trituration of the residue with water gave a solid which was dried to yield 1.17 g (90.7%); TLC on alumina (microplate) with ether showed only the desired **26**. This material was recrystallized from 2-propanol (15 ml) and dried to give 0.90 g (69.7%), mp 154–155°. Anal. ($C_{27}H_{30}N_2$) C, H, N.

***cis*- and *trans*-2-(4,4'-Difluorobenzhydryl)-3-formamidoquinuclidine (27).** A solution of 6.0 g (0.0183 mol) of 2-(4,4'-difluorobenzhydryl)-3-quinuclidinone[2] in 40 ml of formamide was treated with 6.0 g of ammonium formate and heated overnight at 172° in an oil bath. The cooled solution was treated with excess potassium carbonate and poured into 1 l. of water. This solution was extracted several times with ether, which was then dried ($MgSO_4$) and concentrated in vacuo to yield 5.39 g of a glassy material: ir max ($CHCl_3$) 5.95 μ (s); TLC on alumina (microplate) with 5% 2-propanol–ether showed two components in about equal amounts. Recrystallization from 2-propanol gave 3.40 g: mp 179–190°; ir max (Nujol) 3.08 (m), 5.94 (s), 6.05 μ (s); ir max ($CHCl_3$) 5.93 μ (s). Anal. ($C_{21}H_{22}F_2N_2O$) C, H, N.

3-Benzhydrylbicyclo[2.2.2]octan-2-one Oxime (28). 3-Benzhydrylbicyclo[2.2.2]octan-2-one,[2] 1.0 g (0.0034 mol), was treated with 7 ml of water, 7 ml of 10% aqueous potassium hydroxide solution, 15 ml of ethanol, and 1.7 g of hydroxylamine hydrochloride and refluxed for 45 min. The solution was cooled and the resulting solid was collected and dried to yield 0.95 g: mp 185–190°; ir max (Nujol) 3.08–3.25 μ (s). Anal. ($C_{21}H_{23}NO$) C, H, N.

2-Amino-3-benzhydrylbicyclo[2.2.2]octane (29). A solution of 2.9 g (0.0095 mol) of 3-benzhydrylbicyclo[2.2.2]octan-2-one oxime in 50 ml of THF was added dropwise to a refluxing suspension of 2.5 g (0.065 mol) of $LiAlH_4$ in 50 ml of THF and refluxing was continued overnight. The cooled solution was treated with saturated sodium sulfate solution and the salts were removed by filtration and washed with THF. The filtrate was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 and dried ($MgSO_4$). Removal of solvent in vacuo gave 1.8 g of a slightly yellow solid residue. This material was combined with 1.0 g from a previous run and sublimed on a kugelrohr at 120–130° (10×10^{-5} mm) to give 1.5 g of a white solid, mp 130–132°. Anal. ($C_{21}H_{25}N$) C, H, N.

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Butyrophenones as Hypotensive Agents. Derivatives of 4-Aryl-4-(hydroxymethyl)cyclohexylamine

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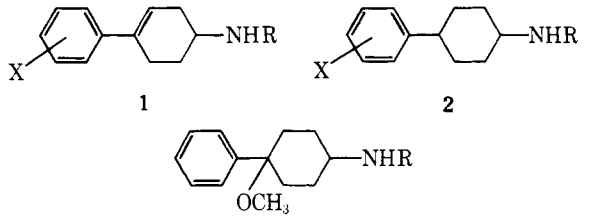
The preparation of butyrophenone derivatives of 4-aryl-4-(hydroxymethyl)cyclohex-1-ylamines starting from the corresponding 4-cyano-4-phenylcyclohexan-1-ones is described. Substitution was varied in both rings; both isomers of 4-phenyl-4-(hydroxymethyl)cyclohex-1-ylamine were characterized. Those derivatives which carried *p*-fluoro substitution on the butyrophenone exhibited hypotensive activity in the rat with diminished CNS activity compared to compounds lacking the hydroxymethyl group. The effect of substitution on the 4-aryl ring is discussed.

It has been shown previously that the butyrophenone derivatives of the amines **1–3** [R = $CH_2CH_2CH_2C(=O)(p\text{-}C_6H_4F)$] exhibit interesting neuroleptic activity in various animal screens.[1] In theory at least, these compounds are metabolically intraconvertible by well-known pathways. Thus, reduction of the styrene double bond of **1** leads into series **2**; the benzylic *tert*-methoxyl group of **3** could, under acidic conditions, eliminate to afford the olefin **1**.

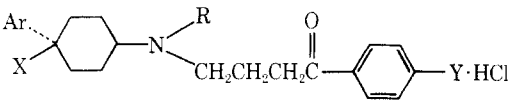


We thus considered it of some interest to ascertain the effect on biological activity of blocking these potential intraconversions. Such simple reactions should be prevented by attachment of an additional carbon atom to the benzilic position. We chose as our initial goal compounds in which this additional substituent was present as a hydroxymethyl group.

Synthesis. Hydroxyacetate **4** was converted to its mesylate in straightforward manner by means of mesyl chloride in pyridine. Treatment of **5** with sodium azide in DMF followed by reduction of the crude intermediate with lithium aluminum hydride led to reduction of both the azide and acetate groups; there was obtained amino alcohol **6** in which the configuration about C_1 had been inverted. The isomeric hydroxyacetate **8** was subjected to the same series of reactions to afford an amino alcohol (**10**) which was clearly different from **6** (Scheme I). Each of these compounds was then converted to the butyrophenone by condensation with the 2,2-dimethylpropylene ketal of 4'-chloro(*p*-fluoro)butyrophenone, followed by deketalization. General screening revealed that **7** elicited a blood pressure lowering effect in the rat while the CNS responses to this agent were markedly reduced from the prototypes **1–3** (see Table I). The isomeric compound **11**, on the other hand, failed to lower blood pressure at the standard screening dose of 50 mg/kg. This observation led us to study the effect of substitution on the aromatic rings of **7** on biological activity.

