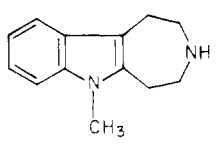
Synthesis of Some 5-Phenylhexahydroazepino[4,5-*b*]indoles as Potential Neuroleptic Agents

Arthur J. Elliott,* Elijah H. Gold, and Henry Guzik

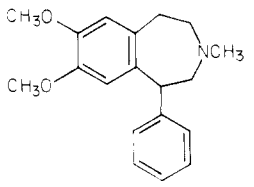
Chemical Research Department—Medicinals, Schering-Plough Pharmaceutical Research Division, Bloomfield, New Jersey 07003. *Received April 14, 1980*

5-Phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**3a**) and five derivatives have been prepared and screened for neuroleptic activity. None of the compounds antagonized methamphetamine aggregate toxicity in mice. A number of compounds, including **3a** and its 3-methyl derivative **3d**, showed activity in the antidepressant screens.

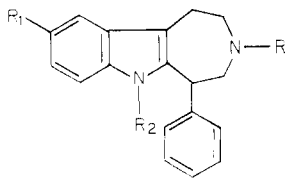
The synthesis and biological activity of a series of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles have been reported.[1] Of these, 6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (1) antagonized the aggressiveness of



1



2



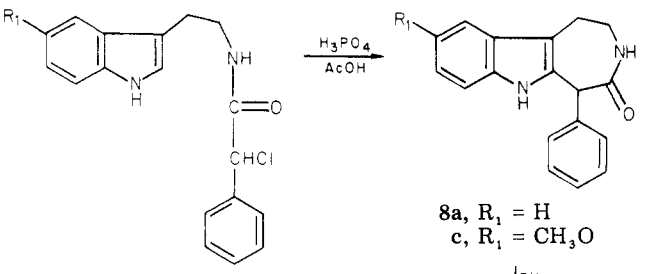
3a, R_1 = H; R_2 = H; R_3 = H
b, R_1 = H; R_2 = CH_3; R_3 = H
c, R_1 = CH_3O; R_2 = H; R_3 = H
d, R_1 = H; R_2 = H; R_3 = CH_3
e, R_1 = H; R_2 = CH_3; R_3 = CH_3
f, R_1 = CH_3O; R_2 = H; R_3 = CH_3

fighting mice, was active in blocking conditioned avoidance, was hypothermic, anorexigenic, and displayed tryptamine-like activity in mice. However, in chronic schizophrenics, 1 did not show neuroleptic activity.[2]

The clinical efficacy of Sch 12679 (**2**) in the management of aggressive mental retardates[3] prompted the synthesis of a number of 5-phenyl-1,2,3,4,5,6-hexahydroazepino-[4,5-*b*]indoles (**3a–f**) for pharmacological evaluation. We hoped that incorporation of a phenethylamine pharmacophore would impart clinically useful neuroleptic activity.

Chemistry. A literature search uncovered two syntheses of **3a** but no biological data was reported. The first method[4] involved the cyclization of the adduct (**6a**) of tryptamine and styrene oxide using PPA. We chose to use the benzyl derivative of tryptamine (**4a**) and to debenzylate before cyclization. This eliminated mixtures containing bisadducts. We could not, however, improve over the reported cyclization yield (22%). The second method[5] involved reaction of tryptamine with phenylchloroacetyl chloride, followed by cyclization and reduction of the amide carbonyl (Scheme I). This method proved

Scheme I

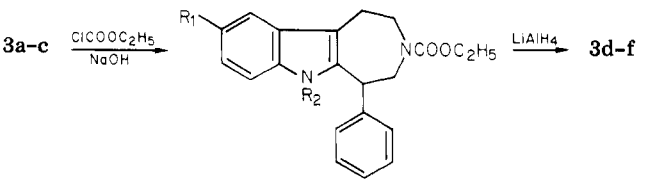


7a, R_1 = H
c, R_1 = CH_3O

8a, R_1 = H
c, R_1 = CH_3O

3a,c

Scheme II



9a, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = CH_3O; R_2 = H

quite efficient for larger scale preparations.

