3-Aryl- and 3-Hydroxy-3-aryloctahydropyrido[2,1-*c*][1,4]oxazines. Synthesis, Stereochemistry, and Central Nervous System Pharmacological Actions

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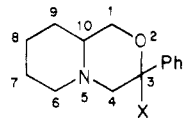
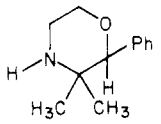
A series of substituted 3-aryl- and 3-hydroxy-3-aryloctahydropyrido[2,1-*c*][1,4]oxazines has been synthesized for purposes of investigating potentially useful CNS pharmacological actions of this novel heterocyclic system. The preferred conformation of the bicyclic system of the parent compounds, **1** and **2**, has been shown to be trans with equatorial orientation of the 3-phenyl substituent in each compound. The various substituted aryl analogues of this series are depressants of motor activity in mice, and certain analogues exhibit significant anticonvulsant and appetite suppressant activity in test animals.

We report here the results of a structure–activity relationship study of the influence of phenyl substituents on the central nervous system (CNS) actions of 3-phenyl- (**1**) and 3-hydroxy-3-phenyloctahydropyrido[2,1-*c*][1,4]-oxazines (**2**). A previous report[3] describing the CNS



1, X = H
2, X = OH



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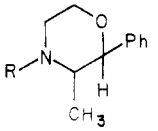
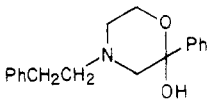


4, R = H (phenmetrazine)
5, R = CH_3 (phendimetrazine)



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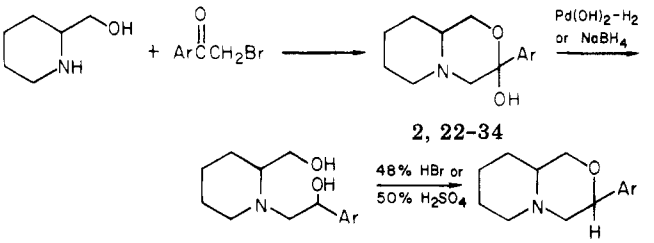
actions of **1** and **2** indicated that these compounds possess a depressant action demonstrated by a reduction of locomotor activity of mice. The potential for therapeutic utility of the central actions of the octahydro[2,1-*c*]-[1,4]oxazines is indicated by the various CNS pharmacological actions reported for related 2-arylmorpholines, such as psychomotor stimulation and anorexia (**3**–**5**)[4,5] and anticonvulsant activity (**6**).[6]

Synthesis. The desired phenyl-substituted analogues of **1** and **2** were prepared according to the pathway illustrated in Scheme I. Treatment of 2-piperidinemethanol with the appropriately substituted 2-bromoacetophenone provided quantitative yields of the hemiketal product (analogues of **2**). There was no evidence to suggest the presence of the keto alcohol tautomer. Reductive cleavage of the hemiketal provided diol intermediates which were cyclized to the appropriate analogues of **1** under acidic conditions. Optimal conditions for conversion of the hemiketals to the diols involved the use of 10% $Pd(OH)_2$ on C [10:1 (w/w) hemiketal to catalyst], 1 N H_2SO_4 as solvent, and 48 psi of H_2 for 24 h. The haloaryldiol intermediates were prepared from the appropriate hemiketal by $NaBH_4$ reduction to avoid aromatic dehalogenation which occurs under catalytic reductive conditions. Cyclization of diol intermediates was accomplished in refluxing 48% HBr for a 2-h reaction period. The methoxyaryl analogues **14**–**17** were synthesized from the appropriate diols by refluxing in 50% H_2SO_4 (20–45 min) so as to avoid O-demethylation. Other cyclization procedures, including refluxing in Ac_2O or heating in either Me_2SO or

Scheme I



2, 22–34

1, 7–21

$POCl_3$, were evaluated and found to be unsatisfactory as compared to the HBr or H_2SO_4 catalyzed procedures (see Table I).

