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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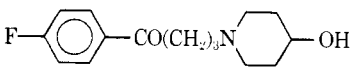
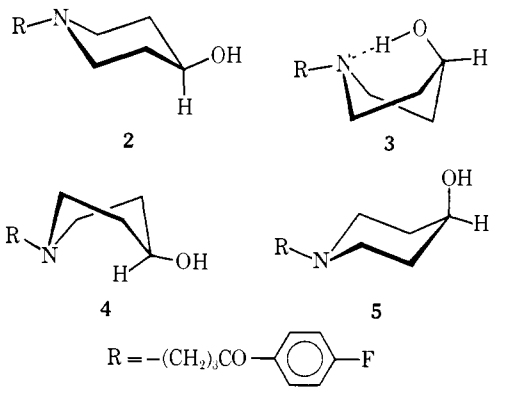
4-(4-Hydroxypiperidino)-4′-fluorobutyrophenone (**1**) has been reported to produce moderate tranquilization properties in mice, rats, cats, dogs, and human subjects.[1] There is no knowledge concerning how the drug is bound to the receptor site. Unlike the majority of the active antipsychotic butyrophenone-type 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).

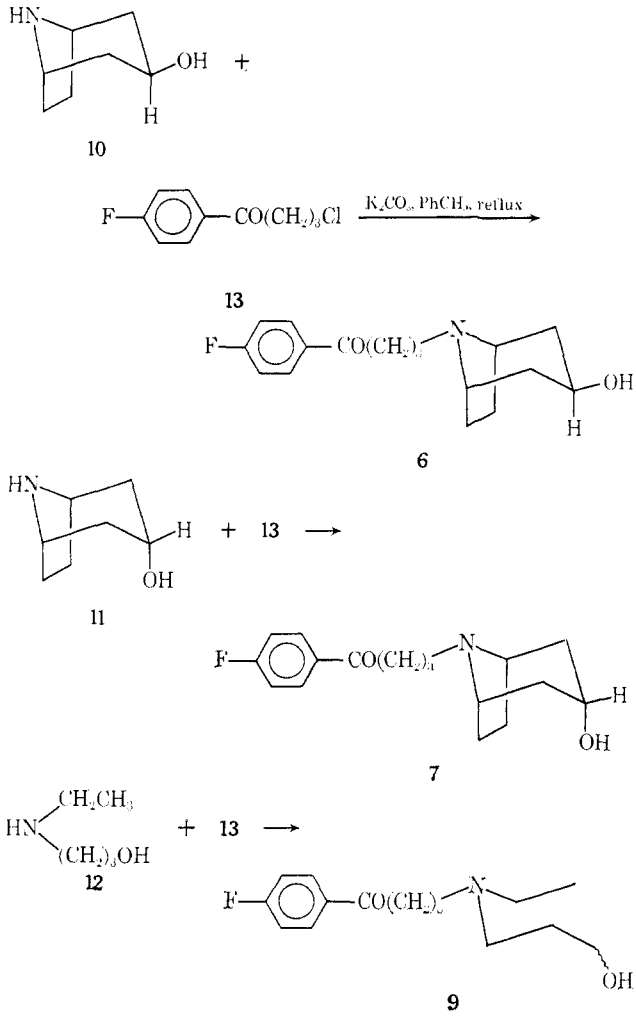
(2) N. M. Gabel and L. G. Abood [*J. Med. Chem.*, **8**, 616 (1965)] have correlated the availability of the N electron pair of some piperidine compounds to their anticholinergic psychotomimetic potency. However, the orientation of the N electron pair and, in turn, the spatial disposition of the N substituent 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).

SCHEME I



SCHEME II

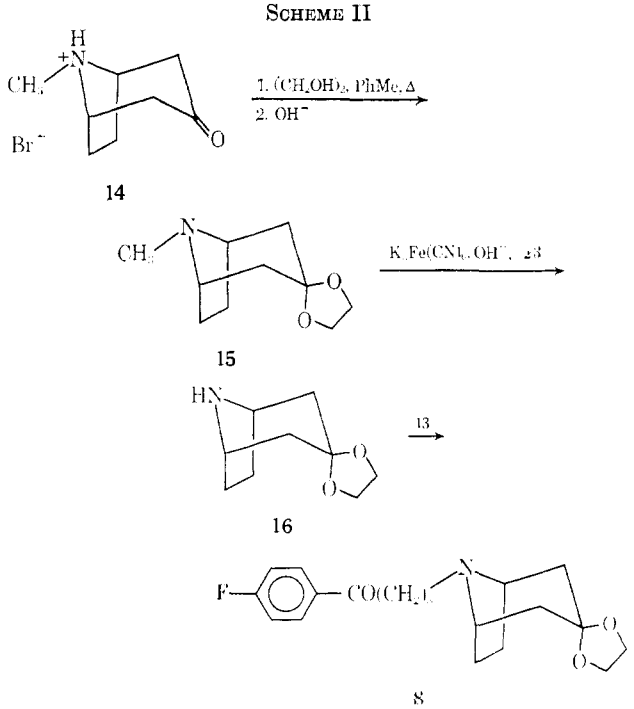
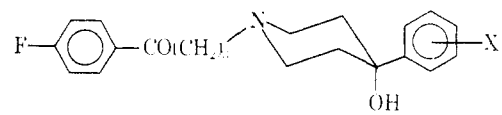


