Psilocin Analogs. III. Synthesis of 5-Methoxy- and 5-Hydroxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles

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A number of tetrahydro-β-carbolines were prepared with oxygen substituents at C-5. This class of compounds represents a hybrid between two naturally occurring groups of hallucinogenic molecules, the 4-hydroxytryptamines and the 6- and 7-oxygenated β-carbolines.

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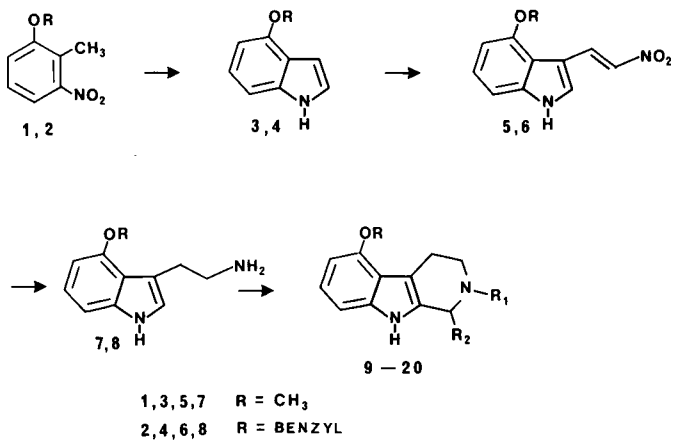
The hallucinogenic character of certain 4-oxygenated indoles (*e.g.*, psilocin and its *N,N*-diethyl counterpart, CZ-74) has been well established (1-4). That other hydroxytryptamines possess this property has only recently been appreciated (5). Isomeric 5-oxygenated compounds such as 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) and the *N,N*-diisopropyl homolog are also active hallucinogens in humans (6,7). However, the state of mind induced by these two classes of compounds is qualitatively different (1,7). The prototypes for these substances occur in nature. Psilocin, its dihydrogen phosphate ester (psilocybin), and various *N*-demethylated analogs have been discovered in certain fungal genera of the Strophariaceae (8,9). Preparations of various vascular plants containing 5-MeO-DMT have long been used by South American Indians for social, medicinal and religious purposes (10,11). Some of these latter plants, *e.g.*, species of *Banisteriopsis* Morton and *Virola* Warburg, have also been shown to contain cyclized tryptamine derivatives, *i.e.*, 6- and 7-methoxy-β-carboline alkaloids (12-15). Of the many species of these genera chemically studied, only the Asian *Banisteriopsis argentea* Spring ex Juss has been reported (16) to contain the isomeric β-carboline, 5-methoxytetrahydroharman **15** (17). Only a few only 5-oxygenated β-carbolines are known to occur in nature. These include the reserpine analog venenatine from *Alstonia venenata* R.Br (18) and the heteroyohimbine alkaloid mitragynine from *Mitragyna speciosa* Korth (19). The latter species has been implicated as an opium substitute in Southeast Asia (20). In commentting on the pharmacology of mitragynine, Hoffer and Osmond stated "....it would not be suprising if this alkaloid resembled psilocybin it its psychological activity..." (21). Brimblecombe and Pinder (21a) have expressed a similar opinion, "...in view of its structural relationship to yohimbine, the harmala alkaloids, and the 4-methoxytryptamines, it is likely that mitragynine is hallucinogenic."

The role of β-carbolines in the production of hallucinogenic states has been studied (22). Naranjo (23) has reported that such effects are elicited by several substances such as 6-methoxytetrahydroharman, its positional isomer tetrahydroharmine, and the aromatized derivative, harmine. Certain β-carbolines have also been implicated as inhibitors of monoamine oxidase (24), cholinesterase (25), and as potential endogenous benzodiazepine ligands (26). Interactions with adrenergic (27) and serotonergic (28,29) sites have been reported. In view of the above, one might envisage interesting biodynamic activities in 5-oxygenated tetrahydroharmans, *i.e.*, cyclized psilocin derivatives.