Stereochemical Studies. The bicyclic octahydropyrido[2,1-*c*][1,4]oxazine system provides a more rigid stereochemical framework than found in the 2-arylmorpholines. Hence, an analysis of the stereochemistry of **1** and **2** may provide useful information regarding the steric aspects of the CNS actions of these compounds and their substituted phenyl analogues. The octahydropyrido[2,1-*c*][1,4]oxazine system can display interconversion of cis–trans ring fused chair conformers via inversion about the bridgehead N. However, the presence of strong Bohlmann bands (2700–2800 cm^{-1}) in the IR spectra of **1** and **2** suggests a preference for the trans-fused conformers. The presence of Bohlmann bands in the IR spectra of related bicyclic systems serves as a reliable indicator for trans stereochemistry.[7] Reports of the preferred conformations of perhydro[1,2-*c*][1,3]oxazine[8] and 3-substituted quinolizidines[9] have indicated a trans fusion for these molecules. One would expect contributions of trans fusion to the preferred conformations of **1** and **2** to be even greater than for these related systems because of the absence of nonbonded interactions between C-(10)–H_{ax} and C(2) substituents in the octahydropyrido-[2,1-*c*][1,4]oxazines. Evidence for a preferred equatorial orientation of the phenyl substituent in **1** was provided by the appearance of an ABX pattern for the C(4)-methylene protons and the C(3)–H_{ax} in the NMR spectrum, δ 2.1 and 3.1 and δ 4.65 (J = 3 and 11 Hz), respectively. A singlet (δ 7.25) for the aromatic protons of **1** is also indicative of equatorial Ph in that it is consistent with the results obtained in comparing the NMR spectra of 3(e)- and 3(a)-phenylquinolizidine.[9] Analysis of pseudocontact deshielded NMR spectra of **1** utilizing the lanthanide shift reagent $Eu(fod)_3$[10] supports the configurational assignment for this compound. The signals for the α protons of the oxazine ring, $H_{1(a)}$, $H_{3(a)}$, and $H_{4(e)}$, experienced significantly greater deshielding than the β protons as the ratio of $Eu(fod)_3$ to **1** is increased. These data are interpreted on the basis of the reasonable assumption that the lanthanide shift reagent is preferentially complexed with the basic N

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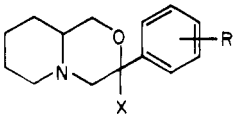
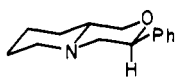
Table I. 3-Aryl- and 3-Hydroxy-3-aryloctahydropyrido[2,1-c][1,4]oxazines



