

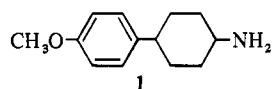
# Partly Reduced Biphenyls as Central Nervous System Agents. 1. 4-Arylcyclohex-3-enylamines

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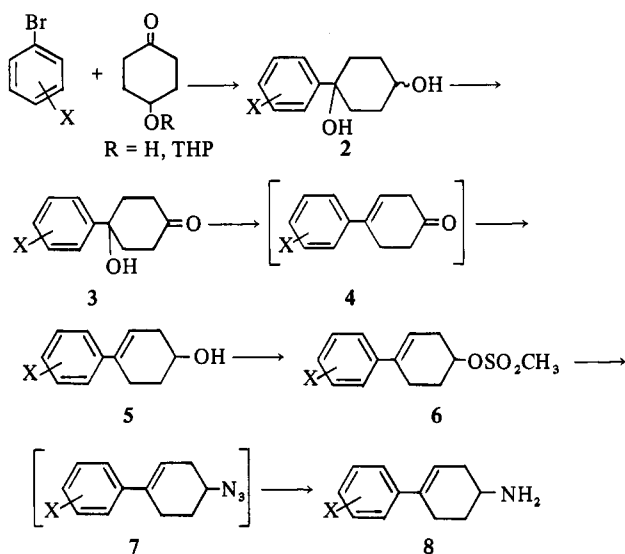
A series of 4-arylcyclohex-3-en-1-ones was prepared in several steps from 4-hydroxycyclohexanone and the appropriate Grignard reagents. The ketones were elaborated to the corresponding 4-arylcyclohex-3-en-1-ylamines. These were converted to several derivatives, including piperidines and 4'-fluoro-4-butyrophenones. 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  $\Delta^3$  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.



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

Scheme I



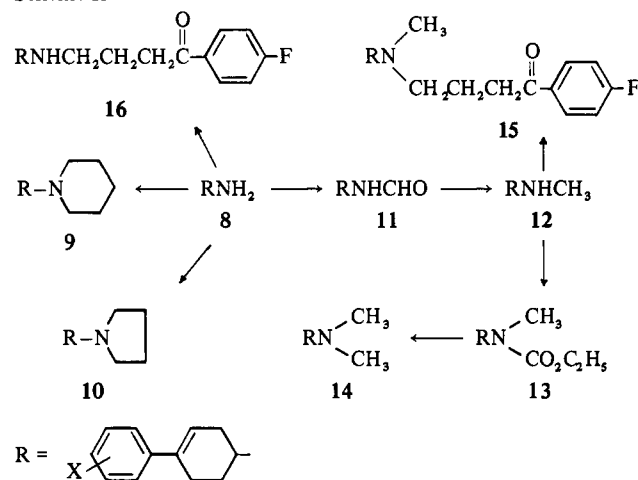
In the initial work, the requisite carbon skeleton was established by reaction of hydroxycyclohexanone with an excess of the appropriate Grignard reagent (method A). It was subsequently found advantageous to carry out this condensation on the tetrahydropyranyl ether of the hydroxy ketone (method B); 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  $\Delta^3$ -enone; in no case was any isomerization observed. Reduction of the ketone by means of  $\text{NaBH}_4$  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  $\text{MeSO}_2\text{Cl}$  in pyridine led cleanly to the mesylates; these were subjected to displacement by  $\text{NaN}_3$  in DMF. The last intermediates were then reduced directly with  $\text{LiAlH}_4$  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  $\alpha,\omega$ -dihalides and the mono- and dimethyl compounds by the acylation-reduction sequence shown in Scheme II. The known potentiation

Scheme II

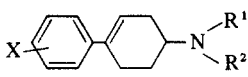


often obtained on preparation of 4-(4'-fluorophenyl)butyrophe-  
none derivatives<sup>4</sup> led us to prepare these analogs as well.

