Partly Reduced Biphenyls as Central Nervous System Agents. 1. 4-Arylcyclohex-3-enylamines

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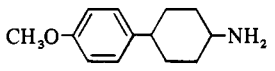
A series of 4-arylcyclohex-3-en-1-ones was prepared in several steps from 4-hydroxycyclohexanone and the appropriate Grignard reagents. The ketones were elaborated to the corresponding 4-arylcyclohex-3-en-1-ylamines. These were converted to several derivatives, including piperidines and 4'-fluoro-4-butyrophenones. 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 the course of general screening, arylcyclohexylamine (1) was found to exhibit interesting activity on various parameters of the CNS assay. We thus set about the preparation of analogs in order to delineate the scope of this lead. The synthetic route we chose led through the corresponding Δ^3 compounds. The finding that these, too, possessed activity led us to prepare derivatives of these as well. This communication describes that work; the reduced compounds are reported in a subsequent paper.



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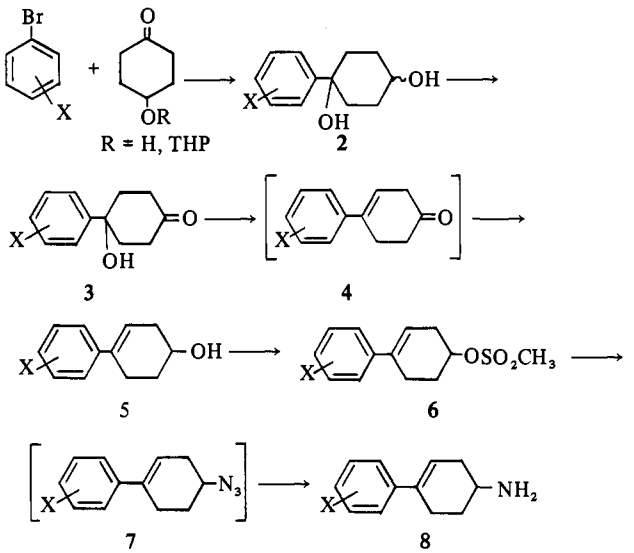
Synthesis. Though arylcyclohexylamines with functionality at the 4 position are known, the methods used to prepare these lack versatility.[1,2] The recent availability of a convenient method for large-scale preparation of 4-hydroxycyclohexanone[3] led us to design a route based on this intermediate.

Scheme I

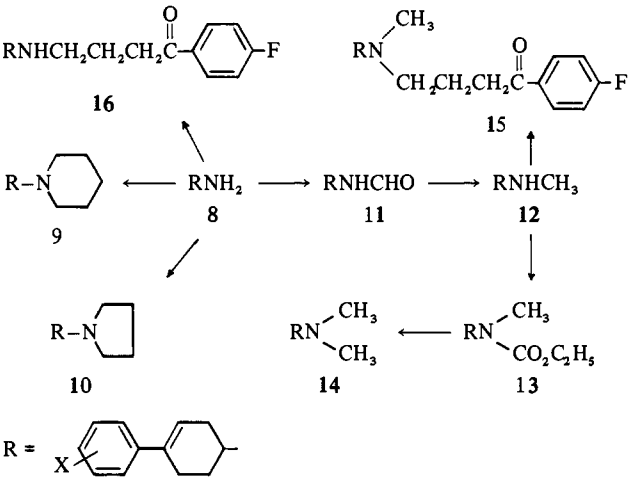


In the initial work, the requisite carbon skeleton was established by reaction of hydroxycyclohexanone with an excess of the appropriate Grignard reagent (method A). It was subsequently found advantageous to carry out this condensation on the tetrahydropyranyl ether of the hydroxy ketone (method B); this modification not only conserved aryl halide but avoided the insoluble salts which tended to reduce yields. In order to facilitate purification and characterization, the first-obtained mixture of isomeric diols was oxidized directly to the hydroxy ketone by means of Jones reagent. Brief exposure of that product to neat trifluoroacetic acid (TFA) led cleanly to the Δ^3-enone; in no case was any isomerization observed. Reduction of the ketone by means of $NaBH_4$ gave the unsaturated alcohol. Application of this scheme to the *p*-thioanisyl analog led to considerable over oxidation on treatment with Jones reagent; it proved possible in this case to carry out the dehydration selectively (TFA) to go directly from the diol to the unsaturated alcohol.

