Psilocin Analogs II. Synthesis of 3-[2-(Dialkylamino)ethyl]-, 3-[2-(*N*-Methyl-*N*-alkylamino)ethyl]-, and 3-[2-(Cycloalkylamino)ethyl]indol-4-ols

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Structural alteration of the N^b-substituents of psilocin (3-[2-dimethylamino)ethyl]indol-4-ol) (**12a**) has led to a number of compounds containing known pharmacophoric groups. Further, it is hoped that the subtle changes in the nature of these substituents may lead to a clearer understanding of the structure-activity relationships of the 4-hydroxytryptamine hallucinogens.

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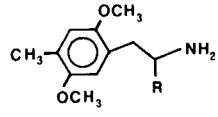
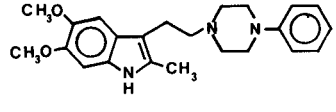
The 4-oxygenated indoles present an interesting class of substances. This is because a) they rarely occur in nature (1-4) and b) compounds containing such a nucleus often present a unique pharmacological profile. A striking example of the latter can be seen by the clinical comparison of 4-hydroxy-*N,N*-dimethyltryptamine (psilocin) and its 5-hydroxy counterpart, bufotenin. While psilocin is an active hallucinogenic agent in humans with an oral dose of 5-10 mg. (5), bufotenin is not hallucinogenic with oral doses up to 100 mg. (6), and considerable controversy exists as to whether the latter is in fact psychotomimetic (7,8). Why the transposition of the hydroxyl group from C-5 to C-4 in these substances creates such a difference in biological activity is an intriguing question. The difference in lipophilicity between the two molecules has been offered as a possible explanation (8,9). That the electronic character of these compounds may influence their biological activities has also been postulated (10) and debated (11). Comparative molecular conformations (12) may also play a role. It may be that psilocin could exist as a unique ionophore at physiological *p*H possessing special membrane and cellular transport properties. Because of the ease with which psilocin enters the central nervous system through the gastrointestinal tract (8), compounds designed around such a nucleus may prove to have valuable pharmacological effects. Such a concept is not without precedent. The powerful psychotomimetic 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane (**1**) (DOM, "STP") is 80-100 times as active as mescaline on a dose-response basis (13). Yet, simple homologation to produce 2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane (**2**) yields a substance deviod of hallucinogenic effects (14,15). This compound has shown promise as an antidepressant agent with minimal side effects (15-17).



1 DOM, R = CH_3
2 BL-3912A, R = C_2H_5

Compounds containing a substituted piperazinyl moiety have found numerous applications as medicinal agents. For example, oxypertine (**3**) and its analogs possess significant neuroleptic (18) and adrenolytic (19) activities. *N*-Aralkyl substituted 4-(substituted-phenyl)piperidin-4-ols (of which haloperidol is representative) are also clinically useful antipsychotic agents (20). Similar piperazine and piperidine groups attached to indoles *via* 3-alkyl side-chains have been reported to have antihypertensive (21), tranquilizing (22), and antiinflammatory (23) activities. Hybrid molecules with such groups attached to a 4-hydroxyindole moiety might be expected to have interesting medicinal properties.



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The chemistry of the 4-hydroxyindoles, particularly those substituted with a 3-aminoalkyl side-chain, presents an interesting challenge due to their instability in both chemical (4, 24-26) and biological systems (27). The earlier discovery (24) that most of the product amines could be purified by sublimation or distillation *in vacuo* greatly facilitated their isolation. In the pure crystalline state these materials can be stored for long periods at freezer temperatures.

The synthesis of the glyoxylamides and the amines was essentially as reported earlier (24). Attempts to prepare the

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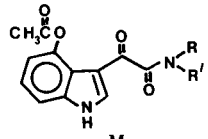
Table I