Initial screening results suggested that the most interesting activity resided in the 4-(4'-fluorophenyl)butyrophe-  
none of the primary amine as well as the piperidine. Most primary  
amines were thus taken on to the butyrophe-  
none 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<sup>a</sup>

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

<sup>a</sup>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. <sup>b</sup>Procedures for measuring acute toxicity (LD<sub>50</sub>) and the effect of the compound on overt behavior, loss of righting reflex (LRR<sub>50</sub>), traction (Tr<sub>50</sub>), chimney (Ch<sub>50</sub>), dish (D<sub>50</sub>), pedestal (P<sub>50</sub>), and antagonism of nicotine-induced tonic extensor convulsions (TE) and death (L) have been described previously.<sup>5</sup> <sup>c</sup>The procedure for measuring the effect on uptake of [<sup>14</sup>C]serotonin<sup>6</sup> and [<sup>3</sup>H]norepinephrine<sup>7</sup> 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. <sup>d</sup>BuF denotes –CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO(*p*-FC<sub>6</sub>H<sub>4</sub>).

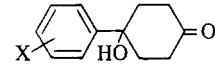
the most marked effect is on nicotine-induced convulsions and death; it is of interest that the *p*-fluoro compound is the only nonbutyrophenone in this series to show inhibition of the uptake of labeled norepinephrine and 5-hydroxytryptamine. The piperidines generally mimic the primary amines in their 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<sub>3</sub> 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<sub>4</sub>Cl. 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<sub>2</sub>O was allowed to stand at room temp for 4 hr. The solution was then

Table II. 4-Aryl-4-hydroxycyclohexanones

					
Compd	X	Method	Yield, %	Mp, °C	Formula <sup>a</sup>
3a	<i>o</i> -CH <sub>3</sub>	A	21	122–124	C <sub>13</sub> H <sub>16</sub> O <sub>2</sub>
	<i>o</i> -CH <sub>3</sub>	B	38	120–124	
3b	<i>m</i> -CH <sub>3</sub>	A	31	118–119.5	C <sub>13</sub> H <sub>16</sub> O <sub>2</sub> <sup>b</sup>
	<i>m</i> -CH <sub>3</sub>	B	56	115–118	
3c	<i>p</i> -CH <sub>3</sub>	A <sup>d</sup>	35	109–111	C <sub>13</sub> H <sub>16</sub> O <sub>2</sub> <sup>c</sup>
	<i>p</i> -CH <sub>3</sub>	B	55	104–107	
3d	<i>m</i> -OCH <sub>3</sub>	A	32	110–112	C <sub>13</sub> H <sub>16</sub> O <sub>3</sub>
3e	<i>p</i> -Cl	A <sup>e</sup>	34	137.5–139	C <sub>12</sub> H <sub>13</sub> ClO <sub>2</sub>
3f	<i>p</i> -F	A	35	115–117	C <sub>12</sub> H <sub>13</sub> FO <sub>2</sub> <sup>h</sup>
3g	<i>o</i> -CF <sub>3</sub>	A <sup>f</sup>	17	118–120	C <sub>13</sub> H <sub>13</sub> F <sub>3</sub> O <sub>2</sub>
3h	<i>m</i> -CF <sub>3</sub>	A	33	110–112	C <sub>13</sub> H <sub>13</sub> F <sub>3</sub> O <sub>2</sub>
3i	<i>p</i> -CF <sub>3</sub>	A <sup>g</sup>	36	156–162	C <sub>13</sub> H <sub>13</sub> F <sub>3</sub> O <sub>2</sub> <sup>i</sup>
	<i>p</i> -F, <i>o</i> -CH <sub>3</sub>	B	53	156–158	C <sub>13</sub> H <sub>13</sub> FO <sub>2</sub>

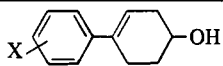
<sup>a</sup>Satisfactory analyses were obtained for C and H unless noted.

