Partly Reduced Biphenyls as Central Nervous System Agents. 2. *cis*- and *trans*-4-Arylcyclohexylamines

Daniel Lednicer,* D. Edward Emmert, Robert Lahti, and Allan D. Rudzik

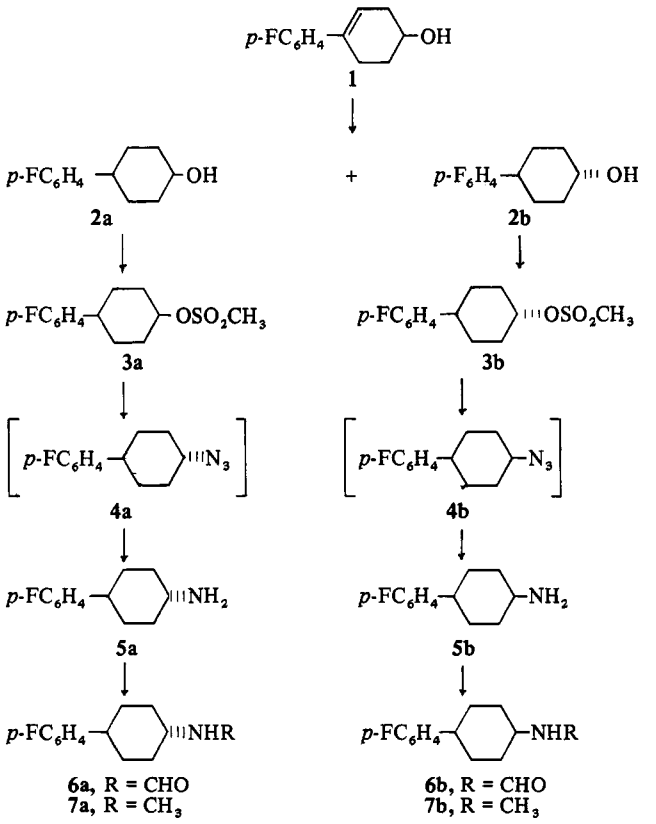
Research Laboratories of The Upjohn Company, Kalamazoo, Michigan. *Received May 2, 1972*

Both isomers of 4-(*p*-fluorophenyl)cyclohexylamine were prepared and their stereochemical identities determined. A series of *trans*-4-arylcyclohexylamines was synthesized by a stereoselective route starting from the Grignard reaction product of 4-hydroxycyclohexanone with substituted bromobenzenes. The amines were then converted to piperidines and 4'-fluoro-4-butyrophenones. The products were tested in a series of assays for CNS activity; the last compounds were particularly active on both overt behavior and biochemical parameters.

In view of the interesting CNS activity shown by derivatives of 4-arylcyclohex-3-en-1-ylamines,[1] we decided to investigate the corresponding analogs fully saturated in the cyclohexane ring. Such compounds might show differences from the earlier reported series due to changes in lipophilicity and to altered geometry of the molecule.

Synthesis. For our initial work we deliberately chose a route that would afford both the cis and trans isomers, for two reasons. First, earlier work suggested that both isomers of phenylcyclohexylamines showed biological activity;[2] thus we had no *a priori* reason to go in either direction. Perhaps equally important was the fact that we felt that any structural assignment would rest on firmer grounds with both isomers in hand (Scheme I).

Scheme I

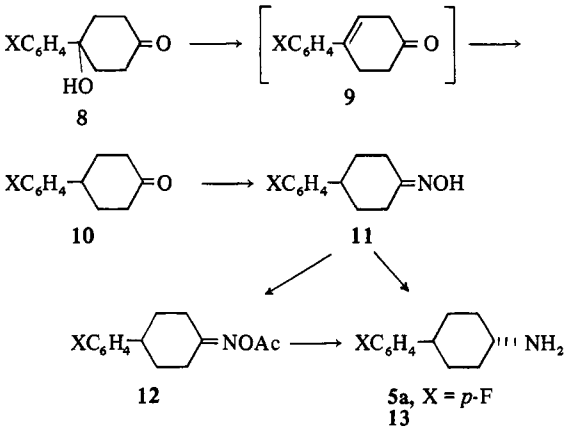


Catalytic reduction of the unsaturated alcohol **1**[1] afforded a mixture of isomeric products separable by chromatography. The less polar, lower melting isomer predominated slightly. This isomer showed CHOH in the nmr both at lower field (δ 4.11) and as a sharper band ($W_{1/2}$, 8 Hz) than the higher melting alcohol (δ 3.62, $W_{1/2}$, 18 Hz); both relative position[3] and band width[4] lead to the assignment of the former to the cis series and the latter to the trans series.

Each of the epimeric alcohols was then converted to the mesylate. These were subjected to SN_2 displacement with NaN_3 to afford the azides of opposite configuration. Reduction by means of $LiAlH_4$ completed the preparation of the isomeric amines **5a** and **5b**. Each of these was then taken on to the corresponding *N*-methyl compound (**7a**, **7b**) *via* its formamide.

Screening of derivatives of the two bases showed the trans series to be more interesting. We thus developed a stereoselective route for their preparation (Scheme II).

