trans-3-**Amino-6-phenyl-1-benzylpiperidine** (*trans*-**16**). *trans*-**15** (5.08 g, 0.01 mol) was added to 25 ml of 6 *N* HCl and the mixture was heated on a steam bath for 20 min, cooled in ice, and extracted with three 50-ml portions of ether. The aqueous acidic solution was made basic with 6 *N* NaOH and extracted with $CHCl_3$ which was washed with H_2O, dried (Na_2SO_4), and evaporated. The solid residue was recrystallized from acetonitrile to yield *trans*-**16** (2.2 g, 80%): mp 132–133°. Anal. ($C_{18}H_{22}N_2$) C, H, N.

trans-1-**Benzyl-3-dimethylamino-6-phenylpiperidine** (**1**). Sodium cyanoborohydride (0.600 g, 0.0096 mol) was added to a cold stirred solution of *trans*-**16** (1.0 g, 0.0037 mol) and 4 ml (0.049 mol) of 37% formaldehyde in 30 ml of acetonitrile. A slight evolution of heat occurred followed by the separation of an oily layer. After 15 min of stirring, a few drops of glacial acetic acid were added until the mixture exhibited a pH of 7. Stirring was continued for 48 hr during which time the pH was maintained near neutrality by the occasional addition of a few drops of glacial acetic acid. The solvent was evaporated, 20 ml of 20% NaOH was added to the residue, and the basic mixture was extracted with three 50-ml portions of ether. The combined ether extracts were washed with 20 ml of 0.5 *N* KOH and extracted with three 20-ml portions of 15% HCl. The acidic extracts were combined, made basic with solid KOH, and extracted with three 50-ml portions of ether which were combined, dried ($MgSO_4$), and evaporated to afford crude **1** which was recrystallized from petroleum ether–ether to yield 0.60 g (55%) of **1** as a white crystalline solid: mp 58–60°; NMR ($CDCl_3$) 2.15 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{20}H_{26}N_2$) C, H, N.

The dihydrochloride of **1** was prepared for biological testing by addition of ethanolic HCl to an ether solution of **1**. Solvent was evaporated in vacuo and the product was recrystallized from ethanol–ether to afford **1** dihydrochloride: mp 248–250°. Anal. ($C_{20}H_{28}N_2Cl$) C, H, N.

cis-1-**Benzyl-3-dimethylamino-6-phenylpiperidine** (**2**). To a solution of *cis*-**16** (1.50 g, 0.0056 mol) in 20 ml of acetonitrile was added 5.0 ml (0.06 mol) of 37% formaldehyde. The solution was cooled and stirred vigorously and 0.700 g (0.011 mol) of sodium cyanoborohydride was added in one portion. The pH was adjusted to 7 by the addition of a few drops of glacial acetic acid and was stirred at room temperature for 48 hr. Acetonitrile was removed by evaporation in vacuo and the residue was triturated with 20% NaOH followed by extraction with three 50-ml portions of ether. The combined ether extracts were extracted with three 20-ml portions of 15% HCl which were combined, made basic with solid NaOH, and extracted with three 50-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and evaporated to yield an oil which slowly solidified. The solid was recrystallized from petroleum ether–cyclohexane to afford **2** (1:1 g, 67%): mp 39–40°; NMR 2.15 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{20}H_{26}N_2$) C, H, N.

The dihydrochloride of **2** was prepared for biological testing by adding ethanolic HCl to an ether solution of **2**. Evaporation of the solvent in vacuo and recrystallization from ethanol–ether afforded **2** dihydrochloride: mp 153–156°. Anal. ($C_{20}H_{28}N_2Cl \cdot H_2O$) C, H, N, O.