<sup>b</sup>Calcd: C, 76.44; H, 7.90. Found: C, 76.93; H, 8.49. <sup>c</sup>Calcd: C, 76.44; H, 7.90. Found: C, 77.04; H, 8.16. <sup>d</sup>Recrystallized from cyclohexane. <sup>e</sup>Recrystallized from Me<sub>2</sub>CO–C<sub>6</sub>H<sub>12</sub>. <sup>f</sup>Prepared via the organolithium reagent. <sup>g</sup>Recrystallized from C<sub>6</sub>H<sub>6</sub>. <sup>h</sup>Calcd: C, 69.21; H, 6.29. Found: C, 69.50; H, 6.76. <sup>i</sup>Calcd: C, 60.63; H, 5.76. Found: C, 60.46; H, 5.07.

washed in turn with satd aqueous NaHCO<sub>3</sub> 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 III. 4-Arylcyclohex-3-en-1-ols

				
Compd	X	Yield, %	Mp, °C	Formula <sup>a</sup>
5a	<i>o</i> -CH <sub>3</sub>	99	<i>b</i>	
5b	<i>m</i> -CH <sub>3</sub>	89	61–61.5	C <sub>13</sub> H <sub>16</sub> O
5c	<i>p</i> -CH <sub>3</sub>	72	96.5–97.5	C <sub>13</sub> H <sub>16</sub> O
5d	<i>m</i> -OCH <sub>3</sub>	91	<i>b</i>	
5e	<i>p</i> -SCH <sub>3</sub>	35	127–130	C <sub>13</sub> H <sub>16</sub> OS
5f	<i>p</i> -Cl	62	108–111.5	C <sub>12</sub> H <sub>13</sub> ClO
5g	<i>p</i> -F	96	73–74.5	C <sub>12</sub> H <sub>13</sub> FO
5h	<i>o</i> -CF <sub>3</sub>	85	83–85	C <sub>13</sub> H <sub>13</sub> F <sub>3</sub> O
5i	<i>m</i> -CF <sub>3</sub>	95	<i>b</i>	
5j	<i>p</i> -CF <sub>3</sub>	58	103.5–105.5	C <sub>13</sub> H <sub>13</sub> F <sub>3</sub> O
5k	<i>p</i> -F, <i>o</i> -CH <sub>3</sub>	97	36–41 <sup>c</sup>	

<sup>a</sup>Satisfactory analyses obtained for C, H. <sup>b</sup>Could not be crystallized. <sup>c</sup>Could not be satisfactorily recrystallized.

was obtained on extraction of the filtrate with Et<sub>2</sub>O; 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<sub>2</sub>CO. The solvent was removed *in vacuo* (minimum heat), and the residue was dissolved in H<sub>2</sub>O and Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O, aqueous NaHCO<sub>3</sub>, and brine and taken to dryness. The residue was then chromatographed over Florisil<sup>†</sup> (elution with 5%, then 20% Me<sub>2</sub>CO–Skellysolve B<sup>§</sup>). The crystalline fractions were recrystallized from Me<sub>2</sub>CO–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<sub>3</sub>. The precipitate was dissolved in Et<sub>2</sub>O and washed into neutrality with NaHCO<sub>3</sub>. Following washes with H<sub>2</sub>O 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<sub>4</sub>. 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<sub>2</sub>CO–SSB and 8 l. of 10% Me<sub>2</sub>CO–SSB). The more polar fractions were combined and recrystallized from Me<sub>2</sub>CO–SSB.

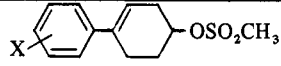
**4-Arylcyclohex-3-en-1-ol Methanesulfonates (Table IV).** A solution of 3.06 g of the alcohol in 10 ml of pyridine was cooled in ice. Three ml of CH<sub>3</sub>SO<sub>2</sub>Cl was then added, and the solution was allowed to stand in the cold overnight. The mixture was then diluted with water, and the oil extracted with Et<sub>2</sub>O. The organic layer was washed with 2.5 *N* HCl, H<sub>2</sub>O, and NaHCO<sub>3</sub>. 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<sub>6</sub>H<sub>6</sub> and H<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O 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<sub>4</sub> 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<sub>2</sub>O, 1 ml of 15% NaOH, and 3 ml of H<sub>2</sub>O. The precipitated solid was removed by filtration, and the filtrate taken to dryness. The residue was dissolved in a small amount of Et<sub>2</sub>O and treated with an excess of 4.9 *N* HCl in Et<sub>2</sub>O. 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<sub>2</sub>Et was

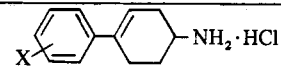
Table IV. 4-Arylcyclohex-3-en-1-ols Methanesulfonates

