EXHIBIT 1004

The product was chromatographed on neutral alumina to give the ketone (0.39 g): mp 185–190°, undepressed by the sample prepared as in (i); ν_{max} 3378, 3215, 2083, 1704, and 1642 (weak) cm^{-1}.

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Synthesis and Pharmacological Activity of Alkylated Tryptamines[1]

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A series of 3-(N-alkylaminoalkyl-α-methyl)indoles has been prepared either by reductive amination of 3-indolylacetone and 3-indolylbutanone, or by reduction of 3-alkylaminoacylindoles. Introduction of a single methyl group into the aliphatic nitrogen of α-methyltryptamine gave a compound that caused the arousal of motor activity in reserpinized mice in much shorter time than the parent substance. Introduction of a higher group or a second methyl substituent brings about decrease in physiological activity, while elongation of the aliphatic side chain results in complete loss of action.

DL-α-Methyltryptamine (I) has been found to produce LSD-like symptoms in human volunteers.[3] It has been shown that I can be metabolized by converting I to its 6-hydroxy derivative or deaminated to 3-indolylacetone.[4]

The onset of action exerted by I is relatively slow, and the symptoms last longer than those produced by N,N-dialkyltryptamines. The investigations by Vane *et al.*,[5] indicate that the reversal of reserpine-induced ptosis in mice may be a feature common to all tryptamines while the stimulation of spontaneous locomotion in reserpinized mice is restricted to the α-alkylated congeners only.

In a more detailed study of the reversal of reserpine-induced ptosis and the stimulation of spontaneous activity, we have observed that after administration of I the first measure develops rather quickly when compared to the second one which builds up gradually (see Figure 1). The delay between the two effects suggests that the stimulation of motor activity might be due to a metabolite formed slowly from the administered drug. This presumably active metabolite cannot be 6-hydroxy-α-methyltryptamine or indolylacetone since both compounds proved to be inactive in the spontaneous locomotion tests (Table I).

A possible formation of an active metabolite could involve the N-methylation of the side chain of I giving rise to N,α-dimethyltryptamine (N,α-DMT) and N,N,α-trimethyltryptamine (N,N,α-TMT), compounds that might either be active themselves or provide a link toward an active metabolite. This hypothesis has been further substantiated by the fact that the optically active *d* isomer of I exerts a significantly stronger effect than the *l* form, thus pointing to a selective enzymatic pathway of metabolism.[6,7]

We decided to prepare and test a series of N,α-alkyltryptamines and related compounds to determine the effect of changes in the side chain on the physiological activity of these compounds. The synthetic approach followed three routes.

(1) Reaction of indolylmagnesium bromide (III) with propylene oxide, bromination of the resulting 3-indolyl-2-propanol (IV), and condensation of V with an alkylamine. The yield of IV was erratic and only a small amount of N,Nα-trimethyltryptamine (VI, R = R′ = CH_3) was obtained by this method.

(2) Reduction of 3-(2-dimethylaminopropionyl)indole (X) with lithium aluminum hydride. X was prepared from 1,3-di(2-chloropropionyl)indole (IX) and dimethylamine. Bromination of 3-propionylindole (VII)[8] afforded the bromo derivative (VIII) in low yield, contrary to the results with 3-acetylindole.[9]

(3) Reductive amination of 3-indolylacetone (XI)[10] with primary alkylamines. This method gave N,α-DMT (VI, R = H; R′ = CH_3) and the corresponding N-ethyl and N-isopropyl derivatives in acceptable yields. Analogously 1-(3-indolyl)-3-butanone afforded the homologous 3-(3-alkylaminobutyl)indoles.

In connection with this and other investigations a number of tryptamines were required. The preparation of previously unreported N-hexyl- and 6-hydroxy-N,N-diethyl derivatives is described in the Experimental Section of this paper.

(1) Portions of this study were presented at the 46th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 1962, and at the 33rd Meeting of the Israel Chemical Society, Be'er Sheva, Dec 1963.

(2) Visiting Scientist, Clinical Neuropharmacology Research Center, National Institute of Mental Health, May 1961–1963. Israel Institute for Biological Research, Ness Zionah, Israel.

(3) H. B. Murphree, R. H. Dippy, E. H. Jenney, and C. C. Pfeiffer, *Clin. Pharmacol. Therap.*, **2**, 722 (1961).