Treatment with $MeSO_2Cl$ in pyridine led cleanly to the mesylates; these were subjected to displacement by NaN_3 in DMF. The last intermediates were then reduced directly with $LiAlH_4$ to afford finally the desired amines.

Turning next to modification of the amine, we initially held the bicyclic moiety constant at *p*-fluorophenylcyclohex-3-enyl. The heterocyclic compounds were obtained by alkylation with the corresponding α,ω-dihalides and the mono- and dimethyl compounds by the acylation–reduction sequence shown in Scheme II. The known potentiation

Scheme II

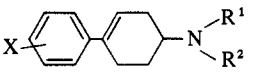


often obtained on preparation of 4-(4'-fluoro)butyrophenone derivatives[4] led us to prepare these analogs as well.

Initial screening results suggested that the most interesting activity resided in the 4-(4'-fluoro)butyrophenone of the primary amine as well as the piperidine. Most primary amines were thus taken on to the butyrophenones and selected compounds to the piperidines.

Pharmacology. The compounds prepared in this series were then tested for their effects on both behavioral (see footnote *b*, Table I) and biochemical CNS end points (see footnotes *a–c*, Table I for methodology). A brief perusal of the results quickly shows that the different activity profiles among these agents makes comparison difficult. Thus, though the primary amines (**8c,f,g,i**) show undeniable effects on overt behavior, as defined by Table I, footnote *b*,

Table I. Pharmacology of 4-Arylcyclohex-3-en-1-ylamines[a]



X	R^1	R^2	Compd	LD_{50}[b]	LRR_{50}[b]	Tr_{50}[b]	Ch_{50}[b]	D_{50}[b]	P_{50}[b]	Nicotine TE[b]	Nicotine L[b]	Effect on amines[c] [^{3}H]NE heart	Effect on amines[c] 5-[^{14}C]HT spleen
p-CH_3	H	H	8c	45	>50	>25	16	7	14	>25	>25	95	93
p-Cl	H	H	8f	>12.5	>12.5	>12.5	>12.5	9.9	>12.5	11	9	88	86
p-F	H	H	8g	>12.5	>12.5	>12.5	>12.5	>12.5	>12.5	3.5	3.5	62	48
m-CF_3	H	H	8i	>50	>50	>50	>50	12	25	10	10	98	84
o-CH_3	$(CH_2)_5$		9a	142	79	>25	20	11	11	4	4	102	126
m-CH_3	$(CH_2)_5$		9b	142	>100	>100	32	14	32	3.2	3.2	100	114
p-CH_3	$(CH_2)_5$		9c	>100	>100	100	8	56	40	63	63	113	132
m-OCH_3	$(CH_2)_5$		9d	126	>50	>50	50	>50	>50	8	8	104	104
m-CF_3	$(CH_2)_5$		9e	178	>100	40	10	>25	>25	3.2	3.6	105	117
p-F	$(CH_2)_4$		10	>100	>100	40	8	4	6	3	3	90	70
p-F	CHO	H	11	>100	>100	>100	25	25	45	16	16	74	71
p-F	CH_3	H	12	200	>100	89	>50	1.3	5	1.1	25	80	75
p-F	CH_3	CH_3	14	178	>100	80	56	5.6	63	9	8	98	86
p-F	CH_3	BuF[d]	15	>50	>50	8	1.8	0.9	3.6	3.6	3.2	12	46
o-CH_3	BuF	H	16a	>200	>200	25	8	0.71	5	0.4	0.45	60	102
m-CH_3	BuF	H	16b	>200	178	25	1.1	0.28	0.5	1.8	2.2	87	105
p-CH_3	BuF	H	16c	>200	>200	40	1.6	8	16	9	9	87	120
m-OCH_3	BuF	H	16d	>200	>200	50	1.8	0.5	3.6	1.4	1.6	33	99
p-Cl	BuF	H	16e	>100	>100	56	4	0.1	5	16	9	131	110
p-F	BuF	H	16f	>50	>50	7	0.8	0.2	0.56	1.3	1.6	8	49
o-CF_3	BuF	H	16g	>200	>200	63	2	0.4	6.3	1.6	1.8	36	77
m-CF_3	BuF	H	16h	>25	>25	>25	7	18	18	6	7	33	69
p-CH_3S	BuF	H	16i	>200	>100	63	1.4	0.84	5.0	0.32	0.32	37	74
p-F, *o*-CH_3	BuF	H	16j	>200	>200	126	5.6	0.7	3.6	1.3	1.8	78	85