Methylation of the azepino nitrogen was accomplished by reaction with ethyl chloroformate, followed by $LiAlH_4$ reduction (Scheme II) Attempts at a one-step methylation using HCHO–HCOOH gave extensive decomposition. The new compounds derived from 1-methyltryptamine and 5-methoxytryptamine were prepared by analogous procedures.

Pharmacology. The compounds were tested for neuroleptic activity using antagonism of methamphetamine aggregate toxicity (MAT) in mice. In addition, the compounds were screened in mice for other CNS activity as follows: antagonism of acetic acid induced writhing (analgesia), pentylenetetrazole-induced convulsions (anticonvulsant), and tetrabenzazine (TBZ) induced ptosis (antidepressant). The compounds were also tested in rats for inhibition of muricidal activity (antidepresant).

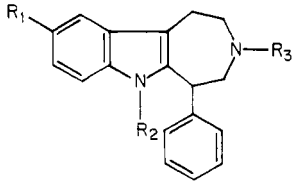
Discussion

None of the compounds was active in the MAT, writhing, or pentylenetetrazole tests (ED_{50} > 30 mg/kg). The lack of activity in MAT at this high dose makes it unlikely that any of the compounds tested have significant neuroleptic activity. All presently useful neuroleptic agents would have shown complete protection at the screening dose. For example, chloropromazine has an ED_{50} of 0.3 mg/kg. Interestingly, several of the compounds blocked TBZ-induced ptosis in mice or muricidal behavior in rats (but not both), indicating the potential for antidepressant activity (Table I). Methylation of the indole nitrogen removed all activity.

(1) Hester, J. B.; Tang, A. H.; Keasling, H. H.; Veldkamp, W. *J. Med. Chem.* **1968**, *11*, 101.
(2) Gallant, D. M.; Bishop, M. P.; Bishop, G.; O'Meallie, L. *Curr. Ther. Res.* **1967**, *9*, 579.
(3) Albert, J. M.; Elie, R.; Cooper, S. F.; Clermont, A.; Langlois, Y. *Curr. Ther. Res.* **1977**, *21*, 786.
(4) McLean, S.; Dmitrienko, G. I.; Szakolcai, A. *Can. J. Chem.* **1976**, *54*, 1262.
(5) Freter, K. *Liebigs Ann. Chem.* **1969**, *721*, 101.

0022-2623/80/1823-1268$01.00/0

Table I



compd	R_1	R_2	R_3	TBZ[a,e]	muricide[b,e]
3a	H	H	H	>30	2.1 (1.9-2.2)
3b	H	CH_3	H	>30	>10
3c	CH_3O	H	H	>30	12.2 (9.8-15.6)
3d	H	H	CH_3	1.0 (0.85-1.24)	>10
3e	H	CH_3	CH_3	>30[c]	>10[c]
3f	CH_3O	H	CH_3	1.9 (1.7-2.1)[d]	>10[d]
imipramine				2.0 (1.8-2.2)	20.2 (18.8-23.8)

[a] ED_{50}, mg/kg po (mouse), to reverse tetrabenazine ptosis. [b] ED_{50}, mg/kg ip (rat), to block muricidal behavior. [c] Tested as the HCl salt. [d] Tested as the maleate salt. [e] 95% confidence limits.

In an acute behavioral and toxicity study, rats were treated with **3a** at doses from 10 to 300 mg/kg, po. Increased pupil size and tremors were noted at 30 mg/kg, while salivation and cyanosis occurred at 100 mg/kg. The compound was lethal at 300 mg/kg. Compound **3d** was much less toxic acutely, showing only a decrease in motor activity and slight ptosis at 300 mg/kg.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian CFT-20 spectrometer, and mass spectra were determined with a Varian MAT CH5. Microanalyses were performed by the Physical Analytical Services Department of the Schering-Plough Corp.

5-Phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (3a). This compound was prepared by both literature methods,[4,5] but the amide procedure[5] was preferred.

