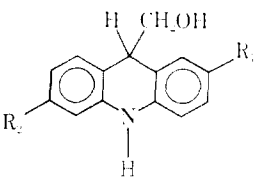
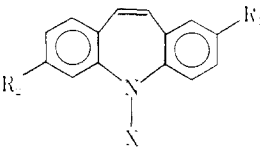
TABLE II



No.	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses	Recrystn solvent
7	F	H	85	148–149	$C_{14}H_{12}FNO$	C, H, N	PhH
8	Cl	H	90	119–120	$C_{14}H_{12}ClNO$	C, H, N	PhH–hexane
9	OCH_3	Cl	75	151–153 (153–154)[a]	$C_{15}H_{14}ClNO_2$		PhH–hexane

[a] Reference 2.

TABLE III



No.	X	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses	Recrystn solvent
10	H	F	H	30	175–177	$C_{13}H_{10}FN$	C, H, N	Cyclohexane
11	$(CH_2)_3N(CH_3)_2 \cdot C_4H_4O_4$[a]	F	H	15	153–154	$C_{23}H_{25}FN_2O_4$	C, H, N	EtOH–Et_2O
12	H	Cl	H	30	168–170	$C_{13}H_{10}ClN$	C, H, N	Cyclohexane
13	$(CH_2)_3N(CH_3)_2 \cdot C_4H_4O_4$[a]	Cl	H	50	125–128	$C_{23}H_{25}ClN_2O_4$	C, H, N	PhH–Et_2O
14	H	OCH_3	Cl	30	173–175 (176)[b]	$C_{14}H_{12}ClNO$		Cyclohexane
15	$(CH_2)_3N(CH_3)_2$	OCH_3	Cl	65	82–85 (88)[b]	$C_{20}H_{23}ClN_2O$	C, H, N	PhH–hexane
16	$(CH_2)_3N(CH_3)_2 \cdot C_4H_4O_4$[a]	H	H	50	146–148 (148–149)[c]	$C_{23}H_{26}N_2O_4$		PhH

[a] Maleate salt. [b] Reference 2. [c] P. N. Craig, B. M. Lester, A. J. Saggiomo, C. Kaiser, and C. R. Zirkle, *J. Org. Chem.*, **31**, 135 (1961).

9-Acridinecarboxaldehydes.– In a typical reaction, a mixture of 23.4 g (0.11 mole) of 2-fluoro-9-methylacridine, 35.3 g (0.24 mole) of N,N-dimethyl-4-nitrosoaniline, 20 drops of piperidine, and 150 ml of 2-pentanol was refluxed for 5 hr. The mixture was cooled, and the residue was filtered and washed with 95% EtOH. The nitrone was not purified but was used directly. A stirred slurry of crude nitrone in 300 ml of 12% HCl was heated on a steam bath for 5 min. Filtration gave the hydrochloride which was treated with excess 20% NaOAc solution to liberate the base, (21 g crude). Recrystallization from MeCN gave 16 g (65%).

9-Hydroxymethyl-9,10-dihydroacridines.– In a typical example, to a stirred suspension of 9.0 g of LAH in 200 ml of Et_2O under N_2, 18.9 g (0.084 mole) of 2-fluoro-9-acridinecarboxaldehyde was added in portions. After completion of addition, the mixture was stirred and refluxed for 3 hr. The mixture was cooled and worked up in the usual manner. The yield was 16.1 g (85%).

5H-Dibenz[*b*,*f*]azepines.– A mixture of 15 g of sea sand, 15 g of P_2O_5, and 50 ml of xylene under N_2 was heated to reflux and 2 g (0.009 mole) of 2-fluoro-9-hydroxymethyl-9,10-dihydroacridine was added quickly; the mixture was refluxed for 2 hr. Longer reflux time, in our hands, resulted in isolation of only 9-methylacridines (*cf.* ref 2). The mixture was cooled and extracted (PhH), the organic layer was dried ($CaSO_4$), and the solvent was removed under reduced pressure. The residue was taken up in PhH and chromatographed on an alumina column packed in hexane; PhH was used as the eluent. The yield after one recrystallization from cyclohexane was 0.6 g (30%).