Compd	X	R	Mp, °C	Recrystn solvent[a]	Formula[b]
1	H	H	212-214	Ace	$C_{14}H_{19}NO\cdot HCl$
7	H	4-F	206-208	Ace-Et_2O	$C_{14}H_{18}FNO\cdot HCl$
8	H	4-Cl	255-257	Ace	$C_{14}H_{18}ClNO\cdot HCl$
9	H	4-Br	275-277	Ace	$C_{14}H_{18}BrNO\cdot HCl$
10	H	2-CF_3	222-224	PhH-Et_2O	$C_{15}H_{18}F_3NO\cdot HCl$
11	H	3-CF_3	218-219	PhH	$C_{15}H_{18}F_3NO\cdot HCl$
12	H	4-CF_3	239-241	Ace-Et_2O	$C_{15}H_{18}F_3NO\cdot HCl$
13	H	4-CH_3	220-222	Ace-Et_2O	$C_{15}H_{21}NO\cdot HCl$
14	H	3-OCH_3	173-174	PhH	$C_{15}H_{21}NO_2\cdot HCl$
15	H	4-OCH_3	191-193	PhH	$C_{15}H_{21}NO_2\cdot HCl$
16	H	3,4-$(OCH_3)_2$	209-210	PhH-Et_2O	$C_{16}H_{23}NO_3\cdot HCl$
17	H	3,4,5-$(OCH_3)_3$	257-259	Ace	$C_{17}H_{25}NO_4\cdot HCl$
18	H	3-OH	199-200	EtOH-Et_2O	$C_{18}H_{19}NO_2\cdot HBr$
19	H	4-OH	243-244	EtOH-Et_2O	$C_{18}H_{19}NO_2\cdot HBr$
20	H	3-OAc	181-183	Ace-Et_2O	$C_{16}H_{21}NO_3\cdot HCl$
21	H	4-NHAc	264-265	Ace	$C_{16}H_{22}N_2O_2\cdot HCl$
2	OH	H	166-167	Ace-Et_2O	$C_{14}H_{19}NO_2\cdot HCl$
22	OH	4-F	155-157	Ace-Et_2O	$C_{14}H_{18}FNO_2\cdot HCl$
23	OH	4-Cl	168-170	Ace	$C_{14}H_{18}ClNO_2\cdot HCl$
24	OH	4-Br	177-179	Ace	$C_{14}H_{18}BrNO_2\cdot HCl$
25	OH	2-CF_3	163-164	EtOAc-Et_2O	$C_{15}H_{18}F_3NO_2\cdot HCl$
26	OH	3-CF_3	172-174	Ace-Et_2O	$C_{15}H_{18}F_3NO_2\cdot HCl$
27	OH	4-CF_3	198-199	Ace-Et_2O	$C_{15}H_{18}F_3NO_2\cdot HCl$
28	OH	4-CH_3	160-161	Ace	$C_{15}H_{21}NO_2\cdot HCl$
29	OH	3-OCH_3	140-141	Ace	$C_{15}H_{21}NO_3\cdot HCl$
30	OH	4-OCH_3	151-153	Ace	$C_{15}H_{21}NO_3\cdot HCl$
31	OH	3,4-$(OCH_3)_2$	161-163	Ace	$C_{16}H_{23}NO_4\cdot HCl$
32	OH	3,4,5-$(OCH_3)_3$	154-155	Ace-Et_2O	$C_{17}H_{25}NO_5\cdot HCl$
33	OH	3-OAc	153-154	Ace-Et_2O	$C_{16}H_{21}NO_4\cdot HCl$
34	OH	4-NO_2	202-204	Ace	$C_{14}H_{17}N_2O_4\cdot HCl$

[a] Ace = acetone, PhH = benzene. [b] Analyzed for C, H, and N.

atom of 1.[11] Evidence for a 3(a)-hydroxy-3(e)-phenyl configuration for 2 was obtained from an examination of



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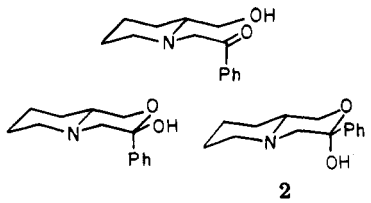
the IR and NMR spectra of this compound. A significant amount of intramolecular H-bonded species was noted in the IR spectrum (dilution studies) of 2. Only the trans conformer of 2 having C(3)–OH_{ax} is capable of forming intramolecular H bonds. The appearance of the signal for $H_{1(a)}$ downfield relative to that for $H_{1(e)}$ in the NMR spectrum of 2 can be explained in terms of deshielding of the former proton by the C(3)–OH_{ax}. Pseudocontact deshielded NMR spectra of 2 utilizing Eu(fod)$_3$ indicated greater deshielding of the α protons of the oxazine ring of this compound, providing further evidence for the axial orientation of the C(3)–OH since preferential interaction of the shift reagent and 2 would be expected to occur at the OH function.[11] The possibility that a tautomeric equilibrium could contribute significantly to the structure of the hemiketal 2 was considered. Tautomeric inter-



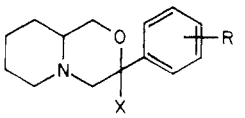
2

conversion could conceivably give rise to configurational inversion at C(3). Examination of the solid (KBr) and solution (CCl_4) IR spectra of 2 failed to reveal any carbonyl absorption. The methyl ketal of 2 was prepared (2 refluxed in CH_3OH–HCl for 8 h) in order to prevent tautomeric interconversion. Comparison of the NMR spectral characteristics of 2 and its methyl ketal derivative in solvents of different polarity ($CDCl_3$ and pyridine-d_5) and at variable temperature (25–100 °C) revealed no alterations of the signal patterns for the C(4)-methylene protons (AB q) or for the C(1)-methylene protons (AB pattern). These data suggest a similar conformational and configurational structure for the methyl ketal of 2 and, further, a homogeneity for the structure of the hemiketal 2. The lack of a tautomeric interconversion in a series of 2-arylmorpholine hemiketals has also been reported for those derivatives containing a tertiary N.[6]

