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

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Received October 4, 1976

The synthesis of four dialkyl and three cycloalkyl analogs of psilocin (**4**, R = CH_3), a hallucinogenic principle found in certain fungi, is described. The synthetic route involves four transformations starting with 6,7-dihydroindol-4(5*H*)one (**1**).

J. Heterocyclic Chem., 14, 71 (1977).

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 = CH_3) and its corresponding dihydrogenphosphate ester (psilocybin). These two substances have subsequently been detected in various species of the genera *Psilocybe* (Fr.) Quél., *Panaeolus* (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).

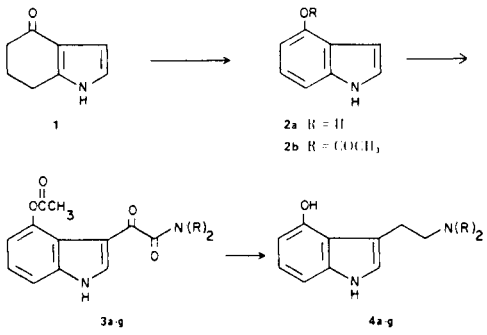
Troxler, Seemann and Hofmann (16) synthesized a number of analogs of **4** with variations in the position of the oxygen substituent as well as modifications of the ethylamino side chain. The diethyl analog of psilocin (Sandoz CZ-74) reached clinical trial (17) and was found to be as active as psilocin 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(5*H*)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

Scheme I



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 diisopropyl analog (**4d**) could not be induced to crystallize as the free base but was converted to the hydrochloride salt by careful addition of 0.1*N* 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

Physical Data for the Amides **3**

Compound	Yield	R	M.p. (solvent)	Formula	Analyses
3a	74%	ethyl	150-151 (ether)	$C_{16}H_{18}N_2O_4$ (302.34)	Calcd: C, 63.56; H, 6.00; N, 9.27 Found: C, 63.57; H, 5.87; N, 8.95
3b	78%	*n*-propyl	130-131 (ether/cyclohexane)	$C_{18}H_{22}N_2O_4$ (330.40)	Calcd: C, 65.44; H, 6.71; N, 8.48 Found: C, 65.10; H, 6.79; N, 8.35
3c	77%	*n*-butyl	123-125 (cyclohexane/hexane)	$C_{20}H_{26}N_2O_4$ (358.45)	Calcd: C, 67.02; H, 7.31; N, 7.82 Found: C, 66.77; H, 7.62; N, 7.64
3d	35%	*iso*-propyl	204-206 (ethyl acetate/hexane)	$C_{18}H_{22}N_2O_4$ (330.40)	Calcd: C, 65.44; H, 6.71; N, 8.48 Found: C, 65.08; H, 6.76; N, 8.26
3e	55%	pyrrolidyl	174-176 (chloroform/hexane)	$C_{16}H_{16}N_2O_4$ (300.33)	Calcd: C, 63.98; H, 5.38; N, 9.32 Found: C, 63.67; H, 5.58; N, 9.02
3f	60%	piperidyl	177-178 (chloroform/hexane)	$C_{17}H_{18}N_2O_4$ (314.35)	Calcd: C, 64.96; H, 5.77; N, 8.91 Found: C, 64.89; H, 5.59; N, 8.62
3g	80%	morpholidyl	190-191 (ethyl acetate/hexane)	$C_{16}H_{16}N_2O_5$ (316.33)	Calcd: C, 60.75; H, 5.10; N, 8.86 Found: C, 60.80; H, 5.10; N, 8.88