Physical Data for the Amides



Compound No.	R, R'	Yield	M.p.	Formula	Analyses
8	H, *t*-butyl	87%	212-213° (ethyl acetate/hexane)	$C_{16}H_{18}N_2O_4$ (302.33)	Calcd: C, 63.57; H, 6.00; N, 9.26. Found: C, 63.41; H, 6.12; N, 9.24.
9	benzyl, benzyl	66%	139-141° (ethyl acetate/hexane)	$C_{26}H_{22}N_2O_4$ (426.50)	Calcd: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.07; H, 5.19; N, 6.45.
10	*iso*-butyl, *iso*-butyl	84%	152-154° (ethyl acetate/hexane)	$C_{20}H_{26}N_2O_4$ (358.42)	Calcd: C, 67.02; H, 7.31; N, 7.81. Found: C, 66.90; H, 7.51; N, 7.93.
11	*sec*-butyl, *sec*-butyl	33%	syrup	$C_{20}H_{26}N_2O_4$ (358.42)	Calcd: C, 67.02; H, 7.31; N, 7.81. Found: C, 65.54; H, 7.74; N, 6.84.
12	methyl, methyl	80%	204-205° (THF)	$C_{14}H_{14}N_2O_4$ (274.28)	Calcd: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.16; H, 5.18; N, 10.51.
13	methyl, ethyl	73%	179-180° (ether)	$C_{15}H_{16}N_2O_4$ (288.31)	Calcd: C, 62.49; H, 5.60; N, 9.72. Found: C, 62.58; H, 5.47; N, 9.56.
14	methyl, *n*-propyl	63%	95° (ethyl acetate/hexane)	$C_{16}H_{18}N_2O_4$ (302.33)	Calcd: C, 63.57; H, 6.00; N, 9.26. Found: C, 63.19; H, 5.90; N, 9.18.
15	methyl, *iso*-propyl	79%	211-212° (chloroform/hexane)	$C_{16}H_{18}N_2O_4$ (302.33)	Calcd: C, 63.57; H, 6.00; N, 9.26. Found: C, 63.73; H, 5.90; N, 9.28.
16	methyl, *n*-butyl	60%	syrup	$C_{17}H_{20}N_2O_4$ (316.37)	Calcd: C, 64.54; H, 6.37; N, 8.86. Found: C, 63.83; H, 6.56; N, 8.24.
17	methyl *iso*-butyl	64%	142-145° (ethyl acetate/hexane)	$C_{17}H_{20}N_2O_4$ (316.37)	Calcd: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.34; H, 6.46; N, 8.69.
18	methyl, *sec*-butyl	35%	138-140° (ether/hexane)	$C_{17}H_{20}N_2O_4$ (316.37)	Calcd: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.30; H, 6.32; N, 8.82.
19	methyl, *t*-butyl	48%	225-226° (THF)	$C_{17}H_{20}N_2O_4$ (316.37)	Calcd: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.64; H, 6.48; N, 8.75.
20	methyl, cyclopentyl	48%	163-164° (ethyl acetate/hexane)	$C_{18}H_{20}N_2O_4$ (328.40)	Calcd: C, 65.84; H, 6.14; N, 8.53. Found: C, 64.72; H, 6.19; N, 8.47.
21	2,6-dimethylpiperidyl	30%	196-197° (ethyl acetate/hexane)	$C_{19}H_{22}N_2O_4$ (342.41)	Calcd: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.35; H, 6.70; N, 7.87.
22	4-phenylpiperidyl-	52%	229-230° (ether/hexane)	$C_{23}H_{22}N_2O_4$ (390.45)	Calcd: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.58; H, 5.77; N, 6.98.
23	4-hydroxy-4-(*p*-fluoro-phenyl)piperidyl-	78%	210° (ethyl acetate/hexane)	$C_{23}H_{21}FN_2O_5$ (424.44)	Calcd: C, 65.09; H, 4.99; N, 6.60. Found: C, 65.45; H, 5.16; N, 6.52
24	*N*-methylpiperazino-	59%	216-217° (ethyl acetate)	$C_{17}H_{19}N_3O_4$ (329.39)	Calcd: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.95; H, 5.80; N, 12.76.

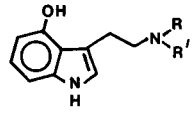
parent substance, 4-hydroxytryptamine (**6**) have met with limited success (4), although stable salts of this compound have been reported (28). Hydrogenolysis of the dibenzylamine **9a** proved sluggish. Thin-layer chromatographic evidence suggests that one *N*-benzyl group is removed rapidly (< 0.1 hour). However, the rate of hydrogenolysis (> 24 hours) of the second benzyl group could not be enhanced by a variety of catalysts or *p*H modifications of the reaction mixtures. Since 4-hydroxytryptamine is so unstable (4), hydrogenolyses mixtures were treated with acetic anhydride and pyridine to provide the stable *N,O*-diacetate (**7**) isolated by preparative thin-layer chromatography in low yield.

