ω-Azabicyclic Butyrophenones

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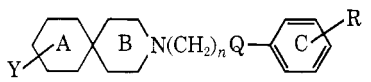
A group of ω-azabicyclic butyrophenones has been prepared and evaluated pharmacologically. All compounds studied in which the azabicyclic structure was nonaromatic were effective CNS depressants. The 4,7-bridged isoindolines were the most potent of the group.

We have previously described the synthesis and neuroleptic properties of a series of ω-azaspiranylbutyrophenones[1] of the general structure I. In this



I

study it was shown that the most potent compounds were those in which R–C was *p*-fluorophenyl, Q was carbonyl, $n = 3$, and the azaspiranyl structure AB was bicyclic. Opening of ring A to give disubstituted piperidines or the elimination of ring A greatly decreased or abolished neuroleptic properties. Based on these observations, a group of compounds, in which various azabicyclic structures were substituted in lieu of the azaspiranyl rings on *p*-fluorobutyrophenone, have been prepared and evaluated pharmacologically.

The compounds reported were prepared by refluxing the appropriate azabicyclic secondary amine with 4-chloro-4′-fluorobutyrophenone in an inert solvent, such as toluene or xylene, for periods up to 1 week. During the course of the study several new isoindolines and 3-azabicyclo[3.2.0]heptane were prepared.

Our previous experiences with isoindolines[2-4] have shown that the stability of these ring systems increases with the degree of saturation of the ring; isoindoline itself is the least stable. An N substituent, such as alkyl- or dialkylaminoalkyl, also increases stability. All of these derivatives can be obtained in good to excellent yields by the reduction of the corresponding imides with lithium aluminum hydride (LAH) except the bases in which the N substituent is hydrogen. In these cases the yields are markedly reduced. This generalization was further verified in the preparation of the new isoindoline ring systems, Table I, **4**, **5**, and **6**, in which the yields were 19, 9, and 12%, respectively. 3-Azabicyclo[3.2.0]heptane was obtained in a 23% yield by reduction of the imide[5] with LAH in ether.

One obvious reason for the low yields obtained is the insolubility of these imides in ether. Imides corresponding to ring systems AB **5** and **6** (Table I) were reduced as slurries in ether. Ring system **4** and one preparation of **6** were prepared by continuously extracting all imide into the LAH solution, with only slight improvement in yields.

Pharmacology.—Compounds prepared and evaluated are listed in Table I, along with pertinent physical data. The compounds were screened for gross effects in Wistar rats by methods previously described.[1] The data are summarized in Table II. From these data it can be said in general that when ring A is aromatic (**4**, **10**, **11**) tranquilizing activity is lost and the effects observed are convulsant. The single exception to this is the indoline derivative **10**, which had little activity.

All of the saturated azabicyclic structures, or those containing one double bond, yielded substituted butyrophenones that had good to excellent central nervous system (CNS) depressant properties and exhibited periods of duration from medium to long. Compound **9**, containing the smallest azabicyclic ring studied, had good CNS depressant properties, but a shorter duration of effect than the larger ring systems. This compound was considerably more soluble than the others which may account for its quicker onset and shorter duration of action.

Of the group of compounds studied, the 4,7-bridged isoindolines, **1**, **5**, and **6**, exhibited the greatest potency. Compound **1** was selected for more extensive investigation. The choice over **5** and **6** was primarily based on chemical reasons because of the better yields obtained in the preparation of the starting isoindoline base. When compared with chlorpromazine (CPZ) in mice, **1** caused a decrease in spontaneous motor activity at 3 mg/kg while 12.7 mg/kg of CPZ was required. In mice **1** caused lacrimation at 6 mg/kg, tremors at 12.5 mg/kg, and ptosis at 25 mg/kg. It was active against tremorine-induced convulsions at 10 mg/kg. Compounds **1**, as well as **2** and **3**, were clinically effective tranquilizers when administered orally at doses of 10–20 mg bid or tid.[6]

R substituents, other than fluorine, at the *para* position of ring C decreased CNS depressant properties (**12**); the quaternary salts (**13–16**) were devoid of CNS depressant properties. The structural relationship of the azaspiranylbutyrophenones to γ-aminobutyric acid has been pointed out and discussed.[1] The present study of azabicyclic butyrophenones strengthens that hypothesis. The *p*-fluoro group is apparently essential to confer maximum CNS depressant effects as well as the antiinflammatory activity observed with some of the azaspiranylbutyrophenones.

