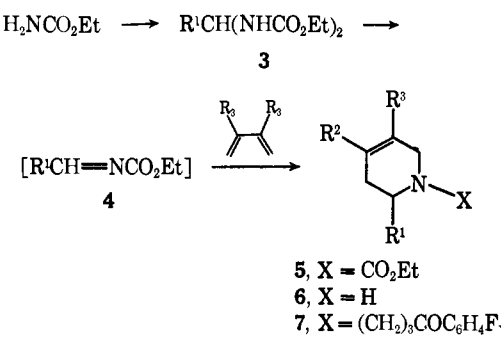

(ip) to mice and gross behavioral changes were observed, essentially according to the protocol described by Irwin.[10] All proved to be CNS depressants; in addition, **10** gave some indications of CNS stimulation. The most potent depressants were **12** and **13**; both showed some activity at 5 mg/kg. Compd **1** when tested in these laboratories displays activity at 2.5 mg/kg. Compd **12** also showed decreases of 11, 22, and 54% of normal responses at doses of 2.5, 5, and 10 mg/kg, resp, in the Sidman avoidance procedure.[11] All of the compds were lethal at doses greater than 100 mg/kg.

Experimental Section

Representative Procedure. 4′-Fluoro-4-[4-methyl-2-(4-methoxyphenyl)-1,2,3,6-tetrahydro-1-pyridyl]butyrophenone·HCl (11).—A stirred mixt of 0.10 mole of (*p*-methoxyphenyl)-methylenebis(ethylurethane), 2 ml of $BF_3 \cdot 2EtO$, and 200 ml of C_6H_6 was heated to reflux as 0.15 mole of isoprene was added dropwise. The mixt was refluxed an addnl hr, then cooled, washed with H_2O, and dried ($MgSO_4$). Removal of solvent and distn of the residue afforded 23.6 g (81%) of ethyl 1,2,3,6-tetrahydro-2-(4-methoxyphenyl)-4-methyl-1-pyridinecarboxylate (**14**), bp 137–139° (0.09 mm). *Anal.* C, H, N. Hydrolysis was effected by maintaining a mixt of the carbamate, excess KOH, and ethylene glycol at 150° for 12 hr, cooling, dilu with H_2O, and extn into Et_2O. The washed and dried (K_2CO_3) Et_2O soln was evapd *in vacuo*, and the crude amine was used directly. A stirred mixt of the amine, 1.5 mole equiv of γ-chloro-*p*-fluorobutyrophenone, 2 equiv of Na_2CO_3, 100 mg of KI, and 100 ml of 1,2-dimethoxyethane was refluxed 12 hr, at the end of which time tlc analysis demonstrated the consumption of starting amine. The cooled mixt was dild with several vol of H_2O and extd with Et_2O. The dried (K_2CO_3) Et_2O exts were then satd with HCl gas to ppt 45–60% yields of brown, somewhat tacky **11**. Two recrystn from MeOH–Et_2O afforded white needles of **11**, mp 159–161°.

(10) S. Irwin in "Animal and Clinical Pharmacological Techniques in Drug Evaluation," H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Philadelphia, Pa., 1964, pp 36–54.

(11) M. Sidman, *Science*, **118**, 157 (1953).

Central Nervous System Active Butyrophenones. 2. Methyl-Branched γ-Aminobutyrophenones

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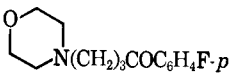
The chemistry and pharmacology of the potent neuroleptic, haloperiodol (**1**),[1,2] have been studied extensively. Simpler analogs of **1** have also been studied. For example, **2** has been found[3] to be a potent MAO inhibitor. In these laboratories, **2** has been found to be approximately 0.1 as potent a sedative as **1**. Reviews of the pharmacology of **1** indicate that alkyl branches or



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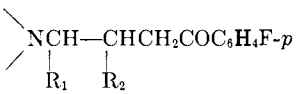
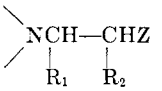
unsaturation in the carbonyl side chain lead to diminished activity.[2] Since it has been shown[4] that **1** is metabolized by cleavage α to N, followed by degradation to *p*-fluorophenylacetic acid, we were interested in examining the possible effects of Me substituents on this process and on the duration of action of related drugs. Accordingly, we present here the preparation and properties of some simple model compounds **3** in which R_1 and R_2 are alternately CH_3 and H.