(4) S. Szara, *Federation Proc.*, **20**, 885 (1961); *Experientia*, **17**, 76 (1961).

(5) J. R. Vane, H. O. J. Collier, S. J. Corne, E. Marley, and P. B. Bradley, *Nature* **191**, 1068 (1961).

(6) We are indebted to Dr. H. Schwarz of Sandoz Pharmaceuticals for these isomers.

(7) After completion of the present study a similar observation has been reported for α-ethyltryptamine: G. Vogel and L. Ther, *Arzneimittel-Forsch.*, **13**, 779 (1963).

(8) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).

(9) K. Bodendorf and A. Walk, *Arch. Pharm.*, **294**, 484 (1961).

(10) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952).

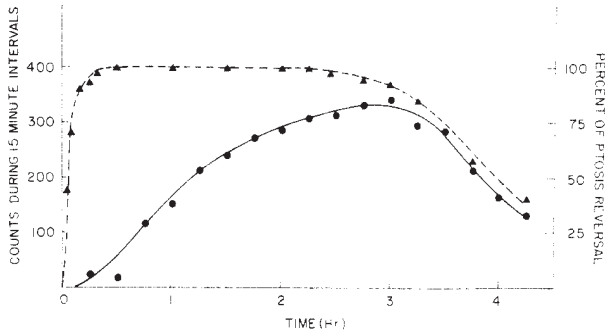


Figure 1.—Activity cage counts (●–●–●) and ptosis reversal score (▲–▲–▲) in reserpinized mice (4 mg/kg) after administration of α-methyltryptamine hydrochloride (20 mg/kg).

An attempt was made to obtain the N,N-dialkyltryptamines directly from III and an appropriate dialkylaminoalkyl chloride or mesylate. In the case of dimethylaminoethyl chloride or mesylate the tryptamine was isolated in 8% yield. With diethylaminoethyl and diisopropylaminoethyl chlorides only traces were obtained. The failure of this reaction may be explained by the formation and subsequent reaction of $Alk_2NCH_2CH_2MgCl$.[11]

Pharmacological Findings. General Procedure.—Reserpine solution (0.4 mg/ml) was prepared by dilution of Serpasil® (Ciba) with a mixture containing 25% ethanol, 25% propylene glycol, and 50% saline. This solution (0.2 ml ip) had been administered to white mice averaging 20 g. Eighteen hours later 10 animals were given a buffered solution of the compound tested and the extent of ptosis reversal was scored every 3–5 min during the first 30 min, and every 15 min later. Simultaneously four identically treated mice were placed in an activity cage,[12] and a second group of four injected with the buffered solution served as controls. The number of light-beam breaks were recorded at 15-min intervals.

Results

The tested compounds fall under three classes: (1) active in both ptosis reversal and evoking spontaneous locomotion, (2) active in ptosis reversal only, and (3) inactive in both tests. To the first group, generally, belong α-alkylated tryptamines with no substituents in the aromatic ring (with the possible exception of the 5 position[13]) and bearing but hydrogen or methyl at the aliphatic nitrogen. The second category consists of various ring-substituted tryptamine derivatives with the exception of 4-fluorotryptamines and 6-hydroxy-α-methyltryptamine. Indole derivatives with modifications in the side chain constitute the third class (Table I).

N-Methylation of I brought about a significant change in the pattern of spontaneous locomotion of reserpinized mice. The motor activity began almost immediately after the administration of N,α-DMT and reached the peak after 45–60 min (Figure 2). The parallelism of the developing and declining of both phenomena is obvious. For comparison a similar

(11) It has been reported recently by C. R. Ganellin and H. F. Ridley [*Chem. Ind.* (London), 1388 (1964)] that indolylmagnesium iodide and dimethylaminoethyl chloride in anisole gave 25% yield of dimethyltryptamine.

(12) W. J. Kinnard and C. J. Carr, *J. Pharmacol.*, **121**, 354 (1957).

(13) A. Kalir and S. Szara, *J. Med. Chem.*, **6**, 716 (1963).

