Psilocin Analogs. 1. Synthesis of 3-[2-(Dialkylamino)ethyl]- and 3-[2-(Cycloalkylamino)ethyl]indol-4-ols

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The synthesis of four dialkyl and three cycloalkyl analogs of psilocin (4, R = CH₃), a hallucinogenic principle found in certain fungi, is described. The synthetic route involves four transformations starting with 6,7-dihydroindol-4(5H)-one (1).


The rediscovery (1,2) of the ceremonial use of certain agarics in Mexico led Hofmann and collaborators to a phytochemical investigation of the species involved (3). Animal and human testing (4) of various fractions from extracts of cultivated Psilocybe mexicana Heim resulted in the isolation of two psychoactive principles. Structural studies and confirmation by synthesis (5-7) showed these compounds to be 3-[2-(dimethylamino)ethyl]indol-4-ol (psilocin, 4, R = CH₃) and its corresponding dihydrogenphosphate ester (psilocybin). These two substances have subsequently been detected in various species of the genera Psilocybe (Fr.) Quél., Psilocybe (Fr.) Quél. and Conocybe Fayod (8).

The hallucinogenic effects of psilocin and psilocybin have been well documented (9-12). Delay, Pichot and Lempérière (13) have commented on the possible psychotherapeutic role of these substances, although the length and intensity of the experience might preclude their use in all but the most special circumstances. Structural modification using psilocin as a template might lead to compounds having mood-enhancing qualities instead of hallucinogenic effects. Such an approach has been utilized by Shulgin, Sargent and Naranjo (14) in an extensive program of the structural modification of mescaline. Some success in the use of these analogs as adjuncts to psychotherapy has been reported by Naranjo (15).

Troxler, Seemann and Hofmann (16) synthesized a number of analogs of 4 with variations in the position of the oxygen substituent as well as modifications of the ethylamino side chain. The diethyl analog of psilocin (Sandoz CZ-74) reached clinical trial (17) and was found to be as active as psilocin but with a shorter duration.

Psilocin has been synthesized by a number of routes (7, 18-21). Hofmann's original synthesis has recently been repeated by Ono, Shimamine and Takahashi (22).

An attractive entry into 4-hydroxyindole chemistry is via dehydrogenation (23) of 6,7-dihydroindol-4(5H)-one, 1. Compound 1 has been prepared from 1,3-cyclohexanedione (24) and by a three step synthesis from pyrrole (18). Extensive exploitation of this route has not occurred although a notable exception is the work of Remers, Roth, Gibs and Weiss (25,26).

Compound 1 was conveniently aromatized with 10% palladium on carbon in refluxing p-cymene. The 4-hydroxyindole thus obtained was acetylated to provide crystalline 4-acetoxyindole (2b). Compound 2b was then
converted to the glyoxylamides (3) and thence to the amines (4) by the method of Speeter and Anthony (27). (Scheme I). The entire sequence results in the production of modest yields of the amines (4) through crystalline intermediates without the need for chromatographic purification at any step.

Early experiments on the isolation of the amines (4) from the reduction mixtures demonstrated their lability in the presence of impurities. Filtration of hydrolyzed reduction complexes led to rapid decomposition of the amines with formation of deep blue pigmented solutions. A similar reaction occurred during attempted chromatography of the crude amines on silicic acid. However, it was found that work-up of the reduction mixtures in an inert atmosphere minimized pigment formation. The amines were then purified by either distillation or sublimation in vacuo. The pure amines were found to be stable when stored in an anhydrous atmosphere at -15°. The disopropyl analog (4d) could not be induced to crystallize as the free base but was converted to the hydrochloride salt by careful addition of 0.1N hydrochloric acid to a solution of the amine in methanol.

The proton magnetic resonance spectra appear to be characteristic for this type of compound (28). The spectra of 3a-3d exhibit a doubling up of signals for the amide alkyl substituents due to the partial double bond character.

