Synthesis and Characterization of 5*H*-1,3-Dioxolo[4,5-*f*]indoleethylamines

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Twelve new *N,N*-dialkylated-5,6-methylenedioxytryptamines and *N*-cyclopropyl-5,6-methylenedioxytryptamine were prepared as hybrids of known psychoactive phenylethylamines and tryptamines. Novel, more convenient syntheses of *N*-methyl- and *N*-benzylcyclopropylamine are described.

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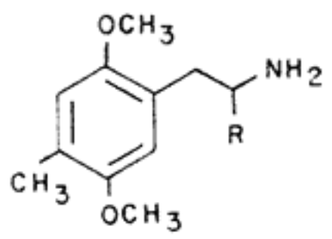
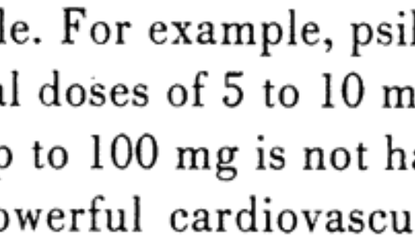
Since the end of the last century tens of phenethylamines and homologues, notably phenylisopropylamines, have been synthesized and evaluated for psychotomimetic activity directly in man [1] and indirectly, using model systems [2]. Variation in aromatic ring substituents provides a wide range of potencies [1,3] and qualitative effects [1,2]. On the other hand, the psychotomimetic activity of the powerful psychotomimetic 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane (**1**) [3,4] is lost upon homologation to **2** [5,6]; the latter compound is an antidepressant with minimal side effects [6,7].



1 R = CH_3
2 R = C_2H_5

Our knowledge of psychopharmacological structure-activity relationships (SAR) of indolealkylamines is relatively limited [8,9,10] compared to such knowledge of phenylethylamines, changes in aromatic ring substituents can produce profound changes in potency and psychopharmacological profile. For example, psilocin (**3**) is hallucinogenic in man at oral doses of 5 to 10 mg [11] while bufotenin (**4**) at doses of up to 100 mg is not hallucinogenic [12], and is instead a powerful cardiovascular stimulant [13,14]. However, there are indications that the effects of varying substitution on basic nitrogen are different in the phenylethylamines and indoleethylamines. In the phenylethylamines, for example, *N*-methylation or *N,N*-dimethylation of mescaline abolishes hallucinogenic activity [15]. Similarly, 2-alkylamino-1-(3,4-methylenedioxyphenyl)propanes **5** showed rapidly decreasing psychotomimetic potencies as the number of carbon atoms in the alkyl substituent R increased from one to eight [16]. In the indolealkylamines, Shulgin and Carter found that replacing the *N*-methyl groups of orally inactive (but parenterally active) *N,N*-dimethyltryptamine (DMT) and its 5-methoxy analogue [17] with *N*-isopropyl groups gave compounds which were orally active in the 20-50 mg and 6-10 mg ranges respectively [18]. The authors suggested that steric hindrance by the *N*-isopropyl groups slowed oxidative deamination by MAO. Replacement of the *N*-methyl groups of psilocin with *N*-isopropyl groups resulted in only a slight decrease in oral activity [8]. Thus, while increasing the size of *N*-alkyl substituents on *N*-alkyl phenylethylamines eliminates the compounds' psychopharmacological activity, there are indications that variation of the substituents on the basic nitrogen of indolealkylamines may produce intriguing effects.



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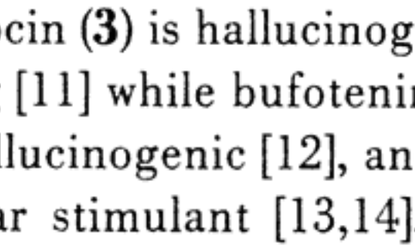

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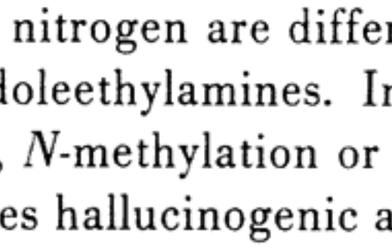


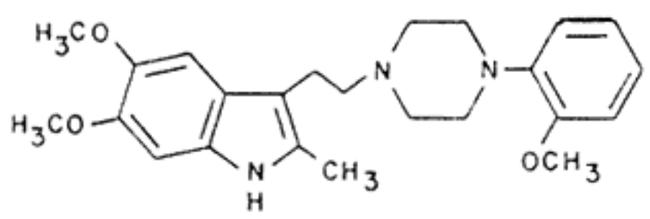
5a R = H

Among the phenylisopropylamines, compounds bearing a methylenedioxy substituent (in particular, the parent, **5a**) show unusual psychopharmacological profiles. Quantitatively, **5a** is approximately three times as potent as its dimethoxy counterpart [19]. Qualitatively, Shulgin described it [20] as "unusual among the hallucinogens in that it leads not to the usual mescaline-like state of visual and sensory distortion, but rather a state of sensory amplification and enhancement without appreciable sympathomimetic stimulation." In contrast, 2-amino-1-(3,4-dimethoxyphenyl)propane elicited extensive visual distortions and gross body tremor after intravenous injections of approximately 700 mg [19]. The unusual qualities of **5a** have inspired its use as an adjunct to psychotherapy [21,22,23,24].