TABLE I

Compd	MED, mg/kg po (mice): Behavior depression	Muscle relaxation
1	10	10
6	150	300
7	150	75
8	150	150
9	100–300	300
17	5	5–10
18	5	5–10

tinent data of haloperidol (**17**) and trifluperidol (**18**) are also given for comparison.

Of the two tests, muscle relaxation is more sensitive and thus gives a better indication of the CNS activity of the compounds. Compounds **6–8** possess about the same behavior depression potency. However, the muscle relaxation test definitely shows the potency order: **7** > **8** > **6**. These results suggest that **5** is the conformation responsible for the CNS activities of **1**. This is borne out by the activities of **17** and **18**. In the



17, X = 4-Cl
18, X = 3-CF$_3$

molecules of these two compounds, the substituted phenyl rings have the preference of occupying the equatorial disposition, forcing the hydroxyl group to assume the axial position.[6]

The markedly reduced activities of **6–8** seem to be associated with the ethylene bridge of the tropane ring. If both the N and the O atoms are involved in binding the receptor and/or in causing the pharmacological response, it becomes evident that the ethylene bridge seems to prevent this to some extent. The low activities of **9** in both tests indicate that the N substituents poorly mimic the pharmacological conformation of the piperidine ring of **1**.

Experimental Section[7]

N-Alkylation. General Procedure.—Compounds **6–9** were synthesized by this general method (see Table II). A mixture of the amine (20–25 mmol), 4-chloro-4′-fluorobutyrophenone (**13**, 30 mmol), anhydrous K_2CO_3 (5–10 g), and PhMe (30–50 ml) was refluxed overnight. The hot reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was fractionated on kugelrohr to remove the by-product *p*-fluorobenzoylcyclopropane and any unreacted starting amine. The products were obtained as higher boiling fractions. The liquid products were purified by repeated kugelrohr distillation, and the solid materials by recrystallizing from appropriate solvents.

Compound **7** was obtained in two crystalline forms. The procedure of obtaining them is described below.

4′-Fluoro-4-nortropinobutyrophenone (7).—A mixture of nortropine (**11**, 3.18 g, 25 mmol), chloride **13** (5.6 g, 28 mmol), anhydrous K_2CO_3 (7 g), and PhMe (30 ml) was refluxed overnight and filtered. Evaporation of the filtrate afforded an oil (8 g), which was kugelrohr distilled at 0.001 mm. A mixture (1.7 g) of *p*-fluorobenzoylcyclopropane and unreacted 11 was collected at 100° (air bath) and the product at 140° (air bath) (5.5 g, 67% yield). The product thus obtained was redistilled under the

(6) J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, pp 207, 209–231. Conformational energy "best values": C_6H_5, 3.0; OH, 0.52 (aprotic solvents) and 0.87 kcal (hydrogen-donor solvents).

(7) Melting points were determined on a Thomas–Hoover Unimelt and are uncorrected. Microanalyses were conducted by the Aldrich Analytical Division on an F and M Model 185 CHN analyzer. Yields of products were based on results of one single reaction. No attempt was made to obtain maximum yields.

TABLE II

Compd	Yield, %	Mp, °C	Kugelrohr distn,[a] °C (mm)	n_D (°C)	Formula	Analyses
6	72	86.0–87.5			$C_{17}H_{22}FNO_2$	C, H, N
6	67	Two forms: 58–61, 81.5–83.0			$C_{17}H_{22}FNO_2$	C, H, N
8	55		110–120 (1×10^{-3})	1.5366 (20)	$C_{19}H_{24}FNO_3$	C, H, N
9	51		117 (7×10^{-5})	1.5345 (23.5)	$C_{15}H_{22}FNO_2$	C, H, N

[a] Temperatures given are those of the air bath, at which the materials were collected.

same conditions. A small syrupy fraction was collected at 140°, which solidified upon standing. It was recrystallized from C_6H_6–petroleum ether (bp 30–60°) as white, fine prismatic needles, mp 58–61°. The second fraction was collected at 155° and recrystallized twice from C_6H_6–petroleum ether as prismatic granules, mp 81.5–83.0°. The ir spectra of the two substances in solid state (Nujol mull) were markedly different, but were superimposable in solution ($CHCl_3$): 2.9 (broad), 3.4, 5.95, 11.98 μ.