Scheme II

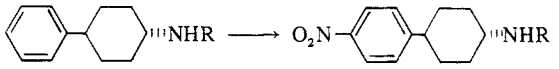


Catalytic reduction of the ketone **9** (X = *p*-F) afforded the cyclohexanone **10**. This was taken on to the oxime by standard means and that product acetylated by means of Ac_2O in pyridine. Reduction to the trans amine was accomplished by (a) Li, *tert*-BuOH, and NH_3 on the oxime **11**, (b) the same conditions on the acetate **12**, or, finally, (c) with diborane on the acetate. In each case the final purified sample of amine was identical with that obtained by the previous route. The selectivity of the reduction methods was b > a > c; in subsequent experiments with halogenated aromatics, however, we found the Birch conditions to lead to extensive removal of halogen.

This route was then used to prepare a series of *trans*-cyclohexylamines starting from the 4-aryl-4-hydroxylcyclohexanones described previously;[1] several additional starting ketones were prepared for the present work by the earlier procedure.

To include in this series a compound with a markedly electron-deficient aromatic ring we set about preparing the nitro compound. Acetylation of the amine **14** led cleanly to the corresponding amide; this last was nitrated in workable yield with a mixture of nitric and trifluoroacetic acid.

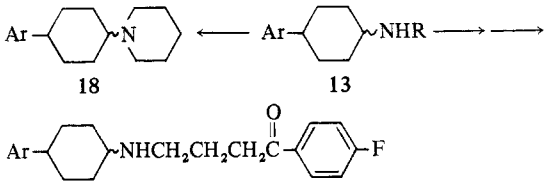
This reagent proved superior to the classical nitric-sulfuric mixed acid in avoiding the strongly oxidizing conditions. Hydrolysis with strong acid gave the desired primary amine.



14, R = H
15, R = Ac

16, R = Ac
13m, R = H

The piperidine analogs of many of the amines were obtained in straightforward manner by reaction of the latter with 1,5-diiodopentane. Alkylation of the amines with the 2,2-dimethylpropylene ketal of 4′-chloro-4-fluorobutyrophenone followed by hydrolysis gave the butyrophenone derivatives.



18 13

17

Pharmacology. Table I shows the effects of the compounds prepared in these series on both behavioral and biochemical end points. The primary amines all produced effects on overt behavior but the most potent activity was their ability to antagonize nicotine-induced tonic extensor convulsions and lethality. The butyrophenone derivatives produced marked effects on overt behavior and all were potent antagonists of nicotine-induced convulsions and death. The *p*-fluorobutyrophenone derivative **(17a)** was one of the most active compounds on overt end points and most potent in blocking norepinephrine and 5-hydroxytryptamine uptake. It should be noted that the cis *p*-fluoro compound **(17a′)** was less than 0.1 as active as the trans **(17a)** derivative. Six of the derivatives **(17e, 17g, 17h, 17j, 17k, 17m)** produced potent effects on norepinephrine uptake with little or no effect on 5-hydroxytryptamine uptake. In the *p*-fluoro-*N*-methyl series the cis form **(17o)** was similarly much less active than the trans isomer **(17n)**.

In general, using antagonism of nicotine-induced convulsions and death, the compounds of the present series show 2 to 20 times the potency of the corresponding previously reported[1] Δ^4 analogs. The effect of substitution on the aromatic ring on rank order of potency, however, varies in these two series.

It is of note, though, that the most potent agent in this series, the *trans-p*-fluorobutyrophenone **(17i)**, shows ED_{50}'s of the same order of magnitude as the most potent compound in the Δ^4 series. That amine also carried a *p*-fluoro and a butyrophenone grouping **(16f** in the previous paper).

Experimental Section†

cis- and *trans*-**4-(*p*-Fluorophenyl)cyclohexanol (2a and 2b).** A mixture of 11.42 g of the unsaturated alcohol and 0.10 g of 10% Pd/C in 200 ml of EtOAc was shaken under H_2 until 1 equiv of gas had been taken up (10 min). The catalyst was collected on a filter and the filtrate taken to dryness. The residual oily solid was chromatographed on 1 l. of Florisil‡ (elution with 8 l. of 4% and 6 l. of 10% Me_2CO–Skellysolve B).§ The crystalline fractions were combined on the basis of their tlc to afford first the crude cis alcohol followed by the trans alcohol. The former was recrystallized from petroleum ether (cooling in freezer) to give 5.52 g of solid, mp 40–43°. *Anal.* C, 74.19; H, 7.79. Found: C, 74.70; H, 8.08. The trans alcohol obtained above was recrystallized from ether–Skellysolve B to yield 3.50 g of solid, mp 120.5–123.5°. *Anal.* ($C_{12}H_{15}FO$) C, H.

trans-**4-(*p*-Fluorophenyl)cyclohexanol Methanesulfonate (3b).** To an ice-cooled solution of 3.50 g of the alcohol in 30 ml of pyridine there was added 3.5 ml of methanesulfonyl chloride. Following 6 hr standing in the cold, the mixture was poured into water. The precipitated solid was recrystallized twice from aqueous methanol to give 4.22 g of trans mesylate, mp 90–92.5°, mmp with cis mesylate, 72–90°. *Anal.* ($C_{13}H_{17}FO_3S$) C, H.