TABLE I: EFFECT OF INDOLE DERIVATIVES ON SPONTANEOUS LOCOMOTION AND PTOSIS REVERSAL IN RESERPINIZED MICE

No.	Compd	Dose, mg/kg[a]	Spontaneous locomotion[b]	Max % of ptosis reversal/min
1	α-Methyltryptamine[c]	1	i	40/25
		2.5	i	55/25
		5	i	80/30
		10	sa	90/30
		15	a	95/45
2	*d*-α-Methyltryptamine	15	a	95/35
3	*l*-α-Methyltryptamine	15	sa	80/45
4	α-Ethyltryptamine[c]	16	sa	85/40
5	N,α-Dimethyltryptamine[d]	20		
6	N-Ethyl-α-methyltryptamine[d]	20	i	25/30
		30	sa	60/25
7	N-Isopropyl-α-methyltryptamine[d]	25	i	15/25
8	N,N,α-Trimethyltryptamine[d]	25	sa	30/20
		30	sa	40/25
9	N,N-Dimethyltryptamine[e]	30	i	65/15
10	N,N-Diethyltryptamine[f]	30	i	55/25
		35	i	65/30
11	4-Chloro-α-methyltryptamine[g]	35	i	40/35
12	4-Hydroxy-α-methyltryptamine bimaleate·CH_3OH[g]	30	i	45/20
13	4,α-Dimethyltryptamine bimaleate[g]	50	i	60/20
14	6-Hydroxy-α-methyl tryptamine[g]	14	i	0
15	4-Fluoro-N,N-diethyltryptamine[h]	30	i	0
16	4-Fluoro-N-morpholinyltryptamine[h]	30	i	0
17	4-Fluoro-N-piperidyltryptamine[h]	30	i	0
18	5-Fluoro-N,N-dimethyl tryptamine[i]	17	i	35/15
19	5-Fluoro-N,N-diethyltryptamine[i]	20	i	65/10
20	6-Fluoro-N,N-dimethyltryptamine[j]	17	i	50/25
21	5-Hydroxytryptamine creatinine sulfate[e]	58	i	15/10
22	6-Hydroxytryptamine[g]	30	i	45/10
23	6-Hydroxy-N,N-dimethyltryptamine[k]	17	i	40/15
24	6-Hydroxy-N,N-diethyltryptamine[d]	30	i	15/8
25	5-Hydroxytryptophan[e]	100	i	0
26	6-Hydroxytryptophan[g]	10–50	i	0
27	3-Indolylacetone[l]	50	i	0

[a] Hydrochlorides were used unless otherwise specified (**12**, **13**, **21**, and **25–27**), in which case the doses refer to the dry weight of the particular substance. [b] i = inactive (the photocell counts never reached 100 in any of the 15-min intervals during the 90-min test period); sa = slightly active (photocell counts in the same intervals reached a value between 100 and 200); a = active (photocell counts in the above intervals reached 200 or more). [c] R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuszkovicz, *J. Org. Chem.*, **25**, 1548 (1960). [d] See Experimental Section. [e] Commercial product. [f] R. B. Barlow and I. Khan, *Brit. J. Pharmacol.*, **14**, 99 (1959). [g] Kindly supplied by Sandoz Pharmaceuticals. [h] M. Bentov, Z. Pelchowicz, and A. Levy, *Israel J. Chem.*, **2**, 25 (1964). [i] Z. Pelchowicz, A. Klauszyner, and M. Bentov, *J. Chem. Soc.*, 5418 (1961). [j] M. Bentov, A. Kaluszyner, and Z. Pelchowicz, *J. Chem. Soc.*, 2825 (1962). [k] F. Troxler, F. Seeman, and A. Hofmann, *Helv. Chim. Acta*, **42**, 2073 (1959). [l] See ref 10.

experiment was performed with *d*-amphetamine (Figure 3). It can be clearly seen that the effect on both measures starts immediately after administration of the drug without the characteristic delay seen after α-methyltryptamine (Figure 1). Although in the case of amphetamine the spontaneous locomotion was relatively more pronounced than in the case of N,α-DMT, the trend was the same. It may be pointed out that both I[14] and N,α-DMT[15] are monoamine oxidase (MAO) inhibitors so the difference in the activity pattern shown by our experiments might be due to factors which are not related to MAO action. Possibilities like the above-mentioned formation of a metabolite, different rate of 6-hydroxylation, difference in the penetration through the blood–brain barrier, and selective action on chemoreceptors might be quoted as factors explaining these differences. The data available at present do not allow definite conclusions to be drawn regarding the mechanisms underlying the phenomena presented.

Replacement of the methyl group in N,α-DMT by a bulkier ethyl or isopropyl radical, as well as the introduction of a second methyl substituent caused a sharp decrease in the motor activity along with slight decrease of the potency on ptosis reversal.