Given the unusual and perhaps therapeutically useful psychopharmacological properties of methylenedioxy-substituted phenylisopropylamines (*e.g.* **5a**), and given indications that indolealkylamine activity is retained or even enhanced on going from smaller *N*-alkyl groups (*e.g.* methyl) to larger groups (*e.g.* isopropyl), it seemed that preparation of a series of *N,N*-dialkyl methylenedioxytryptamines would be of interest. The ready availability of 5,6-methylenedioxyindole (see below) prompted the study of a series of the corresponding tryptamines.

Prior to the inception of this work, fewer than a dozen *N,N*-dialkyl-5,6-methylenedioxytryptamines had been re-

ported, and these all bore 2-(4-(substituted-aryl)piperazinyl)ethyl side chains. The patents decribing these compounds, which resemble the clinically useful dimethoxy analogue oxypertine (**6**), claim that they are CNS depressants [25] or sedatives and hypotensives [26].



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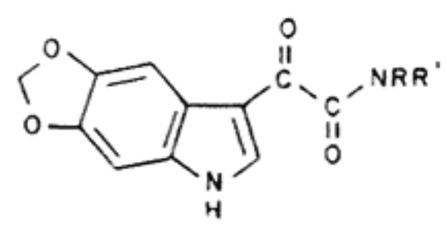
During the course of this work, syntheses of the *N,N*-dimethyl and *N,N*-diisopropyl analogues **7** and **16** were reported [27]. Evaluation of these compounds by behavior disruption of rats using the Sidman Avoidance schedule indicated that **7** and **16** were both less active than DMT. Serotonin antagonism values (pA_2) for **7** and DMT as measured by contraction of rat fundus muscle were equal within experimental uncertainty. No human pharmacology was reported for **7** or **16** [28].

Five ring-substituted *N*-cyclopropyltryptamines have been reported as potent MAO inhibitors. Winn and co-workers [29] synthesized the unsubstituted compound and its 5- and 7-methoxy analogues and found that *N*-cyclopropyltryptamine was more potent than pargyline as an MAO inhibitor. Chimenti and co-workers [30] reported syntheses of 5,6-dimethoxy- and 6,7-dimethoxy-*N*-cyclopropyltryptamines and preliminary results which indicate partial selectivity of the inhibitors between mitochondrial and bovine plasma MAO. Herein the synthesis of *N*-cyclopropyl-5,6-methylenedioxytryptamine (**8**) is reported.

Literature procedures [31] were followed to prepare 6,β-dinitro-3,4-methylenedioxystyrene from piperonal in good yield. Previous workers have used iron in either hot acetic acid [31,33] or hot ethanol and acetic acid [32] to cyclize reductively this dinitrostyrene to 5,6-methylenedioxyindole in fair to moderate yields. In the present work, as in a reported synthesis of 5,6-dimethoxyindole [34], the dinitrostyrene was hydrogenated over palladium on carbon to give 5,6-methylenedioxyindole in 50-64% yields over four runs.