3

Chemistry.—Michael addition of secondary amines to either methyl methacrylate or methyl crotonate afforded β-amino esters (**4**, Z = CO_2CH_3). Reduction to the alcohols (**4**, Z = CH_2OH) with LAH, followed by reaction with $SOCl_2$ in PhH, provided the Cl compounds (**4**, Z = CH_2Cl). Conversion to the Grignard reagent, followed by reaction with *p*-fluorobenzonitrile, proved exceedingly troublesome but finally proceeded in acceptable yield using extended reaction times and THF as the solvent. The compds and intermediates, some of which have been reported in the literature, prepared are listed in Table I.



4

Pharmacology.—Compds **8**, **12**, **16**, **20**, **24**, and **28** showed varying degrees of CNS depression when tested in mice (ip).[5] Compd **8** was the most active, showing depression at doses of 100 mg/kg; **28** was the least potent, showing very little activity below the convulsant dose level of *ca.* 300 mg/kg. The lethal dose varied somewhat, ranging from 100 mg/kg for **12** to *ca.* 1000 mg/kg for **16** and **28**. No relationship between activity and the position of the Me group in isomeric pairs could be discerned. As expected, in every case the unbranched compds (*i.e.*, $R_1 = R_2 = H$) were more active; somewhat discouraging was the observation that no increase in the duration of activity with **8**, **12**, **16**, **20**, **24**, and **28** could be observed.

Experimental Section

The following procedure is representative.

***dl*-α-Methyl-3-azabicyclo[3.2.2]nonone-3-propionate·HCl (21).**—A soln of 24.04 g (0.20 mole) of 3-azabicyclo[3.2.2]nonane,

(1) Haloperidol.

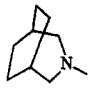
(2) P. A. J. Janssen in "Medicinal Chemistry," Vol. 4-II, M. E. Gordon, Ed., Academic Press, New York, N. Y., 1967.

(3) R. F. Squires and J. B. Lassen, *Biochem. Pharmacol.*, **17**, 369 (1968).

(4) G. A. Braun, G. I. Poos, and W. Soudijn, *Eur. J. Pharmacol.*, **1**, 58 (1967).

(5) S. Iwrin in "Animal and Clinical Pharmacological Techniques in Drug Evaluation," H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Philadelphia, Pa., 1964, pp 36–54.