5-(3-Dimethylaminopropyl)-5H-dibenz[*b*,*f*]azepines.– A mixture of 1.0 g (0.0047 mole) of 2-fluoro-5H-dibenz[*b*,*f*]azepine, 0.78 g of NaH (58% in an oil dispersion) and 70 ml of xylene were refluxed 2 hr under N_2. To this mixture was added dropwise a solution of 4.7 g (0.04 mole) of 3-N,N-dimethylaminopropyl chloride in 50 ml of xylene and the mixture was refluxed for 20 hr. The reaction mixture was treated with H_2O and extracted with Et_2O, the organic layer was dried ($CaSO_4$) and evaporated under reduced pressure, and the residue was chromatographed over alumina as described above. The oil obtained from the PhH eluent was treated with 0.27 g (0.023 mole) of maleic acid dissolved in 10 ml of EtOAc. Cooling overnight at −5° produced 0.25 g (15%) which was recrystallized from EtOH–Et_2O.

1,3-Dihydro-1-methyl-5,6- (and 5,7-) diaryl-2H-1,4-diazepin-2-ones

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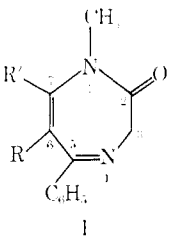
Received April 11, 1969

Although a number of 2H-1,4-benzodiazepin-2-ones closely related to diazepam have been reported to show CNS depressant properties,[1] the monocyclic 1,3-



I

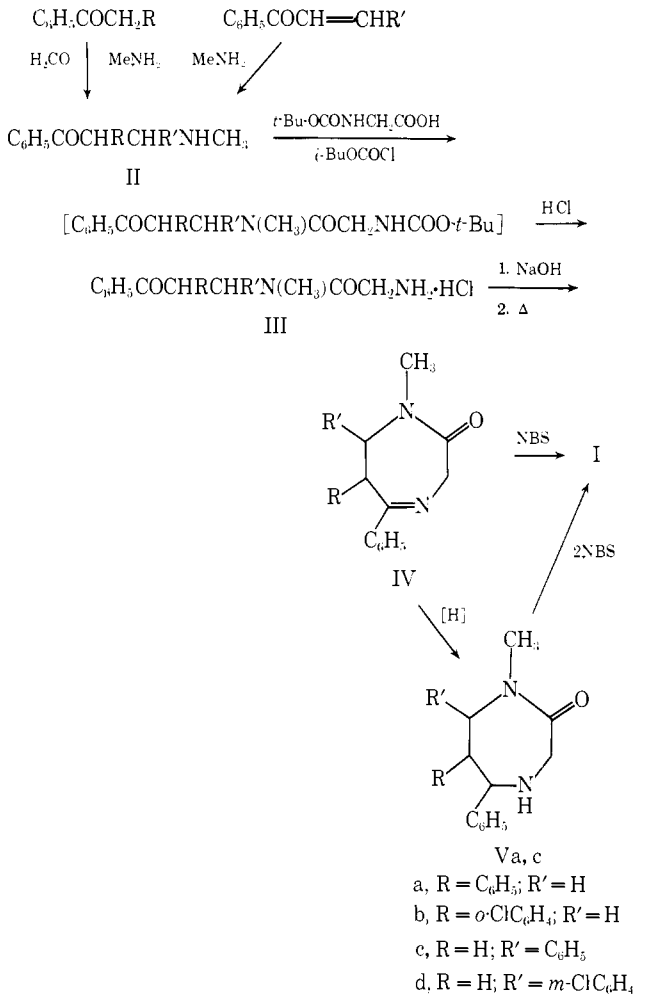
dihydro-2H-1,4-diazepin-2-one ring system I has not been described. This paper describes the preparation

(1) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, p 237.

and properties of four compounds of type I with aryl groups in the 5,6 and 5,7 positions.

The compounds were prepared as illustrated in Chart I. The Mannich bases II were treated with *t*-

CHART I



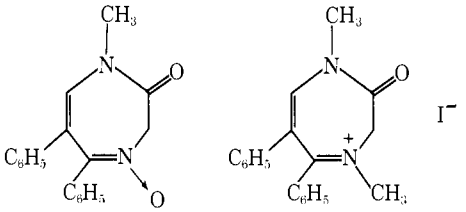
a, R = C_6H_5; R′ = H
b, R = *o*-ClC_6H_4; R′ = H
c, R = H; R′ = C_6H_5
d, R = H; R′ = *m*-ClC_6H_4

butoxycarbonylglycine and isobutyl chloroformate by the mixed anhydride peptide synthesis.[2] Removal of the blocking group gave the β-(aminoacetamido)propiophenone hydrochlorides (III). Cyclization of III to IV was accomplished either by heating the free bases, neat, or in toluene with a catalytic amount of *p*-toluenesulfonic acid. The structures of these 1,3,6,7-tetrahydro-2H-1,4-diazepin-2-ones (IV) were established by analytical and spectral data.