Table I

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>R</th>
<th>M.p. (solvent)</th>
<th>Formula</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>74%</td>
<td>ethyl</td>
<td>150-151 (ether)</td>
<td>C_{16}H_{16}N_{2}O_{4}</td>
<td>Calcd: C, 63.56; H, 6.00; N, 9.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(302.34)</td>
<td>Found: C, 63.57; H, 5.87; N, 8.95</td>
</tr>
<tr>
<td>3b</td>
<td>78%</td>
<td>n-propyl</td>
<td>130-131 (ether/</td>
<td>C_{18}H_{22}N_{2}O_{4}</td>
<td>Calcd: C, 65.44; H, 6.71; N, 8.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cyclohexane)</td>
<td>(330.40)</td>
<td>Found: C, 65.10; H, 6.79; N, 8.35</td>
</tr>
<tr>
<td>3c</td>
<td>77%</td>
<td>n-butyl</td>
<td>123-125 (cyclo-</td>
<td>C_{20}H_{26}N_{2}O_{4}</td>
<td>Calcd: C, 67.02; H, 7.31; N, 7.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hexane/hexane)</td>
<td>(358.45)</td>
<td>Found: C, 66.77; H, 7.62; N, 7.64</td>
</tr>
<tr>
<td>3d</td>
<td>35%</td>
<td>iso-propyl</td>
<td>204-206 (ethyl</td>
<td>C_{18}H_{23}N_{2}O_{4}</td>
<td>Calcd: C, 65.44; H, 6.71; N, 8.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetate/hexane)</td>
<td>(330.40)</td>
<td>Found: C, 65.08; H, 6.76; N, 8.26</td>
</tr>
<tr>
<td>3e</td>
<td>55%</td>
<td>pyrrolidyl</td>
<td>174-176 (chlo-</td>
<td>C_{16}H_{16}N_{2}O_{4}</td>
<td>Calcd: C, 63.98; H, 5.38; N, 9.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>roform/hexane)</td>
<td>(300.33)</td>
<td>Found: C, 63.57; H, 5.58; N, 9.02</td>
</tr>
<tr>
<td>3f</td>
<td>60%</td>
<td>piperidyl</td>
<td>177-178 (chlo-</td>
<td>C_{17}H_{18}N_{2}O_{4}</td>
<td>Calcd: C, 64.96; H, 5.77; N, 8.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>roform/hexane)</td>
<td>(314.35)</td>
<td>Found: C, 64.89; H, 5.59; N, 8.62</td>
</tr>
<tr>
<td>3g</td>
<td>80%</td>
<td>morphol</td>
<td>190-191 (ethyl</td>
<td>C_{16}H_{16}N_{2}O_{5}</td>
<td>Calcd: C, 60.75; H, 5.10; N, 8.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>didyl</td>
<td>acetate/hexane)</td>
<td>(316.33)</td>
<td>Found: C, 60.80; H, 5.10; N, 8.88</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>R</th>
<th>M.p. (solvent)</th>
<th>Formula</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>50%</td>
<td>ethyl</td>
<td>103-104 (ethyl</td>
<td>C_{14}H_{20}N_{2}O</td>
<td>Calcd: C, 72.38; H, 8.68; N, 12.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetate/hexane)</td>
<td>(232.33)</td>
<td>Found: C, 72.46; H, 8.73; N, 11.91</td>
</tr>
<tr>
<td>4b</td>
<td>51%</td>
<td>n-propyl</td>
<td>96-97 (ethyl</td>
<td>C_{16}H_{22}N_{2}O</td>
<td>Calcd: C, 73.80; H, 9.29; N, 10.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetate/hexane)</td>
<td>(260.39)</td>
<td>Found: C, 73.81; H, 9.27; N, 10.75</td>
</tr>
<tr>
<td>4c</td>
<td>35%</td>
<td>n-butyl</td>
<td>74-75 (ethyl</td>
<td>C_{18}H_{26}N_{2}O</td>
<td>Calcd: C, 74.95; H, 9.73; N, 9.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetate/hexane)</td>
<td>(288.44)</td>
<td>Found: C, 74.88; H, 9.86; N, 9.66</td>
</tr>
<tr>
<td>4d</td>
<td>47%</td>
<td>iso-propyl</td>
<td>263 dec. (methanol/</td>
<td>C_{16}H_{25}N_{2}ClO</td>
<td>Calcd: C, 64.74; H, 8.49; N, 9.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ether) (b)</td>
<td>(296.86)</td>
<td>Found: C, 64.56; H, 8.48; N, 9.29</td>
</tr>
<tr>
<td>4e</td>
<td>50%</td>
<td>pyrrolidyl</td>
<td>193-195 (ethyl</td>
<td>C_{14}H_{18}N_{2}O</td>
<td>Calcd: C, 73.01; H, 7.88; N, 12.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetate/hexane)</td>
<td>(230.31)</td>
<td>Found: C, 72.98; H, 7.92; N, 12.05</td>
</tr>
<tr>
<td>4f</td>
<td>42%</td>
<td>piperidyl</td>
<td>180-181 (ethyl</td>
<td>C_{15}H_{20}N_{2}O</td>
<td>Calcd: C, 73.73; H, 8.25; N, 11.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acetate/hexane)</td>
<td>(244.35)</td>
<td>Found: C, 73.67; H, 8.56; N, 11.38</td>
</tr>
<tr>
<td>4g</td>
<td>46%</td>
<td>morphol</td>
<td>177-178 (ethyl</td>
<td>C_{14}H_{18}N_{2}O_{2}</td>
<td>Calcd: C, 68.27; H, 7.36; N, 11.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>didyl</td>
<td>acetate/hexane)</td>
<td>(246.31)</td>
<td>Found: C, 68.36; H, 7.44; N, 11.30</td>
</tr>
</tbody>
</table>