cis-**4-(*p*-Fluorophenyl)cyclohexanol Methanesulfonate (3a).** Methanesulfonyl chloride (5.0 ml) was added to an ice-cooled solution of 5.52 g of the alcohol in 40 ml of pyridine. Following 6 hr standing in the cold, the mixture was poured into water. The precipitated solid was collected on a filter and recrystallized twice from aqueous methanol. There was obtained 6.65 g of cis mesylate, mp 98–100°. *Anal.* ($C_{13}H_{17}FO_3S$): C, 57.33; H, 6.29. Found: C, 56.79; H, 6.57.

trans-**4-(*p*-Fluorophenyl)cyclohexylamine Hydrochloride (5a).** A mixture of 6.65 g of the cis mesylate and an equal weight of NaN_3 in 65 ml of DMF was stirred in an oil bath at 90–95° for 12 hr. The mixture was taken to dryness on the rotary evaporator at 2 mm, and the residue dissolved in H_2O and C_6H_6. The organic layer was washed well with H_2O and brine to give 4.84 g of crude azide.

A solution of the azide in 75 ml of THF was added to a well-stirred suspension of 2.40 g of LAH in 25 ml of THF. Following 1 hr stirring at room temp and 2 hr at reflux, the mixture was cooled in ice. There was added in turn 2.40 ml of H_2O, 2.40 ml of 15% NaOH, and 6 ml of H_2O. The precipitated solid was collected on a filter, and the filtrate taken to dryness. The residual solid was dissolved in Et_2O and treated with 3.6 *N* ethereal HCl. The solid was recrystallized twice from MeOH–EtOAc to give 3.05 g of solid, mp >330°. *Anal.* ($C_{12}H_{17}ClFN$) C, H, Cl.

cis-**4-(*p*-Fluorophenyl)cyclohexylamine Hydrochloride (5b).** A mixture of 4.22 g of the trans mesylate and an equal weight of NaN_3 in 45 ml of DMF was heated at 95° for 12 hr. The mixture was worked up as in the case of the isomer, and the azide reduced by means of LAH (2.10 g). The amine hydrochloride was isolated exactly as above. A single recrystallization from MeOH–EtOAc gave 2.88 g of the cis amine hydrochloride, mp 237–238.5°. *Anal.* ($C_{12}H_{17}ClFN$) C, H, Cl.

trans-**4-(*p*-Fluorophenyl)cyclohexylformamide (6a).** A mixture of 2.86 g (0.0125 mole) of the amine hydrochloride, 2.35 ml of Et_3N, 15 ml of H_2O, and 60 ml of CH_2Cl_2 was stirred at room temp until the solid completely dissolved. The organic layer was separated, diluted with C_6H_6, and taken to dryness.

The residue was suspended in 27 ml of ethyl formate and the mixture stirred under reflux for 40 hr. The solvent was then removed *in vacuo*, and the residue recrystallized from C_6H_6. There was obtained 2.26 g (82%) of solid, mp 139–142.5°. *Anal.* ($C_{13}H_{16}FNO$) C, H.

cis-**4-(*p*-Fluorophenyl)cyclohexylformamide (6b).** A mixture of 2.50 g (0.011 mole) of the amine hydrochloride, 2.1 ml of Et_3N, 13 ml of H_2O, and 55 ml of CH_2Cl_2 was stirred at room temp until the solid was all in solution. The organic layer was separated, diluted with C_6H_6, and taken to dryness. A mixture of the residue and 29 ml of ethyl formate was heated at reflux for 42 hr. The solvent was then removed *in vacuo*, and the residue recrystallized from EtOAc–C_6H_{12}. There was obtained 1.96 g of product, mp 121–124°, 81% yield. *Anal.* ($C_{13}H_{16}FNO$): C, 70.56; H, 7.29. Found: C, 71.03; H, 7.49.

trans-*N*-**Methyl-4-(*p*-fluorophenyl)cyclohexylamine (7a).** A solution of 2.26 g (0.010 mole) of the amide in 67 ml of THF was added to 0.56 g of $LiAlH_4$ in 10 ml of THF over 10 min. Following 4 hr stirring under reflux, the mixture was cooled in ice and treated, in turn, with 0.6 ml of H_2O, 0.6 ml of 15% NaOH, and 1.8 ml of H_2O. The precipitated salts were collected on a filter, and the filtrate was taken to dryness. The residue obtained from the latter was dissolved in ether and treated with an excess of satd HCl in Et_2O. The precipitated solid was recrystallized from CH_2Cl_2–EtOAc to give 1.98 g of hygroscopic product, mp 213–215°. *Anal.* ($C_{13}H_{19}ClFN$) C, H, Cl.

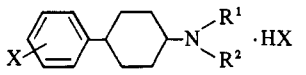
cis-*N*-**Methyl-4-(*p*-fluorophenyl)cyclohexylamine Hydrochloride**

†All melting points are uncorrected and reported as observed on a Thomas-Hoover capillary mp apparatus. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Company for elemental and spectral analyses. Analytical results indicated by element symbols were within ±0.4% of the theoretical values.