Pharmacology. Testing was carried out on the isolated guinea pig ileum which was prepared according to a standard method.[8] The ileum was bathed in Tyrodes solution at 37° and bubbled with air. Tissues were allowed to stabilize for a minimum of 15 min before introduction of agonists. Histamine and acetylcholine were then added at 3-min intervals until reproducible contractions were obtained. Antagonists were allowed to remain in contact with the ileal tissue for 15 min prior to the addition of 4×10^{-6} *M* histamine or 4×10^{-7} *M* acetylcholine. The ED_{50} values cited in the discussion are the results of three determinations at three dose levels. The values in parentheses are standard errors.

Acknowledgment. The authors are grateful to Dr. Ronald T. Borchardt for the histamine *N*-methyltransferase data. Portions of this work were supported by Grant GM 15477 from the National Institutes of Health and by grant from the Graduate School of the University of Minnesota.

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Synthesis and Biological Actions of 2-Substituted Quinolizidines†,[1]

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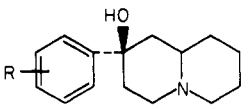
A series of 2-substituted quinolizidines was synthesized and tested for their effects on motor activity in mice. In the 2-aryl-2-hydroxyquinolizidines (**5** and **6**) a difference was noted in potency between the axial and equatorial aryl analogs. A significant difference in activity was also found between the epimeric 2-(4-fluorobenzoyl)quinolizidines (**10c** and **11c**).

The structure–activity relationship (SAR) of haloperidol (**1**) has been studied in great detail since the utility of this drug as a major tranquilizer was affirmed.[2] The stereochemical requirements for biological activity of the butyrophenone series have not been as well defined.[3] Considering the quinolizidine ring as a semirigid nucleus to which appropriate substituents are added, the compounds **2** could be considered as haloperidol analogs with two fixed stereochemical centers. Before attempting the synthesis of **2**, several model chemical systems, **3** and **4**,

† Dedicated to the memory of Professor Edward E. Smissman.

Table I. 2-Hydroxy-2-phenylquinolizidines



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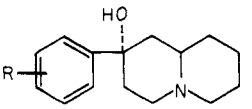

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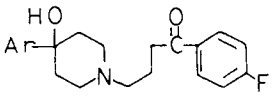
Compd	R and position	^{1}H NMR[a] hydroxyl	Bonded[b] hydroxyl	Mp, °C	Yield, %	Formula[c]
5a	4-Cl	~3.0	3.15	153-156[d]	28.3	$C_{15}H_{20}ClNO$
6a	4-Cl	3.1	2.95	98-99[d]	13.5	$C_{15}H_{20}ClNO$[h]
5b	4-CF_3	~2.0	3.10[g]	187-188.5[e]	34.8	$C_{16}H_{20}F_3NO$
6b	4-CF_3	4.2	2.98	107-108[f]	6.7	$C_{16}H_{20}F_3NO$
5c	3-Cl	~2.0	3.10	125-127[e]	40.8	$C_{15}H_{20}ClNO$
6c	3-Cl	3.0	2.96	107-111[f]	12.1	$C_{15}H_{20}ClNO$
5d	3-CF_3	3.0	3.10	103[f]	15.0	$C_{16}H_{20}F_3NO$
6d	3-CF_3	3.6	2.95	115-117[f]	10.7	$C_{16}H_{20}F_3NO$

[a] All spectra were run in $CDCl_3$ and chemical shifts reported in parts per million downfield from an internal standard of Me_4Si. [b] All ir spectra were run in CCl_4 and reported in μ. [c] All compounds were analyzed for C, H, N, and, if present, Cl except for 5a and 6a and the results were witnin 0.4% theory. [d] From ligroine (bp 100-115°). [e] From cyclohexane. [f] From petroleum ether (bp 38-49°). [g] Very poor solubility in CCl_4. [h] C: calcd, 67.78; found, 67.25.



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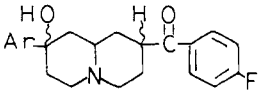
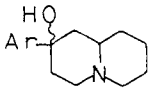


2

were explored. This report is concerned with the synthesis and initial screening of these monosubstituted quinolizidines.