Catalytic hydrogenation of IVa and IVc resulted in the uptake of 1 molar equiv of hydrogen and gave the hexahydro-2H-1,4-diazepin-2-ones (Va and c).

Treatment of the 1,3,6,7-tetrahydro-2H-1,4-diazepin-2-ones (IV) with 1 molar equiv of NBS resulted in bromination and dehydrobromination to give, in one step, the 1,3-dihydro-2H-1,4-diazepin-2-ones (I). Compound Ia was also obtained by treatment of the hexahydro-2H-1,4-diazepin-2-one (Va) with 2 molar equiv of NBS.

Two additional derivatives of Ia, the N-oxide VI and the methiodide VII, were prepared. Conversion of Ia to VI did not appreciably change the ir and nmr spectral characteristics. On the other hand, the nmr spectrum of the methiodide VII shows a marked downfield shift of the six NCH_3 protons as well as of the vinyl proton.



The carbonyl band in the ir spectrum is also shifted to lower wavelength. These shifts indicate that the positive charge in the salt VII is delocalized.

Pharmacological Results.—The 5,6- and 5,7-diaryl-2H-1,3,6,7-tetrahydro- and -2H-1,3-dihydrodiazepin-2-ones were administered to male Swiss albino mice at a dose of 250 mg/kg ip and observed during a period of 2 hr for prominent signs of CNS depression such as motor depression, ptosis, loss of reflex activity (prehensile, pinnal, corneal, righting), flaccidity, or catatonia. None of the compounds showed interesting activity in this procedure.

Experimental Section

The preparation of the compounds is described below in general procedures when possibe. Physical properties are given in Tables I–III. The ir spectra were determined on a Perkin-Elmer spectrophotometer (Model 21); the uv spectra were taken on a Cary 11 recording spectrophotometer and the nmr spectra were obtained on a Varian A-60 spectrometer with TMS as an internal standard. The mass spectra were taken on an AEI MS-9 mass spectrometer. The melting points were measured in open capillaries in a Hershberg apparatus and are uncorrected. When analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

β-Aminopropiophenone Hydrochlorides (II·HCl, Table I).—Compounds **1** and **2** were prepared from the desoxybenzoins, H_2CO, and $MeNH_2$ by a literature procedure.[3] Compounds **3** and **4** were prepared by treating chalcone and *m*-chlorochalcone with excess $MeNH_2$.

1,3,6,7-Tetrahydro-2H-1,4-diazepin-2-ones (IV, Table II).—The β-(aminoacetamido)propiophenone hydrochlorides (III) were prepared from the β-aminopropiophenones (II) by the following procedure which is based on a modification of a literature procedure.[2]

A solution of 21 g (0.12 mol) of *t*-butoxycarbonylglycine, 13.3 ml (0.12 mol) of N-methylmorpholine, and 120 ml of dry THF was stirred and cooled to −15°, and then 16.2 ml (0.12 mol) of isobutyl chloroformate was added. The mixture was stirred for 1–2 min and then 0.12 mol of the β-aminopropiophenone (liberated from the hydrochloride) was added in about 10 ml of THF. The mixture was stirred for 1 hr at −15° and filtered, and the filtrate was evaporated to an oil. The oil was dissolved in Et_2O and washed with dilute HCl, H_2O, $NaHCO_3$, and H_2O. The Et_2O solution was dried ($MgSO_4$), filtered, and evaporated. To the residual oil was added 75 ml of concentrated HCl, and the solution was allowed to stand for 30 min and then evaporated at reduced pressure to give a thick oil which solidified after treatment with Et_2O. Since the resulting β-(aminoacetamido)-propiophenone hydrochlorides were difficult to purify, they were converted into the bases with aqueous alkali for use in the next step. The bases were cyclized by one of the two methods listed below.

Method A.—The β-(aminoacetamido)propiophenones were heated in a bath at 135–140° at 0.2–0.5 mm for 1 hr. After cooling, the glassy residues were treated with Et_2O to give the

(2) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **89**, 5012 (1967).