					
Compd	X	Yield, %	Mp, °C	Recrystn solvent	Formula <sup>a</sup>
6a	<i>o</i> -CH <sub>3</sub>	67	35–37	PE <sup>b</sup>	C <sub>14</sub> H <sub>18</sub> O <sub>3</sub> S
6b	<i>m</i> -CH <sub>3</sub>	90	45–47	Et <sub>2</sub> O–PE	C <sub>14</sub> H <sub>18</sub> O <sub>3</sub> S
6c	<i>p</i> -CH <sub>3</sub>	82	85–87	SSB	C <sub>14</sub> H <sub>18</sub> O <sub>3</sub> S <sup>c</sup>
6d	<i>m</i> -OCH <sub>3</sub>	77	59–62	Et <sub>2</sub> O–PE	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub> S
6e	<i>p</i> -SCH <sub>3</sub>	90	136–138	CH <sub>2</sub> Cl <sub>2</sub> –SSB	C <sub>12</sub> H <sub>18</sub> O <sub>3</sub> S <sub>2</sub>
6f	<i>p</i> -Cl	84	96–98	C <sub>6</sub> H <sub>12</sub>	C <sub>13</sub> H <sub>15</sub> ClO <sub>3</sub> S
6g	<i>p</i> -F	51	80–81.5	SSB	C <sub>13</sub> H <sub>15</sub> FO <sub>3</sub> S
6h	<i>o</i> -CF <sub>3</sub>	95	88–90	SSB	C <sub>14</sub> H <sub>15</sub> F <sub>3</sub> O <sub>3</sub> S
6i	<i>m</i> -CF <sub>3</sub>	99	<i>d</i>		
6j	<i>p</i> -CF <sub>3</sub>	69	99–100	H <sub>2</sub> O–MeOH	C <sub>14</sub> H <sub>15</sub> F <sub>3</sub> O <sub>3</sub> S
6k	<i>p</i> -F, <i>o</i> -CH <sub>3</sub>	98	<i>d</i>		

<sup>a</sup>Satisfactory analyses obtained for C, H, unless otherwise noted.

<sup>b</sup>Petroleum ether. <sup>c</sup>Calcd: C, 63.13; H, 6.81. Found: C, 62.77; H, 6.95. <sup>d</sup>Could not be crystallized; single spot on tlc (silica gel–CH<sub>2</sub>Cl<sub>2</sub>).

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

				
Compd	X	Yield, %	Mp, °C	Formula
8a	<i>o</i> -CH <sub>3</sub>	50	272–294.5	C <sub>13</sub> H <sub>18</sub> CIN <sup>h</sup>
8b	<i>m</i> -CH <sub>3</sub>	66	250–259	C <sub>13</sub> H <sub>18</sub> CIN <sup>i</sup>
8c	<i>p</i> -CH <sub>3</sub>	55	311–313	C <sub>13</sub> H <sub>18</sub> CIN <sup>c</sup>
8d	<i>m</i> -OCH <sub>3</sub>	61	232–235	C <sub>13</sub> H <sub>18</sub> CINO <sup>b</sup>
8e	<i>p</i> -SCH <sub>3</sub>	60	>300	C <sub>13</sub> H <sub>18</sub> CINS <sup>b</sup>
8f	<i>p</i> -Cl	54	260–265	C <sub>12</sub> H <sub>15</sub> Cl <sub>2</sub> N <sup>d</sup>
8g	<i>p</i> -F	57	261–266	C <sub>12</sub> H <sub>15</sub> ClF <sub>2</sub> N <sup>e</sup>
8h	<i>o</i> -CF <sub>3</sub>	61	247–248	C <sub>13</sub> H <sub>15</sub> ClF <sub>3</sub> N <sup>b</sup>
8i	<i>m</i> -CF <sub>3</sub>	49	256–258	C <sub>13</sub> H <sub>15</sub> ClF <sub>3</sub> N <sup>d,g</sup>
8j	<i>p</i> -CF <sub>3</sub>	34 <sup>f</sup>	250–254	C <sub>13</sub> H <sub>15</sub> BrF <sub>3</sub> N <sup>d,g</sup>
8k	<i>p</i> -F, <i>o</i> -CH <sub>3</sub>	58	246–250	C <sub>13</sub> H <sub>17</sub> ClFN <sup>b</sup>