(1) C. H. Grogan, C. F. Geschickter, M. E. Freed, and L. M. Rice, *J. Med. Chem.*, **8**, 62 (1965).

(2) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **20**, 1687 (1955).

(3) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **77**, 616 (1955).

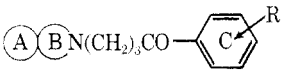
(4) C. H. Grogan and L. M. Rice, *J. Med. Chem.*, **6**, 802 (1963).

(5) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **23**, 1100 (1957).

(6) C. F. Geschickter, personal communication.

TABLE I

ω-AZABICYCLIC BUTYROPHENONES



No.	Ring system AB	C	R	Bp, °C (mm)	Yield, %	Formula	% calcd Carbon	% calcd Hydrogen	% calcd Nitrogen	% found Carbon	% found Hydrogen	% found Nitrogen
1	Isoindoline,[4] perhydro-4-methyl-4,7-epoxy	Phenyl	*p*-F	150 (0.12)	57	$C_{19}H_{24}FNO_2$[a]	71.90	7.62	5.99[b]	72.15	7.80	5.77[b]
2	Isoindoline,[2] 3a,4,7,7a-tetrahydro	Phenyl	*p*-F	135–140 (0.2)	49	$C_{18}H_{22}FNO$[c]	75.23	7.72	6.61[b]	75.14	7.68	6.48[b]
3	Isoindoline,[2] perhydro	Phenyl	*p*-F	...	*d*	$C_{18}H_{25}ClFNO$[d]	...	...	...	...	...	...
4	Isoindoline, 5,6-dichloro	Phenyl	*p*-F	155–165 (0.1)	45	$C_{18}H_{16}Cl_2FNO$	61.38	4.58	20.13[e]	61.50	4.62	20.29[e]
5	Isoindoline, 4,7-methano-3a,4,-7,7a-tetrahydro	Phenyl	*p*-F	...	*f*	$C_{19}H_{23}ClFNO$[f]	67.95	6.90	10.56[g]	68.28	6.93	10.27[g]
6	Isoindoline, 4,7-ethano-3 4,-7,7a-tetra-hydro	Phenyl	*p*-F	...	*g*	$C_{20}H_{25}ClFNO$[g]	68.66	7.20	5.43[b]	68.78	7.37	5.64[b]
7	3-Azabicyclo-[3.2.2]nonane	Phenyl	*p*-F	150–160 (0.3)	73	$C_{18}H_{24}FNO$[h]	74.71	8.36	6.57[b]	74.58	8.54	6.39[b]
8	*d*-Camphidine[7]	Phenyl	*p*-F	...	42[i]	$C_{20}H_{29}ClFNO$[i]	...	...	...	...	...	...
9	3-Azabicyclo-[3.2.0]heptane	Phenyl	*p*-F	...	*j*	$C_{16}H_{21}ClFNO$[j]	...	...	...	...	...	...
10	Indoline	Phenyl	*p*-F	155–165 (0.18)	45	$C_{18}H_{18}FNO$[k]	76.30	6.40	6.70[b]	75.90	6.62	7.01[b]
11	Isoquinoline, 1,2,3,4-tetra-hydro	Phenyl	*p*-F	150–160 (0.2)	41	$C_{19}H_{20}FNO$[l]	76.74	6.78	4.71	76.47	6.51	5.03
12	No. 1	Phenyl	*p*-Cl	...	59[m]	$C_{19}H_{25}Cl_2NO_2$[m]	...	...	...	...	...	...
13	No. 1	Phenyl	*p*-F	...	88[n]	$C_{20}H_{27}ClFNO_2$[n]	...	...	...	...	...	...
14	No. 1	Phenyl	*p*-Cl	...	86[o]	$C_{20}H_{27}Cl_2NO_2$[o]	...	...	...	...	...	...
15	No. 1	Phenyl	*p*-Iso-propyl	...	83[p]	$C_{23}H_{34}Cl_2NO_2$[p]	...	...	...	...	...	...
16	No. 1	2-Thienyl	H	...	84[q]	$C_{18}H_{26}ClNO_2S$[q]	...	...	...	...	...	...