Table I

Physical Data for the Amides



H

Compound No.	R,R′	Yield (%)	Corrected Mp °C (recrystallization solvents)	Formula (mol weight)	Analyses % Calcd./Found C	H	N
7a	methyl, methyl	41 (a)	225.5-226.5 (ethyl acetate-ethanol)	$C_{13}H_{12}N_2O_4$ (260.25)	59.99 59.84	4.65 4.74	10.77 10.74
9a	methyl, isopropyl	51	203-204 (d) (acetone)	$C_{15}H_{16}N_2O_4$ (288.31)	62.49 62.36	5.59 5.61	9.72 9.47
10a	methyl, cyclopropyl	59	211-213 (chloroform-hexane)	$C_{15}H_{14}N_2O_4 \cdot ¼H_2O$ (290.79)	61.96 61.95	5.02 5.03	9.63 9.59
11a	pyrrolidyl	41	229.5-231.5 (ethanol)	$C_{15}H_{14}N_2O_4$ (286.29)	62.93 62.89	4.93 4.98	9.78 9.71
12a	morpholinyl	58	268.5-270.5 (chloroform-hexane)	$C_{15}H_{14}N_2O_5$ (302.28)	59.60 59.95	4.67 4.34	9.27 9.25
14a	piperidyl	46	238.5-240.5 (acetone-ethyl acetate)	$C_{16}H_{16}N_2O_4$ (300.32)	63.99 63.84	5.37 5.42	9.33 9.35
15a	methyl, (cyclopropyl)methyl	43	160-161 (ethyl acetate-hexane)	$C_{16}H_{16}N_2O_4$ (300.32)	63.99 63.82	5.37 5.40	9.33 9.26
16a	isopropyl, isopropyl	38 (b)	278-278.5 (ethyl acetate-hexane)	$C_{17}H_{20}N_2O_4$ (316.36)	64.54 64.63	6.37 6.47	8.85 9.14
18a	methyl, benzyl	57	206-207 (ethyl acetate-hexane)	$C_{19}H_{16}N_2O_4$ (336.35)	67.85 67.47	4.80 4.76	8.33 8.35
19a	4-phenylpiperazino	44	269.5-271.5 (acetonitrile-water)	$C_{21}H_{18}N_2O_4$ (363.40)	66.83 66.39	5.07 5.14	11.03 11.03
20a	4-(4-fluorophenyl)-piperazino	41	280.5-281 (ethanol-ethyl acetate)	$C_{21}H_{18}N_3O_4F$ (395.39)	63.79 63.81	4.59 4.54	10.63 10.70
21a	cyclopropyl, benzyl	37	183.5-184.5 (acetone-hexane)	$C_{21}H_{18}N_2O_4$ (362.38)	69.60 69.42	5.00 5.03	7.73 7.72
22a	4-benzylpiperazino (c)	35	231.5-232 (ethyl acetate)	$C_{22}H_{21}N_3O_4$ (391.43)	66.49 67.24	5.32 5.29	12.08 10.65

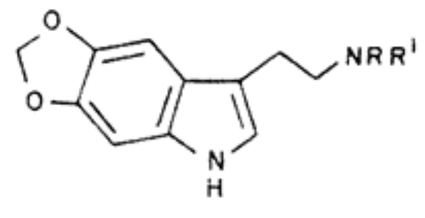
(a) Lit [28] 79% yield, mp 217-220° uncorrected. (b) Lit [28] 81% yield, mp 278-280° uncorrected. (c) A satisfactory analysis could not be obtained for this compound, yet by tlc it appeared to be pure and it was reduced cleanly to the corresponding amine **22**, Table II.

The tryptamine side chain was built using the general two-step procedure of Speeter and Anthony [35]. Treatment of crude 5,6-methylenedioxyindoleglyoxyl chloride (from oxalyl chloride and the indole) with various secondary amines [36] gave *N,N*-dialkyl-5,6-methylenedioxyindoleglyoxylamides, which are presented in Table I. An ethereal solution of *N*-methyl(cyclopropylmethyl)amine, standardized and characterized as the hydrogen oxalate salt, was prepared from cyclopropanecarboxylic acid chloride *via* the amide. Only one well-documented preparation of *N*-methylcyclopropylamine has appeared in the literature [37]; it involves a three-step conversion of cyclopropylamine to *N*-methylcyclopropylamine hydrogen oxalate by way of air- and moisture-sensitive triphenylphosphine cyclopropylimine in an overall yield of 54%. In the present work, the same overall conversion was accomplished by a different route in three steps in the same overall yield, but none of the intermediates was air-or moisture-sensitive (Scheme I).

Under Schotten-Baumann conditions cyclopropylamine was converted to its crystalline carbobenzyloxy derivative **23** in 79% yield. In dimethylformamide **23** could be deprotonated with sodium hydride and the resulting salt alkylated with excess methyl iodide [38] to give **24** in 95% yield. The carbobenzyloxy group of **24** was removed hydrogenolytically and an ethereal solution of *N*-methylcyclopropylamine was obtained; this solution was standardized by precipitation of the known [37] hydrogen oxalate salt **25** from an aliquot. Attempts to reduce **23** with lithium aluminum hydride afforded a low yield of **25**. Presumably,