The key intermediates to this series, the cyano ketones **15**, were prepared by a modification of a previously reported route,[2] which involves decarboxylation of the product of Dieckmann cyclization (**14**) of the double Michael adducts of methyl acrylate and arylacetonitriles (**13**). Treatment of the cyano ketone with ethylene glycol in refluxing benzene afforded the ketals **16**. In view of the hindered nature of the nitrile, it is perhaps not surprising that reflux in ethylene glycol with base was required to effect hydrolysis of these last to the acids.[3] Reduction with lithium aluminum hydride[4] followed by deketalization and

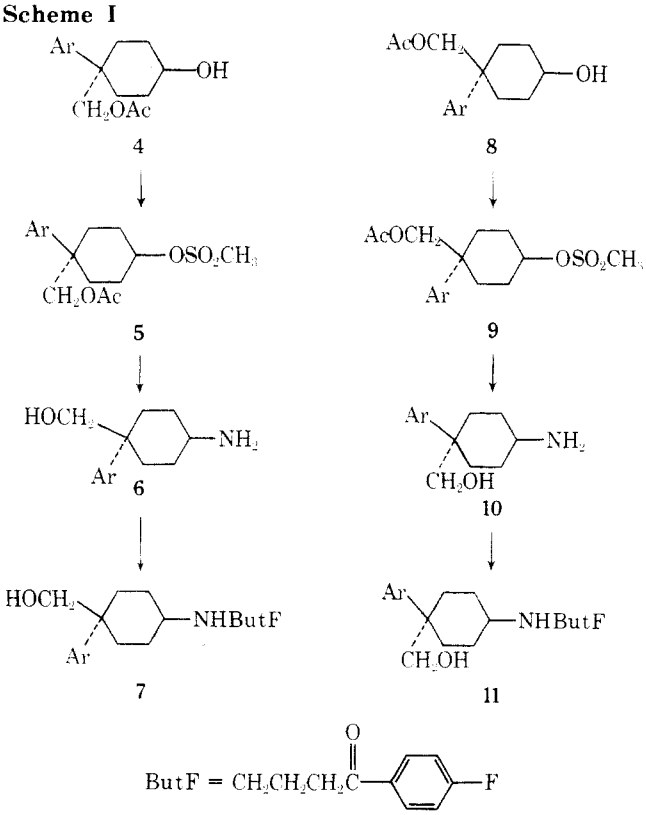
Table I. Pharmacological Activity of Butyrophenones[a]



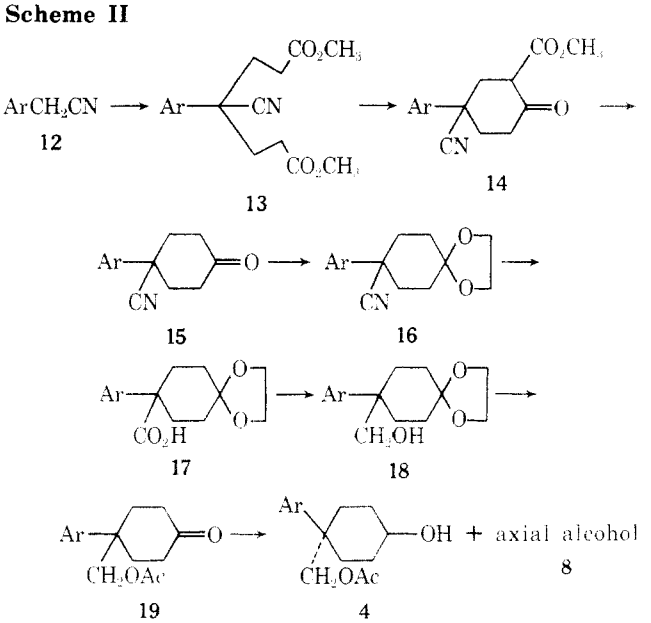
Compd	Ar	X	Y	R	Nicotine TR_{50}[c]	Nicotine TE_{50}[d]	Nicotine L_{50}[e]	Hypotensive act., potency ($p = 0.05$)[f]
7a	C_6H_5	CH_2OH	F	H	200	7	8	7 (12–3)
7b	p-ClC_6H_4	CH_2OH	F	H	71	18	18	36 (60–21)
7c	p-FC_6H_4	CH_2OH	F	H	142	2	3.2	12 (23–7)
7d	p-$CH_3OC_6H_4$	CH_2OH	F	H	63	3.2	3.2	100
7e	1-Naphthyl	CH_2OH	F	H	>200	7	8	10 (16–4)
11[b]	C_6H_5	CH_2OH	F	H	>100	36	36	[g]
21a	C_6H_5	CH_2OAc	F	H	71	16	16	10 (18–5)
21b	p-$CH_3OC_6H_5$	CH_2OAc	F	H	>50	15	15	38 (65–18)
24	C_6H_5	CH_2OH	F	CH_3	100	32	36	
30	C_6H_5	CH_3	F	H	50	10	10	8 (13–2)
33a	C_6H_5	CH_2OH	H	H	>200	>200	>200	
33b	C_6H_5	CH_2OH	CH_3	H	>200	71	79	
33c	C_6H_5	CH_2OH	OCH_3	H	>200	63	63	
33d	C_6H_5	CH_2OH	Cl	H	56	25	25	
3a	p-FC_6H_5	OCH_3	F	H	23	3.2	3.2	
Haloperidol					20	9	10	NT[h]
Chlorpromazine					6.3	0.9	1.1	NT
Clonidine					NT	NT	NT	1600 (3100–900)

[a] Configuration of all compounds as shown above except 11. [b] C_6H_5 and N are cis. [c] Fraction response. [d] Antagonism of nicotine-induced tonic extensor convulsions. [e] Antagonism of nicotine-induced lethality. [f] Compound **7d** is 100 by definition. [g] Inactive at screening dose. [h] Not tested.