(3) J. Matti, A. M. Laval-Vergès, and I. Emöd, *Bull. Soc. Chim. Fr.*, 1176 (1963).

TABLE I

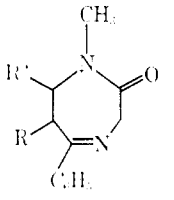
$C_6H_5COCHRCHR'NHCH_3 \cdot HCl$

II·HCl

No.	R	R'	Yield, %	Mp, °C dec	Formula[b]
1	C_6H_5	H	46	147–149[a]	$C_{16}H_{18}ClNO$
2	o-ClC_6H_4	H	55	132–136	$C_{16}H_{17}Cl_2NO$
3	H	C_6H_5	74	137–138	$C_{16}H_{18}ClNO$
4	H	m-ClC_6H_4	96	134–136	$C_{16}H_{17}Cl_2NO \cdot 0.5H_2O$[c]

[a] Lit.[4] mp 163°. [b] C: calcd, 60.2; found, 60.7. [c] All compounds were analyzed for C, H, Cl, N.

TABLE II

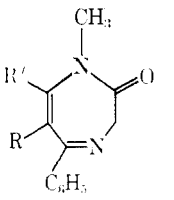


IV

No.	R	R'	Yield, %	Method	Mp, °C	Formula	Analyses
5	C_6H_5	H	60	A	101–121		
			42	B	116–126	$C_{18}H_{18}N_2O$[a]	C, H, N
6	o-ClC_6H_4	H	74	A	125–134	$C_{18}H_{17}ClN_2O$	C, H, Cl, N
7	H	C_6H_5	59	B	131–134	$C_{18}H_{18}N_2O$	C, H, N
8	H	m-ClC_6H_4	77	A	139–140	$C_{18}H_{17}ClN_2O$	C, H, Cl, N

[a] Ir ($CHCl_3$) 6.02 μ; nmr ($CDCl_3$) no NH proton and a three-proton ABC pattern; uv (MeOH) 242 mμ shifted to 265 mμ in acid solution; mass spectrum, M⁺ 278.

TABLE III



I

No.	R	R'	Yield, %	Mp, °C	Formula	Analyses
9	C_6H_5	H	52	147–148	$C_{18}H_{16}N_2O$[a]	C, H, N
10	o-ClC_6H_4	H	46	193–196	$C_{18}H_{15}ClN_2O$	C, H, Cl, N
11	H	C_6H_5	82	145–146	$C_{18}H_{16}N_2O$	C, H, N
12	H	m-Cl-C_6H_4	32	134.5–135.5	$C_{18}H_{15}ClN_2O$	C, H, Cl, N

[a] Ir ($CHCl_3$) 5.95 and 6.13 μ; nmr ($CDCl_3$) δ 3.27 (s, 3, NCH_3), 4.54 (s, 2, NCH_2CO), 6.97 (s, 1, $=CH-$); mass spectrum, M⁺ 276; uv (MeOH) 247 mμ (log ε 4.24) and 305 mμ (sh) reversibly shifted to 255 and 365 mμ in acid solution.

products as white solids which were then recrystallized from EtOH.

Method B.—A solution of the β-(aminoacetamido)propiophenone (0.018 mol) was dissolved in 750 ml of dry PhMe, 0.1 g of TsOH was added, and the mixture was refluxed under a Dean-Stark H_2O separator for 2 hr. The mixture was filtered and evaporated to give an oil. Addition of a small amount of Et_2O caused the oil to solidify. The solid was collected and recrystallized from EtOH.

1,3-Dihydro-2-H-1,4-diazepin-2-ones (I, Table III).—A mixture of 0.01 mol of the tetrahydrodiazepinone (IV), 0.1 g (0.0005 mol) of benzoyl peroxide, and 1.8 g (0.01 mol) of recrystallized NBS in 100 ml of CCl_4 was refluxed on a steam bath for 45 min. The orange solid which separated was collected and slurried in H_2O. The mixture was made alkaline and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a solid product which was recrystallized from EtOH.

When the hexahydrodiazepinone (Va) was treated with 2 molar equiv of NBS by the above procedure, the dihydrodiazepinone (Ia) was obtained in a 22% yield.