Table II

Physical Data for the Amines

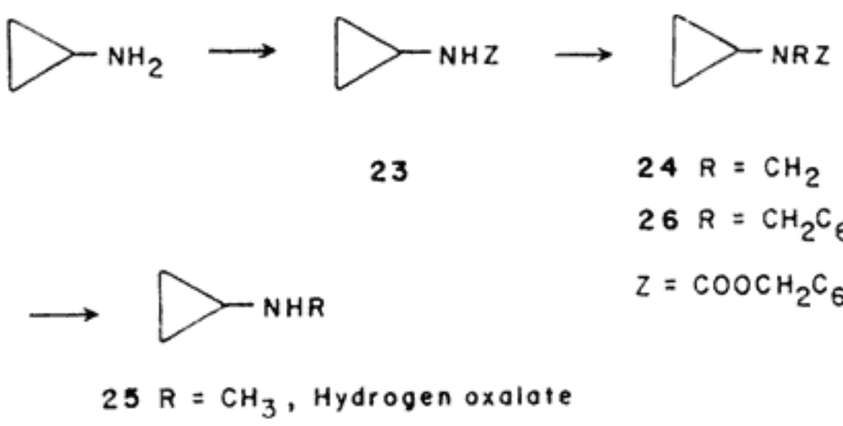


Compound No.	R,R'	Method of Synthesis	Yield (%)	Corrected Mp °C (recrystallization solvents)	Formula (mol weight)	Analyses % Calcd./Found C	H	N
7	methyl, methyl	(a)	38 (e)	115.5-117 (ethyl acetate/hexane)	$C_{13}H_{16}N_2O_2$ (232.29)	67.22 67.15	6.94 7.17	12.46 12.40
8	cyclopropyl, H	(b)	49	188-189 (d) (isopropanol-ether)	$C_{14}H_{17}ClN_2O_2 \cdot ¼H_2O$ (285.24)	58.95 58.94	6.18 6.25	9.82 9.72
9	methyl, isopropyl	(a)	33	87-89 (benzene-cyclohexane)	$C_{15}H_{20}N_2O_2$ (260.34)	69.20 68.71	7.75 7.65	10.76 10.47
10	methyl, cyclopropyl	(a)	53	82.2-85 (ether-cyclohexane)	$C_{15}H_{18}N_2O_2$ (258.32)	69.75 69.53	7.02 7.31	10.84 10.64
11	pyrrolidyl	(a)	25	110.5-112.5 (ether)	$C_{15}H_{18}N_2O_2$ (258.32)	69.75 69.66	7.02 7.06	10.84 10.99
12	morpholinyl	(a)	68	117.5-119 (ethyl acetate-hexane)	$C_{15}H_{18}N_2O_3$ (274.32)	65.68 65.49	6.61 6.85	10.21 10.17
13	methyl, cyclobutyl	(c)	18	106-106.5 (cyclohexane-hexane)	$C_{16}H_{20}N_2O_2$ (272.35)	70.56 70.43	7.40 7.18	10.28 10.06
14	piperidyl	(a)	58	150-152 (ethyl acetate-hexane)	$C_{16}H_{20}N_2O_2$ (272.35)	70.56 70.58	7.40 7.66	10.28 10.28
15	methyl, (cyclopropyl)methyl	(a)	22	124-127.5 (THF-ether)	$C_{16}H_{21}ClN_2O_2 \cdot ¼H_2O$ (313.31)	61.34 61.32	6.92 6.70	8.94 9.07
16	isopropyl, isopropyl	(a)	60 (f)	93-94.5 (ether-hexane)	$C_{17}H_{24}N_2O_2$ (288.39)	70.80 70.99	8.39 8.84	9.71 9.71
17	methyl, cyclopentyl	(c)	66	108-109 (cyclohexane)	$C_{17}H_{22}N_2O_2$ (286.37)	71.30 71.23	7.75 7.82	9.78 9.71
18	methyl, benzyl	(a)	61	99-101 (cyclohexane)	$C_{19}H_{20}N_2O_2$ (308.38)	74.00 73.80	6.54 6.65	9.08 9.00
19	4-phenylpiperazino	(a)	46	131.5-133 (g) (THF-hexane)	$C_{21}H_{23}N_3O_2$ (349.43)	72.18 71.88	6.63 6.54	12.03 12.03
20	4-(4-fluorophenyl)piperazino	(a)	58	174-175.5 (THF-hexane)	$C_{21}H_{22}FN_3O_2$ (367.43)	68.65 68.73	6.04 6.08	11..44 11.39
21	cyclopropyl, benzyl	(a)	52	216-218 (d) (ethanol-ether)	$C_{21}H_{23}ClN_2O_2$ (370.87)	68.01 67.84	6.25 6.38	7.55 7.42
22	4-benzylpiperazino	(a)	74	122-123 (ether-hexane)	$C_{22}H_{25}N_3O_2$ (361.46)	72.55 72.43	6.97 6.95	11.63 11.40

(a) Lithium aluminum hydride reduction of corresponding glyoxylamide. (b) Hydrogenation of **21**. (c) Hydrogenation of **18** in presence of carbonyl compound. (d) Hydrochloride salt. (e) Lit [28] 48% yield, mp 109-110° uncorrected. (f) Lit [28] 16% yield, mp 85-86° uncorrected. (g) Lit [26] mp 141.0-143.2°.

23 met the same fate as other cyclopropylamides with a free NH which have suffered ring opening on reduction with lithium aluminum hydride [38]. For this reason, *N*-benzylcyclopropylamine was required for synthesis of **8**. Deprotonated **23** could also be alkylated with benzyl bromide to give **26** in 96% yield. Hydrogenolytic removal of the carbobenzyloxy group left *N*-benzylcyclopropylamine [39] in 77% yield after distillation.