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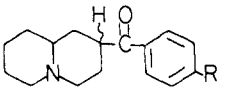

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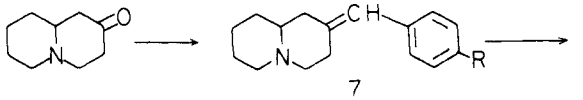
Chemistry. The 2-hydroxy-2-arylquinolizidines were prepared by Grignard addition to quinolizidin-2-one.[4,5] The resulting diastereoisomers of 2-hydroxy-2-arylquinolizidines, **5** and **6**, were identified by the location of the bonded and nonbonded hydroxyl in the ir and ^{1}H NMR spectra. When the ir spectra were determined as 2% (w/v) solution in CCl_4, **6** showed the presence of intramolecular bonded hydroxyl while isomer **5**, which is only capable of intermolecular hydrogen bonding, possessed no bonded hydroxyl group. The equatorial hydroxyl proton is consistently more deshielded in the ^{1}H NMR than is the axial hydroxyl proton. The spectral data are listed in Table I and are in agreement with the results of Lingard.[6]

The synthesis of the 2-benzoylquinolizidines, 4, is outlined in Scheme I. The Wittig reaction performed on quinolizidin-2-one gave compound **7** which was hydroxylated via hydroboration followed by hydrogen peroxide–sodium hydroxide treatment to yield compounds **8** and **9**. In all cases the ^{1}H NMR absorption and coupling pattern for the benzylic hydrogen were characteristic of the equatorial and axial nature of the benzyl hydroxyl group in compounds **8** and **9**, respectively. The benzylic proton in **8** appeared at ca. δ 4.3 as a doublet, J = 6 Hz, while the benzylic proton in **9** appeared at ca. δ 4.7 as a doublet, J = 10 Hz. It is interesting to note that when the sequence was performed on a large scale, with R = F, difficulty was encountered in the hydroboration step. In the usual reaction the products are isolated as borane complexes, as indicated by strong absorption at 4.17 μ in the ir, and an initial separation is performed by chromatography on silica gel. The complex is then destroyed by treatment with aqueous HCl and the equatorial products **8** and axial products **9** are recovered as diastereomeric mixtures, as indicated by wide melting points (Table III). When **7** (R = F) was hydroxylated and chromatographed the primary product from the column was the borane complex of **9**. After liberation of the free base, compound **9** was separated into its diastereoisomers **9c** and **9d**. The original silica gel column was washed with a more polar solvent to yield primarily **8** which was recovered as its diastereoisomers **8c** and **8d**. The purified diastereoisomers gave identical ^{1}H NMR spectra while the ir spectra showed minor differences. Compounds **8** and **9** were individually oxidized using Jones reagent to the desired ketones, **10** and **11**, respectively. The stereochemistry of **11** was proven by base-catalyzed epimerization to **10**. Tables II–IV list the properties of the

Scheme I



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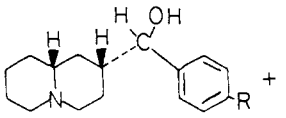

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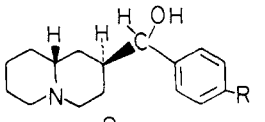

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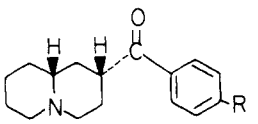

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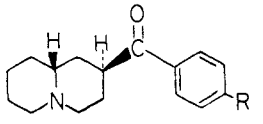

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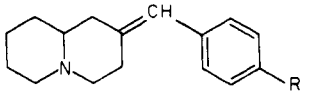
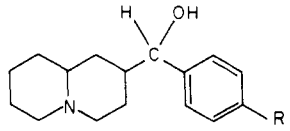
Table II. 2-Benzalquinolizidines



Compd	R	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
7a	H	215-216 dec	EtOAc	75	$C_{16}H_{21}N$·HCl
7b	Cl	77-78	EtOH-H_2O	65	$C_{16}H_{20}ClN$
7c	F	170-173	95% EtOH	63	$C_{16}H_{20}FN$·$C_6H_3N_3O_7$

[a] See footnote c in Table I.