Hexahydro-1-methyl-5,6-diphenyl-2H-1,4-diazepin-2-one (Va).—A mixture of 0.56 g (0.002 mol) of IVa, 0.1 g of 10% Pd–C, and 25 ml of EtOH was hydrogenated at room temperature and atmospheric pressure. After the calculated amount of H_2 had been absorbed (3 hr), the catalyst and solvent were removed to give 0.5 g (90%) of the product as a white solid, mp 141–142.5°, ir ($CHCl_3$) 6.09 μ. *Anal.* ($C_{18}H_{20}N_2O$) C, H, N.

Hexahydro-1-methyl-5,7-diphenyl-2H-1,4-diazepin-2-one (Vc).—A mixture of 2.95 g (0.0106 mol) of IVc, 0.5 g of 10% Pd–C, and 125 ml of EtOH was hydrogenated as described above. After removal of the catalyst and solvent, 2.8 g (94%) of the product was obtained as a white solid, mp 124.5–128°. Recrystallization from EtOAc gave the analytical sample, mp 129–130°, ir ($CHCl_3$) 6.12 μ. *Anal.* ($C_{18}H_{20}N_2O$) C, H, N.

1,3-Dihydro-1-methyl-5,6-diphenyl-2H-1,4-diazepin-2-one 4-Oxide (VI).—A mixture of 0.83 g (0.003 mol) of Ia and 0.81 g (0.005 mol) of m-chloroperbenzoic acid in 35 ml of CH_2Cl_2 was stirred for 24 hr and then washed with $NaHCO_3$ and H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated to an orange glass. Two recrystallizations from EtOH gave 0.05 g (6%) of a white solid: mp 208–208.5°; ir ($CHCl_3$) 5.99 and 6.21 μ; nmr ($CDCl_3$) δ 3.33 (s, 3, NCH_3), 4.87 (s, 2, NCH_2CO), 6.83 ppm (s, 1, $CH=$). *Anal.* ($C_{18}H_{18}N_2O_2$) C, H, N.

1,3-Dihydro-1,4-dimethyl-2-oxo-5,6-diphenyl-2H-1,4-diazepinium Iodide (VII).—A solution of 0.28 g (0.001 mol) of Ia, 5 ml of MeI, and 5 ml of Me_2CO was allowed to stand at room tem-

perature overnight. The yellow solid which had separated was collected and recrystallized from MeCN to give 0.35 g (83%) of a yellow solid: mp 223.5° dec; ir (Nujol mull) 5.85 and 6.22 μ; nmr (d_6-DMSO) δ 3.50 (s, 6, $2NCH_3$), 4.73 (s, 2, NCH_2CO), 8.09 ppm (s, 1, $CH=$). *Anal.* ($C_{19}H_{19}IN_2O$) C, H, I, N.

Acknowledgments.—We wish to thank Mr. L. Brancone and associates for the microanalyses, Mr. W. Fulmor and Mr. G. O. Morton for the interpretation of the nmr spectra, and Dr. J. Karliner for the mass spectra. We also thank Dr. E. N. Greenblatt, Mrs. A. K. Pajares, and Mrs. Josephine Kurowski for the pharmacological testing.

Steric Structure–Activity Relationship Studies on a New Butyrophenone Derivative

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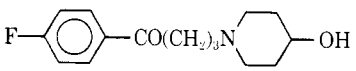
Received May 5, 1969

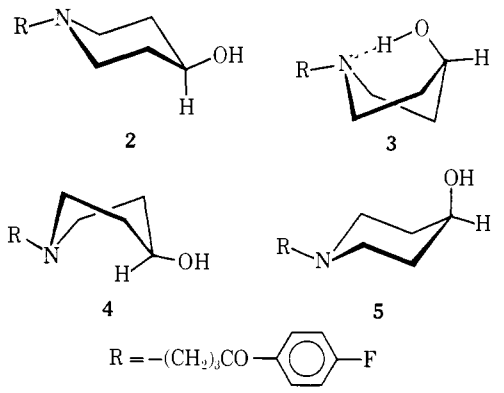
4-(4-Hydroxypiperidino)-4′-fluorobutyrophenone (**1**) has been reported to produce moderate tranquilization properties in mice, rats, cats, dogs, and human subjects.[1] There is no knowledge concerning how the drug is bound to the receptor site. Unlike the majority of the active antipsychotic butyrophenone-type compounds, it possesses only minimal antiemetic activity. We assume that this unique activity and other properties are related to the structure of this molecule *per se*. The objective of this study is to look for possible steric requirements of the hydroxyl group orientation.