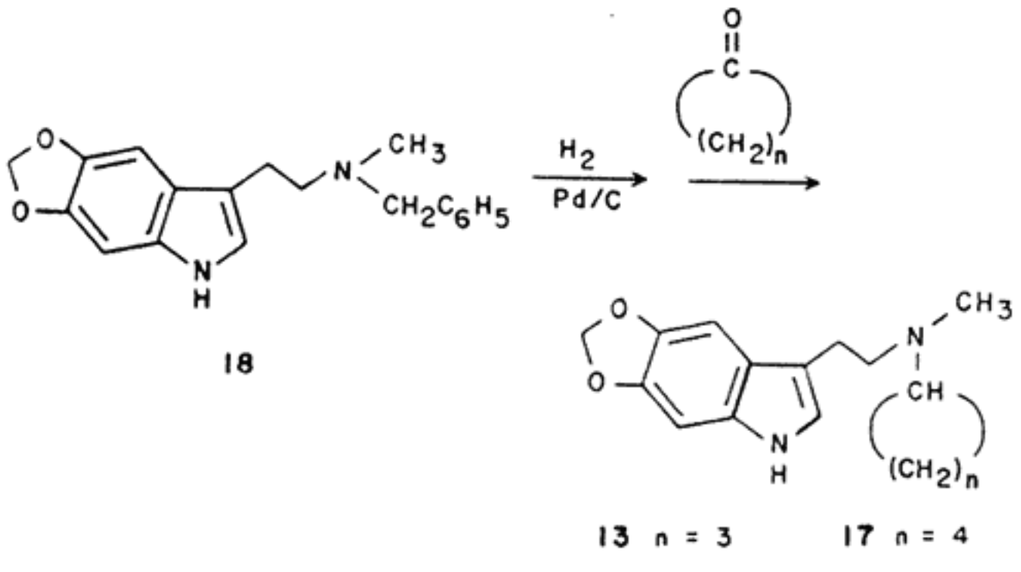
Scheme I



Other workers [40] have noted that secondary indole-3-glyoxylamides with different alkyl groups on amide nitrogen exhibit splitting of alkyl signals in proton magnetic resonance spectra due to restricted rotation about the amide bond. Similar splittings were seen in pmr spectra of compounds **9a, 10a, 15a, 18a**, and **21a**. Thin layer chromatograms of these amides, developed at ambient temperature, showed ill-resolved streaks rather than round spots. When such chromatograms were developed in a freezer, at −20°, the streaks were replaced by pairs of round spots. Similar temperature-dependent effects have been seen in the reverse-phase high-pressure liquid chromatograms of peptides containing proline residues [41].

The glyoxylamides were reduced with excess lithium aluminum hydride in refluxing THF. Those amines with larger, symmetrical alkyl substituents crystallized readily, while those with smaller or different substituents sometimes took weeks to crystallize. All products exhibited pmr spectra consistent with the proposed structures. Amines **13** and **17** were synthesized according to Scheme II. Attempts to synthesize **9** by this method met with limited success, perhaps because the product crystallized with difficulty. The hydrochloride of amine **21** was rapidly debenzylated by catalytic hydrogenation to give the hydrochloride of amine **8**.

Scheme II



EXPERIMENTAL

Proton magnetic resonance spectra were obtained from a Varian EM-360 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee and by the Microanalytical Laboratory, Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan. Melting points are corrected. Unless otherwise stated, yields of novel compounds refer to yields of analytically pure products. Thin-layer chromatograms were obtained on 250 μ layers of silica gel GF on glass plates; the amides were run with 5% methanol or 2-propanol in chloroform or methylene chloride, the amines with 1-2% concentrated ammonium hydroxide in methanol. Visualization was by short wave uv unless otherwise stated. All solvents were reagent grade. Tetrahydrofuran was distilled from benzophenone-sodium prior to use. Dimethylformamide was stored over 4Å molecular sieves. All of the symmetrically substituted seconadary amines and *N*-methylbenzylamine were from commercial sources. Unless otherwise specified, the *N*-methylalkylamines were synthesized according to [36].

5,6-Methylenedioxyindole.

A solution of 19.12 g (0.082 mole) of 6,β-dinitro-3,4-methylenedioxystyrene in 55 ml of absolute ethanol, 40 ml of acetic acid and 300 ml of ethyl acetate was shaken with 4.0 g of 10% palladium on charcoal under 40 to 55 psig hydrogen for 45 minutes. The mixture was then filtered through Celite under nitrogen. The pale green filtrate was shaken with a slurry of 40 g of sodium hydrogen carbonate in 100 ml of water. The organic phase was separated and was dried over magnesium sulfate before it was filtered. The dark green filtrate was concentrated *in vacuo* to leave a greensih black solid which was triturated with four fresh 100 ml portions of boiling cyclohexane, the boiling supernatants being combined in the same beaker. The combined supernatants were allowed to cool to room temperature before the crystalline product (8.3 g, 64% yield, mp 107-110°, lit [31] mp 108-110°; lit [33] mp 110°) was collected by filtration.