Scheme I

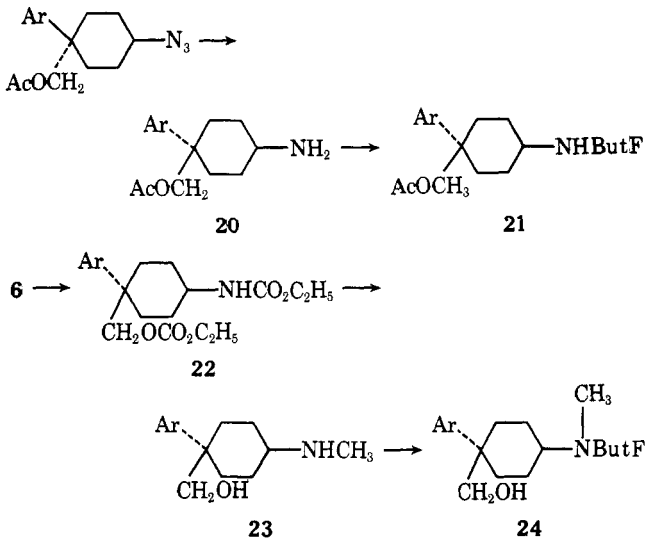


Scheme II



then acetylation afforded the ketoacetates **19** (Scheme II). Reduction of the ketone with sodium borohydride in 95% 2-propanol afforded both the isomeric alcohols in a ratio from 4 to 5 to 1, with the equatorial alcohol predominating. We have shown elsewhere[5] that in the case of **4a** (X = H), the phenyl group in this alcohol occupies the unusual axial position. The major alcohols, obtained by chromatography, were then converted to the p-fluorobutyrophenones by the transformations depicted in Scheme I. It should be noted that the hydroxymethyl group and the amine in these products bear the cis relationship.

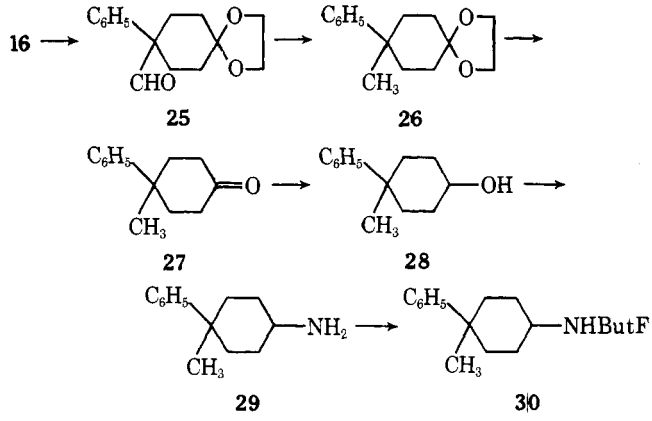
Catalytic reduction of the azides obtained from the alkylation of two of the mesylates (**5**, Ar = C_6H_5, p-$C_6H_4OCH_3$) afforded the O-acylated analogs of **6** (**20**). Amine **7** (Ar = C_6H_5) was converted to the carbamate, carbonate ester **22**; reduction by means of lithium aluminum hydride afforded the N-methyl compound **23**. Each of the above was in turn converted to the corresponding p-fluorobutyrophenone.



20 21 22 23 24

We next wished to study the effect of elimination of oxygen on the carbon at the quaternary center. Treatment of cyanoketal **16** (Ar = C_6H_5) with a stoichiometric amount of lithium aluminum hydride followed by hydrolysis of the intermediate imine under controlled conditions[6] yielded the aldehyde ketal **25.** This compound was converted to the methyl analog by Wolf–Kishner reduction. Removal of the ketal group followed by reduction with sodium borohydride afforded a 3:2 mixture of equatorial and axial alcohols; attempts to resolve this mixture were not successful. The total mixture was then subjected to the transformations outlined in Scheme III to afford the amine **29,** apparently

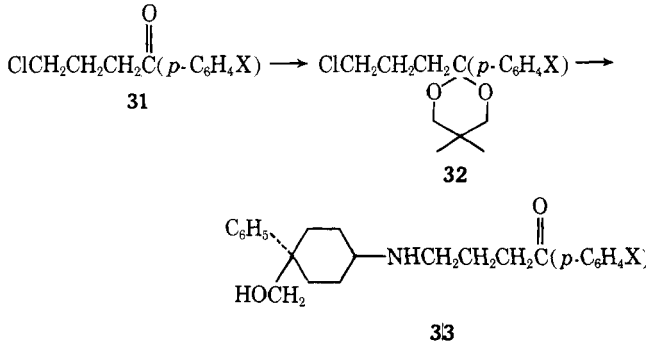
Scheme III



25 26 27 28 29 30

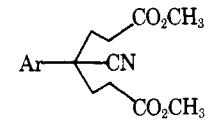
as a single product. The lack of reference compounds led us to remain noncommittal as to the stereochemistry of that product. This, too, was then carried on to the *p*-fluorobutyrophenone.