Table II

Physical Data for the Amines **4**

Compound	Yield	R	M.p. (solvent)	Formula	Analyses
4a	50%	ethyl	103-104 (ethyl acetate/hexane) (a)	$C_{14}H_{20}N_2O$ (232.33)	Calcd: C, 72.38; H, 8.68; N, 12.06 Found: C, 72.46; H, 8.73; N, 11.91
4b	51%	*n*-propyl	96-97 (ethyl acetate/hexane)	$C_{16}H_{24}N_2O$ (260.39)	Calcd: C, 73.80; H, 9.29; N, 10.76 Found: C, 73.81; H, 9.27; N, 10.75
4c	35%	*n*-butyl	74-75 (ethyl acetate/hexane)	$C_{18}H_{28}N_2O$ (288.44)	Calcd: C, 74.95; H, 9.78; N, 9.71 Found: C, 74.88; H, 9.86; N, 9.66
4d	47%	*iso*-propyl	263 dec. (methanol/ether) (b)	$C_{16}H_{25}N_2ClO$ (296.86)	Calcd: C, 64.74; H, 8.49; N, 9.44 Found: C, 64.56; H, 8.48; N, 9.29
4e	50%	pyrrolidyl	193-195 (ethyl acetate/hexane)	$C_{14}H_{18}N_2O$ (230.31)	Calcd: C, 73.01; H, 7.88; N, 12.17 Found: C, 72.98; H, 7.92; N, 12.05
4f	42%	piperidyl	180-181 (ethyl acetate/hexane) (c)	$C_{15}H_{20}N_2O$ (244.35)	Calcd: C, 73.73; H, 8.25; N, 11.47 Found: C, 73.67; H, 8.56; N, 11.38
4g	46%	morpholidyl	177-178 (ethyl acetate/hexane)	$C_{14}H_{18}N_2O_2$ (246.31)	Calcd: C, 68.27; H, 7.36; N, 11.38 Found: C, 68.36; H, 7.44; N, 11.30

(a) Rf erence 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 C_5H, C_6H and C_7H 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 III

Proton Magnetic Resonance Parameters for the Amides **3**

Compound	Solvent	Chemical Shift, ppm δ
3a	Deuteriochloroform	7.53 (br s, 1H, N_1H), 7.10 (s, 1H, C_2H), 7.05 (m, 3H, C_5H, C_6H, C_7H), 3.36 (m, 4H, J = 8 Hz, ethyl CH_2), 2.45 (s, 3H, acetate CH_3), 1.20 (t, 3H, J = 8 Hz, ethyl CH_3), 1.06 (t, 3H, J = 8 Hz, ethyl CH_3)
3b	Deuteriochloroform	2.44 (br s, 1H, N_1H), 6.90 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.30 (m, 4H, propyl CH_2), 2.44 (s, 3H, acetate CH_3), 1.62 (m, 4H, propyl CH_2), 0.86 (m, 6H, propyl CH_3)
3c	Deuteriochloroform	7.51 (br s, 1H, N_1H), 6.97 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.30 (m, 4H, butyl CH_2), 2.45 (s, 3H, acetate CH_3), 1.54 (m, 8H, butyl CH_2), 0.97 (m, 6H, butyl CH_3)
3d	Deuteriochloroform plus dimethylsulfoxide-d_6, 1:1	7.86 (br s, 1H, N_1H), 7.20 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.67 (m, 2H, isopropyl CH), 2.42 (s, 3H, acetate CH_3), 1.56 (d, 6H, isopropyl CH_3), 1.18 (d, 6H, isopropyl CH_3)
3e	Deuteriochloroform	8.05 (br s, 1H, N_1H), 7.11 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.50 (m, 4H, pyrrolidyl α-CH_2), 2.42 (s, 3H, acetate CH_3), 1.88 (m, 4H, pyrrolidyl β-CH_2)
3f	Deuteriochloroform plus dimethylsulfoxide-d_6, 10:1	7.91 (br s, 1H, N_1H), 7.20 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.46 (m, 4H, piperidyl CH_2), 2.46 (s, 3H, acetate CH_3), 1.67 (br s, 6H, piperidyl CH_2)
3g	Deuteriochloroform	7.98 (br s, 1H, N_1H), 7.20 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.58 (m, 4H, morpholidyl O-CH_2), 2.86 (br s, 4H, morpholidyl N-CH_2), 2.41 (s, 3H, acetate CH_3)