SCHEME I



The required starting indoles were obtained by the method of Leimgruber and Batcho (30). Condensation of a 2-nitro-6-alkoxytoluene with *N,N*-dimethylformamide dimethylacetal followed by reductive cyclization of the intermediate eneamine with Raney nickel-hydrazine (31) afforded compounds **3** and **4**. A special advantage of this reagent combination is the retention of the benzyl ether (31a) in compound **4**. Alternatively, 4-methoxyindole **3** was prepared by alkylation of 4-hydroxyindole (32) with methyl iodide. The tryptamines **7** and **8** were synthesized by reaction of the indoles with 1-dimethylamino-2-nitroethylene (33,44) and reduction of the intermediate nitrovinyindoles **5** and **6** with lithium aluminum hydride. The products were stable in contrast to the previously reported (34) parent, 4-hydroxytryptamine. The β-carbolines **9**, **11**, **13**

Table I

Physical Data for the β-Carbolines

Compound	Substituents	Yield	Mp			Analyses		
9	R = Bzl	34%	220-222° dec	$C_{18}H_{18}N_2O$•	Calcd:	C 75.22	H 6.66	N 9.72
	$R_1 = R_2 = H$		(THF/hexane)	0.5 H_2O	Found:	C 75.22	H 6.68	N 9.75
				(287.39)				
10	R = Bzl,	72%	192-193°	$C_{19}H_{20}N_2O$	Calcd:	C 78.04	H 6.91	N 9.58
	$R_1 = CH_3$		(EtOAc/hexane)	(292.41)	Found:	C 77.98	H 6.93	N 9.57
	$R_2 = H$							
11	R = Bzl,	68%	184-185° dec	$C_{19}H_{20}N_2O$	Calcd:	C 78.04	H 6.91	N 9.58
	$R_1 = H$,		(EtOAc/hexane)	(292.41)	Found:	C 77.81	H 6.98	N 9.51
	$R_2 = CH_3$							
12	R = Bzl	80%	148-149°	$C_{20}H_{22}N_2O$	Calcd:	C 78.38	H 7.25	N 9.14
	$R_1 = R_2 = CH_3$		(EtOAc/hexane)	(306.44)	Found:	C 78.37	H 7.28	N 9.10
13	$R = CH_3$	49%	213-214°	$C_{12}H_{14}N_2O$	Calcd:	C 71.25	H 6.99	N 13.85
	$R_1 = R_2 = H$		(EtOAc/hexane)	(202.28)	Found:	C 71.33	H 7.03	N 13.80
14	$R = R_1 = CH_3$	69%	214-215°	$C_{13}H_{16}N_2O$	Calcd:	C 72.18	H 7.47	N 12.95
	$R_2 = H$		(EtOAc/hexane)	(216.31)	Found:	C 71.85	H 7.59	N 12.92
15	$R = R_2 = CH_3$	42%	200-202°	$C_{13}H_{16}N_2O$	Calcd:	C 72.18	H 7.47	N 12.95
	$R_1 = H$		(EtOAc/hexane)	(216.31)	Found:	C 71.80	H 7.63	N 12.61
16	$R = R_1 = R_2$	37%	229-31°	$C_{14}H_{18}N_2O$	Calcd:	C 73.00	H 7.89	N 12.16
	$= CH_3$		($MeOH/H_2O$)	(230.34)	Found:	C 72.84	H 7.88	N 11.94
17	$R = R_1 = R_2$	51%	233-235° dec	$C_{11}H_{12}N_2O$•	Calcd:	C 68.21	H 7.17	N 13.26
	= H		(THF/hexane)	0.5 EtOH	Found:	C 68.38	H 7.05	N 12.76
				(211.29)				
18	$R = R_2 = H$	72%	275-277° dec	$C_{12}H_{14}N_2O$•	Calcd:	C 69.69	H 7.08	N 13.55
	$R_1 = CH_3$		(THF)	0.25 H_2O	Found:	C 69.73	H 7.11	N 13.55
				(206.79)				
19	$R = R_1 = H$	76%	134-135°	$C_{12}H_{14}N_2O$•	Calcd:	C 68.21	H 7.17	N 13.26
	$R_2 = CH_3$		(THF/hexane)	0.5 H_2O	Found:	C 68.29	H 7.25	N 12.47
				(211.29)				
20	R = H	86%	156-158° dec	$C_{13}H_{16}N_2O$•	Calcd:	C 69.29	H 7.62	N 12.44
	$R_1 = R_2 = CH_3$		(EtOAc/hexane)	0.5 H_2O	Found:	C 69.23	H 7.84	N 11.29
				(225.32)				

and **15** were obtained by Pictet-Spengler reaction (35) of the tryptamines with glyoxylic or pyruvic acids. The *N*-methyl-β-carbolines were conveniently prepared by alkylation of the secondary amines with lithium aluminum hydride and ethyl formate (36-38, 38a). Compounds **9-12** were catalytically debenzylated to afford the 5-hydroxy-β-carbolines **17-20**.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded with a Varian EM-360 spectrometer and are reported in ppm δ downfield from an internal standard of tetramethylsilane. Mass spectra were obtained with a Varian CH 7 spectrometer with an ionization potential of 70 ev at 140°. Ultraviolet spectra were run on a Hewlett-Packard 8450A spectrometer in ethanol. Elemental analyses were performed by Atlantic Micro Laboratories, Atlanta, Georgia, and by the Analytical Laboratories of Syntex Corporation, Palo Alto, California. Reactions were monitored by thin-layer chromatography on 250 μ layers of silica gel GF on glass plates. Melting points are uncorrected.