Finally, several 4′-chlorobutyrophenones (X = H, Cl, CH_3, OCH_3)[7] were converted to the corresponding neo-



31 32 33

Table II. Dimethyl 4-Aryl-4-cyanopimelates



Compd	Ar	Yield, %	Bp, °C (mm)
13b	*p*-ClC_6H_4	71	186–191 (0.35)
13c	*p*-FC_6H_4	72	177–181 (0.25)
13d	*p*-$CH_3OC_6H_4$	70	205–210 (0.6)
13e	1-Naphthyl	59	209–219 (0.5)

pentyl glycol ketals. Alkylation of **6** with these halides followed by deketalization yielded the analogs in which substitution on the remote aromatic ring was varied.

Pharmacology. The ED_{50} values for the effects of the test compounds on both overt behavior (fraction response) and nicotine-induced tonic extensor convulsions and lethality[8] are recorded in Table I. Compound was administered interperitoneally in solution or suspension in 0.25% methylcellulose to male mice (CF-1) weighing 18–22 g.

Compounds were screened for oral hypotensive activity in normotensive rats at a standard dose of 50 mg/kg by the method of Weeks.[9] Those agents which had lowered blood pressure by 9 mmHg or more after 4 hr following administration of drug were declared active. (Statistical analysis of historical data from this screen indicates this cut-off point would exclude vehicle alone 99% of the time.) Active compounds were retested at two or more dosage levels. The most active compound of the series (**7d**) lowered blood pressure down to a dose of 5.0 mg/kg (mean blood pressure lowering, 18.7 ± 5 mmHg). The potencies of the remaining active compounds relative to **7d,** as determined by parallel bioassay procedures,[10] are recorded in Table I.

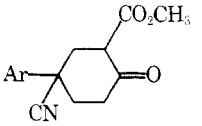
Five of the butyrophenones (**7a,c,d** and **30**) showed fairly potent activity in antagonizing both nicotine-induced end points. Although each of these had some effect on overt behavior, their potency was lower than either haloperidol or the butyrophenones reported by us earlier, e.g., **3a.** There seems further little correlation between potency in the nicotine assay within this series and potency in the hypotensive assay; though **7c** and **7d** are equipotent in nicotine antagonism, the latter is significantly more active as a hypotensive agent.

Aside from modification of the aromatic group attached to the cyclohexane ring, structural requirements for hypotensive activity appear quite stringent. Thus, comparison with the compounds prepared earlier (e.g., **3a**) strongly suggests the necessity for the quaternary center at the carbon bearing the aryl group. Though only a single isomeric pair was prepared (**7a** and **11**), the test results with these compounds indicate that nitrogen and the aromatic ring must bear a trans relationship. The rigid requirement for the *p*-fluorobutyrophenone for hypotensive activity is perhaps the most puzzling observation from this series, for as Table I demonstrates, none of the butyrophenones bearing substitution other than fluorine (**33a–d**) exhibited hypotensive activity at the screening dose.

Experimental Section[11]

Dimethyl 4-Aryl-4-cyanopimelates (13) (Table II). A mixture of 0.124 mol of the appropriate arylacetonitrile and 58 ml of methyl acrylate in 60 ml of *tert*-butyl alcohol was brought to reflux. The heat was removed and there was added quickly 19 ml of 40% methanolic Triton B in 28 ml of *tert*-butyl alcohol. Following 4 hr of heating at reflux the mixture was allowed to cool and was taken up in H_2O and PhH. The organic layer was washed in turn

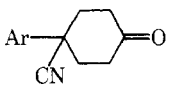
Table III. 4-Aryl-4-cyano-2-carbomethoxycyclohexanones



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
14b	p-ClC_6H_4	87	144.5–147.5	EtOAc–C_6H_{12}	$C_{15}H_{14}ClNO_3$
14c	p-FC_6H_4	92	*a*		
14d	p-$CH_3OC_6H_4$	96	63.5–66	Et_2O–PE[b]	$C_{16}H_{17}NO_4$
14e	1-Naphthyl	74	166.5–168	Me_2CO–SSB	$C_{19}H_{17}NO_3$

[a] Not crystalline. [b] Petroleum ether.

Table IV. 4-Aryl-4-cyanocyclohexanones



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
15b	p-ClC_6H_4	82	94.5–97	Et_2O	$C_{13}H_{12}ClNO$
15c	p-FC_6H_4	67	84–88	Et_2O	$C_{13}H_{12}FNO$
15d	p-$CH_3OC_6H_4$	60	77.5–79.5	Et_2O	$C_{14}H_{15}NO_2$
15e	1-Naphthyl	76	213–215	Me_2CO	$C_{17}H_{15}NO$

with 2.5 *N* HCl, H_2O, and brine and was taken to dryness. The residue was distilled first at 40 mm to remove a forerun and then at 0.5 mm to afford the oily product.

4-Aryl-4-cyano-2-carbomethoxycyclohexanones (14) (Table III). *t*-BuOK. To a solution of 0.00692 mol of the appropriate dimethyl 4-aryl-4-cyanopimelate in 45 ml of THF there was added 1.57 g (0.014 mol) of *t*-BuOK. The mixture was heated at reflux for 4.5 hr, cooled in ice, and treated with 10 ml of 2.5 *N* AcOH. The organic layer was separated and diluted with C_6H_6. That solution was then washed in turn with $NaHCO_3$, H_2O, and brine. The solution was taken to dryness and the product if solid recrystallized.