3,3-Ethylenedioxytropane (15).—A mixture of tropinone hydrobromide (**14**, 30 g, 0.136 mol), ethylene glycol (17.5 g), and PhMe (150 ml) was stirred and refluxed for 47 hr, while water plus the glycol (7 ml) was collected in a Barrett trap. After cooling, the organic layer was decanted, and the black tarry substance was dissolved in 2 *N* KOH (100 ml) and continuously extracted with Et_2O (250 ml) for 6 hr. The Et_2O extract and the PhMe layer were combined, dried, and evaporated *in vacuo*, giving the crude product as a dark liquid (31 g). Two kugelrohr distillations afforded the pure product as a colorless liquid, collected at 45–50° (air-bath temperature) and 0.02 mm, $n^{20}D$ 1.4936. *Anal.* ($C_{10}H_{17}NO_2$) C, H, N.

3,3-Ethylenedioxynortropane (16).—To a mixture of **15** (9.2 g, 50 mmol), NaOH (20 g), and H_2O (80 ml), which was cooled to −10°, was added a warm aqueous solution of $K_3Fe(CN)_6$ [98.8 g, 0.3 mol, in H_2O (170 ml)] at a rate to maintain the reaction mixture at ±3° with efficient stirring. The addition required 60 min. After stirring at room temperature for 43 hr, the mixture was continuously extracted with Et_2O (250 ml) for 72 hr. The Et_2O extract was stirred with KOH pellets for 2 hr, filtered through Celite, and evaporated *in vacuo*. Kugelrohr distillation of the red liquid residue (8 g) gave the product (7 g, 83% yield), collected at 35–40° (0.002 mm). An analytical sample was obtained by redistillation on kugelrohr, as a colorless liquid, collected at 105–110° (5 mm), $n^{19.8}D$ 1.5033. *Anal.* ($C_9H_{15}NO_2$) C, H, N.

Acknowledgments.—The authors are indebted to the Pharmacology Department of the Bristol Research Laboratories, Syracuse, N. Y., for the biological tests.

Synthesis of Compounds with Potential Central Nervous System Stimulant Activity. I. 2-Amino-2-oxazolin-4-one-5-spirocycloalkanes and 2-Amino-2-oxazolin-4-one-5-spiro(4′-piperidines)

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The known activity of many 2-amino-2-oxazolines[1,2] and 2-amino-2-oxazolin-4-ones[3–5] as CNS stimulants

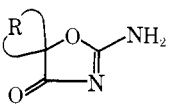
TABLE I

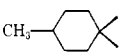
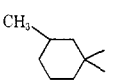
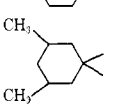
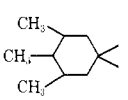
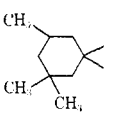
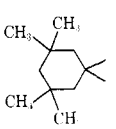
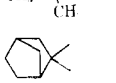
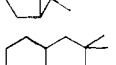
Compd[a]	Min dose causing signif inc in spont motor act., mg/kg Ip	Oral	Approx LD_{50}, mg/kg Ip	Oral
Pemoline	10	10	500	500
1h	50	50	300	300
1j	50	100	750	750
3a	100	200	>1000	>1000

[a] Administered as a 2% suspension in 0.3% trajacanth.

TABLE II

2-AMINO-2-OXAZOLIN-4-ONE-5-SPIROCYCLOALKANES



No.	R	Formula	Mp, °C[a]	Yield, %
1a		$C_6H_8N_2O_2$	188–193	15.0
b		$C_7H_{10}N_2O_2$	215–220	16.2
c		$C_8H_{12}N_2O_2$	220–225	16.0
d		$C_9H_{14}N_2O_2$	248–253	21.3
e		$C_{10}H_{16}N_2O_2$	262–266	31.2
f		$C_9H_{14}N_2O_2$	272–277	11.3
g		$C_9H_{14}N_2O_2$	249–252	30.7
h		$C_{10}H_{16}N_2O_2$	278–282	30.5
i		$C_{11}H_{18}N_2O_2$	296–302	36.4
j		$C_{11}H_{18}N_2O_2$	261–266	25.8
k		$C_{12}H_{20}N_2O_2$	318–321	27.8
l		$C_9H_{12}N_2O_2$	284–289	31.4
m		$C_{12}H_{18}N_2O_2$	248–268	13.3

[a] All compounds melted with decomposition.

(1) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley, and J. McGowin, *J. Med. Chem.*, **6**, 266 (1963).
(2) Lab. Dausse, French Patent 1,426,080 (1966).
(3) L. Schmidt, *Arzneimittel-Forsch.*, **6**, 423 (1956).
(4) H. Najer and R. Giudicelli, *Bull. Soc. Chim. France*, 1231 (1961).
(5) C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1679 (1962).