Central Nervous System Active Butyrophenones. 1. Unsaturated Analogs of γ -Aminobutyrophenones

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The potent neuroleptic 1^1 has been the subject of exhaustive chemical and pharmacological investigation,



during the course of which many structural variants have been prepared.²⁻⁴ We describe herein the prepreasonably be expected to be a facile process. A few such unsaturated analogs of 1 have been reported.^{5,6} For example, 2 was described as a convulsant, having no tranquilizing activity.³



Chemistry.--Condensation of aliphatic or aromatic aldehydes with ethyl carbamates affords methylenebis-(N-urethanes) (3) which, in the presence of boron trifluoride etherate, are converted to the transient dienophiles 4. A Diels-Alder reaction affords 1,2,3,6tetrahydropyridine carbamates (5) convertible to 6 by basic hydrolysis.^{7,8} Alkylation of **6** with the commercially available γ -chloro-*p*-fluorobutyrophenone proved troublesome by a published procedure;⁹ in our hands, use of Na₂CO₃ as the base and refluxing 1,2-dimethoxyethane as the solvent afforded improved and reproducible vields of 7.

		IADDE I		
		$\mathrm{Z}(\mathrm{CH}_2)_3\mathrm{CC}_6\mathrm{H}_4\mathrm{F}$ - p		
Compd	Z ^a	Formula	Mp, °C (HCl salt)	Anal. ^h
8	H ₃ C , CH ₃	$\mathrm{C_{17}H_{22}FNO}\cdot\mathrm{HCl}$	163-164	C, H, N, F
9	$H_{3}C$ H_{3} H_{3} $H_{3}C$ H_{3}	$\mathrm{C}_{23}\mathrm{H}_{26}\mathrm{FNO}\cdot\mathrm{HCl}$	185-187	C, H, N
10	H ₃ C	$\mathrm{C}_{22}\mathrm{H}_{24}\mathbf{FNO}\cdot\mathrm{HCl}$	192-193	C, H, N
11	$H_{3}C$ $N_{C_{6}}H_{1}-OCH_{3}\cdot p$	$C_{23}H_{26}FNO_2 \cdot HCl$	159–161	C, H, N
12	<u></u>	$C_{17}H_{20}FNO \cdot HCl$	166-168	C, H, N, Cl
134		$C_{20}H_{20}FNO\cdot HCl$	215-216 dec	C, H, N

TADLE I

^a Racemates, where present, were unresolved. ^b Anal. results for the indicated elements were within $\pm 0.4\%$ of the calcd values. Spectral data (ir, nmr) were also consistent with the assigned structures. • The required precursor amine was prepd by the procedure of L. A. Carpino and D. E. Barr, J. Org. Chem., 31, 764 (1966).

aration and pharmacology of some related compounds formally derived from 1 by replacement of the hydroxy, aryl-substituted piperidine ring by an unsaturated heterocyclic ring. Dehydration of 1 in vivo might

Compds 8-12 prepared in this way are listed in Table I.

Pharmacology.—Compds 8-13 were administered

(1) Haloperidol.

- (2) P. A. J. Janssen, "Medicinal Chemistry," Vol. 4-II, M. Gordon, Ed., (2) T. A. J. Janssen, Incontinue Constraint of Press, New York, N. Y., 1967, pp 199-248.
 (3) W. J. Welstead, Jr., G. C. Helsley, R. L. Duncan, Jr., A. D. Cale,
 (3) W. J. Welstead, Jr., G. C. Helsley, R. L. Duncan, Jr., A. D. Cale,
- Jr, C. R. Taylor, J. P. DaVanzo, B. V. Franko, and C. D. Lunsford, J. Med. Chem., 12, 435 (1969).

(4) C. H. Grogan and L. M. Rice, ibid., 10, 621 (1967).

(5) P. A. J. Janssen, British Patent 881,894 (Nov 8, 1961); Chem. Abstr., 57, 2146f (1962). (6) P. A. J. Janssen, U. S. Patent 3,030,372 (April 17, 1962); Chem.

Abstr., 59, 2780g (1963).

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(8) M. P. Cava, C. K. Wilkins, Jr., D. R. Dalton, and K. Bessho, J. Org. Chem., 30, 3772 (1965). (9) N. J. Harper, A. B. Simmonds, W. T. Wakama, G. H. Hall, and

D. K. Vallance, J. Pharm. Pharmacol., 18, 150 (1966).



(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-(4methoxyphenyl)-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 BF₃·2EtO, 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 H₂O, and dried (MgSO₄). 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, diln 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*-fluorobutyro-phenone, 2 equiv of Na₂CO₃, 100 mg of KI, and 100 ml of 1,2dimethoxyethane was refluxed 12 hr, at the end of which time the analysis demonstrated the consumption of starting amine. The cooled mixt was dild with several vol of H₂O and extd with Et₂O. The dried (K₂CO₃) Et₂O exts were then satd with HCl gas to ppt 45-60% yields of brown, somewhat tacky 11. Two recrystn from MeOH-Et₂O 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 ex-

(1) Haloperidol.

tensively. Simpler analogs of 1 have also been studied. For example, 2 has been found³ 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

$$\sum_{N(CH_2)_3COC_6H_4F-p}^{O}$$

unsaturation in the carbonyl side chain lead to diminished activity.² Since it has been shown⁴ 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 R₁ and R₂ are alternately CH₃ and H.

$$NCH-CHCH_2COC_{\delta}H_4F-p$$

Chemistry.—Michael addition of secondary amines to either methyl methacrylate or methyl crotonate afforded β -amino esters (4, Z = CO₂CH₃). Reduction to the alcohols (4, Z = CH₂OH) with LAH, followed by reaction with SOCl₂ in PhH, provided the Cl compounds (4, Z = CH₂Cl). 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.



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 \cdot HCl(21). --A soln of 24.04 g (0.20 mole) of 3-azabicyclo[3.2.2]nonane,

⁽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.