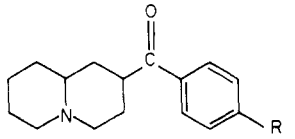
Table III. 2-Benzylhydroxyquinolizidines



Compd	R	Mp, °C	Yield, %	Formula[a]
8a	H	149-156[b]	22.6	$C_{16}H_{23}NO$
9a	H	180-190[c]	8.6	$C_{16}H_{23}NO$
8b	Cl	156-158[c]	6.3	$C_{16}H_{22}ClNO$
9b	Cl	155-168[b]	12.6	$C_{16}H_{22}ClNO$
8c	F	158-166[b]	16.3	$C_{16}H_{22}FNO$
8d	F	175-180[b]		$C_{16}H_{22}FNO$
9c	F	171-172[c]	13.8	$C_{16}H_{22}FNO$
9d	F	197-199.5[d]		$C_{16}H_{22}FNO$

[a] See footnote c in Table I. [b] From cyclohexane. [c] From $CHCl_3$. [d] From benzene.

Table IV. 2-Benzoylquinolizidines



Compd	R	Mp, °C	Yield, %	Formula[a]
10a	H	75-77[b]	30	$C_{16}H_{21}NO$
11a	H	66-67[b]	70	$C_{16}H_{21}NO$
10b	Cl	116-120[c]	62	$C_{16}H_{20}ClNO$
11b	Cl	81-82[b]	87	$C_{16}H_{20}ClNO$
10c	F	107.5-109[b]	65	$C_{16}H_{20}FNO$
11c	F	75.5-77[b]	65	$C_{16}H_{20}FNO$

[a] See footnote c in Table I. [b] From petroleum ether (bp 38-49°). [c] From cyclohexane.

compounds prepared by this scheme.

Screening and Results. Male Swiss-Webster mice (Texas Inbred, Houston, Texas) weighing 20-25 g were used to test for drug effects on forced and spontaneous motor activity after being acclimated to laboratory conditions for 3-4 days. The compounds were dissolved in a minimum amount of 1.5 *M* NaH_2PO_4, diluted with water, and administered intraperitoneally. Haloperidol was dissolved in a minimum amount of 50% (w/v) tartaric acid-water solution. The results that differed from control values at $p < 0.05$ level (Student's *t* test) were considered to be statistically significant.

Acute Toxicity. The acute 7-day intraperitoneal lethal dose effects were determined in mice at each of four dose levels, and the LD_{50} was estimated using the method of Weil.[7]

Forced and Spontaneous Motor Activity. The effect of the compounds on forced motor activity of mice was studied using the rotarod.[8] The wooden rod was rotated at 4 rpm for the first 30 sec, 6 rpm during the next 30 sec, and at progressively increasing speed thereafter at 30-sec intervals (maximum 50 rpm) until the mouse fell. Six animals were tested simultaneously and were given four trials with two spaced 4-6 hr apart, on each of two consecutive days. Thirty minutes prior to the fourth trial, the mice were administered vehicle (controls) or one of the selected doses of the experimental compounds.

The effects of the compounds on the spontaneous motor activity in mice were measured in three photocell cages (Actophotometer, Woodward Research Corp.).[8] Two animals treated with identical doses of the same compound were placed in each photocell cage 10 min after the initiation of the rotarod test, and a 15-min count was recorded beginning 5 min after the animals were placed in the photocell cages. Each dose was tested in a factorial design in each of the three activity cages in order to negate the differences in sensitivity among units.