(a) Reference 16 reports m.p. 104-106°. (b) Characterized as the hydrochloride salt. (c) Reference 16 reports m.p. 182-183°.
of the C-N bond (29). The ABC spin system (30) of the aromatic C₅H, C₆H and C₇H signals is not amenable to first-order analysis. However, approximate parameters were obtained in certain well-resolved cases, e.g., 4f.

**EXPERIMENTAL**

Proton magnetic resonance spectra were obtained with a Varian Associates T-60 spectrometer and are reported in ppm δ downfield from an internal standard of tetramethylsilane. Elemental analyses

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Chemical Shift, ppm δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Deuteriochloroform</td>
<td>7.53 (br s, 1H, N₁H), 7.10 (s, 1H, C₂H), 7.05 (m, 3H, C₅H, C₆H, C₇H), 3.36 (m, 4H, J = 8 Hz, ethyl CH₂), 2.45 (s, 3H, acetate CH₃), 1.20 (t, 3H, J = 8 Hz, ethyl CH₂), 1.06 (t, 3H, J = 8 Hz, ethyl CH₃)</td>
</tr>
<tr>
<td>3b</td>
<td>Deuteriochloroform</td>
<td>2.44 (br s, 1H, N₁H), 6.90 (m, 4H, C₂H, C₅H, C₆H, C₇H), 3.30 (m, 4H, propyl CH₂), 2.44 (s, 3H, acetate CH₃), 1.62 (m, 4H, propyl CH₂), 0.86 (m, 6H, propyl CH₃)</td>
</tr>
<tr>
<td>3c</td>
<td>Deuteriochloroform</td>
<td>7.51 (br s, 1H, N₁H), 6.97 (m, 4H, C₂H, C₅H, C₆H, C₇H), 3.30 (m, 4H, butyl CH₂), 2.45 (s, 3H, acetate CH₃), 1.54 (m, 8H, butyl CH₂), 0.97 (m, 6H, butyl CH₃)</td>
</tr>
<tr>
<td>3d</td>
<td>Deuteriochloroform plus dimethylsulfoxide-d₆, 1:1</td>
<td>7.86 (br s, 1H, N₁H), 7.20 (m, 4H, C₂H, C₅H, C₆H, C₇H), 3.67 (m, 2H, isopropyl CH), 2.42 (s, 3H, acetate CH₃), 1.56 (d, 6H, isopropyl CH₂), 1.18 (d, 6H, isopropyl CH₂)</td>
</tr>
<tr>
<td>3e</td>
<td>Deuteriochloroform</td>
<td>8.05 (br s, 1H, N₁H), 7.11 (m, 4H, C₂H, C₅H, C₆H, C₇H), 3.50 (m, 4H, pyrrolidyl CH₂), 2.42 (s, 3H, acetate CH₃), 1.88 (m, 4H, pyrrolidyl CH₂)</td>
</tr>
<tr>
<td>3f</td>
<td>Deuteriochloroform plus dimethylsulfoxide-d₆, 10:1</td>
<td>7.91 (br s, 1H, N₁H), 7.20 (m, 4H, C₂H, C₅H, C₆H, C₇H), 3.46 (m, 4H, piperidyl CH₂), 2.46 (s, 3H, acetate CH₃), 1.67 (br s, 6H, piperidyl CH₂)</td>
</tr>
<tr>
<td>3g</td>
<td>Deuteriochloroform</td>
<td>7.98 (br s, 1H, N₁H), 7.20 (m, 4H, C₂H, C₅H, C₆H, C₇H), 3.58 (m, 4H, morpholyl O-CH₂), 2.86 (br s, 4H, morpholyl N-CH₂), 2.41 (s, 3H, acetate CH₃)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Chemical Shift, ppm δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Deuteriochloroform</td>