Table IV

Proton Magnetic Resonance Parameters for the Amines **4**

Compound	Solvent	Chemical Shift, ppm δ
4a	Deuteriochloroform	8.05 (br s, 1H, N_1H, exchange with deuterium oxide), 6.81 (m, 2H, C_6H, C_7H), 6.77 (s, sharpening on addition of deuterium oxide, C_2H), 6.52 (dd, 1H, C_5H, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz), 2.80 (m, 4H, α-CH_2, β-CH_2), 2.56 (dd, 4H, J = 7 Hz, ethyl CH_2), 0.97 (t, 6H, J = 7 Hz, ethyl CH_3)
4b	Deuteriochloroform	7.92 (br s, 1H, N_1H, exchange with deuterium oxide), 7.05 (t, 1H, C_6H, $J_{5,6}$ = $J_{6,7}$ = 8 Hz), 6.85 (dd, 1H, C_7H, $J_{5,7}$ = 2 Hz, $J_{6,7}$ = 8 Hz), 6.83 (s, 1H, C_2H, sharpening on addition of deuterium oxide), 6.53 (dd, 1H, C_5H, $J_{5,6}$ = 8 Hz, $J_{5,7}$ = 2 Hz), 2.86 (m, 4H, α-CH_2, β-CH_2), 2.52 (m, 4H, propyl CH_2), 1.53 (m, 4H, propyl CH_2), 0.83 (t, 6H, propyl CH_3, J = 6 Hz)
4c	Deuteriochloroform	7.97 (br s, 1H, N_1H, exchange with deuterium oxide), 6.93 (m, 2H, C_6H, C_7H), 6.73 (s, 1H, C_2H, sharpening on addition of deuterium oxide), 6.52 (dd, 1H, C_5H, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 2 Hz), 2.83 (m, 4H, α-CH_2, β-CH_2), 2.46 (m, 4H, butyl CH_2), 1.30 (m, 8H, butyl CH_2), 0.77 (m, 6H, butyl CH_3)
4d	Deuterium oxide plus dimethylsulfoxide-d_6, 1:1	7.00 (m, 4H, C_2H, C_5H, C_6H, C_7H), 3.55 (m, 2H, isopropyl CH, J = 7 Hz), 3.16 (br s, 4H, α-CH_2, β-CH_2), 1.15 (d, 12H, isopropyl CH_3, J = 7 Hz)
4e	Deuteriochloroform plus acetone-d_6, 1:1	6.95 (m, 3H, C_2H, C_6H, C_7H), 6.53 (dd, 1H, C_5H, J = 7 Hz), 2.98 (br s, 4H, α-CH_2, β-CH_2), 2.60 (m, 4H, pyrrolidyl CH_2), 1.97 (m, 4H, pyrrolidyl CH_2)
4f	Deuteriochloroform	7.92 (br s, 1H, N_1H, exchange with deuterium oxide), 7.03 (t, 1H, C_6H, $J_{5,6}$ = $J_{6,7}$ = 7 Hz), 6.83 (dd, 1H, C_7H, $J_{5,7}$ = 2 Hz, $J_{5,6}$ = 7 Hz), 6.81 (br s, sharpening on addition of deuterium oxide, 1H, C_2H), 6.55 (dd, 1H, C_5H, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 2 Hz), 2.92 (m, 2H, β-CH_2), 2.60 (m, 2H, α-CH_2), 2.53 (m, 4H, piperidyl CH_2)
4g	Deuteriochloroform	7.97 (br s, 1H, N_1H, exchange with deuterium oxide), 6.96 (m, 2H, C_6H, C_7H), 6.85 (s, 1H, C_2H, sharpening on addition of deuterium oxide), 6.62 (dd, 1H, C_5H, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 2 Hz), 3.88 (m, 4H, morpholidyl CH_2), 3.05 (m, 2H, β-CH_2), 2.73 (m, 4H, α-CH_2 and morpholidyl CH_2)

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 thinlayer chromatography on 250 μ layers of silica gel GF on glass plates.

4-Hydroxyindole (**2a**).

Under a nitrogen atmosphere 10 g. (74 mmoles) of 6,7-dihydroindol-4(5*H*)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° 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%), m.p. 96-97° (Literature (18) m.p. 97°).

4-Acetoxyindole (**2b**).

Compound **2a** (7.6 g., 57 mmoles) was dissolved in 200 ml. of pyridine and 150 ml. of acetic anhydride 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%), m.p. 98-100° (Literature (18) m.p. 99°); nmr (deuteriochloroform): ppm δ 8.30 (br s, 1H, N_1H, exchange with deuterium oxide), 7.03 (m, 4H, C_2H, C_5H, C_6H, C_7H), 6.42 (m, 1H, C_3H, collapsing to d on addition of deuterium oxide), 2.41 (s, 3H, acetate CH_3).

4-(Acetoxy)-*N*,*N*-dialkyl- and -*N*,*N*-Cycloalkylindole-3-glyoxylamides (**3a-g**).

To a stirred and cooled (0°) 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 mmoles) in 4.0 ml. of ether. The reaction was stirred at 0° for 5 hours and then a solution of 40% dialkyl- (or cycloalkyl-) amine in ether was added dropwise until the *p*H 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 mmoles) 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 mmoles) 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° 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 0.1*N* hydrochloric acid was added. The solution was concentrated to dryness in a stream of nitrogen. All traces of moisture were removed by evacuation 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.

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