Table V. Acute LD_{50}[a] in Mice of the 2-Substituted Quinolizidines

Compd	LD_{50}, mg/kg ip	95% confidence limits
5a	228.7	194.5-269.0
5b	125.4	0
5c	134.1	114.0-157.7
5d	136.6	129.4-144.2
6a	67.5	57.4-79.4
6b	129.6	101.8-165.0
6c	179.8	169.3-191.0
6d	261.9	211.0-325.3
10c	192.6	166.2-223.5
11c	86.1	69.5-106.5
1	49.7	37.7-65.6

[a] Seven-day intraperitoneal single-dose LD_{50}.

The percent of control activity (spontaneous and forced motor activity) at each dose level of the compounds used was plotted in an attempt to make an early evaluation of the possible types of activity of each compound.

To determine more fully their pharmacologic effects, certain of the compounds were administered to male Wistar rats (175-225 g) by intraperitoneal injection. Gross behavior was observed and measurements were taken of respiratory rate, heart rate, rectal temperature, and pupil size. For each dose tested, three rats were treated and compared with one control.

The LD_{50} values for the 2-substituted quinolizidines were determined and are presented in Table V. All compounds tested were less toxic than haloperidol. Most of the compounds produced convulsions at doses in the lethal range, but only **11c** caused convulsions as intense and prolonged as those seen with haloperidol (1) which produced death as late as 72 hr after a single injection and in some of the survivors, symptoms (tremors, ataxia) persisted for 72 hr or more. Mice receiving the test compounds, however, had either died or recovered completely and were symptom-free within 24 hr after dosing.

The effects on forced and spontaneous motor activity in mice of the substituted quinolizidines are presented in Table VI and VII. The results of forced motor activity studies demonstrated dose-related depression of activity with compounds **5a**, **10c**, and **11c**. Several additional analogs showed depression of forced motor activity but only at very high doses.

The results from the spontaneous motor activity study showed compounds **5a**,**b**,**d**, **10c**, and **11c** produced a dose-related depression. Once again, most of the other analogs produced a depressed motor activity at the largest dose studied, which was approximately one-third of the LD_{50}. This depression may have been related to toxicity. Two compounds, **6a** and **6c**, increased the spontaneous motor activity above that of controls at low doses. In both cases, these compounds were the axial chlorophenyl analogs. The more interesting of these, **6a**, was submitted for gross observation in rats. Outside of a slight decrease in respiration and increase in heart rate the animals appeared normal. No increase in motor activity was noted at a dose of 5 or 30 mg/kg ip. Of considerable interest were the gross observations on the rats treated with **5a**, **10c**, and **11c**.

Compounds **5a** (50 mg/kg), **11c** (25 mg/kg), **10c** (20 mg/kg), and haloperidol (1, 6 mg/kg) were administered ip to rats and showed a significant depression in most observed end points. For **5a** this included decreases in respiration rate, heart rate, and body temperature (-1°) and an increase in pupil size. The rats also showed a decrease in motor activity and ptosis. The maximal effects appeared between 1 and 2 hr with a duration of more than

Table VI. Effects of 2-Substituted Quinolizidine Derivatives on Forced Motor Activity in Mice