<sup>a</sup>Satisfactory analyses obtained for C, H, Cl. <sup>b</sup>Satisfactory analyses obtained for C, H, N. <sup>c</sup>Calcd: C, 69.78; H, 8.11. Found: C, 70.28; H, 8.76. <sup>d</sup>No satisfactory analysis could be obtained; nmr and ir are in agreement with structure. <sup>e</sup>Satisfactory analysis for C, H. <sup>f</sup>Recrystallized from CH<sub>2</sub>Cl<sub>2</sub>–C<sub>6</sub>H<sub>6</sub>. <sup>g</sup>Hydrobromide, Calcd: Br, 24.81. Found: Br, 24.26. <sup>h</sup>Calcd: C, 69.78; H, 8.11. Found: C, 70.06; H, 7.77. <sup>i</sup>Calcd: C, 69.78; H, 8.11. Found: C, 69.50; H, 8.62.

heated at reflux overnight. The resulting solution was taken to dryness. The residue was recrystallized twice from Me<sub>2</sub>CO–Skellysolve B to afford 1.32 g of the amide, mp 105–107°. *Anal.* (C<sub>13</sub>H<sub>14</sub>FNO): C, 71.71; H, 6.44. Found: C, 71.67; H, 7.26.

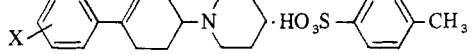
***N*-Methyl-4-(*p*-fluorophenyl)-3-cyclohexen-1-ylamine Hydrochloride (12).** A solution of 2.0 g of the amide in 60 ml of THF was added to a well-stirred suspension of 0.50 g of LAH in 10 ml of THF. Following 4 hr heating at reflux, the mixture was cooled in ice. There was then added in turn 0.5 ml 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<sub>2</sub>Cl<sub>2</sub>–EtOAc to give 1.54 g of product, mp 180–183°. *Anal.* (C<sub>13</sub>H<sub>17</sub>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<sub>2</sub>CO<sub>3</sub>, 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<sub>6</sub>H<sub>6</sub> and H<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O 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

<sup>†</sup>Florisil is a synthetic magnesia silica gel absorbent manufactured by the Floridin Co., Warren, Pa.

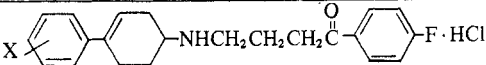
<sup>§</sup>Skellysolve B is a petroleum fraction, mp 60–70°, sold by the Skelly Oil Co.

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

				
Compd	X	Yield, %	Mp, °C	Formula
9a	<i>o</i> -CH <sub>3</sub>	54	160–162	C <sub>25</sub> H <sub>33</sub> NO <sub>3</sub> S <sup>a</sup>
9b	<i>m</i> -CH <sub>3</sub>	63	157–160	C <sub>25</sub> H <sub>33</sub> NO <sub>3</sub> S <sup>b</sup>
9c	<i>p</i> -CH <sub>3</sub>	63	190–193	C <sub>25</sub> H <sub>33</sub> NO <sub>3</sub> S <sup>b</sup>
9d	<i>m</i> -OCH <sub>3</sub>	71	151–155	C <sub>25</sub> H <sub>33</sub> NO <sub>4</sub> S <sup>b</sup>
9e	<i>m</i> -CF <sub>3</sub>	42	155–160	C <sub>25</sub> H <sub>30</sub> F <sub>3</sub> NO <sub>3</sub> S <sup>b</sup>