[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]BuF denotes $-CH_2CH_2CH_2CO(p\text{-}FC_6H_4)$.

the most marked effect is on nicotine-induced convulsions and death; it is of interest that the *p*-fluoro compound is the only nonbutyrophenone in this series to show inhibition of the uptake of labeled norepinephrine and 5-hydroxytryptamine. The piperidines generally mimic the primary amines in their action with possibly slightly increased potency. Not until we come to the butyrophenones do we see a marked increase in potency on overt behavior as well as antagonism nicotine-induced convulsions and death. The potency of the SCH_3 analog (**16i**) on the latter parameter is particularly striking. Finally, note should be taken of the marked inhibition of uptake of amines occasioned by both *p*-fluoro compounds (**15**, **16f**).

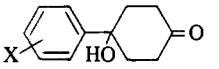
Experimental Section†

4-Arylcyclohexane-1,4-diols. Method A. In a typical experiment a solution of 5.70 g (0.05 mole) of 4-hydroxycyclohexanone in 60 ml of THF was added to an ice-cooled solution of 0.15 mole of the appropriate Grignard reagent with vigorous mechanical stirring. Following 17 hr standing at room temp, the mixture was cooled in ice and treated with 50 ml of aqueous NH_4Cl. The organic layer was separated, washed with water and brine, and taken to dryness.

Method B. A solution of 10.0 g each of 4-hydroxycyclohexanone and dihydropyran and 0.5 g of *p*-TSA in 100 ml of Et_2O was allowed to stand at room temp for 4 hr. The solution was then washed in turn with satd aqueous $NaHCO_3$ and brine and taken to dryness. A solution of the oily residue in 100 ml of THF was then added to 0.10 mole of an ice-cold solution of the appropriate Grignard reagent in 120 ml of THF. Following 17 hr standing at room temp, the mixture was worked up as above. A solution of the residual gum in 100 ml of MeOH was stirred with 10 ml of 2.5 *N* HCl for 1 hr. The bulk of the solvent was removed *in vacuo*, and the precipitated solid was collected on a filter. Additional product

†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.

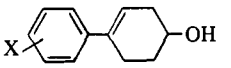
Table II. 4-Aryl-4-hydroxycyclohexanones



Compd	X	Method	Yield, %	Mp, °C	Formula[a]
3a	*o*-CH_3	A	21	122–124	$C_{13}H_{16}O_2$
	o-CH_3	B	38	120–124	
3b	*m*-CH_3	A	31	118–119.5	$C_{13}H_{16}O_2$[b]
	m-CH_3	B	56	115–118	
3c	*p*-CH_3	A[d]	35	109–111	$C_{13}H_{16}O_2$[c]
	p-CH_3	B	55	104–107	
3d	*m*-OCH_3	A	32	110–112	$C_{13}H_{16}O_3$
3e	*p*-Cl	A[e]	34	137.5–139	$C_{12}H_{13}ClO_2$
3f	*p*-F	A	35	115–117	$C_{12}H_{13}FO_2$[h]
3g	*o*-CF_3	A[f]	17	118–120	$C_{13}H_{13}F_3O_2$
3h	*m*-CF_3	A	33	110–112	$C_{13}H_{13}F_3O_2$
3i	*p*-CF_3	A[g]	36	156–162	$C_{13}H_{13}F_3O_2$[i]
	p-F, *o*-CH_3	B	53	156–158	$C_{13}H_{15}FO_2$