Compd	Dose, mg/kg ip	Trial, sec ± SE	% of control	Dose, mg/kg ip	Trial, sec ± SE	% of control
5a	0	209.5 ± 25.7	100	25	149.4 ± 12.2	71.3
	50	56.0 ± 11.1[a]	26.7	100	18.8 ± 9.7[a]	9.7
5b	0	159.3 ± 17.8	100	12.5	183.6 ± 23.7	115.2
	25	160.3 ± 14.2	100.6	50	50.2 ± 4.8[a]	31.5
5c	0	243.3 ± 15.9	100	12.5	207.5 ± 15.8	88.6
	25	195.9 ± 19.7	83.6	50	80.3 ± 30.5[a]	34.3
5d	0	156.6 ± 31.0	100	12.5	167.8 ± 26.6	107.2
	25	153.7 ± 29.3	98.1	50	88.6 ± 38.8	56.6
6a	0	226.7 ± 14.5	100	5	240.0 ± 20.9	105.9
	10	231.7 ± 10.0	101.9	25	198.7 ± 19.3	87.6
6b	0	183.7 ± 18.7	100	12.5	182.5 ± 9.4	99.3
	25	169.6 ± 26.2	92.3	50	153.4 ± 29.3	83.5
6c	0	224.5 ± 16.4	100	15	216.7 ± 10.8	96.5
	30	235.7 ± 17.1	105.0	60	115.5 ± 26.2[a]	51.4
6d	0	184.5 ± 29.6	100	25	180.6 ± 24.3	97.9
	50	185.5 ± 24.6	100.5	100	54.6 ± 14.1[a]	29.6
10c	0	201.7 ± 16.8	100	15	53.4 ± 21.0[a]	26.5
	30	30.7 ± 24.2[a]	15.2	60	9.8 ± 4.8[a]	4.8
11c	0	218.1 ± 12.8	100	6.25	143.3 ± 9.4[a]	65.6
	12.5	121.1 ± 21.7[a]	55.5	25	50.2 ± 14.2[a]	23.0
1	0	71.5 ± 15.1	100	2.5	71.0 ± 13.3	99.3
	5	56.8 ± 32.7	79.4	10	18.9 ± 9.4[a]	26.4

[a] $p < 0.05$.

Table VII. Effects of 2-Substituted Quinolizidine Derivatives on Spontaneous Motor Activity in Mice

Compd	Dose, mg/kg ip	Activity counts per 15 min ± SE	% of control	Dose, mg/kg ip	Activity counts per 15 min ± SE	% of control
5a	0	366.0 ± 99.2	100	25	71.0 ± 24.8[a]	19.4
	50	66.3 ± 25.8[a]	18.1	100	19.3 ± 10.1[a]	2.6
5b	0	609.7 ± 279.4	100	12.5	548.7 ± 64.4	90.0
	25	239.7 ± 148.7	39.3	50	106.7 ± 22.9	17.5
5c	0	416.7 ± 145.5	100	12.5	460.3 ± 28.8	110.5
	25	374.3 ± 139.9	89.9	50	309.7 ± 121.6	74.3
5d	0	313.0 ± 37.7	100	12.5	220.0 ± 106.8	70.3
	25	141.3 ± 76.2	45.1	50	110.7 ± 67.3	35.4
6a	0	143.7 ± 47.0	100	5	757.0 ± 91.7[a]	526.8
	10	631.7 ± 134.7[a]	439.6	25	32.2 ± 9.2	22.5
6b	0	830.3 ± 121.7	100	12.5	413.0 ± 97.2	49.7
	25	686.7 ± 136.9	82.7	50	375.7 ± 134.7	45.2
6c	0	306.7 ± 52.0	100	15	511.3 ± 47.0	166.7
	30	475.0 ± 77.2	154.9	60	136.0 ± 68.1	44.3
6d	0	522.3 ± 159.5	100	25	621.3 ± 46.2	119.0
	50	580.0 ± 192.1	111.0	100	28.7 ± 5.5[a]	5.5
10c	0	520.7 ± 103.7	100	15	1.3 ± 0.7[a]	2.5
	30	5.0 ± 4.5[a]	9.6	60	0.0 ± 0.0[a]	0
11c	0	421.7 ± 112.6	100	6.25	403.0 ± 221.5	95.6
	12.5	204.7 ± 90.4	48.5	25	43.0 ± 11.2[a]	10.2
1	0	130.3 ± 50.0	100	2.5	36.0 ± 22.0	27.6
	5	1.7 ± 0.9	13.0	10	0.3 ± 0.3	0.2

[a] $p < 0.05$.