In 1977, Büchi and Mak (29) reported the direct preparation of 3-(2-nitrovinyl)indoles *via* acid catalyzed reaction of indoles with 1-dimethylamino-2-nitroethylene. With slight modification, this method led to a 78% yield of 4-acetoxy-3-(2-nitrovinyl)indole (**5**). Reduction of compound **5** with lithium aluminum hydride proceeded rapidly in refluxing tetrahydrofuran but work-up (in a dry, inert atmosphere) followed by acetylation provided compound **7** in only 26% yield.

Preliminary experiments aimed at the syntheses of 3-[2-(monoalkylamino)ethyl]indol-4-ols have been disappointing. While the preparation of 4-acetoxy-*N*-(*t*-butyl)-indole-3-glyoxylamide (**8**) proceeded in high yield, reduc-

Table II

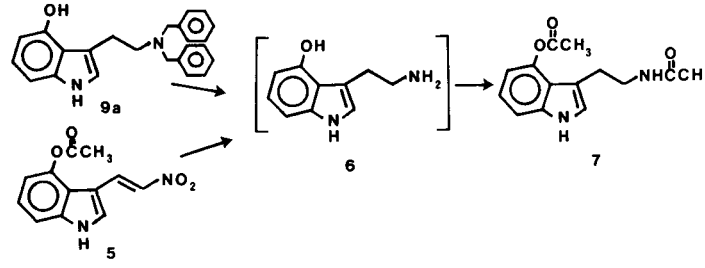
Physical Data for the Amines



Compound No.	R, R'	Yield	M.p.	Formula	Analyses
9a	benzyl, benzyl-	54%	234-237° dec. (a) (methanol/ether)	$C_{24}H_{25}N_2ClO$ (392.94)	Calcd: C, 73.36; H, 6.41; N, 7.13. Found: C, 73.08; H, 6.42; N, 6.93.
10a	*iso*-butyl, *iso*-butyl-	80%	275-277° (a) (methanol/ether)	$C_{18}H_{29}N_2ClO$ (329.91)	Calcd: C, 66.54; H, 9.00; N, 8.62. Found: C, 66.70; H, 9.13; N, 8.61.
11a	*sec*-butyl, *sec*-butyl-	66%	197-199° (a) (ethanol/ether)	$C_{18}H_{29}N_2ClO$ (329.91)	Calcd: C, 66.54; H, 9.00; H, 8.62. Found: C, 66.53; H, 9.00; N, 8.54.
12a	methyl, methyl-	56%	169-170 (b) (ethyl acetate/hexane)	$C_{12}H_{16}N_2O$ (204.30)	Calcd: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.66; H, 7.99; N, 13.85.
13a	methyl, ethyl-	41%	118-119° (ethyl acetate/hexane)	$C_{13}H_{18}N_2O$ (218.30)	Calcd: C, 71.53; H, 8.31; N, 12.84. Found: C, 71.64; H, 8.51; N, 12.90.
14a	methyl, *n*-propyl-	54%	162-163° (a) (methanol/ether)	$C_{14}H_{21}N_2ClO$ (268.84)	Calcd: C, 62.56; H, 7.89; N, 10.42. Found: C, 62.23; H, 7.79; N, 10.18.
15a	methyl, *iso*-propyl	74%	123-124° (ethyl acetate/hexane)	$C_{14}H_{20}N_2O$ (232.32)	Calcd: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.06; H, 8.52; N, 11.75.
16a	methyl, *n*-butyl-	34%	183-185° (a) (methanol/ether)	$C_{15}H_{23}N_2ClO$ (282.87)	Calcd: C, 63.69; H, 8.21; N, 9.91. Found: C, 63.54; H, 8.01; N, 9.86.
17a	methyl, *iso*-butyl-	54%	syrup	$C_{15}H_{22}N_2O$ (246.37)	Calcd: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.84; H, 8.62; N, 11.27.
18a	methyl, *sec*-butyl-	48%	syrup	$C_{15}H_{22}N_2O$ (246.37)	Calcd: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.73; H, 8.59; N, 12.95.
19a	methyl, *t*-butyl-	60%	150-153° (ethyl acetate/hexane)	$C_{15}H_{22}N_2O$ (246.37)	Calcd: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.05; H, 9.04; N, 11.30.
20a	methyl, cyclopentyl-	60%	155° dec. (ethyl acetate/hexane)	$C_{16}H_{22}N_2O$ (258.38)	Calcd: C, 74.38; H, 8.58; N, 10.84. Found: C, 73.99; H, 8.86; N, 10.76.
21a	2,6-dimethylpiperidyl-	47%	169-170° dec. (ether/hexane)	$C_{17}H_{24}N_2O$ (272.40)	Calcd: C, 74.96; H, 8.88; N, 10.24. Found: C, 74.83; H, 8.91; N, 10.20.
22a	4-phenylpiperidyl-	55%	165-167° dec. (ethyl acetate/hexane)	$C_{21}H_{24}N_2O$ (320.44)	Calcd: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.40; H, 7.49; N, 8.25.
23a	4-hydroxy-4-(*p*-fluorophenyl)-piperidyl-	45%	188-190° dec. (ethyl acetate/hexane)	$C_{21}H_{23}FN_2O_2$ (354.43)	Calcd: C, 71.16; H, 6.54; N, 7.91. Found: C, 70.82; H, 6.76; N, 7.43.
24a	*N*-methylpiperazino	63%	217-218° dec. (THF/hexane)	$C_{15}H_{21}N_3O$ (259.36)	Calcd: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.27; H, 8.30; N, 16.13.