<td>8.05 (br s, 1H, N₁H, exchange with deuterium oxide), 6.81 (m, 2H, C₆H, C₇H), 6.77 (s, sharpening on addition of deuterium oxide, C₃H), 6.52 (dd, 1H, C₆H, J₅,₆ = 8 Hz, J₆,₇ = 2 Hz), 2.80 (m, 4H, α-CH₂, β-CH₂), 2.56 (dd, 4H, J = 7 Hz, ethyl CH₂), 0.97 (t, 6H, J = 7 Hz, ethyl CH₃)</td>
</tr>
<tr>
<td>4b</td>
<td>Deuteriochloroform</td>
<td>7.92 (br s, 1H, N₁H, exchange with deuterium oxide), 7.05 (t, 1H, C₆H, J₅,₆ = J₆,₇ = 8 Hz), 6.85 (dd, 1H, C₇H, J₅,₇ = 2 Hz, J₆,₇ = 8 Hz), 6.83 (s, 1H, C₅H, sharpening on addition of deuterium oxide), 6.53 (dd, 1H, C₆H, J₅,₆ = 8 Hz, J₆,₇ = 2 Hz), 2.86 (m, 4H, α-CH₂, β-CH₂), 2.52 (m, 4H, propyl CH₂), 1.53 (m, 4H, propyl CH₂), 0.83 (t, 6H, propyl CH₃), J = 6 Hz)</td>
</tr>
<tr>
<td>4c</td>
<td>Deuteriochloroform</td>
<td>7.97 (br s, 1H, N₁H, exchange with deuterium oxide), 6.93 (m, 2H, C₆H, C₇H), 6.73 (s, 1H, C₅H, sharpening on addition of deuterium oxide), 6.52 (dd, 1H, C₆H, J₅,₆ = J₆,₇ = 2 Hz), 2.83 (m, 4H, α-CH₂, β-CH₂), 2.46 (m, 4H, butyl CH₂), 1.30 (m, 8H, butyl CH₂), 0.77 (m, 6H, butyl CH₃)</td>
</tr>
<tr>
<td>4d</td>
<td>Deuterium oxide plus dimethylsulfoxide-d₆, 1:1</td>
<td>7.00 (m, 4H, C₅H, C₆H, C₇H), 3.55 (m, 2H, isopropyl CH, J = 7 Hz), 3.16 (br s, 4H, α-CH₂, β-CH₂), 1.15 (d, 12H, isopropyl CH₃, J = 7 Hz)</td>
</tr>
<tr>
<td>4e</td>
<td>Deuteriochloroform plus acetone-d₆, 1:1</td>
<td>6.95 (m, 3H, C₂H, C₅H, C₇H), 6.53 (dd, 1H, C₆H, J = 7 Hz), 2.98 (br s, 4H, α-CH₂, β-CH₂), 2.60 (m, 4H, pyrrolidyl CH₂), 1.97 (m, 4H, pyrrolidyl CH₂)</td>
</tr>
<tr>
<td>4f</td>
<td>Deuteriochloroform</td>
<td>7.92 (br s, 1H, N₁H, exchange with deuterium oxide), 7.03 (t, 1H, C₆H, J₅,₆ = J₆,₇ = 7 Hz), 6.83 (dd, 1H, C₅H, J₅,₇ = 2 Hz, J₆,₇ = 7 Hz), 6.81 (br s, sharpening on addition of deuterium oxide, 1H, C₂H), 6.55 (dd, 1H, C₆H, J₅,₆ = 7 Hz, J₆,₇ = 2 Hz), 2.92 (m, 2H, β-CH₂), 2.60 (m, 2H, α-CH₂), 2.53 (m, 4H, piperidyl CH₂)</td>
</tr>
<tr>
<td>4g</td>
<td>Deuteriochloroform</td>
<td>7.97 (br s, 1H, N₁H, exchange with deuterium oxide), 6.96 (m, 2H, C₅H, C₇H), 6.85 (s, 1H, C₅H, sharpening on addition of deuterium oxide), 6.62 (dd, 1H, C₆H, J₅,₆ = 7 Hz, J₆,₇ = 2 Hz), 3.88 (m, 4H, morpholyl CH₂), 3.05 (m, 2H, β-CH₂), 2.73 (m, 4H, α-CH₂ and morpholyl CH₂)</td>
</tr>
</tbody>
</table>
were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and by the Microanalytical Laboratory, Department of Chemistry and Chemical Engineering, Michigan Technological University. Melting points are corrected. Reactions were monitored by thin-layer chromatography on 250 \( \mu \) layers of silica gel GF on glass plates.