TABLE I
YCHR$_1$CHR$_2$Z

Compd	Y	R$_1$	R$_2$	Z	Bp (mm), °C	Mp, °C	Formula	Anal.[a] or reference
5	Piperidyl	H	CH_3	CO_2CH_3		163-164[b]		*c*
6	Piperidyl	H	CH_3	CH_2OH	35 (0.02)			*d*
7	Piperidyl	H	CH_3	CH_2Cl	52 (2)		$C_9H_{18}ClN$	C, H, N, Cl
8	Piperidyl	H	CH_3	$CH_2COC_6H_4F$-*p*		122–123[e]	$C_{16}H_{22}FNO \cdot C_4H_4O_4$	C, H, N
9	Piperidyl	CH_3	H	CO_2CH_3	37–38 (0.02)			*f*
10	Piperidyl	CH_3	H	CH_2OH	110 (15)[g]			*g*
11	Piperidyl	CH_3	H	CH_2Cl		155–157[b]	$C_9H_{18}ClN \cdot HCl$	C, H
12	Piperidyl	CH_3	H	$CH_2COC_6H_4F$-*p*	140–142 (0.6)		$C_{16}H_{22}FNO$	C, H, N
13	Morpholinyl	H	CH_3	CO_2CH_3		175–177[b]		*c*
14	Morpholinyl	H	CH_3	CH_2OH	60 (0.1)			*h*
15	Morpholinyl	H	CH_3	CH_2Cl	32 (0.02)		$C_8H_{16}ClNO$	C, H, N, Cl
16	Morpholinyl	H	CH_3	$CH_2COC_6H_4F$-*p*		124–125[c]	$C_{15}H_{20}FNO_2 \cdot C_4H_4O_2$	C, H, N
17	Morpholinyl	CH_3	H	CO_2CH_3		168–170[b]	$C_9H_{17}NO_3 \cdot HCl$	C, H, N
18	Morpholinyl	CH_3	H	CH_2OH	70 (0.02)		$C_8H_{17}NO_2$	C, H, N
19	Morpholinyl	CH_3	H	CH_2Cl	48 (0.03)		$C_8H_{16}ClNO$	C, H, N
20	Morpholinyl	CH_3	H	$CH_2COC_6H_4F$-*p*	141 (0.06)		$C_{15}H_{20}FNO_2$	C, H, N
21		H	CH_3	CO_2CH_3		178–179[b]	$C_{13}H_{23}NO_2 \cdot HCl$	C, H, N, Cl
22		H	CH_3	CH_2OH		41–44	$C_{12}H_{22}NO$	C, H, N
23		H	CH_3	CH_2Cl	65 (0.04)		$C_{12}H_{22}ClN$	C, H, N, Cl
24		H	CH_3	$CH_2COC_6H_4F$-*p*		143–144[e]	$C_{19}H_{26}FNO \cdot C_4H_4O_4$	C, H, N
25		CH_3	H	CO_2CH_3	117 (0.04)		$C_{13}H_{23}NO_2$	C, H, N
26		CH_3	H	CH_2OH	95–96 (0.02)		$C_{12}H_{23}NO$	C, H, N
27		CH_3	H	CH_2Cl	78 (0.02)		$C_{12}H_{22}ClN$	C, H, N
28		CH_3	H	$CH_2COC_6H_4F$-*p*		68–70	$C_{19}H_{26}FNO$	C, H, N

[a] For new compds, anal. of the indicated elements were within ±0.4% of the calcd values. Nmr and ir spectra were also consistent with the assigned structures. Racemates were not resolved. [b] HCl salt. [c] A. Vystrčil and S. Hudeček, *Chem. Listy*, **44**, 262 (1950); *Chem. Abstr.*, **45**, 5625c (1951). [d] P. Bieber, *Ann. Chim. (Paris)*, **9**, 674 (1954). [e] Maleate salt. [f] K. Osugi, *Yakugaku Zasshi*, **75**, 1549 (1955). [g] C. Mannich and Ph. Horkheimer, *Arch. Pharm. (Weinheim)*, **264**, 167 (1926). [h] E. Profft and H. Oberender, *J. Prakt. Chem.*, **25**, 225 (1964).

20.02 g (0.20 mole) of methyl methacrylate, 45 ml of MeOH, and 0.1 g of NaOMe was kept at room temp for 3 days. Dilu with H_2O, extn with Et_2O, evapn of the dried (K_2CO_3) Et_2O exts, and distn afforded 30.16 g (66%) of colorless liquid, bp 85–88° (0.09 mm). A sample in Et_2O was satd with HCl to ppt **21**, mp 178–179°. Three recrystn from MeOH–Et_2O did not raise the mp.

dl-**β-Methyl-3-azabicyclo[3.2.2]nonane-3-propanol (22).**—A soln of 22.53 g (0.10 mole) of amino ester in 150 ml of Et_2O was added dropwise to a stirred suspension of 3.8 g of LAH in 350 ml of Et_2O. After the addn was complete, the mixt was refluxed 1 hr, cooled, and worked up in the usual manner. Removal of solvent afforded 17.63 g (90%) of anal. pure white crystals of **22**, mp 41–44°.