5,6-Methylenedioxy-*N*,*N*-(disubstituted)indole-3-glyoxylamides (for all compounds in Table I except for **10a, 15a** and **21a**).

To a stirred, ice-cooled mixture of 1.61 g (10.0 mmoles) of 5,6-methylenedioxyindole in 20 ml of ether under nitrogen was added over the course of 10-20 minutes a solution of 1.75 ml (20 mmoles) of oxalyl chloride in 5 ml of ether, the temperature of the reaction mixture being kept between 0 and 5°. The stirred mixture was stored at 0° for 20-30 minutes before it was filtered into a sintered-glass funnel. The brick-red powder thus collected was washed with two 5 ml portions of ether before it was dried *in vacuo* for ½ hour. The yield of crude 5,6-methylenedioxyindole-3-glyoxyl chloride was 85-90%. The crude chloride was dissolved in 100 ml of dry tetrahydrofuran and the resulting solution was stirred under nitrogen while being cooled to *ca.* 0°. An ethereal solution of the desired secondary amine was added until the reaction attained *p*H > 9. Solvents were then removed under reduced pressure and the residue was partitioned between 100 ml each chloroform and water (more chloroform was used if some solid remained). The organic phase was separated, dried over magnesium sulfate, and filtered, and the filtrate concentrated *in vacuo*. The resides were recrystallized from the appropriate solvent(s). In the preparation of **22a** it was discovered that the crude product contained some hydrogen chloride, and a solution of the crude product in ethyl acetate containing a little methanol had to be washed with aqueous sodium carbonate before pure product could be isolated.

5,6-Methylenedioxy-*N*-methyl-*N*-cyclopropylindole-3-glyoxylamide (**10a**) (**15a** and **21a** were prepared in a similar manner).

A 250 ml 3-neck flask equipped with stir bar, immersion thermometer and dropping funnel was flushed with nitrogen and the flask was charged with 40 ml of a 0.298 *M* solution of *N*-methylcyclopropylamine (12.0 mmoles) in ether and 1.74 ml of diisopropylethylamine (10.0 mmoles). The dropping funnel was charged with a solution of crude 5,6-methylenedioxyindole-3-glyoxyl chloride in 100 ml of tetrahydrofuran, made from

10.0 mmoles of the indole by the previous procedure. The contents of the flask were stirred rapidly and were cooled to −20°, after which point the glyoxyl chloride solution was added dropwise over the course of 15 minutes, the temperature of the reaction mixture varying from −30° to −15°. At addition's end the cooling bath was removed and the mixture was allowed to warm to 0° before solvents were removed *in vacuo*. The dark brown residue was partitioned between 100 ml each of chloroform and water. The aqueous phase was extracted with 25 ml of chloroform. United chloroform extracts were washed successively with 50 ml of ice-cold 10% aqueous sodium hydrogen sulfate and 50 ml of water before they were dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. The beige solid residue (2.3 g) was stirred with 20 ml of boiling chloroform and the resulting mixture was stored at room temperature overnight before 10 ml of hexane was added. The beige solid was collected by filtration: yield, 1.71 g (59% based on 5,6-methylenedioxyindole). Even after drying the product overnight under oil-pump vacuum at room temperature elemental analysis indicated the presence of 0.25 molecule of water per molecule of **10a**. This hydration did not seem to interfere with subsequent reduction to the amine **10**.

N-Carbobenzyloxycyclopropylamine (**23**).

A mixture of 400 ml of toluene, 400 ml of water, 56.3 g (0.33 mole) of carbobenzyloxy chloride and 36.1 g (0.34 mole) of sodium carbonate was stirred with a paddle stirrer and was cooled to 5°. Cyclopropylamine (19.6 g, 0.344 mole) was added dropwise, the temperature of the reaction rising as high as 21°. The reaction was monitored by quenching aliquots with concentrated aqueous ammonium hydroxide and looking for the disappearance of benzyl carbamate by tlc (silica, 5% 2-propanol in methylene chloride, uv light: R_f of **23** *ca.* 0.75). About a half hour after addition's end the aqueous layer was separated and was extracted with 160 ml of ethyl acetate. Combined organic layers were washed with brine before they were dried over magnesium sulfate. The resulting mixture was filtered and the filtrate concentrated *in vacuo* to leave 62 g of a pale yellow oil. Addition of 100 ml of hexane initiated crystallization. The white flakes were collected by filtration: yield, 52.0 g (79% based on cyclopropylamine, 82% based on carbobenzyloxy chloride), mp 55.5-56.5°. An analytical sample from cyclohexane/hexane exhibited mp 56.0-57.0°.