Similar spectral characteristics were noted for the substituted phenyl derivatives of 1 and 2, suggesting similar conformational and configurational preferences for all members of the series.

Pharmacology. Earlier studies of the CNS effect of 1 and 2 indicated that these compounds were depressants of activity in mice in the 10–40-mg/kg range.[3] Hence, the substituted aryl derivatives of 1 and 2 were also evaluated for effects on the spontaneous locomotor activity in mice as a quantitative measure of CNS effects. Selected members of each series (1 and 2) were screened for anticonvulsant activity in protecting mice from maximal electroshock or metrazole seizures. The neurotoxicity of these same compounds was also evaluated with a rotorod performance test. The effects of 1, 2, 8, 11, 23, and 26 on food consumption in rats were also evaluated in order to determine if these analogues possessed anorexic activity. These particular derivatives of 1 and 2 were chosen on the basis of their structural relationships with phendime-

Table II. Effects of 3-Aryl- and 3-Hydroxy-3-aryloctahydropyrido[2,1-c][1,4]oxazines on Spontaneous Locomotor Activity in Mice



X = H			X = OH		
Compd	R	Redn of act. at 40 mg/kg ip[a]	Compd	R	Redn in act. at 40 mg/kg ip[a]
1	H	+++	2	H	++
7	4-F	+++	22	4-F	++
8	4-Cl	+++	23	4-Cl	+++
9	4-Br	+++	24	4-Br	++
10	2-CF_3	+++	25	2-CF_3	++
11	3-CF_3	+++	26	3-CF_3	+++
12	4-CF_3	+++	27	4-CF_3	++
13	4-CH_3	+	28	4-CH_3	+++
14	3-OCH_3	+	29	3-OCH_3	++
15	4-OCH_3	+++	30	4-OCH_3	+
16	3,4-$(OCH_3)_2$	++	31	3,4-$(OCH_3)_2$	++
17	3,4,5-$(OCH_3)_3$	++	32	3,4,5-$(OCH_3)_3$	+
18	3-OH	−	33	3-OAc	−
19	4-OH	+++	34	4-NO_2	−
20	3-OAc	−			
21	4-NHAc	+++			
Chlorpromazine hydrochloride (5 mg/kg)		+++[b]			
Sodium phenobarbital (20 mg/kg)		c			

[a] +++, reduction in activity not significantly different from chlorpromazine hydrochloride (5 mg/kg, $p < 0.05$); ++, reduction in activity significantly different from saline (ip, $p < 0.05$); +, reduction in activity but within the standard deviation of saline; −, no reduction in activity. [b] Produced a 83.6% reduction in spontaneous locomotor activity. [c] Produced approximately 215% increase in spontaneous locomotor activity.

trazine, chlorphentermine, and fenfluramine.

Results and Discussion

The effects of the substituted phenyl analogues of 1 and 2 on spontaneous locomotor activity in mice are summarized in Table II. At the highest dose level tested (40 mg/kg), those compounds exhibiting measurable activity were found to be depressants. As might be expected, relative lipophilicity appears to play a role in determining the potency of depression of activity as evidenced by the greater activity of the analogues of 1 as compared to 2 and by the enhancement of depressant activity produced by incorporation of a lipophilic moiety (halophenyl, trifluoromethylphenyl). This generalization, however, fails to explain the strong activity depressant effects of the 4′-OH (19) and 4′-NHAc (21) analogues. It also appears that positional isomerism in the phenyl group is an important structural effect, as evidenced by the differences in activity of the 3′- and 4′-OMe (14 and 15) analogues. These differences are minimal in the same analogues of the hemiketal 2 series. A number of the compounds studied exhibited a dose-dependent, biphasic response with regard to spontaneous locomotor activity. The 4′-trifluoromethylphenyl analogue 27 produced significant stimulation of activity at 20 mg/kg and significant depression at 40 mg/kg. However, the 4′-CF_3 analogue of 1 failed to elicit a biphasic response. The 3′-hydroxyphenyl analogue 18 was a depressant of activity at the 20 mg/kg level but not at the 40 mg/kg dose. A similar profile of central activity is seen with certain hallucinogenic agents.[12]