4-Hydroxyindole (2a).

Under a nitrogen atmosphere 10 g (74 mmole) of 6,7-dihydroindol-4(5H)one (24) and 2.5 g of 10% palladium on carbon were stirred and refluxed in 250 ml of \( p \)-cymene for 24 hours. The reaction was cooled to 40\( ^\circ \) and the catalyst removed by filtration through Celite. The filtered solid was washed with 100 ml of methanol and the combined filtrate and washings were concentrated under reduced pressure. The residue was crystallized from cyclohexane, 7.6 g (77%), mp 96-97\( ^\circ \) (Literature (18) mp 97\( ^\circ \)).

4-Acetoxyindole (2b).

Compound 2a (7.6 g, 57 mmole) was dissolved in 200 ml of pyridine and 150 ml of acetic anhydride was added. The reaction was stored at room temperature for 18 hours. The solvent was distilled in vacuo and the residue co-distilled with two 100 ml portions of toluene. The solid residue was recrystallized from cyclohexane to give 8.07 g (81%), mp 98-100\( ^\circ \) (Literature (18) mp 99\( ^\circ \): nmr (deuterochloroform) ppm 8.30 (br s, 1H, \( N_2 \)H, exchange with deuterium oxide), 7.03 (m, 4H, \( C_2 \)H, \( C_5 \)H, \( C_8 \)H, \( C_7 \)H), 6.42 (m, 1H, \( C_3 \)H, collapsing to d on addition of deuterium oxide), 2.41 (s, 3H, acetyl CH3). 4-(Acetoxy)-N,N-dialkyl- and -N,N-Cycloalkylindole-3-glyoxylamides (3a-g).

To a stirred and cooled (0\( ^\circ \)) solution of 0.5 ml (5.9 mmole) of oxalyl chloride in 3.0 ml of dry ethyl ether was added dropwise a solution of compound 2b (500 mg, 2.85 mmole) in 4.0 ml of ether. The reaction was stirred at 0\( ^\circ \) for 5 hours and then a solution of 40% dialkyl- (or cycloalkyl)-amine in ether was added dropwise until the pH was 8.9. The reaction was diluted with chloroform (100 ml) and shaken with 30 ml of 5% sodium bisulfate solution, 30 ml of saturated sodium bicarbonate solution and 30 ml of saturated sodium chloride solution. After drying, (magnesium sulfate) the organic solution was concentrated under reduced pressure. The residue was recrystallized from the appropriate solvent.

3-[2-Dialkyl-(or Cycloalkyl)-amino]ethyl]indol-4-ols (4a-g).

To a stirred suspension of lithium aluminum hydride (13 mmole) in 10 ml of tetrahydrofuran (previously distilled over sodium) under a nitrogen atmosphere at room temperature was added dropwise a solution of the above amide (3a-g) (2.0 mmole) in 5-10 ml of tetrahydrofuran at such a rate as to maintain a gentle reflux. After the addition (7-10 minutes) the reaction was refluxed for an additional 15 minutes. The reaction was cooled to 40\( ^\circ \) and the excess reagent and complex decomposed by dropwise addition of 1.0 ml of ethyl acetate and then 2-3 ml of water. The mixture was filtered in an anhydrous nitrogen atmosphere and the filtrate concentrated under reduced pressure. The residue was either distilled (4a-d) or sublimed (4e-g) in vacuo and then recrystallized.

3-[2-(Diisopropylamino)ethyl]indol-4-ol Hydrochloride (4d).

The oily free base of 4d obtained by distillation of the crude amine, (0.5 mmole) was dissolved in 2.0 ml of methanol and one equivalent of 0.1N hydrochloric acid was added. The solution was concentrated to dryness in a stream of nitrogen. All traces of moisture were removed by evaporation on the oil pump. The solid residue was recrystallized from methanol/ether.

Acknowledgments.

We thank Dr. Lois Durham of the NMR Laboratory, Department of Chemistry, Stanford University, Stanford, California, for her stimulating discussion concerning the nmr spectra. We also wish to thank Dale T. Leslie for his consultation regarding mycological matters.

REFERENCES AND NOTES

(21) M. Julia and F. Ricalens, *ibid.*, 275, 613 (1972).