dl-**3-(3-Chloro-2-methylpropyl)-3-azabicyclo[3.2.2]nonane (23).**—A stirred, refluxing soln of 5.92 g (0.030 mole) of **22** in 50 ml of C_6H_6 was treated dropwise with a soln of 10 ml of $SOCl_2$ in 10 ml of C_6H_6. The mixt was then refluxed overnight, concd to *ca.* 0.5 vol by distn, and poured into excess ice water. The aq layer was extd thoroughly with C_6H_6, then covered with Et_2O, and made strongly basic (pH 10) by the addn of solid K_2CO_3. The Et_2O ext was sepd, and the aq mixt was extd thoroughly with Et_2O. The combined Et_2O exts were dried (K_2CO_3) and evapd *in vacuo*. The residue (6.23 g) was distd to provide 4.23 g (66%) of **23**, bp 65–67° (0.04 mm). This material could be kept in the freezer for several days without change but irreversibly solidified over a period of weeks.

dl-**β-Methyl-γ-*N*-(3-azabicyclo[3.2.2]nonyl)-*p*-fluorobutyrophenonemaleate (24).**—A soln of 4.21 g (0.020 mole) of **23** in 50 ml of anhyd THF was added dropwise to 0.54 g (0.022 g-atom) of Mg. Shortly after the addn was begun, the mixt was heated and maintained at reflux throughout the remainder of the addn and for an addnl 12 hr. The resulting brown solu was cooled, treated dropwise with a solu of 2.42 g (0.020 mole) of

p-fluorobenzonitrile in 50 ml of THF, and then refluxed for 12 hr. The cooled mixt was decompd with aq NH_4Cl and extd with Et_2O. The Et_2O soln was extd with cold 1 *N* HCl. The aq exts were washed with Et_2O, made strongly alk with solid K_2CO_3, and extd with Et_2O. The exts were washed with H_2O, dried (K_2CO_3), and added to a soln of maleic acid in Et_2O. The ppt which formed was filtered, washed with Et_2O, and recrystd from $CHCl_3$–Et_2O to provide 1.45 g (17%) of **24** as white needles, mp 143–144°.

Synthesis and Analgetic Activity of 1,5-Methano-3-methyl-1,2,3,4,5,6-hexahydro-3-benzazocines

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The 1,5-methano-3-methyl-1,2,3,4,5,6-hexahydro-3-benzazocines described in Table I were prepared as possible analgetics and because compound **3** was desired for comparison with an amine of unknown structure obtained from another project. To our knowledge the 1,3-dimethyl,[1] the 1,3-dimethyl-11-oxo,[1] and the 2,6-dioxo[2] derivatives are the only published examples of this ring system. No pharmacological studies on these compds have been reported.

In the present synthetic scheme, hydrogenation of the methyl tosylate quaternary of methyl 5-phenyl-nicotinate[3] and subsequent recovery of the bases gave a mixture of the *cis*- and *trans*-nipecotic esters which were separated as their acid maleate and acid fumarate salts, resp. Their probable configurations were assigned by equilibrating each ester with NaOMe. This procedure gave a 7:3 mixture of esters and the cis diequatorial form was considered to be the favored configuration.[4] Each of the isomeric nipecotic acids was cyclized by polyphosphoric acid to the 6-oxo compd **1** (Table I) in excellent yield. The latter was converted to the compds described by procedures given in the Experimental Section.

The reduction of **1** either catalytically or with LAH gave the cis alcohol **4** which was readily isomerized to the trans alcohol **5** by MsOH. The configurations of these compds were assigned from the coupling constants of the benzylic proton at position 6. The configurations of alcohols **9** and **11** are unknown, but, since all attempts to acetylate **9** failed, its Ph group is probably trans to the bridge; the form in which the OH group is most hindered.