<sup>a</sup>Calcd: C, 70.22; H, 7.88. Found: C, 69.82; H, 8.39. <sup>b</sup>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 <sup>a</sup>
16a	<i>o</i> -CH <sub>3</sub>	190–193	26 <sup>b</sup>	C <sub>23</sub> H <sub>27</sub> ClFNO <sup>c</sup>
16b	<i>m</i> -CH <sub>3</sub>	193–195	45	C <sub>23</sub> H <sub>27</sub> ClFNO
16c	<i>p</i> -CH <sub>3</sub>	207–209	74	C <sub>23</sub> H <sub>27</sub> ClFNO
16d	<i>m</i> -OCH <sub>3</sub>	178–185	40 <sup>b</sup>	C <sub>23</sub> H <sub>27</sub> ClFNO <sub>2</sub>
16e	<i>p</i> -Cl	190–192	45	C <sub>22</sub> H <sub>24</sub> Cl <sub>2</sub> NO
16f	<i>p</i> -F	190–197	38	C <sub>22</sub> H <sub>24</sub> ClF <sub>2</sub> NO <sup>c</sup>
16g	<i>o</i> -CF <sub>3</sub>	157–160	57	C <sub>23</sub> H <sub>24</sub> ClF <sub>4</sub> NO <sup>d</sup>
16h	<i>m</i> -CF <sub>3</sub>	205–208	63	C <sub>23</sub> H <sub>24</sub> ClF <sub>4</sub> NO
16i	<i>p</i> -SCH <sub>3</sub>	171–175	9	C <sub>23</sub> H <sub>27</sub> ClFNO <sub>2</sub> S
16j	<i>p</i> -F, <i>o</i> -CH <sub>3</sub>	218–220	55	C <sub>23</sub> H <sub>26</sub> ClF <sub>2</sub> NO <sup>c</sup>

<sup>a</sup>Satisfactory analyses for C, H, N. <sup>b</sup>Recrystallized from MeOH-EtOAc. <sup>c</sup>Analyzed for C, H only. <sup>d</sup>Calcd: C, 62.51; H, 5.47. Found: C, 62.01; H, 5.15.

CH<sub>2</sub>Cl<sub>2</sub>. This last solution was washed with 2.5 *N* HCl and taken to dryness. The solid was recrystallized twice from CH<sub>2</sub>Cl<sub>2</sub>-EtOAc to give 1.68 g (56%) of product, mp 178–180°. *Anal.* (C<sub>23</sub>H<sub>27</sub>ClF<sub>2</sub>NO): 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<sub>3</sub>N 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<sub>2</sub>O and H<sub>2</sub>O. The organic layer was separated, washed with H<sub>2</sub>O 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<sub>16</sub>H<sub>26</sub>FNO<sub>2</sub>) C, H.

***N,N*-Dimethyl-4-(*p*-fluorophenyl)-3-cyclohexene-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<sub>2</sub>O 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<sub>2</sub>Cl<sub>2</sub>-EtOAc to afford 0.92 g

of solid, mp 165–168°. *Anal.* (C<sub>14</sub>H<sub>19</sub>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<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub>O and Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O 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<sub>16</sub>H<sub>20</sub>FN) C, H.

**4-Arylcyclohex-3-en-1-ylpiperidinium Tosylates (Table VI).** To a solution of 6.7 mmole (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<sub>2</sub>CO<sub>3</sub>. The mixture was stirred overnight at reflux and the solvent then removed *in vacuo*. The residue was taken up in H<sub>2</sub>O and Et<sub>2</sub>O (material insoluble in either phase was discarded). The organic layer was washed with H<sub>2</sub>O 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<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H dissolved in ether. The precipitated tosyl salt was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-EtOAc.

**General Procedure for Preparation of *p*-Fluorobutyrophenones (Table VII).** A suspension of 10 mmole 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<sub>2</sub>CO<sub>3</sub>, 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<sub>6</sub>H<sub>6</sub> and H<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O 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<sub>2</sub>O and recrystallized to constant mp from MeOH–2.5 *N* HCl.

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## References

- (1) D. V. Nightingale, J. D. Kerr, J. A. Gallagher, and M. Maienthal, *J. Org. Chem.*, **17**, 1017 (1952).
- (2) M. Carissimi, R. Dambrossio, E. Grumelli, E. Milla, and F. Ravenna, *Farmaco, Ed. Sci.*, **21**, 155 (1966).
- (3) D. E. Emmert and D. Lednicer, *Org. Prep. Proced.*, **1**, 127 (1969).
- (4) P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).
- (5) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DeVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964).
- (6) R. A. Lahti, P. A. Platz, and B. J. McAllister, *ibid.*, **13**, 681 (1970).
- (7) J. W. Daly, C. R. Creveling, and B. Witkop, *ibid.*, **9**, 273 (1966).