5 hr. With **11c** decreases in respiration, heart rate, and rectal temperature (−2.9°) were recorded. Slight ptosis was noted and an increase in salivation occurred between 0.5 and 1 hr. No effect was seen after 2 hr. The most active compound was the 2-equatorial (4-fluorobenzoyl)quinolizidine (**10c**), which produced effects between 0.5 and 1 hr consisting of a decrease in motor activity, startle response, and grip strength.[9] The decreased respiration and heart rate were in the order of those seen with 1 when observed in the same time period. A decrease in body temperature was noted for **10c** (−3°) and 1 (−2°). Significant ptosis occurred in rats given **10c** within 10 min after administration and lasted 3 hr. Ptosis also occurred with 1.

A direct comparison of results with the test compounds vs. those obtained with haloperidol (1) on forced and spontaneous motor activity is complicated by the very low control values seen with 1. One possible contributory factor is that animals in this experiment were injected with a solution containing as much as 10 mg of tartaric acid. It is possible that the tartaric acid was responsible for the relatively lethargic appearance and performance of these animals.

Preliminary screening results in mice suggest the biological activity of the 2-substituted quinolizidines is dependent on conformational parameters. In the 2-hydroxyl-2-arylquinolizidine series (3) the equatorial aryl axial hydroxyl analogs, **5a–d**, appear consistently more effective in decreasing motor activity than their isomeric counterparts. In the 2-benzoylquinolizidine series (4) only two compounds were screened, and although both showed activity, the equatorial 4-fluorobenzoyl analog **10c** was significantly more potent than its axial isomer, **11c**. When selected members of these series were tested in rats and gross observations were made the same pattern appeared to occur.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were

performed by Atlantic Microlab, Inc., Atlanta, Ga. Satisfactory ir and ^1H NMR spectra were obtained for all compounds reported. Ir spectra were recorded on a Perkin-Elmer Model 700 and Beckman IR 8 spectrophotometer as KBr pellets or liquid film. Hydrogen bonding studies were done on a Beckman 4250 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM 360 spectrometer in $CDCl_3$ using Me_4Si as an internal standard. Chromatography was performed on Brinkman silica gel whereas TLC was done on silica G with 254 fluorescent indicator (Analtech uniplates).

2-Hydroxy-2-(4-chlorophenyl)quinolizidine (5a and 6a). To the Grignard reagent prepared from Mg (2.88 g, 0.12 g-atom) and *p*-chlorobromobenzene (22.9 g, 0.12 mol) in THF (120 ml) was added quinolizidin-2-one[4,5] (8.4 g, 0.055 mol) in THF (50 ml) under N_2. The reaction mixture was heated under reflux for 1 hr, concentrated on a rotary evaporator, and poured over ice (200 g) with the aid of Et_2O. The mixture was acidified with 5 *N* HCl and extracted with Et_2O. The aqueous phase was made alkaline with NaOH solution (50%) and extracted with Et_2O, and the combined organic layer was dried ($MgSO_4$). Concentration of the organic layer gave 12.5 g of crude product which was chromatographed on silica gel (700 g) using Et_3N–MeOH–C_6H_6 (3:5:92) as eluting solvent. Compound **5a**, 4.6 g, was the first product off the column. The second product **6a**, 1.8 g, showed a single product on TLC. The recrystallization solvent, yield, and physical constants for these products and the other compounds **5** and **6** are given in Table I.

2-Benzaloctahydroquinolizidine (7a). To a suspension of triphenylbenzylphosphonium chloride (39.4 g, 0.10 mol), prepared by heating triphenylphosphine with benzyl chloride,[10] in 200 ml of Et_2O was added the phenyllithium (65 ml, 1.8 *M*, 0.11 mol) while stirring under a N_2 atmosphere and with cooling. The addition took 45 min. To the red suspension was added quinolizidin-2-one (15.5 g, 0.10 mol) in Et_2O (50 ml). The reaction mixture was cooled and treated with water and the organic layer separated. The aqueous phase was extracted with Et_2O and the combined organic layer was dried ($MgSO_4$). Removal of the solvent followed by distillation gave 17.2 g of **7a**: bp 134–138° (0.8 mm). The recrystallization solvent, yield, and physical constants for **7a** are given in Table II along with data for **7b** and **7c** which were prepared in a similar manner.