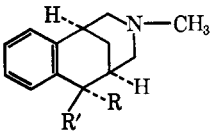
Pharmacology.—Behavioral, neurologic, and autonomic actions were assessed in preliminary dose-ranging studies in mice using the method of Irwin.[5]

Groups of 3 mice were treated orally with the compd dissolved or suspended in 0.4 ml of a 0.5% carboxymethylcellulose vehicle/20-g mouse, and a dose of 100 mg/kg was used for primary screening.

Analgetic activity was determined by the ability of the compds to alter the nociceptive response to pinching the tail with a forcep[6] in the initial dose-ranging studies,

TABLE I

1,5-METHANO-3-METHYL-1,2,3,4,5,6-HEXAHYDRO-3-BENZAZOCINES



No.	R	R1	Salt[a]	Mp, °C	Crystn,[b] solvent	Yield, %	Formula[c]
1		O[d]		61–63	H	87	$C_{13}H_{15}NO$
2		O[d]	HCl	253–256	E–EA		$C_{13}H_{16}ClNO$
3	H	H[e]	HCl	243–245	E–EA	59	$C_{13}H_{18}ClN$
4	H	OH[f,g,h]		78–80	I	80	$C_{13}H_{17}NO$
5	OH	H[i]		88–89	H	75	$C_{13}H_{17}NO$
6	H	C_2H_5COO[h]		85–87	I	60	$C_{16}H_{21}NO_2$
7	H	C_2H_5COO	HCl	211–212	A		$C_{16}H_{22}ClNO_2$
8	C_2H_5COO	H[i,j]	HCl	199–201	E–EA	35	$C_{16}H_{22}ClNO_2$
9	C_6H_5	OH[k,l]	M	180–181	E	75	$C_{23}H_{25}NO_5$
10	C_6H_5	H[i]	HCl	278–280	A–E		$C_{19}H_{22}ClN$
11	$C_6H_5CH_2$	OH[k,m]	HCl	246–248	E	38	$C_{20}H_{24}ClNO$
12	$C_6H_5CH_2$	OAc[k]		134–135	E–I		$C_{22}H_{25}NO_2$

[a] M = acid maleate. [b] A, CH_3CN; E, EtOH; EA, EtOAc; H, hexane; I, *i*-Pr_2O. [c] Analytical results were within ±0.4% for C, H, and N for all compounds listed. [d] R + R1 = 0. [e] Base prepd from **1** by Wolf-Kishner reduction in diethylene glycol 5 hr at 175°. [f] Prepd by LAH reduction of **1** in Et_2O. [g] Prepd by reduction of **1** with Pt in AcOH contg NH_4OAc, yield 60%. [h] Nmr $J_{H_6H_5}$ = 6.5 Hz. [i] Nmr $J_{H_6H_5}$ = 0 Hz. [j] Prepd from **5** as described for **6**. [k] Configuration unknown. [l] Prepd from **1** and PhLi in Et_2O. The free base formed cryst solvates with Et_2O, EtOAc, and with MeCN all melting at 90–120°. [m] Prepd from **1** and PhMgCl in Et_2O.

(1) K. Mitsuhashi, S. Shiotani, R. Oh-uchi, and K. Shiraki, *Chem. Pharm. Bull.*, **17**, 434 (1969).

(2) R. Hill, C. Glassick, and L. Fliedner, *J. Amer. Chem. Soc.*, **81**, 737 (1959).

(3) M. Julia, H. Pinhas, and J. Ingolen, *Bull. Soc. Chim. Fr.*, 2387 (1966).

(4) G. Settimj, M. Carani, F. Gatta, and S. Chiavarelli, *Gazz. Chim. Ital.*, **100**, 703 (1970), have shown this to be the case with 3,5-diphenyl-4-piperidones.

(5) S. Irwin, "Clinical Pharmacological Techniques," J. H. Nodine and P. S. Siegler, Ed., Yearbook Medical Publishers, Inc., Chicago, Ill., 1964, Chapter 4.

(6) C. Bianchi and J. Francheschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).