NaH. Sodium hydride (0.22 mol, 9.0 g) was washed free of mineral oil with $C_6H_5CH_3$. To this there was then added a solution of 0.0735 mol of the appropriate dimethyl 4-aryl-4-cyanopimelate in 500 ml of $C_6H_5CH_3$. The mixture was heated at reflux for 5 hr, cooled in ice, and worked up exactly as above.

4-Aryl-4-cyanocyclohexanones (15) (Table IV). A mixture of 0.0545 mol of the appropriate 4-aryl-4-cyano-2-carbomethoxycyclohexanone in 400 ml of AcOH and 200 ml of 10% H_2SO_4 was stirred mechanically on the steam bath for 48 hr. The mixture was then allowed to cool and diluted with water. This mixture was extracted thoroughly with C_6H_6. The organic layer was washed with H_2O, $NaHCO_3$, and brine and taken to dryness. The residual solid was then recrystallized.

4-Aryl-4-cyanocyclohexanone Ethylene Ketals (16) (Table V). A mixture of 0.098 mol of the appropriate 4-aryl-4-cyanocyclohexanone, 5.6 ml (6.23 g, 0.1 mol) of ethylene glycol, and 0.24 g of *p*-TSA in 175 ml of C_6H_6 was heated at reflux under a Dean-Stark trap for 6 hr. The solution was then allowed to cool and washed in turn with $NaHCO_3$, H_2O, and brine. The residue which remained when the organic layer was taken to dryness was then recrystallized.

4-Aryl-4-carboxycyclohexanone Ethylene Ketals (17) (Table VI). A mixture of 0.0696 mol of the appropriate 4-aryl-4-cyanocyclohexanone ethylene ketal and 15.0 g (0.27 mol) of KOH in 150 ml of ethylene glycol was heated at reflux overnight. The resulting solution was allowed to cool, diluted to 800 ml with H_2O, and washed once with Et_2O. The aqueous layer was covered with Et_2O and cautiously acidified. The organic layer was separated and the aqueous layer washed twice more with Et_2O. The extracts were combined and taken to dryness. The residue was then recrystallized.

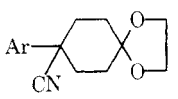
4-Acetoxymethyl-4-arylcyclohexanones (19) (Table VII). A solution of 0.0123 mol of the appropriate 4-aryl-4-carboxycyclohexanone ethylene ketal in 80 ml of THF was added dropwise to 0.50 g (0.013 mol) of $LiAlH_4$ in 10 ml of THF (*caution:* this reaction almost invariably takes off violently about 40 min after the start of the addition). The mixture was heated at reflux for 6 hr and then cooled in ice. There was added in turn 0.5 ml of H_2O, 0.5 ml of 15% NaOH, and 1.5 ml of H_2O. The inorganic solid was collected on a filter and rinsed with Et_2O and the filtrate was taken to dryness.

A solution of 0.068 mol of the crude hydroxy ketal and 20 ml of 2.5 *N* HCl in 200 ml of acetone was stirred at room temperature for 20 hr. The bulk of the solvent was then removed in vacuo and the residue taken up in H_2O and Et_2O. The organic layer was washed with $NaHCO_3$, H_2O, and brine and taken to dryness.

The residue was then dissolved in 60 ml of pyridine and 30 ml of Ac_2O. Following 20 hr standing at room temperature the mixture was poured onto ice–H_2O. The precipitated gum was extracted with Et_2O. The organic layer was washed in turn with H_2O, 2.5 *N* HCl, H_2O, $NaHCO_3$, and brine and taken to dryness. The residue, when solid, was then recrystallized.

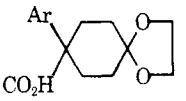
4-Acetoxymethyl-4-arylcyclohexanols (4) (Table VIII). To a solution of 0.037 mol of the appropriate 4-acetoxymethyl-4-arylcyclohexanone in 100 ml of 95% *i*-PrOH there was added 1.42 g of $NaBH_4$. Following 2 hr stirring at room temperature the bulk of the solvent was removed in vacuo. The residue was then taken up in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was then chromato-

Table V. 4-Aryl-4-cyanocyclohexanone Ethylene Ketals



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
16b	p-ClC_6H_4	79	124–126.5	C_6H_{12}	$C_{15}H_{16}ClNO_2$
16c	p-FC_6H_4	93	91–93.5	SSB	$C_{15}H_{16}FNO_2$
16d	p-$CH_3OC_6H_4$	92	101–103.5	CH_2Cl_2–SSB	$C_{16}H_{19}NO_3$
16e	1-Naphthyl	92	166–167	EtOAc–C_6H_{12}	$C_{19}H_{19}NO_2$

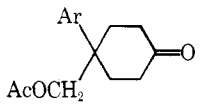
Table VI. 4-Aryl-4-carboxycyclohexanone Ethylene Ketals



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
17b	*p*-ClC_6H_4	82	162.5–164.5	CH_2Cl_2–SSB	$C_{15}H_{17}ClO_4$
17c	*p*-FC_6H_4	93	117–122	*a*	
17d	*p*-$CH_3OC_6H_4$	83	154–155.5	CH_2Cl_2–SSB	$C_{16}H_{20}O_5$
17e	1-Naphthyl	78	174–177	EtOAc–C_6H_{12}	$C_{19}H_{20}O_4$

[a] Could not be satisfactorily recrystallized.

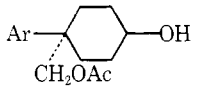
Table VII. 4-Acetoxymethyl-4-arylcyclohexanones



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
19b	*p*-ClC_6H_4	66	*a*		
19c	*p*-FC_6H_4	54	80–84	Et_2O	$C_{15}H_{17}FO_3$
19d	*p*-$CH_3OC_6H_4$	68	86.5–88	Et_2O–SSB	$C_{16}H_{20}O_4$
19e	1-Naphthyl	79	63–66	Et_2O[b]	$C_{19}H_{20}O_3$[c]

[a] Amorphous gum, characterized by NMR. [b] Wet Et_2O. [c] Calculated for $C_{19}H_{20}O_3 \cdot 0.5H_2O$.