4-Methoxyindole (**3**).

A). A mixture of 2 g (15 mmoles) of 4-hydroxyindole (32), 2.2 g (16 mmoles) anhydrous potassium carbonate and 1.0 ml (16 mmoles) of methyl iodide in 150 ml of methyl ethyl ketone and 25 ml of methanol was stirred and refluxed for 2 hours. Another 1.0 ml (16 mmoles) of methyl iodide was added and after a total reaction time of 6.0 hours the mixture was cooled to room temperature, filtered, and the filtrate concentrated under reduced pressure. The residue was partitioned between 200 ml of ether and 50 ml of water. The organic layer was dried (magnesium sulfate), filtered and the solvent removed *in vacuo* to leave a light green crystalline residue, 2.1 g (95%), mp 67° (lit (39) mp 69.5°).

B) Compound **3** was also obtained in 70% yield from 2 nitro-6-methoxytoluene as described below for the benzyloxy case.

4-Benzyloxyindole (**4**).

To a stirred solution of 5.0 g (20.6 mmoles) 2-nitro-6-benzyloxytoluene (40) in 35 ml of *N,N*-dimethylformamide was added 3.0 ml (22.7 mmoles) of dimethylformamide dimethylacetal and 2.0 ml (24 mmoles) of pyrrolidine. The reaction mixture was stirred under a nitrogen atmosphere at 125° for 3.0 hours. The solvent was distilled under reduced pressure at 70° and the dark red, oily residue dissolved in 25 ml of tetrahydrofuran and 25 ml of methanol. Raney-nickel (5 g, ROC/RIC Chemical Corp.) was added and the mixture stirred under a nitrogen blanket at 50-60° and four 1.0 ml aliquots of 85% hydrazine hydrate added at 30 minute intervals. After 2.5 hours total reaction time the mixture was cooled to room temperature and filtered (Celite). The filtrate was concentrated and the dark residue chromatographed over a column of silica gel G using 30% ether in hexane as eluant. Product fractions were combined and concentrated to leave a white crystalline solid, mp 70° (lit (40) mp 72-74°) (68% yield).

E-3-(2-Nitrovinyl)-4-methoxyindole (**5**).

To a mixture of 2.3 g (15.65 mmoles) of 4-methoxyindole and 1.8 g (15.65 mmoles) of 1-dimethylamino-2-nitroethylene (44) was added 40 ml

of anhydrous trifluoroacetic acid. The reaction was stirred at room temperature under a nitrogen atmosphere for 30 minutes. The reaction mixture was poured into excess saturated aqueous sodium bicarbonate and the mixture extracted with two portions of 300 ml of ethyl acetate. The yellow organic phase was dried (magnesium sulfate), filtered and concentrated. The residue was recrystallized from ethyl acetate/hexane to give 1.9 g (56%) red crystals, mp 189-190° dec; nmr (10% dimethylsulfoxide d-6 in deuteriochloroform): ppm δ 8.60 (d, 1H, α-olefin, $J_{\alpha,\beta}$ = 14 Hz), 8.00 (d, 1H, β-olefin, $J_{\beta,\alpha}$ = 14 Hz). 7.76 (br s, 1H, N_1H), 7.16 (M, 3H, C_2H, C_6H, C_7H), 6.69 (dd, 1H, C_5H, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 2 Hz), 4.00 (s, 3H, OCH_3).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$(218.23): C, 60.54; H, 4.63; N, 12.84. Found: C, 60.38; H, 4.68; N, 12.73.

E-3-(2-Nitrovinyl)-4-benzyloxyindole (**6**).

Compound **6** was prepared as described for the methoxy case in 76% yield, mp 158-159° dec; nmr (deuteriochloroform): ppm δ 8.70 (d, 1H, α-olefin, $J_{\alpha,\beta}$ = 14 Hz), 7.88 (d, 1H, β-olefin, $J_{\beta,\alpha}$ = 14 Hz), 7.65 (br, s, 1H, N_1H), 7.33 (m, 9H, C_2H, C_6H, C_7H, benzyl ϕH), 6.76 (dd, 1H, C_5H), $J_{5,6}$ = 6 Hz, $J_{5,7}$ = 2 Hz), 5.29 (s, 2H, benzyl CH_2).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$ (294.33): C, 69.37; H, 4.80; N, 9.52. Found: C, 69.15, H, 4.87; N, 9.39.

