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

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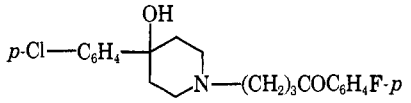
Received February 12, 1971

The potent neuroleptic **1**[1] has been the subject of exhaustive chemical and pharmacological investigation,



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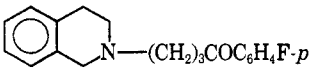
during the course of which many structural variants have been prepared.[2-4] We describe herein the preparation and pharmacology of some related compounds formally derived from **1** by replacement of the hydroxy, aryl-substituted piperidine ring by an unsaturated heterocyclic ring. Dehydration of **1** *in vivo* might reasonably 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]



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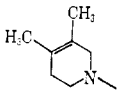
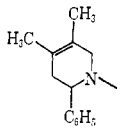
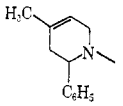
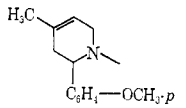
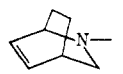
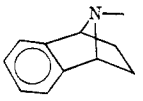
Chemistry.—Condensation of aliphatic or aromatic aldehydes with ethyl carbamates affords methylenebis(*N*-urethanes) (**3**) which, in the presence of boron trifluoride etherate, are converted to the transient dienophiles **4**. A Diels–Alder reaction affords 1,2,3,6-tetrahydropyridine carbamates (**5**) 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 Na_2CO_3 as the base and refluxing 1,2-dimethoxyethane as the solvent afforded improved and reproducible yields of **7**.

TABLE I

$Z(CH_2)_3COC_6H_4F\text{-}p$

Compd	Z[a]	Formula	Mp, °C (HCl salt)	Anal.[b]
8		$C_{17}H_{22}FNO \cdot HCl$	163–164	C, H, N, F
9		$C_{23}H_{26}FNO \cdot HCl$	185–187	C, H, N
10		$C_{22}H_{24}FNO \cdot HCl$	192–193	C, H, N
11		$C_{23}H_{26}FNO_2 \cdot HCl$	159–161	C, H, N
12		$C_{17}H_{20}FNO \cdot HCl$	166–168	C, H, N, Cl
13[c]		$C_{20}H_{20}FNO \cdot HCl$	215–216 dec	C, H, N

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

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., Academic Press, New York, N. Y., 1967, pp 199–248.

(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).

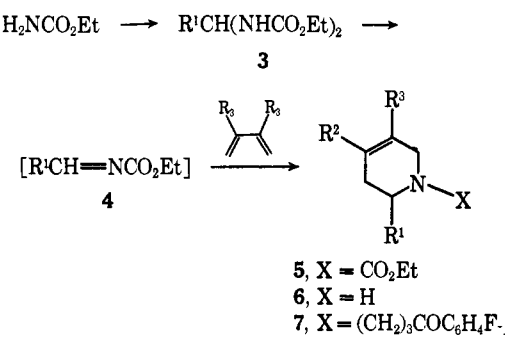
(5) P. A. J. Janssen, British Patent 881,894 (Nov 8, 1961); *Chem. Abstr.*, **57**, 2146*f* (1962).

(6) P. A. J. Janssen, U. S. Patent 3,030,372 (April 17, 1962); *Chem. Abstr.*, **59**, 2780*g* (1963).

(7) R. Merten and G. Muller, *Angew. Chem.*, **74**, 866 (1962).

(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).



5, X = CO_2Et
6, X = H
7, X = $(CH_2)_3COC_6H_4F$-*p*

(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_3·2EtO, 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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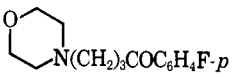
Received February 12, 1971

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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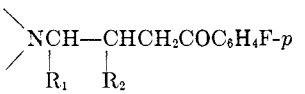
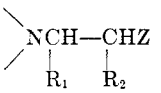
unsaturation in the carbonyl side chain lead to diminished activity.[2] Since it has been shown[4] that **1** is metabolized by cleavage α to N, followed by degradation to *p*-fluorophenylacetic acid, we were interested in examining the possible effects of Me substituents on this process and on the duration 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.



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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.