‡Florisil is a synthetic magnesia silica gel absorbent manufactured by Floridin Co., Warren, Pa.

§Skellysolve B is a petroleum fraction (bp 60–70°) sold by Skelly Oil Co.

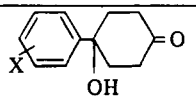
Table I. Pharmacological Testing Results of 4-Arylcyclohexylamines[a]



	X	R^1	R^2	LD_{50}[b]	LRR_{50}[b]	Tr_{50}[b]	Ch_{50}[b]	D_{50}[b]	P_{50}[b]	Nicotine[b] Te	Nicotine[b] L	Effect on amine uptake[c] [^{3}H]NE heart	Effect on amine uptake[c] 5-[^{14}C]HT spleen
13a	*p*-F	H	H									69	87
13a'	*p*-F[d]	H	H									96	121
13i	*p*-OCH_3	H	H	45	>25	>25	14	6	6	>25	>25	33	56
17a	*p*-F	BuF[e]	H	>100	45	10	0.8	0.45	0.63	0.32	0.32	12	44
17a'	*p*-F[d]	BuF	H	126	>50	32	14	5	8	8	9	64	67
17b	*m*-F	BuF	H	>200	>200	89	9	0.8	4.5	0.8	0.9	71	84
17c	*p*-Cl	BuF	H	>200	>200	79	0.28	3.2	6.3	2.0	1.6	67	103
17d	*o*-CH_3	BuF	H	>200	200	63	9	3.6	5.6	1.1	1.1	48	74
17e	*m*-CH_3	BuF	H	>200	>200	36	2.3	0.2	3.1	0.32	0.45	21	85
17f	*p*-CH_3	BuF	H	>100	>100	>100	7.1	4.5	2.5	4.5	5.6	112	108
17g	*o*-OCH_3	BuF	H	>200	>200	100	1.6	0.8	12.5	0.56	1.1	20	90
17h	*m*-OCH_3	BuF	H	>200	>200	71	3.1	0.31	0.7	0.5	0.5	40	87
17i	*p*-OCH_3	BuF	H	178	>100	50	1.3	0.4	2.3	2.0	1.6		
17j	*m*-CF_3	BuF	H	142	>50	42	2.5	0.23	2.5	0.23	0.23	24	81
17k	*p*-CF_3	BuF	H	200	>100	36	2.2	1.4	4.5	1.1	1.1	44	107
17l	*p*-F, *o*-CH_3	BuF	H	>200	>200	45	9	0.9	5.0	1.3	1.4		
17m	*p*-NO_2	BuF	H	>200	>200	71	4.0	2.0	2.8	2.0	2.0	33	77
17n	*p*-F	BuF	CH	89	>50	13	1.3	0.2	1.0	0.56	0.71	16	59
17o	*p*-F[d]	BuF	CH	63	>25	16	>12.5	7.9	>12.5	6.3	7.0	97	90
18d	*o*-CH_3	$(CH_2)_5$		71	45	>25	23	12	18	2.3	2.3	114	100
18e	*m*-CH_3	$(CH_2)_5$		142	71	45	>25	23	>25	9.0	9.0		
18f	*p*-CH_3	$(CH_2)_5$		79	>100	45	10	23	23	6.0	8.0		
18g	*o*-OCH_3	$(CH_2)_5$		79	>50	40	16	16	20	18	18		
18h	*m*-OCH_3	$(CH_2)_5$		>100	79	71	>50	28	40	16	15		
18j	*m*-CF_3	$(CH_2)_5$		142	71	40	14	6.3	>25	2.5	2.5	94	99
18k	*p*-CF_3	$(CH_2)_5$		>200	142	63	15	36	40	2.8	2.8	86	98

[a]Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all the studies reported here. The test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered ip. [b]Procedures for measuring acute toxicity (LD_{50}) and the effect of the compound on overt behavior, loss of righting reflex (LRR_{50}), traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), pedestal (P_{50}), and antagonism of nicotine-induced tonic extensor convulsions (TE) and death (L) have been described previously.[5] [c]The procedure for measuring the effect on uptake of [^{14}C]serotonin[6] and [^{3}H]norepinephrine[7] were carried out using previously described procedures. Test compounds were dissolved or suspended in saline and administered by ip route 1 hr before the intravenous administration of the radioactive materials. All animals were sacrificed 3 hr after the administration of the radioactive compounds. Values are expressed as per cent of control. [d]Cis compounds. Remainders are all trans. [e]BuF denotes $-CH_2CH_2CH_2C(O)C_6H_4F$-*p*.

Table II. 4-Aryl-4-hydroxycyclohexanones



Compd	X	Yield, %	Mp, °C	Formula[a]
8b	*m*-F	40	104–107	$C_{12}H_{13}FO_2$
8g	*o*-OCH_3	50	111–113	$C_{13}H_{16}O_3$
8i	*p*-OCH_3	24	103–104.5	$C_{13}H_{16}O_3$

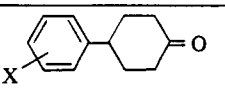
[a]Satisfactory analyses were obtained for C and H.