The anticonvulsant activities of those analogues of 1 and 2 evaluated appear to be restricted to protecting test animals from major convulsions (maximal electroshock) (Table III). In many cases, these analogues were found to potentiate metrazole-induced seizures. The most active compounds of this study were the trifluoromethylphenyl derivatives. The 3′-trifluoromethylphenyl analogues (11 and 26) exhibited the most favorable ED_{50} values which were comparable to the ED_{50} of phenobarbital sodium. Perhaps more important was the finding that the protective indices (TD_{50}/ED_{50}) for 11, 26, and phenobarbital sodium, 3.11, 2.77, and 3.88,[16] respectively, are similar. The 4′-fluorophenyl analogue 7 was also of interest in that it was found to be a potent convulsant in untreated animals at doses of 100 mg/kg.

Evaluation of potential anorexic actions for certain analogues of 1 and 2 indicated that compounds 1, 8, 11, and 26 produced a significant decrease ($p < 0.05$) in food intake in rats at the dose levels tested. Only the phenyl (1) and 4′-chlorophenyl (23) hemiketal derivatives were inactive in this assay. The doses (mmol/kg) of 1, 11, and 26 required to reduce food intake by 50% were 108.4, 55.9, and 29.6, respectively, while for fenfluramine hydrochloride this dose was determined to be 16.8 mmol/kg. It is also pertinent to note that these concentrations of 11 and 26 do not produce significant depression of activity in mice, whereas the anorexic activity of fenfluramine hydrochloride is associated with a depressant effect.[13] The 4′-chlorophenyl analogue 8 was lethal in the test animals at doses of 20 and 40 mg/kg but decreased food intake by 40% at a 34.7 mmol/kg dose level.

In summary, it appears that the most promising compounds prepared in this study are the 3′-trifluoromethylphenyl analogues of 1 and 2. These compounds are effective anticonvulsants and appetite suppressants at dose levels that do not appreciably depress motor activity in mice. Future studies will be directed toward optimizing potential therapeutic actions of appropriate analogues of 1 and 2 via systematic structure–activity relationship analyses.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Spectral data were obtained for all compounds and were utilized in confirming structure. The IR spectra were determined using a Beckman

Table III. Anticonvulsant Activities of Substituted Aryl Derivatives of 1 and 2

Compd	Lowest dose demonstrating act., mg/kg ip: Antimax shock	Lowest dose demonstrating act., mg/kg ip: Antimetrazole	Antimax shock,[a] ED_{50}, mmol/kg	Rotorod toxicity,[a] TD_{50}, mmol/kg
1	100	ia[b]		
2	100	ia		
7	ia	ia		
22	100	ia		
10	30-100	300	258.9 (214.3-298.0)	715.7 (480.3-823.6)
25	30-100	ia	186.0 (166.5-203.7)	546.6 (484.1-599.3)
11	30-100	ia	84.6 (69.7-109.0)	262.6 (222.2-287.9)
26	30-100	ia	78.7 (60.4-91.2)	217.9 (192.4-236.8)
12	30-100	300	290.8 (227.0-346.0)	407.8 (288.1-490.5)
27	100	ia	202.1 (171.8-262.0)	468.0[c] (431.6-500.8)
13	ia	ia		
28	100	ia		
29	100	ia		
30	ia	ia		
31	ia	100		
32	ia	300		
Phenobarbital sodium			85.7[d] (59.0-100.3)	332.8[d] (295.8-417.0)

[a] The figures in parentheses are 95% confidence intervals. [b] ia indicates the lack of anticonvulsant activity in doses of 300 mg/kg or less. [c] This value is an LD_{50} value for 28 due to the lethality produced by this compound. [d] See ref 15.