Anal. Calcd. for $C_{11}H_{13}NO_2$ (191.23): C, 69.09; H, 6.85; N, 7.33. Found: C, 69.21; H, 6.78; N, 7.33.

N-Carbobenzyloxy-*N*-methylcyclopropylamine (**24**).

In a 500 ml one-neck flask equipped with stir bar and dropping funnel a solution of 21.00 g (0.110 mole) of **23** in 175 ml of dimethylformamide was stirred under nitrogen whole the flask was cooled in an ice bath. Oil-free sodium hydride (2.74 g, 0.115 mole) was added. After 5 minutes the ice bath was removed; after another 10 minutes the ice bath was returned and over the next 7 minutes 17.4 g (0.122 mole) of iodomethane was added dropwise from the funnel. The ice bath was removed at the end of the addition. After another hour, tlc indicated some **23** was still present (silica, ethyl acetate-hexane 1:2, uv light). More sodium hydride (0.57 g, 0.024 mole) and iodomethane (2.0 ml) were added and the mixture was stirred overnight. Compound **23** was detectable by tlc. The reaction mixture was poured into 1.1 liters of cold water, and the resulting mixture was extracted wtih three 500 ml portions of ethyl acetate. The combined organic phases were washed successively with 500 ml of water and 500 ml of brine before they were dried over magnesium sulfate. The mixture was filtered and the filtrate was concentrated *in vacuo* to leave 23.4 g of crude oily product, which was distilled in a Kugelrohr (70-80°/0.2 mm) to give 21.5 g (95% yield) of clear colorless oil.

Anal. Calcd. for $C_{12}H_{15}NO_2$ (205.26): C, 70.21; H, 7.37; N, 6.83. Found: C, 70.51; H, 7.52; N, 6.80.

N-Carbobenzyloxy-*N*-benzylcyclopropylamine (**26**).

Following a procedure similar to the previous one 3.82 g (20.0 mmoles) of **23** were alkylated using 0.51 g (21.5 mmoles) of oil-free sodium hydride and 3.43 g (20.0 mmoles) of benzyl bromide in 30 ml of dimethylformamide. The crude product (5.56 g) was purified by Kugelrohr distillation (125°/0.05 mm) to give **26** (5.42 g, 96% yield) as a clear colorless oil.

Anal. Calcd. for $C_{18}H_{19}NO_2$ (281.36): C, 76.84; H, 6.81; N, 4.98. Found: C, 77.09; H, 7.14; N, 4.98.

N-Methylcyclopropylamine and its Hydrogen Oxalate Salt **25**.

A solution of 21.2 g (0.103 mole) of **24**, 8.0 ml of concentrated aqueous hydrogen chloride and 250 ml of ethanol was stirred with 2.0 g of 5% palladium on carbon under 1 atmosphere of hydrogen. The disappearance of **24** could be monitored by tlc or gc (220° oven, 6 ft 10% OV-101 column, ret. time 2.4 minutes). When the reaction was complete the mixture was filtered and the acidic filtrate was concentrated *in vacuo*. The residue was partitioned between 50 ml of water and 50 ml of ether. The aqueous phase was extracted with 50 ml of ether, and the combined ether extracts were extracted with 25 ml of 1.0 *N* aqueous hydrogen chloride. The combined aqueous phases were concentrated *in vacuo* to about 15 ml and the residual solution was chilled in ice before it was treated carefully with 25 ml of saturated aqueous sodium hydroxide. The basic solution was extracted with ether in 100 and 50 ml portions. The combined ether extracts were washed with brine before they were dried over magnesium sulfate and filtered.

The filtrate was diluted with dry ether to 250.0 ml in a volumetric flask. A 5.00 ml aliquot was added to 3.0 ml of ethereal 1.0 *M* anhydrous oxalic acid. The white needles which separated were collected on a frit by filtration before they were washed with two 5 ml portions of ether. The product was dried over phosphorus pentoxide and exhibited mp 110.5-112° (lit [37] mp 110-111°), yield, 240 mg, or 1.49 mmoles (72% yield), indicating an amine concentration of at least 0.298 *M* in the ethereal solution.

N-Benzylcyclopropylamine from **26**.

In a procedure similar to the previous one 5.3 g (18.7 mmoles) of **26** was catalytically converted after 12 hours reaction time to 2.11 g (14.3 mmoles, 77% yield) of the clear, colorless amine, bp 103-105°/15 mm (lit [39] bp 80-81°/5 mm).

N-Methylcyclopropanecarboxamide.

This amide and *N*-methyl(cyclopropylmethyl)amine are reported in the patent literature [42] without full experimental details of their preparation.

