

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. (C₂₇H₃₀N₂) 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-quinuclidinone² 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 (MgSO₄) and concentrated in vacuo to yield 5.39 g of a glassy material: ir max (CHCl₃) 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 (CHCl₃) 5.93 μ (s). Anal. (C₂₁H₂₂F₂N₂O) 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. (C₂₁H₂₃NO) 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 LiAlH₄ 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 CH₂Cl₂ and dried (MgSO₄). 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. (C₂₁H₂₅N) C, H, N.

References and Notes

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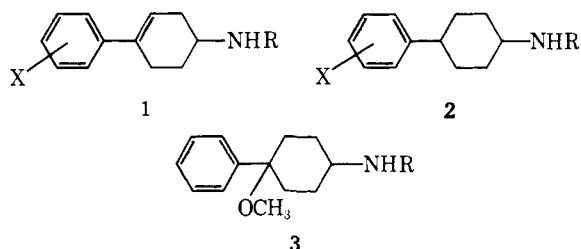
Butyrophenones as Hypotensive Agents. Derivatives of 4-Aryl-4-(hydroxymethyl)cyclohexylamine

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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 = CH₂CH₂CH₂C(=O)(*p*-C₆H₄F)] 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 benzylic 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 fol-

lowed 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 C₁ 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.

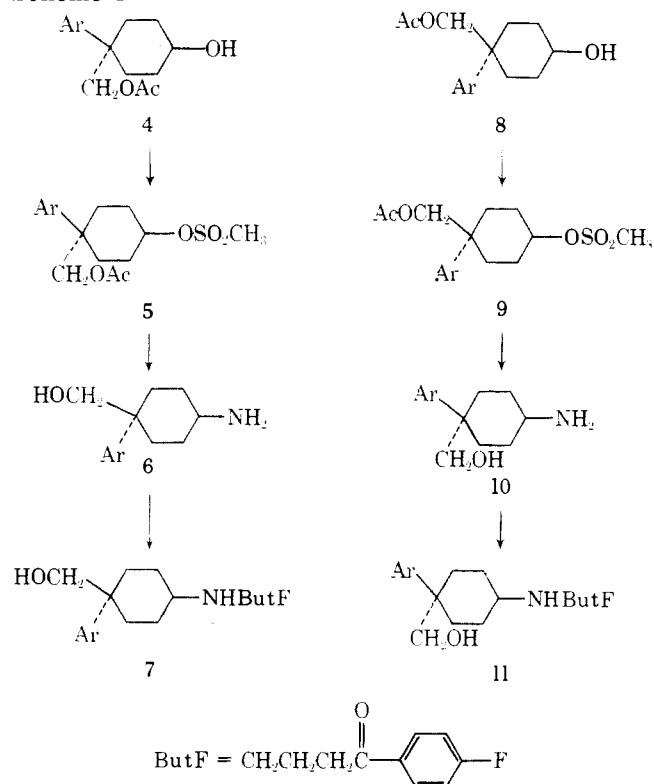
The key intermediates to this series, the cyano ketones **15**, were prepared by a modification of a previously reported route,² which involves decarboxylation of the product of Dieckmann cyclization (**14**) of the double Michael adducts of methyl acrylate and arylacetonitriles (**13**). Treatment of 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 hydride⁴ followed by deketalization and

Table I. Pharmacological Activity of Butyrophenones^a

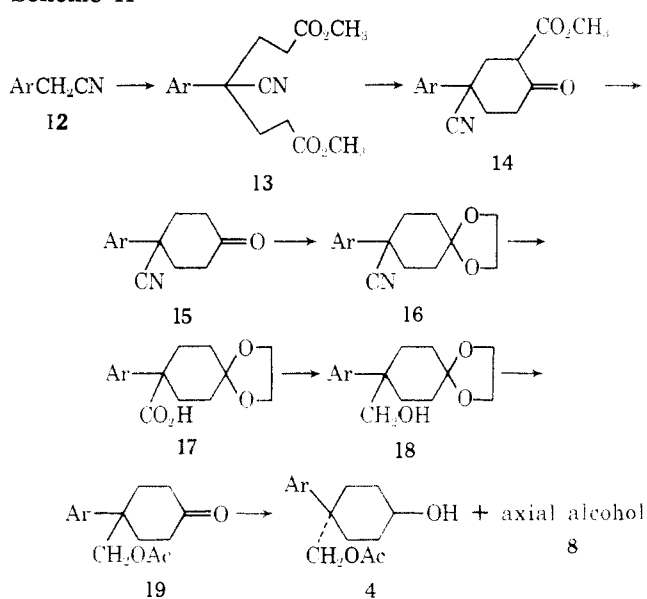
Compd	Ar	X	Y	R	TR ₅₀ ^c	Nicotine		Hypotensive act., potency (<i>p</i> = 0.05) ^f
						TE ₅₀ ^d	L ₅₀ ^e	
7a	C ₆ H ₅	CH ₂ OH	F	H	200	7	8	7 (12-3)
7b	<i>p</i> -ClC ₆ H ₄	CH ₂ OH	F	H	71	18	18	36 (60-21)
7c	<i>p</i> -FC ₆ H ₄	CH ₂ OH	F	H	142	2	3.2	12 (23-7)
7d	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ OH	F	H	63	3.2	3.2	100
7e	1-Naphthyl	CH ₂ OH	F	H	>200	7	8	10 (16-4)
11 ^b	C ₆ H ₅	CH ₂ OH	F	H	>100	36	36	g ^c
21a	C ₆ H ₅	CH ₂ OAc	F	H	71	16	16	10 (18-5)
21b	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ OAc	F	H	>50	15	15	38 (65-18)
24	C ₆ H ₅	CH ₂ OH	F	CH ₃	100	32	36	
30	C ₆ H ₅	CH ₃	F	H	50	10	10	8 (13-2)
33a	C ₆ H ₅	CH ₂ OH	H	H	>200	>200	>200	
33b	C ₆ H ₅	CH ₂ OH	CH ₃	H	>200	71	79	
33c	C ₆ H ₅	CH ₂ OH	OCH ₃	H	>200	63	63	
33d	C ₆ H ₅	CH ₂ OH	Cl	H	56	25	25	
3a	<i>p</i> -FC ₆ H ₄	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)