(7b). A solution of 1.96 g (0.009 mole) of the amide in 60 ml of THF was added to 0.49 g of $LiAlH_4$ in 10 ml of THF over 12 min. Following 4 hr heating at reflux, the mixture was cooled in ice and treated, in turn, with 0.5 ml of H_2O, 0.5 ml of 15% NaOH, and 1.5 ml of H_2O. The solid was removed on a filter, and the filtrate treated as above. The product was recrystallized from CH_2Cl_2–EtOAc to give 1.94 g (90%) of salt, mp 239.5–240.5°. *Anal.* ($C_{13}H_{19}ClFN$) C, H, Cl.

4-Aryl-4-hydroxycyclohexanones (8) (Table II). In a typical experiment a solution of 5.70 g (0.05 mole) of *p*-hydroxycyclohexanone in 60 ml of THF was added to an ice-cooled solution of 0.15 mole of the Grignard reagent in 200 ml of THF. Following 17 hr standing at room temp, the mixture was cooled in ice and treated with 50 ml of satd aqueous NH_4Cl. The organic layer was then separated, treated with water and brine, and taken to dryness.

A solution of the crude mixture of diols in 250 ml of Me_2CO was cooled in an ice bath. Over 5–10 min there was then added 17 ml of Jones reagent. The solvent was removed *in vacuo*, and the residue dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed over Florisil (elution with 5% then 20% Me_2CO in Skellysolve B). The combined crystalline fractions were recrystallized from Me_2CO–Skellysolve B.

Table III. 4-Arylcyclohexanones

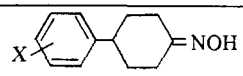


Compd	X	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
10a	*p*-F	80	36–39	PE[b]	$C_{12}H_{13}FO$
10b	*m*-F	90[c]			
10c	*p*-Cl	74	63–65	PE	$C_{12}H_{13}ClO$
10d	*o*-CH_3	87	60–63	PE	$C_{13}H_{16}O$
10e	*m*-CH_3	99[c]			
10f	*p*-CH_3	87	40–46	PE	$C_{13}H_{16}O$
10g	*o*-OCH_3	96	95–97	SSB[d]	$C_{13}H_{16}O_2$
10h	*m*-OCH_3	80	55–58	PE	$C_{13}H_{16}O_2$
10i	*p*-OCH_3	80	74.5–76.5[e]	SSB	
10j	*m*-CF_3	95[c]			
10k	*p*-CF_3	66[f]	44–46.5	PE	
10l	*p*-F, *o*-CH_3	89	96–98	SSB	$C_{13}H_{15}FO$

[a]Satisfactory analyses obtained when formula is given. [b]Petroleum ether. [c]Compound not crystalline; used without purification. [d]Skellysolve B. [e]Lit.[8] mp 75°. [f]Not analyzed; satisfactory ir and nmr.

4-Arylcyclohexanones (10) (Table III). In a typical experiment, the solid hydroxy ketone (5.35 g, 0.024 mole) was added to 25 ml of well-stirred trifluoroacetic acid. Following 10–15 min stirring at room temp, the resulting solution was poured into 400 ml of satd $NaHCO_3$. The precipitate was extracted with Et_2O, and the organic layer washed with $NaHCO_3$ and brine.

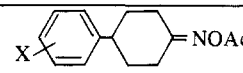
Table IV. 4-Arylcyclohexanone Oximes



Compd	X	Yield, %	Mp, °C	Formula[a]
11a	*p*-F	94	93-96	$C_{12}H_{14}FNO$
11b	*m*-F[b]	43	56-60	$C_{12}H_{14}FNO$
11c	*p*-Cl	88	141-142.5	$C_{12}H_{14}ClNO$
11d	*o*-CH_3	89	143-145	$C_{13}H_{17}NO$
11e	*m*-CH_3	20	94-96	$C_{13}H_{17}NO$
11f	*p*-CH_3	97	140-142	$C_{13}H_{17}NO$
11g	*o*-OCH_3	88	105-108	$C_{13}H_{17}NO_2$
11h	*m*-OCH_3	80	88-91	$C_{13}H_{17}NO_2$
11i	*p*-OCH_3	81	118-119.5	$C_{13}H_{17}NO_2$
11j	*m*-CF_3	47	91-94	$C_{13}H_{14}F_3NO$
11k	*p*-CF_3	74	112-115	$C_{13}H_{14}F_3NO$
11l	*p*-F, *o*-CH_3	93	148-151	$C_{13}H_{16}FNO$

[a]Satisfactory analyses obtained for C, H, N. [b]Product isolated by chromatography on Florisil.