4-Methoxytryptamine Hydrochloride (**7**).

To a stirred suspension of 500 mg (13.16 mmoles) of lithium aluminum hydride in 25 ml of tetrahydrofuran under a nitrogen atmosphere was added dropwise a solution of 1.45 g (6.65 mmoles) of compound **5** in 30 ml of tetrahydrofuran. After the addition the reaction was refluxed for 15 minutes, cooled to room temperature, and water added dropwise to decompose the complex and excess reagent. The mixture was filtered, the filtrate acidified with saturated hydrogen chloride in ether and the solvent distilled under reduced pressure. The residue was recrystallized from ethanol/ether to give 920 mg (65%), mp 216° (lit (41) mp 217-218°).

4-Benzyloxytyptamine Hydrochloride (**8**).

Reduction of compound **6** with lithium aluminum hydride as described above afforded compound **8** in 74% yield, mp 247-248° (dec)(ethanol/-ether).

Anal. Calcd. for $C_{17}H_{19}ClN_2O$ (302.84): C, 67.42; H, 6.34; N, 9.25. Found: C, 67.27; H, 6.38; N, 9.20.

5-Methoxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**13**).

A solution of 480 mg (2.13 mmoles) of 4-methoxytryptamine hydrochloride and 160 mg (2.13 mmoles) of glyoxylic acid in 50 ml of water was stirred and refluxed for 1.0 hour, cooled to room temperature, basefied with 20% sodium hydroxide and extracted with 250 ml of ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated. The residue was recrystallized to give 210 mg of **13** (See Table I for data).

N^2-Methyl-5-methoxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**14**).

To a stirred and refluxing mixture of 150 mg (0.74 mmoles) of compound **13** and 421 mg (11.0 mmoles) of lithium aluminum hydride in 50 ml of tetrahydrofuran was added dropwise a solution of 1.2 ml (15 moles) of ethyl formate in 20 ml of tetrahydrofuran. The reaction was cooled to room temperature, water added cautiously, and the mixture filtered. The filtrate was concentrated under reduced pressure and the residue recrystallized, 110 mg; uv: λ max (log ϵ) 292 (3.50), 277 (3.51), 270 (3.58), 224 (4.24); ms: m/e (relative intensity) 216 (47%) (M^+), 215 (14), 199 (11), 173 (100), 172 (44), 158 (32), 144 (40), 143 (19), 130 (11), 115 (8), 77 (6), 42 (14).

dl-1-Methyl-5-methoxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-β]indole (**15**).

A solution of 346 mg (1.53 mmoles) of 4-methoxytryptamine hydrochloride and 135 mg (1.53 mmoles) of pyruvic acid in 40 ml of water was stirred and refluxed for 1.0 hour. The reaction mixture was cooled to room temperature, basefied with 20% sodium hydroxide, and extracted with 250 ml of ethyl acetate. The organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The solid residue was recrystallized, 140 mg; uv: λ max (log ϵ) 292 (3.53), 280 (3.52), 271 (3.59), 226 (4.25); ms: m/e (relative intensity) 216 (44%), 215 (14), 201 (100), 187 (28), 185 (20), 172 (18), 156 (4), 143 (6), 130 (7), 115 (5), 101 (6), 77 (6), 43 (13).

dl-1,N^2-Dimethyl-5-methoxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**16**).

This material was prepared from compound **15** using lithium aluminum hydride and ethyl formate as described for compound **14**. uv: λ max (log ϵ) 292 (3.42), 277 (3.43), 270 (3.48), 224 (4.17); ms: m/e (relative intensity) 230 (26) (M^+), 216 (18), 215 (100), 199 (24), 187 (30), 172 (21), 158 (7), 143 (5), 130 (6), 115 (11), 91 (7), 77 (6), 56 (9), 42 (24).

Compounds **9-12** were prepared as described for compounds **13-16**, respectively.

5-Hydroxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles (**17-20**).

General Procedure.

A mixture of 0.35 mmoles of benzyl ethers (**9-12**) and 30 mg of 10% palladium on carbon in 30-50 ml of ethanol was shaken under 15 psi of hydrogen pressure for 1.0 hour at room temperature. The catalyst was removed by filtration (Celite) and the filtrate concentrated under reduced pressure. The residues were recrystallized from the appropriate solvent.

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