2-(4-Fluorobenzylhydroxy)quinolizidines (8c,d and 9c,d). To a cold solution of borane in THF (220 ml of 1 *M*, 0.22 mol) under a N_2 atmosphere was added **7c** (27.0 g, 0.11 mol) in THF (125 ml) with stirring. The addition took 2 hr and was followed by stirring at 25° for 24 hr. The reaction mixture was cooled and with stirring aqueous NaOH (36.5 ml of 3 *N*, 0.11 mol) was added followed by the addition of 30% H_2O_2 (37.3 ml, 0.33 mol). The reaction mixture was stirred at 25° for 12 hr. The reaction mixture was concentrated in vacuo, diluted with H_2O, and extracted with Et_2O. The combined Et_2O was dried ($MgSO_4$). Concentration of the organic layer gave 28.6 g of a gum which was chromatographed on silica gel (1 kg) using MeOH–$CHCl_3$ (1:40). The first material from the column appeared to consist of the 2-(*p*-fluorobenzyl)quinolizidine–borane complex. The second material from the column consisted of 7.8 g of a gum of **8–9**–BH_3. Washing the column with Et_3N–MeOH–C_6H_6 (3:6:91) gave 7.2 g of **8–9**. Rechromatography of this latter product on silica gel (1 kg) using Et_3N–MeOH–EtOAc (3:3:94) gave 1.2 g of **8c** and 3.8 g of a mixture of products which by ^1H NMR contained 8 and 9 (1:1). The final fractions from the column consisted of 1.8 g of **8d**. The 7.8 g of the **8–9** complex was stable to silica gel during 7 days of stirring with silica gel (60 g) in MeOH–$CHCl_3$ (1:20). The gum was treated with HCl (18%, 100 ml) and Et_2O with vigorous stirring for 3 days. The aqueous phase was separated and made basic with aqueous NaOH. Extraction was performed with Et_2O. Concentration of the organic layer gave 5.6 g of solid which was chromatographed on silica gel (1 kg) eluting with Et_3N–MeOH–EtOAc (3:3:94). The first solid from the column was **9d** which was fractionally recrystallized from $CHCl_3$ and then benzene to give 0.8 g; this was followed by 1.5 g of a mixture of **8–9** and finally 0.7 g of **9c**. The recrystallization solvent, yield, and physical constants for these products and other compounds **8** and **9** are given in Table III. With compounds **8a,b** and **9a,b** separation of diastereoisomers did not occur which simplified the purification procedure.

2-(4-Fluorobenzoyl)quinolizidine (11c). A mixture of **9c** (0.5 g, 1.9 mmol) and **9d** (0.5 g, 1.9 mmol) was dissolved in acetone (100 ml) by heating. The solution, which became cloudy, was cooled to 0–5° with stirring and Jones reagent (1.8 ml) was added dropwise. Following the addition the mixture was allowed to stir at 0° for 0.5 hr. A few drops of 2-propanol was added to terminate the reaction. The reaction mixture was concentrated in vacuo, treated with aqueous Na_2CO_3 to make alkaline, and extracted with $CHCl_3$. After drying ($MgSO_4$) the solvent was removed and the solid was recrystallized. The recrystallization solvent, yield, and physical constants for this product and other compounds 10 and 11 are given in Table IV.

Epimerization of Axial 2-(4-Fluorobenzoyl)quinolizidine (11c) to Equatorial 2-(4-Fluorobenzoyl)quinolizidine (10c). A sample of **11c** dissolved in absolute EtOH was treated with a few drops of NaOEt. The reaction mixture was immediately analyzed by TLC using Et_3N–MeOH–EtOAc (3:3:94) as eluting solvent. A trace of the axial isomer, **11c**, was present while the major component corresponded to **10c**.

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