Table V. 4-Arylcyclohexanone Oxime Acetates



Compd	X	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
12a	*p*-F	87	84-86	PE[b]	$C_{14}H_{16}FNO_2$
12b	*m*-F	72	62.5-64	SSB	$C_{14}H_{16}FNO_2$
12c	*p*-Cl	89	70-72.5	PE	$C_{14}H_{16}ClNO_2$
12d	*o*-CH_3	80	57-59	PE	$C_{15}H_{19}NO_2$
12e	*m*-CH_3[c]	98	31.5-34		
12f	*p*-CH_3	90	76-79	SSB[b]	$C_{15}H_{19}NO_2$
12g	*o*-OCH_3[d]	99			$C_{15}H_{19}NO_3$
12h	*m*-OCH_3	85	50.5-52	Et_2O-PE	$C_{15}H_{19}NO_3$
12i	*p*-OCH_3	84	81.5-86.5	PE	$C_{15}H_{19}NO_3$
12j	*m*-CF_3[e]	86	42-46	PE	
12k	*p*-CF_3	85	67.5-70	PE	$C_{15}H_{16}F_3NO_2$
12l	*p*-F, *o*-CH_3	89	82-85	SSB	$C_{15}H_{18}FNO_2$

[a]Satisfactory analyses unless shown otherwise. [b]See Table II. [c]Could not be recrystallized. [d]Not crystalline. [e]Satisfactory C, H could not be obtained; ir and nmr satisfactory. For a review of C analyses of fluorinated compounds see ref 9.

A mixture of a solution of the residue in 150 ml of EtOAc and 0.25 g of 10% Pd/C was shaken under H_2 until 1 equiv was absorbed. The catalyst was then removed on a filter, and the filtrate taken to dryness. The residue was recrystallized.

4-Arylcyclohexanone Oximes (11) (Table IV). A mixture of 8.60 g (0.042 mole) of the cyclohexanone, 8.50 g of $NH_2OH \cdot H_2O$, and 19 ml of 45% KOH in 200 ml of EtOH# was heated at reflux for 6 hr. The mixture was then concentrated *in vacuo* and diluted with H_2O. In several cases the product crystallized at this stage. When it did not, the precipitate was extracted with Et_2O and this was washed in turn with H_2O and brine. The organic layer was then taken to dryness and the product recrystallized from Et_2O and SSB.

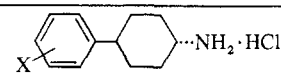
4-Arylcyclohexanone Oxime Acetates (12) (Table V). A solution of 4.43 g (0.016 mole) of the oxime in 25 ml of Ac_2O and 50 ml of pyridine was allowed to stand at room temp overnight. The solution was then poured into ice water. The precipitate if solid was collected on a filter; if not, the mixture was extracted with Et_2O and the organic layer washed, in turn, with H_2O, ice-cold dilute HCl, H_2O, and brine. The organic layer was then taken to dryness *in vacuo*. The solid was then recrystallized.

***trans*-4-Arylcyclohexylamine Hydrochlorides (13) (Table VI).**

a. By Birch Reduction. In a representative experiment, 8.58 g (0.045 mole) of the oxime acetate was dissolved in 90 ml of THF and 27 ml (21 g, 0.28 mole) of *tert*-BuOH. Ammonia (350 ml) was then distilled into the solution from over Na. To this there was then added 1.90 g (0.27 mole) of Li in 3 portions at such a rate that the blue color just persisted. When either the final color faded or 20 min after the last addition, 15 g of solid NH_4Cl was added. The solvent was then evaporated with a stream of N_2. The residue was dissolved in Et_2O and 1 *N* NaOH. The organic layer was separated, washed with H_2O and brine, and taken to dryness. The residue was dissolved in a small amount of Et_2O and treated with an excess of 4.9 *N* HCl in Et_2O. The precipitated solid was recrystallized from MeOH-EtOAc.

b. Diborane Reduction. To an ice-cooled solution of 4.66 g (0.0177 mole) of the oxime acetate in 50 ml of THF there was added dropwise 50 ml (0.05 mole) of 1 *N* B_2H_6 in THF. The solution was allowed to stand in the cold overnight. There was then added dropwise 1 ml of H_2O. The solvent was removed *in vacuo*, and the residue stirred for 2 hr with 100 ml of 0.5 *N* HCl and 50 ml of Et_2O. The organic layer was separated and extracted further with 0.5 *N* HCl and finally H_2O. The combined aqueous portions were made strongly basic and extracted with Et_2O. This last was concentrated to a small volume and treated with an excess of 4.9 *N* HCl in Et_2O. The precipitated solid was recrystallized from MeOH-EtOAc.

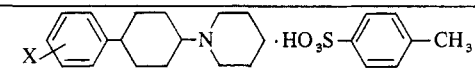
Table VI. *trans*-4-Arylcyclohexylamine Hydrochlorides



Compd	X	Yield, %	Mp, °C	Redn method	Formula[a]
13a	*p*-F	67	>330	a[b]	$C_{12}H_{17}ClFN$
13b	*m*-F	42	>300	b	$C_{12}H_{17}ClFN$
13c	*p*-Cl	86	>300	b	$C_{12}H_{17}Cl_2N$
13d	*o*-CH_3	59	>300	a	$C_{13}H_{20}ClN$
13e	*m*-CH_3	62	285-293	a	$C_{13}H_{20}ClN$
13f	*p*-CH_3	74	>310	a	$C_{13}H_{20}ClN$
13g	*o*-OCH_3	64	>300	a	$C_{13}H_{20}ClNO$
13h	*m*-OCH_3	33	283-284.5	a	$C_{13}H_{20}ClNO$
13i	*p*-OCH_3	20	307-311	a	$C_{13}H_{20}ClNO$
13j	*m*-CF_3[c]	50	223-235	b	
13k	*p*-CF_3[c]	62	>300	b	
13l	*p*-F, *o*-CH_3	66	>300	b	$C_{13}H_{19}ClFN$

[a]Satisfactory analyses obtained for C, H, N unless otherwise indicated. [b]In subsequent runs, using very dry *tert*-BuOH, this reaction led to loss of halogen. [c]Satisfactory analyses could not be obtained; see footnote *e*, Table V.