[a] Hydrochloride, mp 187–188°, from acetone–ether. *Anal.* Calcd for $C_{19}H_{25}ClFNO$: Cl, 10.02. Found: Cl, 9.80. [b] Fluorine analyses. [c] Hydrochloride, mp 137.5–138.5, from acetone–ether. *Anal.* Calcd for $C_{18}H_{23}ClFNO$: Cl, 10.95. Found: Cl, 10.92. [d] As hydrochloride, mp 152–153.5, from acetone–ether. *Anal.* Calcd for $C_{18}H_{25}ClFNO$: Cl, 10.88. Found: Cl, 10.79. [e] Chlorine analyses. [f] As hydrochloride, mp 199–200°, from acetone–ether. [g] As hydrochloride, mp 199–200°, from acetone–ether. [h] Hydrochloride, mp 187–188°, from acetone–ether. *Anal.* Calcd for $C_{18}H_{25}ClFNO$: Cl, 10.88. Found: Cl, 10.78. Methiodide, mp 178–179°, from methanol–ether. *Anal.* Calcd for $C_{19}H_{27}FINO$: I, 29.42. Found: I, 29.61. [i] As hydrochloride, mp 184–185°, from acetone–ether. *Anal.* Calcd for $C_{20}H_{29}ClFNO$: Cl, 10.02. Found: Cl, 9.77. [j] As hydrochloride, mp 139–140°, from acetone–ether. *Anal.* Calcd for $C_{16}H_{21}ClFNO$: Cl, 11.91. Found: Cl, 11.84. [k] Hydrochloride, mp 150–151°, from acetone–ether. *Anal.* Calcd for $C_{18}H_{19}ClFNO$: Cl, 11.09. Found: Cl, 10.95. Methiodide, mp 152–153°, from acetone–ether. *Anal.* Calcd for $C_{19}H_{21}FINO$: I, 29.84. Found: I, 30.03. [l] Hydrochloride, mp 207–209°, from acetone. *Anal.* Calcd for $C_{19}H_{21}ClFNO$: Cl, 10.62. Found: Cl, 10.53. [m] As hydrochloride, mp 167–168°, from acetone–ether. *Anal.* Calcd for $C_{19}H_{25}Cl_2NO_2$: Cl, 19.15. Found: Cl, 18.86. [n] As methochloride, very hygroscopic, mp 204–205°, from acetone–ether. *Anal.* Calcd for $C_{20}H_{27}ClFNO$: Cl, 9.64. Found: Cl, 9.51. [o] As methochloride, very hygroscopic, mp 216–218°, from methanol–ether. *Anal.* Calcd for $C_{20}H_{27}Cl_2NO_2$: Cl, 18.44. Found: Cl, 18.24. [p] As methochloride, very hygroscopic, mp 209–210°, from acetone–ether. *Anal.* Calcd for $C_{23}H_{34}ClNO_2$: Cl, 9.05. Found: Cl, 8.90. [q] As methochloride, very hygroscopic, mp 196–198°, from acetone–ether. *Anal.* Calcd for $C_{18}H_{26}ClNO_2S$: Cl, 9.96. Found: Cl, 9.88.

Experimental Section

Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Melting points were obtained with a Thomas-Hoover capillary-type apparatus and are corrected.

2-[3-(*p*-Fluorobenzoyl)propyl]-4-methyl-4,7-epoxyperhydroisoindoline (1).—4-Methyl-4,7-epoxyperhydroisoindoline[4] (15.3 g, 0.1 mole), 4-chloro-4′-fluorobutyrophenone (10 g, 0.05 mole), and 0.1 g of KI were refluxed for 2 days in 50 ml of toluene. The reaction mixture was cooled, diluted with 3 vol of anhydrous ether, and let stand overnight. Precipitated 4-methyl-4,7-epoxyperhydroisoindoline hydrochloride[4] was removed by filtration and washed with ether. The filtrate and ether washings were stripped at the aspirator until a reddish oil remained. Distillation of the residue *in vacuo* yielded 9 g (57%) of **1** as a colorless oil, bp 150° (0.12 mm).

The **hydrochloride,** obtained by passing anhydrous HCl gas into an ether solution of the base, melted at 184–186 and 187–188° after two recrystallizations from acetone–ether.