IR-33, except for dilution studies which were performed using a Perkin-Elmer Model 257 spectrometer using matched sodium chloride cells of widths 1.091 mm for 0.2 M solutions and 25 mm for 0.002 M solutions. The NMR spectra were taken using a Jeolco C-60HL spectrometer. Mass spectra were obtained using a Du Pont 21-492 mass spectrometer at 70 eV and using the electron-impact technique. Microanalyses are within ±0.4% of theory and were performed by Chemalytics, Inc., Tempe, Ariz., and Galbraith Laboratories, Inc., Knoxville, Tenn. All compounds were tested as their HCl salts except for 18 and 19 which were tested as the HBr salts.

Pharmacological Methods. Compounds subjected to the spontaneous locomotor screen were administered (ip) in three dosage levels (10, 20, and 40 mg/kg) in groups of eight male mice (20–30 g) per dose using distilled water as the vehicle. Test solutions were prepared to deliver the appropriate dose in 1 mL per 100 g of body weight. A group of eight male mice served as the control group and received 0.9% saline, 1 mL per 100 g of body weight. A 10-min stabilization period was employed immediately after administration of the test compound. The animals were then housed singly in photobeam cages containing six beams arranged in a circular fashion. Following a 1-min period during which the animals were not scored, the number of beam interruptions was determined at 10-min intervals for 30 min for both saline controls and treated groups. Significance of the data was determined through an analysis of variance, followed by application of the Duncan multiple range test.[14] Significant differences in effects on activity from saline ($p < 0.05$) and insignificant differences in effects on activity from chlorpromazine hydrochloride ($p < 0.05$) were evaluated for each compound at each dose level tested.

Evaluation of anticonvulsant activity was performed in the anticonvulsant screening project by the Antiepileptic Drug Development Program (NIH). All compounds were tested in male Carworth Farms No. 1 mice and administered ip in three dose levels as the HCl salts in 0.9% saline. Initial testing involved determination of the lowest of the three dose levels required to protect the mice from maximal electroshock and/or subcutaneous metrazole seizures (Table III). Those compounds exhibiting anticonvulsant activity at <100 mg/kg in these initial tests were further evaluated for times of peak effect and median effective doses (probit analysis and Litchfield–Wilcoxon approximation method). The median effective doses for the rotorod (neurotoxicity) test were similarly obtained. Groups of eight mice were utilized in these tests. The times of peak anticonvulsant and neurotoxic effect of 10–12 and 25–27 were 0.5 h.

Adult, male Sprague–Dawley rats weighing approximately 265 g were utilized in evaluating the appetite suppressant activity of certain analogues of 1 and 2. The animals were housed singly in cages and provided with a 12/12 h light–dark cycle in a controlled climate facility. Baseline food consumption was obtained by allowing the animals access to a chow feeder for a 1-h period each day for 14 days. After each feeding period the feeder was removed and weighed. On day 15 animals were randomly grouped (eight to ten animals per group) prior to the feeding period and administered (ip) either saline, fenfluramine hydrochloride, or test compounds in a volume not to exceed 0.4 mL. At 4 min postinjection, feeders were placed in the cages for 1 h, removed, and weighed. Fenfluramine hydrochloride was administered in doses of 2.5, 5.0, and 10.0 mg/kg, while the test compounds were administered in doses of 10, 20, and 40 mg/kg, except for 26 which was tested at 5, 10, and 20 mg/kg levels. Student's t test was used to test for significant differences between the mean food consumption for the pretreatment period and the mean food consumption for the treatment period.

2-Bromoacetophenones. Copper(II) bromide (111.75 g, 0.5 mol) was suspended in 250 mL of EtOAc and the mixture refluxed. The appropriate acetophenone derivative (0.3 mol) in 250 mL of $CHCl_3$ was added rapidly to the refluxing mixture. Refluxing was continued until copious generation of HBr ceased (5–12 h). The mixture was filtered, the filtrate was concentrated in vacuo, and the product, when solid, was recrystallized from MeOH. Oily products were used without further purification.