[a]Satisfactory analyses were obtained for C and H unless noted. [b]Calcd: C, 76.44; H, 7.90. Found: C, 76.93; H, 8.49. [c]Calcd: C, 76.44; H, 7.90. Found: C, 77.04; H, 8.16. [d]Recrystallized from cyclohexane. [e]Recrystallized from Me_2CO–C_6H_{12}. [f]Prepared *via* the organolithium reagent. [g]Recrystallized from C_6H_6. [h]Calcd: C, 69.21; H, 6.29. Found: C, 69.50; H, 6.76. [i]Calcd: C, 60.63; H, 5.76. Found: C, 60.46; H, 5.07.

Table III. 4-Arylcyclohex-3-en-1-ols



Compd	X	Yield, %	Mp, °C	Formula[a]
5a	o-CH_3	99	b	
5b	m-CH_3	89	61-61.5	$C_{13}H_{16}O$
5c	p-CH_3	72	96.5-97.5	$C_{13}H_{16}O$
5d	m-OCH_3	91	b	
5e	p-SCH_3	35	127-130	$C_{13}H_{16}OS$
5f	p-Cl	62	108-111.5	$C_{12}H_{13}ClO$
5g	p-F	96	73-74.5	$C_{12}H_{13}FO$
5h	o-CF_3	85	83-85	$C_{13}H_{13}F_3O$
5i	m-CF_3	95	b	
5j	p-CF_3	58	103.5-105.5	$C_{13}H_{13}F_3O$
5k	p-F, o-CH_3	97	36-41[c]	

[a]Satisfactory analyses obtained for C, H. [b]Could not be crystallized. [c]Could not be satisfactorily recrystallized.

was obtained on extraction of the filtrate with Et_2O; this was combined with the solid.

4-Aryl-4-hydroxycyclohexanones (Table II). Over a period of 10–15 min 30 ml of Jones reagent was added to the crude diol mixture from a run involving 0.10 mole of Grignard reagent in 300 ml of ice-cold Me_2CO. The solvent was removed *in vacuo* (minimum heat), and the residue was dissolved in H_2O and Et_2O. The organic layer was washed with H_2O, aqueous $NaHCO_3$, and brine and taken to dryness. The residue was then chromatographed over Florisil‡ (elution with 5%, then 20% Me_2CO–Skellysolve B§). The crystalline fractions were recrystallized from Me_2CO–Skellysolve B.

4-Arylcyclohex-3-en-1-ols (Table III). a. *Via* **the Hydroxy Ketone.** The solid hydroxy ketone (5.0 g) was added to 30 ml of well-stirred trifluoroacetic acid (TFA). Following 10 min at room temp the resulting solution was poured into 300 ml of satd $NaHCO_3$. The precipitate was dissolved in Et_2O and washed into neutrality with $NaHCO_3$. Following washes with H_2O and brine the solution was taken to dryness.

To a solution of the residue in 100 ml of EtOH (abs) there was added 3.20 g of $NaBH_4$. After 4 hr standing, the bulk of the solvent was removed *in vacuo*. The residue was treated with water and the precipitate collected on a filter. The solid was recrystallized from SSB.

b. *Via* **the Diol.** Crude 4-(*p*-thioanisyl)-1,4-cyclohexanediol (11.0 g) was dissolved in 50 ml of TFA. After 15 min, the solution was treated as above. The crude product was chromatographed on 1.2 l. of Florisil (elution with 3 l. 2.5% Me_2CO–SSB and 8 l. of 10% Me_2CO–SSB). The more polar fractions were combined and recrystallized from Me_2CO–SSB.