3-[3-(*p*-Fluorobenzoyl)propyl]-1,8,8-trimethyl-3-azabicyclo-[3.2.1]octane Hydrochloride (8).—*d*-Camphidine[7] (1,8,8-trimethyl-3-azabicyclo[3.2.1]octane) (15.3 g, 0.1 mole), 10 g (0.05 mole) of 4-chloro-4′-fluorobutyrophenone, and 0.1 g of KI were refluxed for 30 hr in 100 ml of toluene. No isolable product was obtained. The experiment was repeated and the reactants were refluxed for 1 week in 75 ml of xylene. The reaction mixture was diluted with 3 vol of ether and kept overnight at 5°. Precipitated *d*-camphidine hydrochloride[7b] was removed by filtration and washed with ether. The filtrate and washings were stripped at the aspirator. The residual orange oil was dissolved in ether

(7) (a) J. Tafel and K. Eckstein, *Ber.*, **34**, 3283 (1901); (b) K. Rubinstein, K. Hermanson, and N. Elming, *Acta Chem. Scand.*, **17**, 2069 (1963).

TABLE II

SUMMARY OF PHARMACOLOGICAL OBSERVATIONS

No.	LD_{50}, (72 hr), mg/kg[a]	ED_{50}, mg/kg[b]	Remarks[c]
1	~50	<1	Long duration
2	~50	~5	Medium duration
3	~60	~5	Medium duration
4	~50	...	Tremors, convulsions
5	60	2	Long duration
6	60	<2	Long duration
7	100	~20	Medium duration
8	~50	<5	Medium duration
9	75	5	Rapid effect, short duration
10	>200	...	NRR
11	~40	...	Tremors, convulsions

[a] Approximate LD_{50} (72 hr) values were obtained by administering the compounds intraperitoneally to Wistar rats in the weight range 150–250 g. [b] Approximate ED_{50} values were determined in Wistar rats. The effective dose was that which produced noticeable sedation and decreased spontaneous motor activity for at least 1 hr. [c] All of the drugs produced tremors, convulsions, and pseudo-Parkinsonism at high doses. Long duration means for a period greater than 6 hr. Medium duration means for a period from 4–6 hr, and short duration means a period from 1–4 hr. NRR = no remarkable reaction.

and filtered, and gaseous HCl was bubbled in until precipitation was complete. The precipitate was filtered, washed with ether, and dried at 100° to give 42% of **8**, mp 176–180°. Two recrystallizations from acetone–ether gave mp 184–185°.

2-3-(*p*-Fluorobenzoyl)propyl]-4-methyl-4,7-epoxyperhydroisoindoline Methochloride (13).—The quaternary methochlorides **13–16** were readily prepared by refluxing the desired ω-chloroaralkyl ketone with an N-methyl azabicyclic base in ethyl acetate or toluene. The preparation of **13** will illustrate this procedure. 2,4-Dimethyl-4,7-epoxyperhydroisoindoline[3] (8.5 g, 0.05 mole), 4-chloro-4′-fluorobutyrophenone (10 g, 0.05 mole), and 0.1 g of KI were refluxed for 8 hr in 100 ml of anhydrous ethyl acetate. On cooling, the methochloride crystallized and crystallization was completed by adding ether. It was a very hygroscopic material that melted at 203–204.5 and 204–205° after recrystallization from acetone–ether.

4,5-Dichlorophthalimide.[8]—4,5-Dichlorophthalic anhydride (108.5 g 0.5 mole) was treated with a large excess of concentrated aqueous NH_3. Water and NH_3 were boiled off and the residue was heated at 190° in an oil bath for 1 hr to give an essentially quantitative yield of product, mp 210–215°. The material after two recrystallizations from methanol melted at 218–220°.[9]

Anal. Calcd for $C_8H_3Cl_2NO_2$: C, 44.48; H, 1.40; Cl, 32.83. Found: C, 44.59; H, 1.69; Cl, 33.12.

5,6-Dichloroisoindoline.—Into a reaction flask, equipped with stirrer, N_2 inlet, drying tube, and Soxhlet extractor, were introduced 30 g of LAH and 2 l. of absolute ether that had been made free of O_2 and peroxides by distillation from and storage over CaH_2. Finely powdered 4,5-dichlorophthalimide (54 g, 0.25 mole) was placed in the extraction thimble and the imide was extracted into the LAH solution until all had been dissolved (approximately 30 hr). The complex with LAH was greenish brown and largely precipitated onto the walls of the flask. At the end of this period the heat was turned off and the apparatus was flushed with N_2. Distilled water, previously boiled to remove O_2, was added dropwise at such a rate as to maintain gentle reflux of the ether. A gentle stream of N_2 was passed through the apparatus during the decomposition process and the subsequent 4-hr stirring period, When decomposition was complete the ether solution was violet in color. The reaction mixture was filtered rapidly, the inorganic cake was pressed tightly and washed with peroxide-free ether. The filtrate was dried (Na_2SO_4) while under N_2. The next day the ether was stripped and the product was distilled *in vacuo* to yield 9 g (19%) of a pale yellow viscous oil, bp 125–135° (0.7 mm). The material slowly solidified while under N_2 to a pale yellow solid which could not be recrystallized under ordinary laboratory conditions without rapid decomposition as evinced by the rapid color change on exposure to air or ordinary laboratory reagent solvents: yellow → violet → purple → blue → black. Several drops of the viscous oil had been collected during distillation and sealed under N_2. This material gave the following analysis.

