°. This material was recrystallized 3 times from acetone–water for analysis, m.p. 87°.

3-(2-Nitrobutyl)-6-nitroindole.—A vigorous stream of nitrogen was passed through a refluxing mixture of 2.0 g. (9.13 mmoles) of 6-nitrogramine,[22] 40 ml. of 1-nitropropane, and 400 mg. of powdered sodium hydroxide. After the mixture had refluxed for 6 hr. it was cooled, diluted with ether, and washed successively with water and saturated sodium chloride solution. The ether extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Excess nitropropane was removed from the residue by azeotropic distillation first with toluene and then benzene. Crystallization of the residue from benzene–Skellysolve B yielded 1.55 g. (64.5%) of product, m.p. 94–99°. A sample of this material was purified for analysis by Florisil chromatography followed by crystallization from ethyl acetate–Skellysolve B, m.p. 104–105°. The ultraviolet spectrum (ethanol) had λ_{max} 251, 324, and 366 mμ (ε 10,050, 8250, and 7000, respectively) with an inflection at 264 mμ (ε 9700). The infrared spectrum (Nujol) showed NH, 3345 cm.$^{-1}$ and NO_2, 1561 and 1300 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.28; H, 4.73; N, 15.99.

3-(2-Acetylaminobutyl)indole (XIV).—A solution of 3-(2-aminobutyl)indole (30 g., 0.16 mole) in 140 ml. of acetic anhydride was allowed to stand at room temperature, under nitrogen for 18 hr. To the resulting solution was added water (500 ml.) followed by sodium carbonate (102 g.). The mixture which resulted was extracted 3 times with ether; the ether extracts were washed with aqueous sodium bicarbonate and saturated sodium chloride, dried over sodium sulfate, and concentrated to yield 38 g. of a viscous, pale yellow oil. This material was used without purification in the subsequent reaction.

3-(2-Ethylaminobutyl)indole Acetate Salt (I).—A solution of 3-(2-acetylaminobutyl)indole (24.5 g., 0.106 mole) in 500 ml. of tetrahydrofuran was added during 30 min. to a solution of lithium aluminum hydride (76 g.) in 1 l. of tetrahydrofuran. The mixture was then refluxed for 20 hr. and decomposed by successive addition of water (76 ml.), 15% sodium hydroxide solution (76 ml.), and water (228 ml.). The suspension was filtered and the filtrate dried over sodium sulfate and evaporated to dryness to give a yellow oil (21.7 g.). The infrared spectrum showed a very weak amide band which indicated an almost complete reduction. The oil was converted to the acetate salt in ethyl acetate–ether; 20.2 g. (75% yield), m.p. 141.5–142.5° unchanged on recrystallization from methanol–ethyl acetate.

3-(2-Aminobutyl)-1-methylindole Hydrochloride (VII). General Procedure C for the Preparation of 3-(2-Aminobutyl)-indoles.—3-(2-Aminobutyl)indole (44.5 g., 0.237 mole) was added to a mixture of sodamide (0.24 mole) and liquid ammonia (930 ml.) over a period of 30 min. This was followed by the addition of methyl iodide (37 g., 0.25 mole) during 30 min. The ammonia was allowed to evaporate, and the residue was suspended in water (185 ml.) and extracted 5 times with methylene chloride. The extracts were washed twice with brine, dried with anhydrous sodium sulfate, and evaporated to give a yellow oil. An ether solution of this material was acidified with ethereal hydrogen chloride. The resulting hydrochloride was recrystallized from methanol–ether.

Resolution of *d,l*-3-(2-Aminobutyl)-7-methylindole (X).—A solution of *d,l*-3-(2-aminobutyl)-7-methylindole (X) (3.73 g., 0.0184 mole) and dibenzoyl-*d*-tartaric acid monohydrate (6.94 g., 0.0184 mole) in 250 ml. of warm ethanol was allowed to crystallize. The resulting solid was recrystallized 3 times from ethanol to yield the dibenzoyl-*d*-tartrate of *d*-3-(2-aminobutyl)-7-methylindole, m.p. 168°, $[\alpha]_D$ −10° (dimethyl sulfoxide).

Anal. Calcd. for $C_{31}H_{32}N_2O_8$: C, 66.42; H, 5.75; N, 5.00. Found: C, 66.05; H, 6.04; H, 5.25.

Fractional crystallization of the mother liquors from the above crystallization yielded the dibenzoyl-*d*-tartrate of *l*-3-(2-aminobutyl)-7-methylindole, m.p. 170–171.5°, $[\alpha]_D$ −17° (dimethyl sulfoxide).