A solution of methylamine in water (18.7 g of 40%, 0.24 mole of amine) was stirred and cooled to 5°. A solution of 10.45 g (0.100 mole) of cyclopropanecarboxylic acid chloride in 20 ml of ether was added dropwise, keeping the temperature of the reaction between 10 and 20°. After the addition the mixture was stirred at 5 to 10° for 5 minutes before excess salt was added and the cooling bath was removed. After a few more minutes the mixture was extracted with one 50 ml and two 25 ml portions of ether, followed by three 50 ml portions of ethyl acetate. The tlc (silica, 5% 2-propanol in methylene chloride, chlorine gas then potassium iodide-starch) indicated ethyl acetate was a better extraction solvent. The combined organic phases were washed with concentrated aqueous sodium hydrogen sulfate and brine before they were dried over magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to leave a pale yellow oily residue, which was distilled through a short-path still head to give 6.49 g (66% yield) of the amide, bp 124-126°/14 mm, which soon solidified, mp 57.5-61.5° (lit [42] mp 48-51°).

N-Methyl(cyclopropylmethyl)amine.

Under nitrogen a suspension of 3.00 g (0.079 mole) of lithium aluminum hydride in 100 ml of dry ether was stirred with a paddle stirrer in a 500 ml 3-neck flask also equipped with a dropping funnel and reflux condenser. A solution of 6.51 g (0.0656 mole) of *N*-methylcyclopropanecarboxamide in 75 ml of ether was added dropwise over the course of four minutes, keeping the mixture under gentle reflux. Over the next 3½ hours the mixture was heated under reflux and was stirred vigorously. The flask than was cooled in ice and the mixture was hydrolyzed with 3.0 ml of water, 9.0 ml of 10% aqueous sodium hydroxide, and 3.0 ml of water. After a few minutes' stirring the white granular solids were filtered off onto a frit and the filter cake was washed with a total of 100 ml of ether in several portions. The filtrates were dried over magnesium sulfate overnight, and the drying agent was filtered off. The filtrate was diluted with ether to 200.0 ml in a volumetric flask.

A 5.00 ml aliquot was added to 3.0 ml of 1 *M* ethereal anhydrous oxalic acid. After a few minutes the precipitated white powder was filtered onto a frit, and the filter cake was washed with two 5 ml portions of ether before it was dried *in vacuo* over phosphorus pentoxide. Yield of white powder mp 176.5-178°, was 226 mg, or 1.29 mmoles (79% yield), indicating an amine concentration of at least 0.258 *M*. Recrystallization of a 194 mg sample of the powdery salt from ethanol-ether gave 177 mg of flakes, mp 176.5-178°.

Anal. Calcd. for $C_7H_{13}NO_4$ (175.19): C, 47.99; H, 7.48; N, 8.00. Found: C, 48.24; H, 7.55; N, 8.03.

N,N-Dialkyl Substituted-5,6-methylenedioxytryptamines from Corresponding Glyoxylamides (Method A, Table II).

Over a course of 5 to 10 minutes a solution of 1.00 mmoles of glyoxylamide in the minimum volume of tetrahydrofuran (15 to 100 ml) was added dropwise to a stirred suspension of 0.23 g (6.0 mmoles) lithium aluminum hydride in 12 ml of tetrahydrofuran. The mixture was rapidly heated to reflux and was held there until tlc indicated reaction was complete (10 minutes to 2 hours), at which point the mixture was allowed to cool somewhat before it was hydrolyzed carefully with 0.23 ml of water, 0.70 ml of 10% aqueous sodium hydroxide, and 0.23 ml of water. The cooled mixture was filtered through Celite and the filter cake was washed with several portions of tetrahydrofuran, and the combined filtrates were concentrated *in vacuo*. The residues were either subjected to Kugelrohr distillation before recrystallization (**7, 9, 10, 11, 16, 18**) or were recrystallized as the free bases (**12, 14, 19, 20, 22**) or were converted to their hydrochloride salts before recrystallization (**15, 21**).

Debenzylation of **21** to give **8** (Method B, Table II).

A solution of 200 mg (0.540 mmole) of **21** in 50 ml each absolute ethanol and methanol was shaken with 58 mg of 5% palladium on carbon under 50 psi hydrogen for 20 minutes after which time tlc indicated reaction was complete. The mixture was filtered through Celite, the filter cake was washed with chloroform, and the combined filtrates, to which a little benzene was added, were concentrated *in vacuo* to leave 170 mg of amorphous white solid. The crude product was recrystallized and dried *in vacuo* over posphorus pentoxide overnight, yield, 76 mg of beige crystals (49%).

Synthesis of **17** from **18** (illustrative of Method C, Table II).

A solution of 308 mg (1.00 mmole) of **18** and 428 mg (5.1 mmoles) of cyclopentanone in 50 ml of absolute ethanol was shaken with 150 mg of 10% palladium on carbon under 50 psi hydrogen for 24 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was recrystallized from cyclohexane to give 190 mg (66%) of beige crystals.

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