^aConfiguration of all compounds as shown above except 11. ^bC₆H₅ and N are *cis*. ^cFraction response. ^dAntagonism of nicotine-induced tonic extensor convulsions. ^eAntagonism of nicotine-induced lethality. ^fCompound 7d is 100 by definition. ^gInactive at screening dose. ^hNot tested.

Scheme I



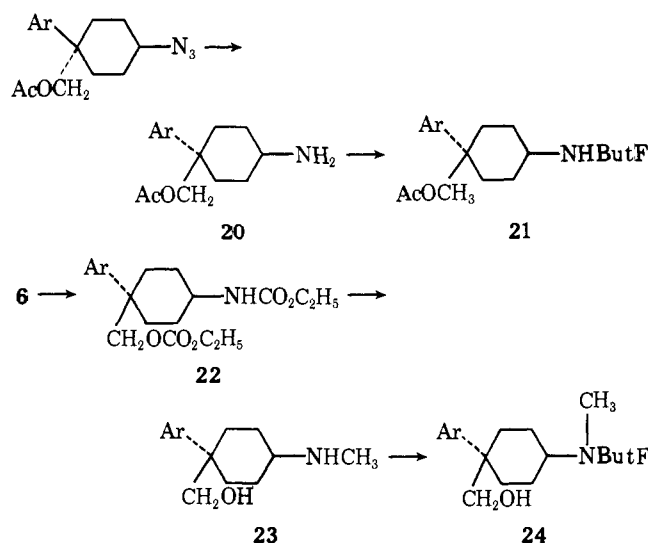
Scheme II



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.

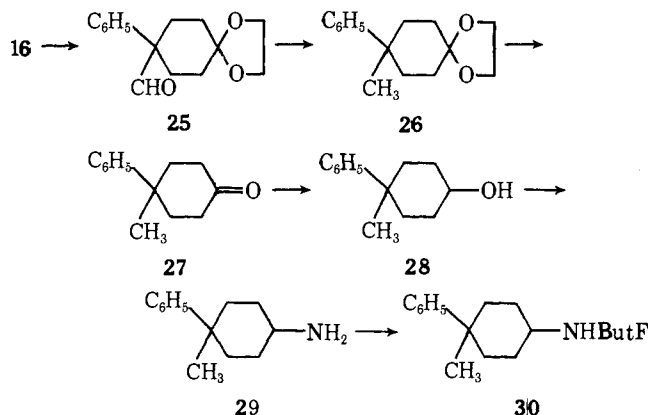
Catalytic reduction of the azides obtained from the alkylation of two of the mesylates (5, Ar = C₆H₅, *p*-C₆H₄OCH₃) afforded the O-acetylated analogs of 6 (20). Amine 7 (Ar = C₆H₅) was converted to the carbamate, carbonate ester 22; reduction by means of lithium aluminum hydride afforded the *N*-methyl compound 23. Each of the above was in turn converted to the corresponding *p*-fluorobutyrophenone.

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 elsewhere⁵ that in the case of 4a (X = H), the phenyl group in this alcohol occupies the unusual axial



We next wished to study the effect of elimination of oxygen on the carbon at the quaternary center. Treatment of cyanoketal 16 (Ar = C₆H₅) with a stoichiometric amount of lithium aluminum hydride followed by hydrolysis of the intermediate imine under controlled conditions⁶ 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



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, CH₃, OCH₃)⁷ were converted to the corresponding neo-