Anal. Calcd. for $C_{31}H_{32}N_2O_8$: C, 66.42; H, 5.75; N, 5.00. Found: C, 66.08; H, 5.71; N, 5.02.

A suspension of the dibenzoyl-*d*-tartrate of *d*-3-(2-aminobutyl)-7-methylindole (1.13 g.) in dilute ammonium hydroxide was stirred with ether. The resulting ether solution was washed with brine, dried over anhydrous potassium carbonate, and concentrated under reduced pressure. Several recrystallizations of the residue from ethyl acetate–Skellysolve B yielded *d*-3-(2-aminobutyl)-7-methylindole, m.p. 115–117°, $[\alpha]_D$ +33° (chloroform).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.09; H, 8.92; N, 13.42.

An ethyl acetate solution of *d*-3-(2-aminobutyl)-7-methylindole (0.598 g.) was acidified with methanolic hydrogen chloride. The resulting salt was recrystallized several times from methanol–ethyl acetate to yield *d*-3-(2-aminobutyl)-7-methylindole hydrochloride, m.p. 238.5–239.5°, $[\alpha]_D$ +24° (methanol).

Anal. Calcd. for $C_{13}H_{19}ClN_2$: C, 65.39; H, 8.02; Cl, 14.85; N, 11.74. Found: C, 65.46; H, 7.80; Cl, 14.64; H, 11.46.

l-3-(2-Aminobutyl)-7-methylindole, m.p. 115.5–117°, $[\alpha]_D$ −35° (chloroform).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.72; H, 9.13; N, 13.37.

l-3-(2-Aminobutyl)-7-methylindole hydrochloride, m.p. 238–239.5°, $[\alpha]_D$ −25° (methanol).

Anal. Calcd. for $C_{13}H_{19}ClN_2$: C, 65.39; H, 8.02; Cl, 14.85; N, 11.74. Found: C, 65.22; H, 7.93; Cl, 14.63; N, 11.92.

These were prepared from the dibenzoyl-*d*-tartrate of *l*-3-(2-aminobutyl)-7-methylindole in a manner similar to that described for the corresponding *d* isomers.

Resolution of *d,l*-3-(2-Aminobutyl)indole (XIII).—A solution of *d,l*-3-(2-aminobutyl)indole (51.8 g.) and *d*-camphor-10-sulfonic acid (79.8 g.) in 840 ml. of boiling isopropyl alcohol was allowed to crystallize. The resulting solid was recrystallized 3 times from isopropyl alcohol to yield 24.7 g. of the *d*-camphor-10-sulfonate of *l*-3-(2-aminobutyl)indole, $[\alpha]_D$ −9° (water). A stirred solution of this solid (20.0 g.) in 1200 ml. of water was treated during 1 hr. with 1.5 equiv. of aqueous sodium hydroxide. The resulting solid was collected by filtration, washed with water, and dried to yield 8.6 g. of *l*-3-(2-aminobutyl)-indole, $[\alpha]_D$ −52° (ethanol). A solution of this material in methanol (50 ml.) was treated with 3.5 ml. of acetic acid. The resulting mixture was concentrated to dryness under reduced pressure, and the residue was recrystallized from a mixture of methanol (75 ml.) and ethyl acetate (300 ml.) to yield the acetate salt of *l*-3-(2-aminobutyl)indole (6.8 g.), m.p. 170.7–173.4°, $[\alpha]_D$ −39° (water).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 68.01; H, 8.48; N, 11.38.

The filtrates from the isolation of the above *d*-camphor-10-sulfonate were concentrated to dryness under reduced pressure. Fractional crystallization of the residue from isopropyl alcohol yielded the *d*-camphor-10-sulfonate of *d*-3-(2-aminobutyl)-indole (16.9 g.), $[\alpha]_D$ +19° (water). This salt (15.0 g.) was converted to the free base, as described for the *l*-salt, which was recrystallized 3 times from ethyl acetate to yield 2.0 g. of *d*-3-(2-aminobutyl)indole. The acetate salt of this compound, m.p. 170–172.1°, $[\alpha]_D$ +37° (water), was prepared in the manner described for the *l*-isomer.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.53; H, 8.07; N, 11.37.

Acknowledgment.—The authors are indebted to Dr. R. W. Rinehart and his associates for microanalyses, to Mrs. B. F. Zimmer and Miss L. M. Pschigoda for ultraviolet and infrared spectra, and to Mr. L. G. Laurian, Mr. D. L. Brown, and Miss A. J. Gibbons for laboratory assistance.

(22) G. Berti and A. DaSettimo, *Gazz. Chim. Ital.*, **90**, 525 (1960).