Anal. Calcd for $C_8H_7Cl_2N$: C, 51.09; H, 3.75; N, 7.45. Found: Cl, 50.86; H, 3.54; N, 7.24.

2-[3-(*p*-Fluorobenzoyl)propyl]-5,6-dichloroisoindoline (4).—5,6-Dichloroisoindoline (7.3 g, 0.039 mole) and 3.9 g (0.019 mole) of 4-chloro-4′-fluorobutyrophenone were refluxed in 50 ml of oxygen-free and water-free toluene for 30 hr. The reaction mixture was cooled and diluted with 3 vol of peroxide-free ether. After standing overnight a violet-blue mass of crystals had separated. These were removed by filtration and the filtrate was stripped of all solvents. The residual blue oil was distilled *in vacuo* to yield 3 g (45%) of a viscous yellow oil, bp 155–165° (0.1 mm). This material likewise rapidly turned purple on exposure to air.

5,6-Dichloroisoindoline Hydrochloride.—The violet-blue crystalline mass, obtained from the preparation of **4**, melted at 132–134° and at 133–134° on recrystallization from acetone–ether. Analyses and its method of obtention indicated that it was the title compound.

Anal. Calcd for $C_8H_8Cl_3N$: Cl, 47.37. Found: Cl, as obtained, 46.8; Cl after 2 days, 34.0.

An immediate modified Fajans' halogen titration[9] gave a value of 15.4 for Cl^- (calcd Cl^-, 15.79).

3-Azabicyclo[3.2.0]heptane.—The reduction of 20 g (0.16 mole) of 3-azabicyclo[3.2.0]heptane-2,4-dione[5] as a slurry in ether with an excess of LAH in ether in the usual manner yielded 3.5 g (23%) of the title base, bp 53–56° (10–11 mm).

Anal. Calcd for $C_6H_{11}N$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.90; H, 11.20; N, 14.26.

The **hydrochloride,** obtained from the preparation of **9**, melted at 198–199° after recrystallization from methanol–ether.

Anal. Calcd for $C_6H_{12}ClN$: Cl, 26.53. Found: Cl, 26.54,

3a,4,7,7a-Tetrahydro-4,7-methanoisoindoline.—Reduction of 54 g (0.33 mole) of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide as a slurry in ether with LAH in ether gave 3.75 g (9%) of the title compound, bp 70–75° (10 mm), together with much polymeric material.

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.63; H, 9.57; N, 10.22.

The **hydrochloride,** obtained from the preparation of **5**, melted at 206–210°. After recrystallization from acetone–ether (slow) it melted at 210–212° dec on slow heating, and at 215–217° dec if put in the bath at 200°.

Anal. Calcd for $C_9H_{14}ClN$: Cl, 20.65; N, 8.16. Found: Cl, 20.47; N, 8.24.

3a,4,7,7a-Tetrahydro-4,7-ethanoisoindoline.—Reduction of 20 g (0.11 mole) of bicyclo[2.2.2]oct-5-ene-2,3-dicarboximide as a slurry in ether with LAH in ether in the usual manner gave a 2 g (12%) yield of the title compound. When 35 g (0.198 mole) of the imide was reduced with LAH by continuously extracting the imide into an ether solution of LAH, there was obtained 5.3 g (18%) of the title compound, bp 72–76° (10–11 mm).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.26; H, 9.87; N, 9.16.

The **hydrochloride,** obtained from the preparation of **6**, melted at 205–206° after recrystallization from methanol–ether.

Anal. Calcd for $C_{10}H_{16}ClN$: Cl, 19.09. Found: Cl, 19.20.

(8) H. D. K. Drew and F. H. Pearman, *J. Chem. Soc.*, 586 (1937), give mp 221°.

(9) C. H. Grogan, L. M. Rice, and E. E. Reid, *J. Org. Chem.*, **20**, 50 (1955).