Table VII. *trans*-4-Arylcyclohexylpiperidine Tosylates



Compd	X	Yield, %	Mp, °C	Formula
18d	*o*-CH_3	34	186-189	$C_{25}H_{35}NO_3S$[a]
18e	*m*-CH_3	33	177-179	$C_{25}H_{35}NO_3S$[a]
18f	*p*-CH_3	64	56-59[d]	$C_{18}H_{27}N$[c]
18g	*o*-OCH_3	74	178-182	$C_{25}H_{35}NO_4S \cdot 0.5H_2O$[a]
18h	*m*-OCH_3	52	150-152	$C_{25}H_{35}NO_4S$[a]
18j	*m*-CF_3	50	171-177	$C_{25}H_{35}F_3NO_3S$[b]
18k	*p*-CF_3	44	186-200	$C_{25}H_{32}F_3NO_2S \cdot 0.5H_2O$[b]

[a]Satisfactory analyses for C, H, N. [b]Satisfactory analyses for C, H, S. [c]Calcd: C, 83.99; H, 10.57; N, 5.44. Found: C, 83.39; H, 10.76; N, 5.44.

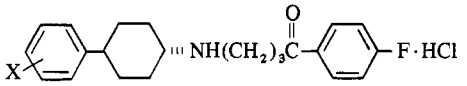
***trans*-4-Phenylcyclohexylamine Acetamide (15).** A solution of the free base obtained from 7.90 g (0.037 mole) of 4-phenylcyclohexylamine hydrochloride[2] in 15 ml of Ac_2O and 30 ml of pyridine was allowed to stand for 2 hr. The resulting mixture was diluted with H_2O, and the solid collected on a filter. A single recrystallization from Me_2CO-C_6H_{12} gave 5.77 g (71%) of amide, mp 158-161°. *Anal.* ($C_{14}H_{19}NO$): C, 77.38; N, 8.81; N, 6.45. Found: C, 76.79; H, 9.49; N, 6.64.

***trans*-*N*-[4-(*p*-Nitrophenyl)cyclohexyl]acetamide (16).** To an ice-cooled solution of 4.67 g (0.0215 mole) of the amide in 25 ml of TFA there was added 9 ml of HNO_3. Following 4 hr standing in the cold, the mixture was poured onto ice. The precipitate was extracted with CH_2Cl_2, and the organic layer washed with $NaHCO_3$. The solid which remained when the organic solution was taken to dryness was chromatographed on 500 ml of Florisil (2 l. each, 20 and 40% Me_2CO-SSB). The higher melting solid fractions were combined and recrystallized from CH_2Cl_2-EtOAc. There was obtained 3.09 g (54%) of crystals, mp 221-224°. *Anal.* ($C_{14}H_{18}N_2O_3$) C, H, N.

***trans*-4-(*p*-Nitrophenyl)cyclohexylamine Hydrochloride (13m).** A solution of 5.25 g (0.02 mole) of the acetamide in 50 ml each of HCl and MeOH was heated at reflux for 3 days. The bulk of the

#It was quite recently found that this can be advantageously replaced by THF.

Table VIII. 4'-Fluoro-4-[4-arylcyclohexylamino]butyrophenone Hydrochlorides



Compd	X	Yield, %	Mp, °C	Formula[a]
17a	*p*-F	43[b]	193-197	$C_{22}H_{26}ClF_2NO$[c]
17a	*p*-F[d]	49[e]	190.5-195	$C_{22}H_{26}ClF_2NO$[f]
17b	*m*-F	55	197-200	$C_{22}H_{26}ClF_2NO$
17c	*p*-Cl	41	214-217	$C_{22}H_{26}Cl_2FNO$[c]
17d	*o*-CH_3	49	194-198	$C_{23}H_{29}ClFNO$[g]
17e	*m*-CH_3	35[b]	195-198	$C_{23}H_{29}ClFNO$
17f	*p*-CH_3	41	227-230	$C_{23}H_{29}ClFNO$[h]
17g	*o*-OCH_3	45	223-235	$C_{23}H_{29}ClFNO_2$
17h	*m*-OCH_3	58	183-185	$C_{23}H_{29}ClFNO_2$
17i	*p*-OCH_3	26[b]	191-193	$C_{23}H_{29}ClFNO_2$
17j	*m*-CF_3	36[b]	197-201	$C_{23}H_{26}ClF_4NO$[f]
17k	*p*-CF_3	26	206-210	$C_{23}H_{26}ClF_4NO$[f]
17l	*p*-F, *o*-CH_3	52	215-218	$C_{23}H_{28}ClF_2NO \cdot 0.5H_2O$
17m	*p*-NO_2	46	231-232	$C_{22}H_{26}ClFN_2O$

[a] Analyses for C, H, N within 0.4% of theoretical values unless specified. [b] Recrystallized from MeOH-EtOAc. [c] Analysis for C, H only. [d] Cis compound. [e] Recrystallized from CH_2Cl_2-EtOAc. [f] Analysis for C, H, Cl. [g] *Anal.* Calcd: C, 70.84; H, 7.50. Found: C, 71.32; H, 8.09. [h] Satisfactory analysis could not be obtained; ir and nmr in agreement with structures.