4-Arylcyclohex-3-en-1-ol Methanesulfonates (Table IV). A solution of 3.06 g of the alcohol in 10 ml of pyridine was cooled in ice. Three ml of CH_3SO_2Cl was then added, and the solution was allowed to stand in the cold overnight. The mixture was then diluted with water, and the oil extracted with Et_2O. The organic layer was washed with 2.5 *N* HCl, H_2O, and $NaHCO_3$. The organic solution was then taken to dryness, and the residue recrystallized.

4-Arylcyclohex-3-enylamines (Table V). In a typical experiment, 0.021 mole of the mesylate and an equal weight of sodium azide in 60 ml of DMF were stirred in an oil bath at 90° for 17 hr. The solvent was then removed under pump vacuum and the residue taken up in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

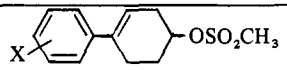
A solution of the residue oil in 100 ml of THF was added dropwise over 40 min to a well-stirred suspension of 1.0 g of $LiAlH_4$ in 10 ml of THF. Following an additional 4 hr stirring at room temp the mixture was cooled in ice. There were then added, in turn, 1 ml of H_2O, 1 ml of 15% NaOH, and 3 ml of H_2O. The precipitated solid was removed by filtration, and the filtrate 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 salt was recrystallized from MeOH–EtOAc.

***N*-[4-(*p*-Fluorophenyl)-3-cyclohexen-1-yl]formamide (11).** A mixture of 1.86 g of the amine free base and 25 ml of HCO_2Et was heated at reflux overnight. The resulting solution was taken to dryness. The residue was recrystallized twice from Me_2CO–Skellysolve B to afford 1.32 g of the amide, mp 105–107°. *Anal.* ($C_{13}H_{14}FNO$): C, 71.71; H, 6.44. Found: C, 71.67; H, 7.26.

***N*-Methyl-[4-(*p*-fluorophenyl)-3-cyclohexen-1-ylamine] Hydrochloride (12).** A solution of 2.0 g of the amide in 60 ml of THF was added to a well-stirred suspension of 0.50 g of LAH in 10 ml of THF. Following 4 hr heating at reflux, the mixture was cooled in ice. There was then added in turn 0.5 ml each of water and 15% sodium hydroxide followed by 1.5 ml of water. The precipitated solid was removed by filtration, and the filtrate taken to dryness. The gummy residue was dissolved in ether and treated with a small excess of 3.6 *N* ethereal HCl. The precipitated solid was recrystallized from CH_2Cl_2–EtOAc to give 1.54 g of product, mp 180–183°. *Anal.* ($C_{13}H_{17}ClFN$) C, H.

4′Fluoro-4-{[4-(*p*-fluorophenyl)-3-cyclohexen-1-yl]methylamino}-butyrophenone Hydrochloride (15). To a suspension of 1.85 g (8.1 mmoles) of the amine hydrochloride in 25 ml of DMF there was added 0.33 g (8.1 mmoles) of 56% NaH. Following 30 min stirring, there was added 1.45 g of KI, 2.40 g of K_2CO_3, and 2.10 g (7.4 mmoles) of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene ketal. The mixture was then stirred overnight in an oil bath at 90°. The solvent was removed under pump vacuum, and the residue taken up in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was stirred for 2 hr with 60 ml of MeOH and 30 ml of 2.5 *N* HCl. The bulk of the MeOH was then removed *in vacuo*. The precipitate was extracted with

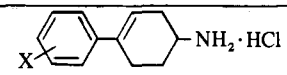
Table IV. 4-Arylcyclohex-3-en-1-ols Methanesulfonates



Compd	X	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
6a	o-CH_3	67	35-37	PE[b]	$C_{14}H_{18}O_3S$
6b	m-CH_3	90	45-47	Et_2O-PE	$C_{14}H_{18}O_3S$
6c	p-CH_3	82	85-87	SSB	$C_{14}H_{18}O_3S$[c]
6d	m-OCH_3	77	59-62	Et_2O-PE	$C_{14}H_{18}O_4S$
6e	p-SCH_3	90	136-138	CH_2Cl_2-SSB	$C_{12}H_{18}O_3S_2$
6f	p-Cl	84	96-98	C_6H_{12}	$C_{13}H_{15}ClO_3S$
6g	p-F	51	80-81.5	SSB	$C_{13}H_{15}FO_3S$
6h	o-CF_3	95	88-90	SSB	$C_{14}H_{15}F_3O_3S$
6i	m-CF_3	99	d		
6j	p-CF_3	69	99-100	H_2O-MeOH	$C_{14}H_{15}F_3O_3S$
6k	p-F, o-CH_3	98	d		