Table VIII. 4-Acetoxymethyl-4-phenylcyclohexanols



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
4b	*p*-ClC_6H_4	39	105–107	Et_2O–SSB	$C_{15}H_{19}ClO_3$
4c	*p*-FC_6H_4	46	80–82.5	Et_2O–SSB	$C_{15}H_{19}FO_3$
4d	*p*-$CH_3OC_6H_4$	45	90–92.5	Et_2O–PE	$C_{16}H_{22}O_4$
4e	1-Naphthyl	51	*a*		

[a] Amorphous gum, characterized by NMR.

graphed on silica gel. Those fractions shown by TLC to consist of less polar material were combined and recrystallized.

4-Acetoxymethyl-4-arylcyclohexanol Methanesulfonates (5 and 9) (Table IX). A solution of the appropriate 4-acetoxymethyl-4-arylcyclohexanol in 10 vol of pyridine was cooled in ice. There was then cautiously added 1 vol of CH_3SO_2Cl. Following 18 hr standing in the cold, the mixture was poured into ice–water. The gum was extracted with Et_2O. The organic layer was washed in turn with H_2O, 2.5 *N* HCl, H_2O, and finally brine and then taken to dryness. The residue, if solid, was then recrystallized.

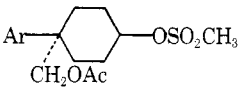
4-Aryl-4-(hydroxymethyl)cyclohexylamine Hydrochlorides (6 and 10) (Table X). A mixture of 0.0145 mol of the appropriate 4-acetoxymethyl-4-arylcyclohexanol methanesulfonate and an equal weight of sodium azide in 10 vol of DMF was stirred overnight in an oil bath at 90°. The solvent was then removed at 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 solution of the residue in 70 ml of THF was added dropwise to 1.10 g (0.029 mol) of $LiAlH_4$ in 20 ml of THF. Following 6 hr stirring at room temperature the mixture was cooled in ice and treated in turn with 1.1 ml of H_2O, 1.1 ml of 15% NaOH, and 3.3 ml of H_2O. The inorganic gel was collected on a filter and rinsed several times with Et_2O and CH_2Cl_2. The combined filtrates were taken to dryness. The residue was dissolved in MeOH and the solution treated with an excess of 5 *N* HCl in Et_2O and taken to dryness. The residue was recrystallized from MeOH–EtOAc.

4-Acetoxymethyl-4-phenylcyclohexylamine Hydrochloride (20a). A mixture of the crude azide obtained from 9.0 g of the crude 4-acetoxymethyl-4-phenylcyclohexanol methanesulfonate and 0.45 g of Pd/C was shaken under H_2 for 3 hr. The catalyst was then removed by filtration and the filtrate taken to dryness. The gummy residue was dissolved in Et_2O and this treated with 6 *N* HCl in Et_2O. The precipitated solid was recrystallized from MeOH–EtOAc to give 2.38 g of product, mp 195.5–198°. Anal. ($C_{15}H_{22}ClNO_2 \cdot 0.5H_2O$) C, H, N.

4-Acetoxymethyl-4-(*p*-methoxyphenyl)cyclohexylamine Hydrochloride (20b). A mixture of the crude azide obtained from 4.50 g (0.0126 mol) of 4-acetoxymethyl-4-(*p*-methoxyphenyl)cyclo-

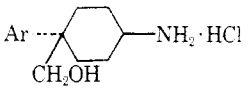
Table IX. 4-Acetoxymethyl-4-arylcyclohexanol Methanesulfonates



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
5a	C_6H_5	85	64–68.5	Et_2O–PE	$C_{16}H_{22}O_5S$
9a	C_6H_5 (isomer)	94	*a*		
5b	*p*-ClC_6H_4	82	120–124	CH_2Cl_2–SSB	$C_{16}H_{21}ClO_5S$
5c	*p*-FC_6H_4	86	95–97	Me_2CO–C_6H_{12}	$C_{16}H_{21}FO_5S$
5d	*p*-$CH_3OC_6H_4$	76	101–102	CH_2Cl_2–SSB	$C_{17}H_{24}O_6S$
5e	1-Naphthyl	90	*a*		

[a] Amorphous gum, characterized by NMR.

Table X. 4-Aryl-4-(hydroxymethyl)cyclohexylamine Hydrochlorides



Compd	Ar	Yield, %	Mp, °C	Formula
6a	C_6H_5	80	260–262	$C_{13}H_{20}ClNO$
10a	C_6H_5 (isomer)	60	215–218	$C_{13}H_{20}ClNO$
6b	*p*-ClC_6H_4	66	303–304.5	$C_{13}H_{19}Cl_2NO$
6c	*p*-FC_6H_4	84	288–290	$C_{13}H_{19}ClFNO$
6d	*p*-$CH_3OC_6H_4$	27	267–269	$C_{14}H_{22}ClNO_2$
6e	1-Naphthyl	33	268–269	$C_{17}H_{22}ClNO$

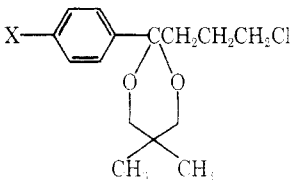
hexanol methanesulfonate and 0.32 g of 10% Pd/C in 150 ml of EtOAc was shaken under H_2 for 6 hr. The catalyst was then removed by filtration and the filtrate taken to dryness in vacuo. The residue was dissolved in Et_2O and this treated with 6 *N* HCl in Et_2O. The precipitate was recrystallized from MeOH–Et_2O to give 2.55 g (64%) of product, mp 191.5–193°. Anal. ($C_{16}H_{24}ClNO_3$) C, H, N.