***N*-Benzyl-1-methyltryptamine (4b).** Benzaldehyde (18.0 g, 0.17 mol) was added to a stirred mixture of 1-methyltryptamine (27.0 g, 0.155 mol) and MeOH (200 mL). After 0.5 h, $NaBH_4$ (3.0 g, 0.079 mol) was added portionwise. The mixture was diluted with H_2O (500 mL) and extracted with EtOAc (500 mL), and the extract was dried (Na_2SO_4) and evaporateed in vacuo. The residual oil was distilled in vacuo (Kugelrohr) to give **4b** as a pale yellow oil (82%). The HCl salt crystallized from MeOH–EtOAc as colorless needles: mp 199–202 °C; MS, M^+ 264 (1%). Anal. ($C_{18}H_{20}N_2$·HCl) C, H, N.

***N*-(2-Hydroxy-2-phenylethyl)-1-methyltryptamine (6b).** Styrene oxide (17.0 g, 0.142 mol) and **4b** (33.0 g, 0.125 mol) were stirred together and heated at 150 °C for 14 h and then allowed to cool. The mixture was dissolved in Et_2O (2 L) and the HCl salt of **5b** was precipitated by the addition of 2.2 M ethereal HCl. The solid was filtered, washed with Et_2O, and dried. Without characterization, **5b** (49.1 g) was dissolved in EtOH (1.5 L) and hydrogenated at 50 psi using 10% Pd/C (7.5 g) for 20 h. The catalyst was filtered and the solvent was evaporated in vacuo. Crystallization from MeOH–EtOAc gave **6b** (37%) as a white powder, mp 154–155 °C. Anal. ($C_{19}H_{22}N_2O$·HCl) C, H, N.

6-Methyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (3b). Compound **6b** (14.0 g, 0.048 mol) was added to a mixture of $CHCl_3$ (500 mL) and PPA (200 mL) and stirred under reflux. After 1.5 h, the mixture was cooled and the $CHCl_3$ was decanted. The PPA was dissolved in H_2O (1 L) and made basic with 6 M NaOH, and the product was extracted into EtOAc (2 × 500 mL). The combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo. Chromatography on silica gel (400 g, $CHCl_3$) gave **3b** (19%), which crystallized from MeCN as a pale-cream powder: mp 122 °C; MS, M^+ 276 (6%); ^1H NMR ($CDCl_3$) 1.71 (s, NH), 2.6–3.3 (m, 6 H), 3.65 (s, 3 H), 4.28 (t, J = 7 Hz, 1 H), 7.0–7.6 (m, 9 H). Anal. ($C_{19}H_{23}N_2$) C, H, N.

***N*-[2-(5-Methoxy-3-indolyl)ethyl]-2-chloro-2-phenylacetamide (7c).** Chlorophenylacetyl chloride (20.4 g, 0.11 mol) was added dropwise with stirring to a solution of 5-methoxytryptamine (39.4 g, 0.21 mol) in CH_2Cl_2 (1 L) at 25 °C. After the addition, stirring was continued for 1 h and the precipitated 5-methoxytryptamine hydrochloride was recovered by filtration. The filtrate was washed, in turn, with 2.7 M HCl (200 mL) and saturated $NaHCO_3$ (200 mL), dried ($MgSO_4$), and then evaporated in vacuo to give **7c** (92% based on recovered tryptamine) as a yellow oil.

9-Methoxy-4-oxo-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (8c). A mixture of **7c** (33.5 g, 0.098 mol), HOAc (140 mL), H_2O (105 mL), and 85% H_3PO_4 (5 mL) was boiled under reflux for 1 h and then cooled in ice. The product was filtered, washed with H_2O, and dried. Crystallization from EtOH gave **8c** (37%) as colorless prisms: mp 253–256 °C; MS, M^+ 306 (100%); ^1H NMR (Me_2SO-d_6) 2.6–3.4 (m, 4 H), 3.77 (s, 3 H), 5.06 (s, 1 H), 6.70 (dd, J = 9 and 2 Hz, 1 H), 6.8–7.4 (m, 7 H), 7.90 (br s, 1 H), 10.73 (br s, 1 H). Anal. ($C_{19}H_{18}N_2O$) C, H, N.