[a]Satisfactory analyses obtained for C, H, unless otherwise noted. [b]Petroleum ether. [c]Calcd: C, 63.13; H, 6.81. Found: C, 62.77; H, 6.95. [d]Could not be crystallized; single spot on tlc (silica gel-CH_2Cl_2).

Table V. 4-Arylcyclohex-3-en-1-ylamine Hydrochlorides



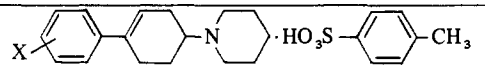
Compd	X	Yield, %	Mp, °C	Formula
8a	o-CH_3	50	272-294.5	$C_{13}H_{18}ClN$[h]
8b	m-CH_3	66	250-259	$C_{13}H_{18}ClN$[i]
8c	p-CH_3	55	311-313	$C_{13}H_{18}ClN$[c]
8d	m-OCH_3	61	232-235	$C_{13}H_{18}ClNO$[b]
8e	p-SCH_3	60	>300	$C_{13}H_{18}ClNS$[b]
8f	p-Cl	54	260-265	$C_{12}H_{15}Cl_2N$[d]
8g	p-F	57	261-266	$C_{12}H_{15}ClFN$[e]
8h	o-CF_3	61	247-248	$C_{13}H_{15}ClF_3N$[b]
8i	m-CF_3	49	256-258	$C_{13}H_{15}ClF_3N$[a]
8j	p-CF_3	34[f]	250-254	$C_{13}H_{15}BrF_3N$[d,g]
8k	p-F, o-CH_3	58	246-250	$C_{13}H_{17}ClFN$[b]

[a]Satisfactory analyses obtained for C, H, Cl. [b]Satisfactory analyses obtained for C, H, N. [c]Calcd: C, 69.78; H, 8.11. Found: C, 70.28; H, 8.76. [d]No satisfactory analysis could be obtained; nmr and ir are in agreement with structure. [e]Satisfactory analysis for C, H. [f]Recrystallized from CH_2Cl_2–C_6H_6. [g]Hydrobromide, Calcd: Br, 24.81. Found: Br, 24.26. [h]Calcd: C, 69.78; H, 8.11. Found: C, 70.06; H, 7.77. [i]Calcd: C, 69.78; H, 8.11. Found: C, 69.50; H, 8.62.

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

§Skellysolve B is a petroleum fraction, mp 60–70°, sold by the Skelly Oil Co.

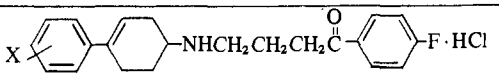
Table VI. 4-Arylcyclohex-3-en-1-ylpiperidinium Tosylates



Compd	X	Yield, %	Mp, °C	Formula
9a	*o*-CH_3	54	160–162	$C_{25}H_{33}NO_3S$[a]
9b	*m*-CH_3	63	157–160	$C_{25}H_{33}NO_3S$[b]
9c	*p*-CH_3	63	190–193	$C_{25}H_{33}NO_3S$[b]
9d	*m*-OCH_3	71	151–155	$C_{25}H_{33}NO_4S$[b]
9e	*m*-CF_3	42	155–160	$C_{25}H_{30}F_3NO_3S$[b]

[a]Calcd: C, 70.22; H, 7.88. Found: C, 69.82; H, 8.39. [b]Satisfactory analyses obtained for C, H, N.