3-Hydroxy-3-aryloctahydropyrido[2,1-c][1,4]oxazines (2 and 22–34). A solution of the appropriate 2-bromoacetophenone (0.1 mol) in Et_2O (100 mL) was mixed with a solution of 2-piperidinemethanol (23.0 g, 0.2 mol) dissolved in warm Et_2O (350 mL). The resulting solution was allowed to stand at room temperature for 24–72 h and the precipitated 2-piperidinemethanol hydrobromide removed by filtration. The filtrate was concentrated in vacuo and the residue taken up in 10% HCl. The acidic solution was extracted with $CHCl_3$, then basified to pH 11 (15% NaOH), and extracted with $CHCl_3$ (3 × 150 mL); the extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was then taken up in Et_2O which was treated with HCl to provide HCl salts (Table I).

1-(2-Hydroxy-2-arylethyl)-2-hydroxymethylpiperidines. Method A. A solution of the appropriate nonhalophenyl analogue of **2** (0.01 mol) in 100 mL of 1 N H_2SO_4 was hydrogenated in the presence of 0.3 g of 10% $Pd(OH)_2/C$ at 20 psi for 24 h. The solution was filtered, alkalinized (15% NaOH), and extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and concentrated in vacuo to yield the diol intermediate which was used in the preparation of the appropriate analogue of **1** without further purification.

Method B. The appropriate halophenyl analogue of **2** (0.011 mol) in 50 mL of absolute EtOH was treated with $NaBH_4$ (1.0 g, 0.025 mol). The reaction was stirred overnight at room temperature, excess hydride destroyed with 10% HCl, the mixture filtered, and the filtrate diluted with 200 mL of H_2O and alkalinized (15% NaOH). The alkaline solution was extracted with $CHCl_3$, the extract dried (Na_2SO_4), and the solvent removed in vacuo to yield the diol intermediate which was used without further purification for the synthesis of **7–9**.

3-Aryloctahydropyrido[2,1-*c*][1,4]oxazines. Method A. A solution of the nonmethoxylated 1-(2-hydroxy-2-arylethyl)-2-hydroxymethylpiperidines (0.023 mol) in 40 mL of 48% HBr was refluxed for 2 h. The solution was concentrated in vacuo and the residue dissolved in H_2O and basified to pH 11 (15% NaOH). The alkaline mixture was extracted thoroughly with Et_2O, and the extract dried (Na_2SO_4) and concentrated. The oily residue was converted to the HCl salt by treatment with ethereal HCl and recrystallized from an appropriate solvent (Table II).

Method B. A solution of the methoxylated phenyldiol intermediates (0.018 mol) was prepared in 50% H_2SO_4 and refluxed for 20, 30, and 40 min for the preparation of **14** and **15**, **16**, and **17**, respectively. The reaction mixture was basified (15% NaOH) and extracted with Et_2O, the extract concentrated, and the residue taken up in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4), and concentrated. The oily residue was converted to the HCl salt using ethereal HCl and recrystallized from an appropriate solvent (Table I).

3-(3-Hydroxyphenyl)octahydropyrido[2,1-*c*][1,4]oxazine (18). A solution of the diol (3.0 g, 0.01 mol) prepared from **29** via $NaBH_4$ reduction in 45 mL of 48% HBr was refluxed for 2 h. The reaction mixture was evaporated to dryness, diluted with H_2O, and treated with NH_4OH. The alkalinized mixture was extracted with Et_2O, and the extract was dried (Na_2SO_4) and concentrated in vacuo to yield 2.1 g (90%) of **18** which was recrystallized from Et_2O–hexane: mp 172–174 °C. The HBr salt of **18** was prepared by dissolving the free base in 48% HBr, evaporating to dryness, and recrystallizing the residue from EtOH–Et_2O: mp 199–200 °C.