1

The most stable conformation for **1** is **2**. Other less stable conformations are **3**, **4**, and **5**.[2] The observed free-energy difference between the axial and the equatorial dispositions of the hydroxyl group of N-methyl-4-piperidinol in D_2O is 0.94 ± 0.05 kcal/mol at 40° and 0.81 ± 0.05 kcal/mol at 80°.[3] The free-energy difference between **2** and **5** should be about the same under similar conditions. There is ample evidence reported in the literature, showing that 4-piperidinols and 4-piperidinones behave like cyclohexanols and cyclohexanones, respectively. The energies of **3** and **4** then should be much higher than those of **2** and **5**. The high energy of the twist or boat form **3** is partially offset by intramolecular hydrogen bonding, which is impossible in **4**.

Conformational analysis of the substrate does not necessarily reveal the actual conformation responsible for the pharmacological responses, especially in cases where the drug receptor can also undergo conformational changes. In this case, the energy of the substrate–receptor complex should be considered. Therefore, a thermodynamically slightly less stable conformation of a substrate may have a better fit to the receptor, so that a complex of lower energy (compared with a complex formed by the substrate in a thermodynamically more stable conformation and the receptor in a less favorable conformation) is formed, and in turn greater response or potency results. Since **1** is tested in intact animals, we know nothing about the nature of the receptor site or about the drug–receptor complex. It is impossible to conclude whether **2** or **5** is the active form, although **3** and **4** may be excluded on the ground of their high energy levels.[4]



2 3 4 5

Four analogs of **1** have been synthesized and tested in mice. Compounds **6**, **7**, and **9** were prepared by N-alkylation of norpseudotropine (**10**), nortropine (**11**), and 3-ethylamino-1-propanol (**12**), respectively, with the chloride **13** (Scheme I). Compound **7** was obtained in two crystalline forms, which gave identical infrared spectra in $CHCl_3$. The higher melting form was used in animal tests. Compound **8** was synthesized as shown in Scheme II. Tropinone hydrobromide (**14**) was converted to the dioxolane derivative **15**, which was demethylated to 3,3-ethylenedioxytropane (**16**). N-Alkylation of **16** gave **8**.

The configuration of C-3 and the conformations of tropine and pseudotropine derivatives have been well established.[5] In both series the piperidine ring exists in the chair form. Hence, if the boat and the twist forms are excluded for consideration on the ground of their high energies, it is most likely that **6** and **7** react with the receptor sites in the conformations shown, which possess an axial and an equatorial hydroxyl group, respectively. In **8**, there is an axial as well as an equatorial oxygen function at C-3; both of these are incorporated in an ether function rather than existing as hydroxyl group. Compound **9** is the 3,4-seco analog of **1** and the ethyl and 3-hydroxypropyl substituents on the nitrogen atom can assume whatever conformation the piperidine ring of **1** may have.

The minimal effective dose (MED) for some CNS activities of **1** and **6–9** are given in Table I. The per-

(1) For evaluation of other pharmacological effects exhibited by **1**, see (a) D. M. Gallant, M. P. Bishop, and R. Guerrero-Figueroa, *Current Therap. Res.*, **10**, 244 (1968); and (b) A. A. Sugerman, *ibid.*, **10**, 533 (1968).

(2) N. M. Gabel and L. G. Abood [*J. Med. Chem.*, **8**, 616 (1965)] have correlated the availability of the N electron pair of some piperidine compounds to their anticholinergic psychotomimetic potency. However, the orientation of the N electron pair and, in turn, the spatial disposition of the N substituent in all compounds discussed in this work are not considered here.

(3) C. Y. Chen and R. J. W. Le Fevre, *Tetrahedron Lett.*, 4057 (1965).

(4) Assuming N-substituted 4-piperidinols behave like cyclohexanol, the energy difference between the twist form **4** and the chair form **2** would be approximately 5.9 kcal/mol. For a discussion of the chair and flexible forms of cyclohexane, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 36–42.

(5) G. Fodor, *Alkaloids*, **6**, 145 (1960); **9**, 269 (1967); also see A. Sinnema, L. Maat, A. J. Van Der Gugten, and H. C. Beyerman, *Rec. Trav. Chim.*, **87**, 1027 (1968).