Ethyl [4-[[(Ethoxycarbonyl)oxy]methyl]-4-phenylcyclohexyl]carbamate (22). A suspension of 2.0 g (0.0083 mol) of 4-phenyl-4-hydroxymethylcyclohexylamine hydrochloride in $CHCl_3$ was shaken with 1 *N* NaOH until all solid dissolved. The solid which remained when the organic layer was taken to dryness was dissolved in 20 ml of pyridine. The solution was cooled in ice and treated with 1.7 ml of $ClCO_2C_2H_5$. Following 18 hr of standing in the cold, the mixture was poured into ice–H_2O. The precipitated solid was recrystallized from Et_2O–petroleum ether to afford 2.32 g (77%) of solid, mp 69–72°. Anal. ($C_{19}H_{27}NO_5$) C, H, N.

***N*-Methyl-4-(hydroxymethyl)-4-phenylcyclohexylamine Hydrochloride (23).** A solution of 9.56 g (0.0274 mol) of ethyl [4-[[(ethoxycarbonyl)oxy]methyl]-4-phenylcyclohexyl]carbamate in 185 ml of THF was added to 2.78 g of $LiAlH_4$ in 50 ml of THF. Following 4 hr heating at reflux the mixture was cooled in ice. There was added, in turn, 2.8 ml of H_2O, 2.8 ml of 15% NaOH, and 8.4 ml of H_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. The residue was dissolved in MeOH, treated with 20 ml of 6 *N* HCl in Et_2O, and taken to dryness. The residue was recrystallized from MeOH–EtOAc to give 5.10 g (73%) of product, mp 204–207°. Anal. ($C_{14}H_{22}ClNO\cdot0.5H_2O$) C, H, N.

4-Formyl-4-phenylcyclohexanone Ethylene Ketal (25). To a well-stirred suspension of 2.74 g (0.072 mol) of $LiAlH_4$ in 170 ml of THF there was added over 20 min a solution of 34.8 g (0.143 mol) of 4-cyano-4-phenylcyclohexanone ethylene ketal in 1700 ml of

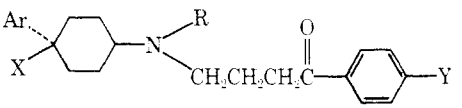
Table XI. 4-Chlorobutyrophenone 2,2-Dimethylpropylene Ketals



Compd	X	Yield, %	Bp (mm), °C	Mp, °C	Recrystn solvent	Formula
32a	H	31.5	117–118 (0.25–0.50)			*a*
32b	CH_3	66.4		78.5–82	PE	$C_{18}H_{23}ClO_2$
32c	CH_3O	30.9	174 (3)	51.5–53.5	PE	*b*
32d	Cl	73.5		87–92	SSB	$C_{15}H_{20}Cl_2O_2$

[a] Characterized by ir and NMR. [b] Unstable. Characterized by ir and NMR.

Table XII. Butyrophenones



Compd	Salt	Ar	X	Y	R	Yield, %	Mp, °C	Recrystn solvent	Formula
7a	HCl	C_6H_5	CH_2OH	F	H	31.9	178–180	MeOH–EtOAc	$C_{23}H_{29}ClFNO_2$
7b	HCl	*p*-ClC_6H_4	CH_2OH	F	H	32.3	188–190	MeOH–EtOAc	$C_{23}H_{28}Cl_2FNO_2$
7c	HCl	*p*-FC_6H_4	CH_2OH	F	H	24.7	196–198	MeOH–EtOAc	$C_{23}H_{28}ClF_2NO_2$
7d	HCl	*p*-$CH_3OC_6H_4$	CH_2OH	F	H	30.3	164–166	MeOH–EtOAc	$C_{24}H_{31}ClFNO_3$
7e	HCl	1-Naphthyl	CH_2OH	F	H	19.5	202–203	MeOH–Me_3CO	$C_{27}H_{31}ClFNO_2$
11[a]	HCl	C_6H_5	CH_2OH	F	H	22.8	*b*		
21a	HCl	C_6H_5	CH_2OAc	F	H	20.5	138–139	EtOAc	$C_{25}H_{31}ClFNO_3$[c]
21b	HCl	*p*-$CH_3OC_6H_4$	CH_2OAc	F	H	46.0[d]	*b*		
24		C_6H_5	CH_2OH	F	CH_3	56.2	91–94	MeOH	$C_{24}H_{30}FNO_2$
30	HCl	C_6H_5	CH_3	F	H	40.5	194–197	MeOH–EtOAc	$C_{23}H_{29}ClFNO$
33a		C_6H_5	CH_2OH	H	H	12.6[d]	100–101	MeOH	$C_{23}H_{29}NO_2$
33b		C_6H_5	CH_2OH	CH_3	H	13.7[d]	123–125	MeOH	$C_{24}H_{31}NO_2$
33c		C_6H_5	CH_2OH	OCH_3	H	19.7[d]	98–99	MeOH	$C_{24}H_{31}NO_3$
33d	HCl	C_6H_5	CH_2OH	Cl	H	47.3	164–167	MeOH–EtOAc	$C_{23}H_{29}Cl_2NO_2$

[a] Aromatic ring and N are cis. [b] Amorphous foam; characterized by ir and NMR. [c] Anal. Calcd for $C_{25}H_{31}ClFNO_3$: C, 67.02. Found: C, 66.46. [d] Isolated by chromatography over silica gel.