(a) Hydrochloride salt. (b) Reference 37 reports m.p. 169°.

tion of this substance with lithium aluminum hydride led to two major products (tlc). The worked-up reaction mixture proved to be exceedingly unstable and attempted separation of the components by distillation or chromatography was not successful. Similar difficulties with lithium aluminum hydride reductions of *N*-(monoalkyl)indole-3-glyoxylamides have been noted by other workers (30,31). Diborane has been used to convert amides to amines (32), but the application of this reagent to indolylglyoxylamides has led to the formation of by-products (33) including indolines (34). The strongly acidic conditions (32) necessary to decompose the intermediate borane-amine complexes would preclude their use with the sensitive 4-hydroxyindole moiety, although a low yield of 4-hydroxytryptamine was obtained *via* pyrolysis of such a complex (4).



SCHEME I

The proton n agnetic resonance spectra of the product amines were consistent with the proposed structures. All of the *N*-methyl-*N*-(alkyl)indole-3-glyoxylamides exhibited a splitting of the *N*-methyl signals due to the rotomeric [partial double-bond character of the amides (35)] nature of these substances.

EXPERIMENTAL

Proton magnetic resonance spectra were obtained with a Varian EM-360 spectrometer. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry and Chemical Engineering, Michigan Technological University and by Integral Microanalytical Laboratories, Inc., Raleigh, North Carolina. Melting points are corrected. Reactions were monitored by thin-layer chromatography on 250 μ layers of silica gel GF on glass plates, glyoxylamides in 5% methanol in chloroform and amines in 1.5% concentrated ammonium hydroxide in methanol. Visualization was by short wave uv. Tetrahydrofuran was distilled from sodium prior to use. Unsymmetrical amines were obtained as reported previously (36).

4-Acetoxy-*N*-(substituted)-indole-3-glyoxylamides (**8-24**).