Table VII. 4′-Fluoro-4-(4-arylcyclohex-3-en-1-ylamino)butyrophenone Hydrochloride



Compd	X	Mp, °C	Yield, %	Formula[a]
16a	*o*-CH_3	190–193	26[b]	$C_{23}H_{27}ClFNO$[c]
16b	*m*-CH_3	193–195	45	$C_{23}H_{27}ClFNO$
16c	*p*-CH_3	207–209	74	$C_{23}H_{27}ClFNO$
16d	*m*-OCH_3	178–185	40[b]	$C_{23}H_{27}ClFNO_2$
16e	*p*-Cl	190–192	45	$C_{22}H_{24}Cl_2NO$
16f	*p*-F	190–197	38	$C_{22}H_{23}ClF_2NO$[c]
16g	*o*-CF_3	157–160	57	$C_{23}H_{24}ClF_4NO$[d]
16h	*m*-CF_3	205–208	63	$C_{23}H_{24}ClF_4NO$
16i	*p*-SCH_3	171–175	9	$C_{23}H_{27}ClFNOS$
16j	*p*-F, *o*-CH_3	218–220	55	$C_{23}H_{26}ClF_2NO$[c]

[a]Satisfactory analyses for C, H, N. [b]Recrystallized from MeOH–EtOAc. [c]Analyzed for C, H only. [d]Calcd: C, 62.51; H, 5.47. Found: C, 62.01; H, 5.15.

CH_2Cl_2. This last solution was washed with 2.5 *N* HCl and taken to dryness. The solid was recrystallized twice from CH_2Cl_2–EtOAc to give 1.68 g (56%) of product, mp 178–180°. *Anal.* ($C_{23}H_{25}ClF_2NO$): C, 68.22; H, 6.22; Cl, 8.70. Found: C, 68.16; H, 6.71; Cl, 8.77.

***N*-Methyl-4-(*p*-fluorophenyl)-3-cyclohexene-1-carbamic Acid Ethyl Ester (13).** To an ice-cooled solution of 3.0 g of the amine free base and 2.15 ml of Et_3N in 30 ml of ether there was added dropwise 1.6 ml of ethyl chloroformate. Following 5 hr standing in the cold the mixture was diluted with Et_2O and H_2O. The organic layer was separated, washed with H_2O and brine, and taken to dryness. The residual solid was recrystallized from a small amount of petroleum ether (cooling in freezer) to give 3.57 g of the carbamate, mp 53–60°. *Anal.* ($C_{16}H_{20}FNO_2$) C, H.

***N,N*-Dimethyl-4-(*p*-fluorophenyl)-3-cyclohexen-1-ylamine Hydrochloride (14).** A solution of 2.57 g of the carbamate in 60 ml of THF was added to a well-stirred suspension of 1.0 g of LAH in 10 ml of THF. Following 4 hr heating at reflux the mixture was cooled in ice and treated in turn with 1 ml each of H_2O and 15% NaOH, followed by 3 ml of water. The solid was removed by filtration, and the filtrate was taken to dryness. The oily crude amine was converted to the hydrochloride with 3.6 *N* ethereal HCl. That solid was recrystallized twice from CH_2Cl_2–EtOAc to afford 0.92 g of solid, mp 165–168°. *Anal.* ($C_{14}H_{19}ClFN$) C, H, Cl.

1-[4-(*p*-Fluorophenyl)-3-cyclohexen-1-yl]pyrrolidine (10). Methanolic NaOMe (4.18 *N*, 2.15 ml) was added to a suspension of 2.02 g of the amine hydrochloride in 35 ml of EtOH. Following 1 hr stirring there was added 2.50 g of K_2CO_3 and 1.95 g of 1,4-dibromobutane. The mixture was heated at reflux for 17 hr and taken to dryness. The residue was dissolved in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residual solid was recrystallized twice from petroleum ether (cooling in freezer). There was obtained 0.86 g of solid, mp 62–65.5°. *Anal.* ($C_{16}H_{20}FN$) C, H.

4-Arylcyclohex-3-en-1-ylpiperidinium Tosylates (Table VI). 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 recrystallzed from CH_2Cl_2–EtOAc.

General Procedure for Preparation of *p*-Fluorobutyrophenones (Table VII). 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.

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