9-Methoxy-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (3c). A mixture of **8c** (10.5 g, 0.034 mol), THF (400 mL), and 1 M BH_3·THF (68 mL) was stirred and boiled under reflux for 4.5 h. The mixture was cooled and the excess BH_3 destroyed by the addition of 2 M NaOH. The solvent volume was reduced in vacuo and H_2O (300 mL) was added. The mixture was extracted with EtOAc (2 × 300 mL) and the combined extracts were evaporated in vacuo. The residual oil was chromatographed on silica gel (400 g, $CHCl_3$–MeOH–NH_4OH, 90:2:0.5), and the product was collected after a forerun of **8c**. Crystallization from MeCN gave **3c** (43%) as off-white prisms: mp 146–148 °C; MS, M^+ 292 (3%); ^1H NMR ($CDCl_3$) 1.84 (s, NH), 2.9–3.5 (m, 6 H), 3.82 (s, 2 H), 4.20 (br, 1 H), 6.71 (dd, J = 9 and 2 Hz, 1 H), 6.8–7.4 (m, 8 H). Anal. ($C_{19}H_{20}N_2O$) C, H, N.

3-Methyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (3d). Compound **3a** (2.62 g, 0.01 mol) in EtOAc (250 mL) was stirred as a two-phase mixture with 2 M NaOH (200 mL). Ethyl chloroformate (2.16 g, 0.02 mol) was added dropwise during 5 min, the layers were separated, and the H_2O layer was washed with EtOAc (100 mL). The combined EtOAc extracts were washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo to give **9a**, which was added, without characterization, to a slurry of $LiAlH_4$ (4 g) in Et_2O (200 mL). The mixture was stirred and boiled under reflux for 18 h, the excess $LiAlH_4$ was destroyed with 0.5 M NaOH, and the inorganics were filtered. The filtrate was dried (Na_2SO_4) and evaporated in vacuo to give **3d** (58%), which crystallized from MeCN as colorless needles: mp 141–142 °C; MS, M^+ 276 (66%); ^1H NMR ($CDCl_3$) 2.52 (s, 3 H), 2.8–3.2 (m, 6 H), 4.44 (t, J = 7 Hz, 1 H), 7.0–7.6 (m, 10 H). Anal. ($C_{19}H_{20}N_2$) C, H, N.

3,6-Dimethyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (3e). Treatment of **3b** as in the above procedure gave **3e** (43%), and the HCl salt crystallized from MeOH–EtOAc as colorless needles: mp 225–227 °C; MS, M^+ 290 (1%); ^1H NMR (Me_2SO-d_6) 2.42 (s, 3 H), 2.6–4.0 (m, 6 H), 2.83 (s, 3 H), 5.10 (br s, 1 H), 6.8–7.6 (m, 9 H). Anal. ($C_{20}H_{22}N_2$·HCl) C, H, N.

9-Methoxy-3-methyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (3f). Treatment of **3c** as outlined above gave **3f** (76%) and the maleate salt crystallized from EtOAc as colorless needles: mp 168–170 °C; MS M^+ 306 (76%); ^1H NMR (Me_2SO-d_6) 2.87 (s, 3 H), 3.0–3.7 (m, 6 H), 3.73 (s, 3 H), 4.67 (br s, 1 H), 5.98 (s, 2 H), 6.64 (dd, J = 9 and 2 Hz, 1 H), 6.9–7.5 (m, 8 H), 10.29 (br s, 1 H). Anal. ($C_{20}H_{22}N_2O$·$C_4H_4O_4$) C, H, N.

Pharmacological Methods. Compounds were administered either intraperitoneally (ip) or orally (po) to male, albino CFI mice (18–22 g), male Charles-River (CD) rats (200–300 g, behavioral and toxicity studies), or male Long-Evans rats (200–300 g, muricide) in a methylcellulose suspension. Experimental procedures have been reported earlier.[6]

Acknowledgment. We thank Dr. L. C. Iorio and his staff for the pharmacological assays.

(6) Elliott, A. J.; Eisenstein, N.; Iorio, L. C. *J. Med. Chem.* **1980**, *23*, 333.