Changes involving the aliphatic moiety of tryptamine resulted in complete disappearance of both effects. Indolylacetone and α-methyl-N-alkylaminopropylindoles were inactive.

Experimental Section[16]

1,3-Bis(2-chloropropionyl)indole (IX).—A solution of 46.8 g (0.4 mole) of indole in 100 ml of toluene was added to a Grignard reagent prepared from 54.5 g (0.5 mole) of ethyl bromide and 12.5 g of magnesium turnings in 125 ml of ether. After 30 min the solution of III was treated with 63.5 g (0.5 mole) of α-chloropropionyl chloride in 50 ml of toluene. After 1 hr of stirring the mixture was poured into ice water-NH_4Cl solution, the organic layer was separated and dried, and the solvents were removed. The residue was recrystallized from ethanol; mp 151–154°, yield 16.0 g (13%).[17]

Anal. Calcd for $C_{14}H_{13}Cl_2NO_2$: C, 56.40; H, 4.40; N, 4.70. Found: C, 56.72; H, 4.68; N, 4.69.

3-(2-Dimethylaminopropionyl)indole (X).—IX (4.5 g, 0.015 mole) was refluxed 1 hr with 10 ml of dimethylamine in 100 ml of ethanol. The solution was concentrated, acidified, and extracted with ether, and the aqueous layer was rendered alkaline. The precipitate was recrystallized from ethanol; mp 192–193°, 2.6 g (80%).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.36; H, 7.61; N, 12.34.

Picrate, mp 157–158° (from methanol).

Anal. Calcd for $C_{19}H_{19}N_5O_8$: N, 15.72. Found: N, 15.38.

When 3-propionylindole[8] was treated with an equivalent amount of bromine in methanol,[9] and the product was refluxed with dimethylamine, a very low yield of X was obtained.

N,N,α-Trimethyltryptamine. Method A.—A solution of 8.8 g (0.05 mole) of IV[18] in 200 ml of ether was treated with 4.4 g of PBr_3 and 4 hr later excess dimethylamine was added. The organic layer was extracted with dilute acid, and the tryptamine was liberated from the aqueous solution and distilled; yield 1.8 (18%) of material boiling at 165° (1.5 mm).

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

(15) D. H. Tedeschi, R. E. Tedeschi, P. J. Fowler, H. Green, and E. J. Fellows, *Biochem. Pharmacol.*, **11**, 481 (1962).

(16) Melting points (determined on a Fisher-Johns apparatus) and boiling points were uncorrected.

(17) Analogous result from III and chloroacetyl chloride has been obtained by D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.*, 1984 (1956).

(18) U. S. Patent 2,908,691 (1959); *Chem. Abstr.*, **56**, 3455 (1962).

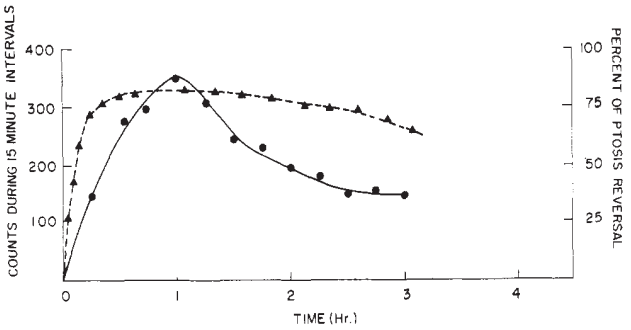


Figure 2.—Activity cage counts (●–●–●) and ptosis reversal score (▲–▲–▲) in reserpinized mice (4 mg/kg) after administration of N,α-dimethyltryptamine hydrochloride (20 mg/kg).

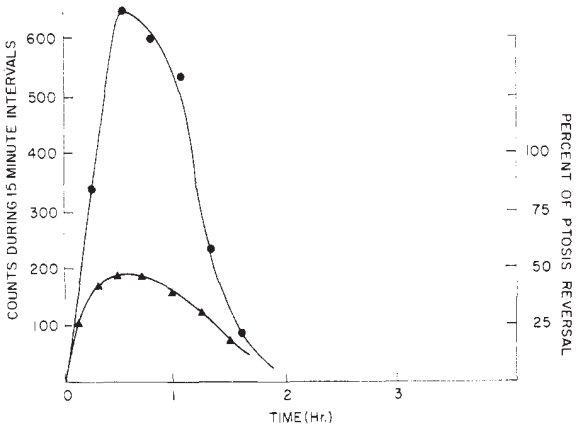


Figure 3.—Activity cage counts (●–●–●) and ptosis reversal score (▲–▲–▲) in reserpinized mice (4 mg/kg) after administration of *d*-amphetamine hydrochloride (3 mg/kg).

Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97. Found: C, 76.89; H, 8.97.

The hydrochloride could not be induced to crystallize and the amine was converted into the bimaleate, mp 139–140° (methanol–ether).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.02; H, 6.87; N, 8.34.

Picrate, mp 177–178° (methanol).

Anal. Calcd for $C_{19}H_{21}N_5O_7$: C, 52.90; H, 4.91; N, 16.24. Found: C, 52.97; H, 4.75; N, 16.25.

Method B.—A solution of 3.0 g of X in 50 ml of tetrahydrofuran (THF) was added to 3.0 g of $LiAlH_4$ in 60 ml of the same solvent and refluxed for 2 hr. The yield of the tryptamine was 1.65 g (59%). The product was identified by melting point and mixture melting point of the bimaleate salt.

N,α-Dimethyltryptamine (VI, R = H; R′ = CH_3).—3-Indolylacetone[10] (3.3 g, 0.019 mole) in 100 ml of ethanol was reduced over Pd–C catalyst in the presence of an excess of methylamine. After 2 hr the catalyst was filtered off and the solution was concentrated, acidified, and extracted with ether, and the aqueous layer was made alkaline. N,α-DMT precipitated as a tan solid, yield 2.2 g (61%), mp 93–94° (hexane–THF), lit.[19] mp 90–91°.

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.88. Found: C, 76.64; H, 8.71; N, 14.59.

Picrate, brick red, mp 207–208° (ethanol).

Anal. Calcd for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.82; H, 4.37; N, 16.73.

Other analogously prepared 3-(N-alkylaminoalkyl-α-methyl)-indoles are found in Table II.

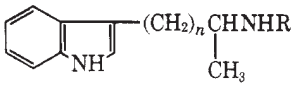
N-Hexyl-3-indoleglyoxylamide.—Oxalyl chloride (15 ml) was added at 0–5° to a solution of 17.6 g (0.15 mole) of indole in 200 ml of ether.[20] The resulting 3-indoleglyoxyl chloride (27.6 g, 88%) was mixed with 30.5 g (*ca.* 0.3 mole) of *n*-hexylamine in 300 ml of ether and the white material was collected, washed with

(19) British Patent 893,707 (1962); *Chem. Abstr.*, **57**, 12438 (1962).

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

TABLE II

3-(N-ALKYLAMINOALKYL-α-METHYL)INDOLES



n	R	Salt	Bp (mm) or mp, °C	Yield, %	Formula	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N
1	C_2H_5	Base	160–163 (0.9)	58	$C_{13}H_{18}N_2$	77.18	8.97			76.38	8.81		
		HCl	188–190		$C_{13}H_{19}ClN_2$	65.39	8.00		11.74	65.10	8.11		12.26
		Picrate	203–205		$C_{19}H_{21}N_5O_7$	52.89	4.91		16.24	52.86	4.60		15.97
1	$CH(CH_3)_2$	HCl	229–230	36	$C_{14}H_{21}ClN_2$			14.03	11.09			13.96	11.44
		Picrate	219–220		$C_{20}H_{23}N_5O_7$	53.93	5.21			54.63	5.63		
2	CH_3	Base	105–106	69	$C_{13}H_{18}N_2$	77.18	8.97		13.85	77.45	8.89		13.25
2	C_2H_5	HCl	169–170	34	$C_{14}H_{21}ClN_2$	66.51	8.37		11.07	66.29	8.19		10.69
2	$CH(CH_3)_2$	HCl	206–207	30	$C_{15}H_{23}ClN_2$	67.51	8.69	13.29		67.29	8.93	13.20	

water, and recrystallized from methanol; yield 32.5 g (90%), mp 156–157°.

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.82; H, 7.37; N, 10.54.