To a stirred solution of 4-acetoxyindole (24) (500 mg., 2.85 mmoles) in 5.0 ml. of diethylether was added 0.5 ml. (5.9 mmoles) of oxalyl chloride. The reaction solution was stored at 4° for 18 hours, diluted with 50 ml. of *n*-hexane, and cooled to −22° for 1.0 hour. The yellow crystalline solid was collected by filtration and dissolved in 10 ml. anhydrous tetrahydrofuran. To this solution was added a solution of 40% dialkyl- or cycloalkylamine in ether until the reaction attained *p*H > 10. The solvents were then removed under reduced pressure and the residue partitioned between 200 ml. of chloroform and 50 ml. of 0.1*N* hydrochloric acid. After washing the organic phase with 50 ml. of saturated aqueous sodium chloride it was dried (magnesium sulfate), filtered, and the filtrate concentrated under reduced pressure. Solid amides were recrystallized from the appropriate solvent, syrupy amides were purified by preparative thin-layer chromatography on 20 × 40 cm glass plates coated with 1000 μ layers of silica gel GF in 5% methanol in chloroform.

3-[2-(Alkyl-substituted-amino)ethyl]indol-4-ols (**9a-24a**).

To a stirred suspension of lithium aluminum hydride (10 mmoles) in 10 ml. of tetrahydrofuran under a nitrogen atmosphere was added dropwise a solution of the above amide (**8-24**) (2.0 mmoles) in 10 ml. of tetrahydrofuran. After the addition the reaction was brought rapidly to reflux and held there for 15 minutes. Thin-layer chromatography usually indicated that complete reduction had taken place at this time. The reaction was cooled to 40° and water added dropwise to decompose the complex and excess reagent. The reaction mixture was then filtered through Celite in a nitrogen atmosphere and the filtrate concentrated under reduced pressure. Where appropriate the residues were distilled *in vacuo* (Kugelrohr apparatus) and then recrystallized or converted to crystalline salts.

3-(2-Nitrovinyl)-4-acetoxyindole (**5**).

To a solution of 175 mg. (1.0 mmole) of 4-acetoxyindole in 1.0 ml. of trifluoroacetic acid was added 116 mg. (1.0 mmole) of 1-dimethylamino-2-nitroethylene (29). The reaction mixture was heated at 55° under a nitrogen atmosphere for 10 minutes during which time the light yellow solution became dark red. The reaction was cooled to room temperature and the solvent distilled under reduced pressure. The resulting red oil was dissolved in 2.0 ml. of chloroform and the solvent removed *in vacuo*. This was repeated with 3.0 ml. of dioxane. Addition of 1.0 ml. of ethyl acetate and scratching induced crystallization of the residue. Hexane (0.25 ml.) was added and the yellow needles collected by filtration and dried *in vacuo* to give 191 mg. of **5** (78%), m.p. 200-203° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_4$ (246.23): C, 58.53; H, 4.09; N, 11.38. Found: C, 58.77; H, 4.12; N, 11.65.

N,O-Diacetyl-4-hydroxytryptamine (**7**).

A).

Compound **5** (335 mg., 1.36 mmoles) was dissolved in 4.0 ml. of tetrahydrofuran and added to a stirred suspension of 300 mg. (7.89 mmoles) of lithium aluminum hydride in 5.0 ml. of tetrahydrofuran. After the addition the reaction was refluxed for 20 minutes, cooled to room temperature, and water added dropwise until gas evolution ceased. The mixture was filtered (Celite, dry nitrogen atmosphere) and the filtrate concentrated under reduced pressure. The resulting clear syrup (slight blue tinge) was dissolved in a mixture of 5.0 ml. of pyridine and 3.0 ml. of acetic anhydride. After standing overnight at room temperature the solvents were distilled under reduced pressure and the residue purified by preparative thin-layer chromatography in 5% methanol in chloroform. The eluted (ethyl acetate) product was crystallized from ethyl acetate/hexane to give 94 mg. (26%), m.p. 150°.

Anal. Calcd. for $C_{14}H_{15}N_2O_3$ (259.29): C, 64.85; H, 5.83; N, 10.80. Found: C, 64.79; H, 6.19; N, 10.66.

B).

Compound **9a** (160 mg., 0.45 mmole) was dissolved in a mixture of 10 ml. of methanol and 10 ml. of ethyl acetate and 80 mg. of 10% palladium on carbon added. The resulting mixture was shaken under 50 psi hydrogen for 14 hours. The catalyst was removed by filtration (Celite, anhydrous nitrogen atmosphere), the filtrate concentrated under reduced pressure, and the residue treated as above with pyridine and acetic anhydride. After chromatographic work-up, compound **7** was obtained in 26% yield, m.p. 150°.

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