MeOH was then removed *in vacuo* and the residue dissolved in 100 ml of hot H_2O. The solution was then made strongly basic and extracted with Et_2O. The organic layer was taken to dryness, the residue dissolved in a small amount of Et_2O and this treated with 4.9 *N* HCl in Et_2O. There was obtained 4.78 g (99%) of hydrochloride. The analytical sample melted at 293-294°. *Anal.* ($C_{12}H_{17}N_2O$) C, H, N.

***trans*-4-Arylcyclohexylpiperidine Tosylates (17) (Table VII).** To a solution of 6.7 mmoles (1.64 g) of the amine hydrochloride in 30 ml of EtOH there was added 1.7 ml of 4.18 *N* NaOMe in MeOH. Following 1 hr stirring, there was added 1 ml (2.17 g) of 1,5-diiodopentane and 1.65 g of K_2CO_3. The mixture was stirred overnight at reflux and the solvent then removed *in vacuo*. The residue was taken up in H_2O and Et_2O (material insoluble in either phase was discarded). The organic layer was washed with H_2O and brine and taken to dryness; in several cases this was recrystallized. The residue was dissolved in ether and treated with 1 equiv of *p*-$CH_3C_6H_4SO_3H$ dissolved in ether. The precipitated tosyl salt was recrystallized from CH_2Cl_2-EtOAc.

General Procedure for Preparation of *p*-Fluorobutyrophenone (Table VIII). A suspension of 10 mmoles of the appropriate amine hydrochloride in 40 ml of DMF was treated with an equivalent (0.43 g) of 57% NaH in mineral oil. At the end of 1 hr there was added 1.70 g of KI, 2.82 g of K_2CO_3, and 2.86 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene ketal. The mixture was stirred overnight in an oil bath at 90°. The solvent was removed under oil pump vacuum and the residue dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue and 20 ml of 2.5 *N* HCl in 40 ml of MeOH was stirred at room temp for 2 hr. The bulk of the solvent was removed *in vacuo* and the solid collected on a filter. The cake was washed once with Et_2O and recrystallized to constant mp from MeOH-2.5 *N* HCl.

***trans*-4'-Fluoro-4-[4-(*p*-fluorophenyl)cyclohexylmethylamino]-butyrophenone hydrochloride (17n)** was prepared in 60% yield by the above procedure. The product was recrystallized from CH_2Cl_2-EtOAc, mp 206-207.5°. *Anal.* ($C_{23}H_{28}ClF_2N$) C, H, N.

***cis*-4'-Fluoro-4-[4-(*p*-fluorophenyl)cyclohexylmethylamino]-butyrophenone hydrochloride (17o)** was prepared in 39% yield by the above procedure. The product was recrystallized from CH_2Cl_2-EtOAc to mp 191.5-193.5°. *Anal.* ($C_{23}H_{28}ClF_2N$) C, H, N.

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Central Nervous System Agents. 4.[1] Analogs of 3-Amino-2-phenylpropiophenone

Robert Bruce Moffett* and Jackson B. Hester

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001.

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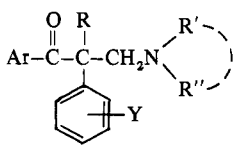
Thirty-one 1-aryl-2-phenyl-3-aminopropanones (I) have been tested in a battery of pharmacological screens designed to detect central nervous system activity. In general these Mannich bases seem to be stimulants. Most of these compounds and intermediates have not been previously reported.

Since the time of Mannich, scattered references have appeared to Mannich bases of the general formula I.[2] A con-



I

siderable number of this type of compound has been tested in animals in our laboratories. In general we have confirmed the reports by Huebner[2g] and Hofmann[2h] of CNS stimulant properties in this series, and we have extended the observations to many new compounds using a battery of pharmacological tests. Table I lists the results of the most significant testing. That many of these compounds are stimulants is shown by the low dose at which stimulation was observed in intact mice as compared with the relatively high dose causing death or loss of righting reflex (generally >100-200 mg/kg). The potency is also indicated by the low dose which prevented nicotine-induced convulsions.

From these data it seems that the most potent stimulants have small substituents on the amine (H, Me, or cyclic with 3 or 4 carbons). While azetidine and pyrrolidine compounds are quite active (**5**, **6**, **16**, **17**, **18**, **19**, and **26**), compounds with the diethylamine group (**4**) or piperidine group (**9**) are much less active. It should be noted, however, that **9** was tested as a free base and thus may be more slowly absorbed