THF. The mixture was stirred at room temperature for 1.75 hr, cooled in an ice bath, and treated in turn with 2.8 ml of H_2O, 2.8 ml of 15% NaOH, and 8.2 ml of H_2O. The inorganic gel was collected on a filter and rinsed with Et_2O. The combined filtrates were then taken to dryness. A solution of the residue in 525 ml of THF and 52.5 ml of 2.5 *N* HCl was stirred at room temperature for 15 min, treated with 17 g of $NaHCO_3$, and taken to near dryness. Et_2O was added to the residue and the organic fraction separated and taken to dryness yielding 34.07 g (96.7%) of crude product, mp 51–66°. A small sample was purified by chromatography over silica gel followed by recrystallization from SSB, mp 68.5–71°. Anal. ($C_{15}H_{18}O_3$) C, H.

4-Methyl-4-phenylcyclohexanone Ethylene Ketal (26). A mixture of 9.38 g (0.038 mol) of 4-formyl-4-phenylcyclohexanone ethylene ketal, 5 ml of $N_2H_4 \cdot H_2O$, and 6.4 g of KOH in 120 ml of ethylene glycol was heated at reflux for 1 hr. Solvent was then allowed to distill until the pot came to 200°. At the end of 5 hr the mixture was allowed to cool, diluted with H_2O, and extracted with Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 750 ml of Florisil (elution with 1% EtOAc–SSB). The crystalline fractions were combined and recrystallized from MeOH–H_2O. There was obtained 5.92 g (67%) of product, mp 48–50°. Anal. ($C_{15}H_{20}O_2$) C, H.

4-Methyl-4-phenylcyclohexanol (28). A solution of 5.92 g (0.0253 mol) of 4-methyl-4-phenylcyclohexanone ethylene ketal and 6 ml of 2.5 *N* HCl in 60 ml of Me_2CO was stirred at room temperature for 20 hr. The solvent was removed in vacuo and the residue dissolved in Et_2O and H_2O. The organic layer was washed with $NaHCO_3$ and brine and taken to dryness.

To a solution of the oily ketone in 50 ml of EtOH there was added 1.25 g of $NaBH_4$. At the end of 5 hr the solvent was removed and the residue worked up as above. The crude product was chromatographed on 500 ml of silica gel (elution with 1% Me_2CO–CH_2Cl_2). There was obtained first 1.14 g of recovered starting ketal, mp 44–48°, followed by 3.08 g (79%) of alcohol, mp 56–72°. The NMR of the last showed a 3:2 ratio of equatorial to axial alcohol.

4-Methyl-4-phenylcyclohexylamine Hydrochloride (29). An ice-cooled solution of 3.08 g (0.0162 mol) of 4-methyl-4-phenylcyclohexanol and 3 ml of CH_3SO_2Cl in 30 ml of pyridine was allowed to stand in the cold overnight. The mixture was diluted with H_2O and then extracted with Et_2O. The organic layer was washed with H_2O, 2.5 *N* HCl, H_2O, and brine and taken to dryness.

A mixture of the gummy mesylate and 3.0 g of NaN_3 in 30 ml of DMF was stirred overnight at 90°. The solvent was removed in vacuo 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.

The crude azide in 60 ml of THF was added to 0.70 g of $LiAlH_4$ in 10 ml of THF. At the end of 4 hr there was added in turn 0.7 ml of H_2O, 0.7 ml of 15% NaOH, and 2.1 ml of h_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. The residue was dissolved in Et_2O and treated with 5 *N* HCl in Et_2O. The resulting solid was recrystallized several times from MeOH–EtOAc to give 1.26 g (35%) of product, mp 313–315°. Anal. ($C_{13}H_{20}ClN$) C, H, N.

4-Chlorobutyrophenone 2,2-Dimethylpropylene Ketals (32) (Table XI). A solution of 0.23 mol of the appropriate 4-chlorobutyrophenone, 0.23 mol of 2,2-dimethyl-1,3-propanediol, and 0.54 g of *p*-TSA in 400 ml of benzene was heated at reflux under a Dean-Stark trap for 20 hr. The solution was allowed to cool, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and taken to dryness. The residue was either recrystallized or distilled to yield desired butyrophenone ketal.

Butyrophenones (7, 11, 21, 24, 30, and 33) (Table XII). A mixture of the free base obtained from 0.0061 mol of the appropriate amine, 1.05 g of KI, 1.80 g of K_2CO_3, and 0.0061 mol of the properly substituted 4-chlorobutyrophenone 2,2-dimethylpropylene ketal in 38 ml of DMF was stirred overnight in an oil bath at 90°. The solvent was then removed under oil pump vacuum. The residue was dissolved in C_6H_6 and water. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue and 10 ml of 2.5 *N* HCl in MeOH was stirred at room temperature for 3 hr. The bulk of the MeOH was removed in vacuo. The residue was washed twice with Et_2O and then extracted with CH_2Cl_2. The CH_2Cl_2 extract was taken to dryness. If crystalline, this salt was then recrystallized.

Alternately, the residue was redissolved in CH_2Cl_2 and washed with base. The solution was then taken to dryness and the free base chromatographed on silica gel. The crystalline fractions were then combined and recrystallized.

Acknowledgment. The authors are indebted to Dr. J. R. Schultz of The Upjohn Co. for statistical treatment of the data from the hypotensive assay.

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(4) This reaction should be treated with caution. A vigorous exotherm was noted in all cases some time *after* addition of acid was complete.
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