N-Hexyltryptamine.—The foregoing compound (13.6 g, 0.05 mole) in 150 ml of dioxane was added dropwise to 11 g $LiAlH_4$ in 200 ml of dioxane, and the mixture was heated. An exothermic reaction began at 55–65°. After 2 hr of refluxing the mixture was cooled, treated with wet dioxane, and filtered, and the solvent was removed under reduced pressure. The remainder was acidified and extracted with ether, and the tryptamine was liberated by adding a solution of NaOH. The product was taken up with ether, distilled at 180–185° (0.2 mm), and recrystallized from petroleum ether (bp 30–60°)–ethyl acetate; yield 2.5 g (20%), mp 82–83°.

Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.63; H, 9.90; N, 11.47. Found: C, 78.77; H, 10.06; N, 11.63.

N,N-Diethyl-6-benzyloxy-3-indoleglyoxylamide.—A solution of 3.0 g (0.0134 mole) of 6-benzyloxyindole (Regis Chemical Co.) in 60 ml of ether was treated with 3.5 ml of oxalyl chloride at 0–5°, and the yellow precipitate was collected and added to 4 ml of diethylamine in 30 ml of ether. The white product was filtered off, washed with water, and recrystallized from ethanol; yield 3.84 g (82%), mp 190–191°.

Anal. Calcd for $C_{21}H_{22}N_2O_3$: N, 8.00. Found: 8.02.

6-Hydroxy-N,N-diethyltryptamine.—The above amide (3.7 g) in 85 ml of dioxane was added to 4.4 g of $LiAlH_4$ in 90 ml of dioxane. The mixture was stirred and refluxed for 5 hr, cooled, and decomposed by addition of methanol and a little water. The inorganic precipitate was filtered off, the filtrate was concentrated and acidified, and traces of insoluble matter were removed by extracting with ether. The base was liberated with NH_3 and extracted with ether, the extract was dried (K_2CO_3), and the solvent was removed. The oily residue of 6-benzyloxy-N,N-diethyltryptamine gave a **picrate,** mp 154–155° (water).

Anal. Calcd for $C_{27}H_{29}N_5O_8$: C, 58.79; H, 5.30; N, 12.70. Found: C, 59.00; H, 5.99; N, 12.53.

The oil (2.7 g) was dissolved in 100 ml of ethanol and debenzylated for 90 min in a Parr apparatus at 4 atm in the presence of 1 g of 10% of Pd–C catalyst. The catalyst was filtered off and the solvent was removed under reduced pressure leaving a solid which was purified by recrystallization from ethyl acetate and methanol; yield 0.8 g (41%), mp 160–161°.

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.39; H, 8.84; N, 12.37.

N-Acetyl-6-benzyloxytryptamine.—6-Benzyloxytryptamine sulfate (2.5 g, 0.008 mole) and 5 ml of acetic anhydride was heated for 5 min in a water bath, then poured into water and filtered off. The product weighed 2.1 g (86%), mp 146–148°. An analytical sample was purified from ethanol; mp 153–154°.

Anal. Calcd for $C_{19}H_{20}N_2O_2$: N, 9.08. Found: N, 9.35.

6-Benzyloxy-N-ethyltryptamine.—A solution of 2.0 g (0.0065 mole) of the preceding compound in 50 ml of THF was added to 1.5 g of $LiAlH_4$ in 50 ml of THF and refluxed with stirring for 2 hr. The complex was decomposed with wet THF and filtered, the filtrate was concentrated, the residue was treated with dilute HCl and filtered again, and the acidic solution was made alkaline, giving 0.4 g (21%) of product, mp 86–87°.

Anal. Calcd for $C_{19}H_{22}N_2O$: N, 9.52. Found: N, 9.80.

Dimethylaminoethyl Methanesulfonate Chloride.—A solution of 44.5 g of dimethylaminoethanol in 150 ml of benzene was treated with 40 ml of methanesulfonyl chloride (Eastman Co.) in 150 ml of the same solvent. The reaction was exothermic and a precipitate appeared. The mixture was cooled, and the solid collected; yield 80.0 g (78%), mp 123–125° (ethanol).

Anal. Calcd for $C_5H_{14}ClNO_3S$: C, 29.48; H, 6.93; N, 6.88. Found: C, 29.42; H, 6.83; N, 6.58.

Acknowledgment.—We are indebted to Mr. H. G. McCann of the Microanalytical Laboratory, National Institute of Arthritis and Metabolic Diseases, for analyses. The skillful assistance of Mrs. Arliene M. Aikens is gratefully appreciated.