3-(4′-Hydroxyphenyl)octahydropyrido[2,1-*c*][1,4]oxazine (19). Treatment of the diol prepared from **30** via $NaBH_4$ reduction, as described for **18**, provided **19**·HBr directly which was recrystallized from EtOH–Et_2O: mp 243–244 °C.

3-(3′-Acetoxyphenyl)octahydropyrido[21-*c*][1,4]oxazine (20). A solution of **18** (2.3 g, 0.01 mol) in 60 mL of Ac_2O was heated on a steam bath for 6 h. Excess Ac_2O was removed in vacuo, the residue washed with H_2O and taken up in $CHCl_3$, and the $CHCl_3$ was washed with H_2O, dried (Na_2SO_4), and concentrated to give 2.67 g (97%) of **20** as a dark oil. The oil was taken up in ether and ethereal HCl added. The HCl salt of **20** was recrystallized from acetone–Et_2O: mp 181–183 °C.

3-(4′-Acetamidophenyl)octahydropyrido[2,1-*c*][1,4]oxazine (21). A solution of 3-(4′-aminophenyl)octahydropyrido[2,1-*c*][1,4]oxazine [prepared by treatment of **34** with $Pd(OH)_2/C$ and H_2 followed by HBr-catalyzed cyclization of the resulting 1-[2-hydroxy-2-(4′-aminophenyl)ethyl]-2-hydroxymethylpiperidine] in 60 mL of Ac_2O was heated on a steam bath for 5 h. Excess Ac_2O was removed in vacuo, and the residue was taken up in 10% HCl, washed with $CHCl_3$, alkalinized, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and concentrated to yield **21** (2.8 g, 90%) which was recrystallized from hexane–Et_2O: mp 165–166 °C. The HCl salt of **21** was prepared using ethereal HCl and recrystallized from acetone: mp 264–265 °C.

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References and Notes

(1) Abstracted in part from a dissertation by G.O.R. presented to the Graduate School of the University of Mississippi.
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(3) T. N. Riley and G. O. Rankin, *J. Med. Chem.*, **19**, 334 (1976).
(4) O. Fanelli, *Arzneim.-Forsch.*, **23**, 810 (1977).
(5) I. R. Innes and M. Nickerson in "The Pharmacological Basis of Therapeutics", 5th ed, L. S. Goodman and A. Gilman, Ed., Macmillan, New York, N.Y., 1975.
(6) A. H. Beckett, W. H. Hunter, and P. Kourounakis, *J. Pharm. Pharmacol.*, **20**, 218S (1968).
(7) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
(8) I. D. Blackburne, A. R. Katritzky, D. M. Read, P. J. Chivers, and T. A. Crabb, *J. Chem. Soc., Perkin Trans. 2*, 203 (1976).
(9) M. E. Rogers, J. Sam, and N. P. Plotnikoff, *J. Med. Chem.*, **17**, 726 (1974).
(10) $Eu(fod)_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium, Pierce Chemicals] in $CDCl_3$ was added to $CDCl_3$ solutions of **1** to provide ratios of $Eu(fod)_3/1$ of 0.197, 0.393, and 0.590 and $CDCl_3$ solutions of **2** to provide ratios of 0.066, 0.132, 0.198, 0.263, and 0.329. The total volume of the sample never exceeded 1.0 mL. All volume measurements were made with a calibrated syringe.
(11) A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackman, *Chem. Rev.*, **73**, 553 (1973).
(12) W. M. Davis, H. T. Hatoum, S. G. Smith, and M. C. Baude in "Psychopharmacology of Hallucinogens", R. C. Stillman and R. E. Willette, Ed., Pergamon Press, New York, N.Y., in press.
(13) A. Abdallah and H. D. White, *Arch. Int. Pharmacodyn. Ther.*, **188**, 271 (1970).
(14) D. B. Duncan, *Biometrics*, **11**, 1 (1955).
(15) "Anticonvulsant Screening Project, Antiepileptic Drug Development Program", DHEW Publication No. (NIH) 76-1093, Bethesda, Md., 1976.