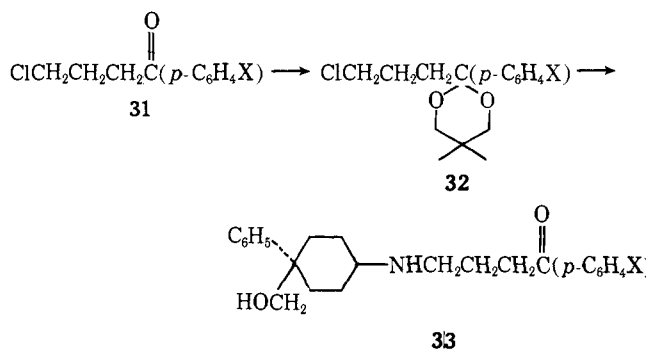


Table II. Dimethyl 4-Aryl-4-cyanopimelates

Compd	Ar	Yield, %	Bp, °C (mm)
13b	<i>p</i> -ClC ₆ H ₄	71	186–191 (0.35)
13c	<i>p</i> -FC ₆ H ₄	72	177–181 (0.25)
13d	<i>p</i> -CH ₃ OC ₆ H 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 ED₅₀ values for the effects of the test compounds on both overt behavior (fraction response) and nicotine-induced tonic extensor convulsions and lethality⁸ 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.

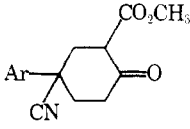
Compounds were screened for oral hypotensive activity in normotensive rats at a standard dose of 50 mg/kg by the method of Weeks.⁹ Those agents which had lowered blood pressure by 9 mmHg or more after 4 hr following administration of drug were declared active. (Statistical analysis of historical data 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.

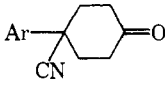
Aside from modification of the aromatic group attached to the cyclohexane ring, structural requirements for hypotensive activity appear quite stringent. Thus, comparison with the compounds prepared earlier (e.g., 3a) strongly suggests the necessity for the quaternary center at the carbon bearing the 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 Section¹¹

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 H₂O 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	<i>p</i> -ClC ₆ H ₄	87	144.5–147.5	EtOAc–C ₆ H ₁₂	C ₁₅ H ₁₄ ClNO ₃
14c	<i>p</i> -FC ₆ H ₄	92	<i>a</i>		
14d	<i>p</i> -CH ₃ OC ₆ H ₄	96	63.5–66	Et ₂ O–PE ^b	C ₁₆ H ₁₇ NO ₄
14e	1-Naphthyl	74	166.5–168	Me ₂ CO–SSB	C ₁₉ H ₁₇ NO ₃

^aNot crystalline. ^bPetroleum ether.**Table IV.** 4-Aryl-4-cyanocyclohexanones


Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
15b	<i>p</i> -ClC ₆ H ₄	82	94.5–97	Et ₂ O	C ₁₃ H ₁₂ ClNO
15c	<i>p</i> -FC ₆ H ₄	67	84–88	Et ₂ O	C ₁₃ H ₁₂ FNO
15d	<i>p</i> -CH ₃ OC ₆ H ₄	60	77.5–79.5	Et ₂ O	C ₁₄ H ₁₅ NO ₂
15e	1-Naphthyl	76	213–215	Me ₂ CO	C ₁₇ H ₁₅ NO

with 2.5 *N* HCl, H₂O, 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 C₆H₆. That solution was then washed in turn with NaHCO₃, H₂O, 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 C₆H₅CH₃. To this there was then added a solution of 0.0735 mol of the appropriate dimethyl 4-aryl-4-cyanopimelate in 500 ml of C₆H₅CH₃. 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% H₂SO₄ 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 C₆H₆. The organic layer was washed with H₂O, NaHCO₃, 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-cyanocyclo-

hexanone, 5.6 ml (6.23 g, 0.1 mol) of ethylene glycol, and 0.24 g of *p*-TSA in 175 ml of C₆H₆ was heated at reflux under a Dean-Stark trap for 6 hr. The solution was then allowed to cool and washed in turn with NaHCO₃, H₂O, and brine. The residue which remained when the organic layer was taken to dryness was then recrystallized.

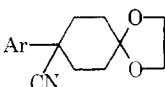
4-Aryl-4-carboxycyclohexanone Ethylene Ketals (17) (Table VI). A mixture of 0.0696 mol of the appropriate 4-aryl-4-cyanocyclohexanone ethylene ketal and 15.0 g (0.27 mol) of KOH in 150 ml of ethylene glycol was heated at reflux overnight. The resulting solution was allowed to cool, diluted to 800 ml with H₂O, and washed once with Et₂O. The aqueous layer was covered with Et₂O and cautiously acidified. The organic layer was separated and the aqueous layer washed twice more with Et₂O. The extracts were combined and taken to dryness. The residue was then recrystallized.

4-Acetoxyethyl-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 LiAlH₄ 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 H₂O, 0.5 ml of 15% NaOH, and 1.5 ml of H₂O. The inorganic solid was collected on a filter and rinsed with Et₂O 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 H₂O and Et₂O. The organic layer was washed with NaHCO₃, H₂O, and brine and taken to dryness.

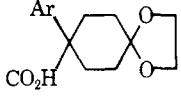
The residue was then dissolved in 60 ml of pyridine and 30 ml of Ac₂O. Following 20 hr standing at room temperature the mixture was poured onto ice–H₂O. The precipitated gum was extracted with Et₂O. The organic layer was washed in turn with H₂O, 2.5 *N* HCl, H₂O, NaHCO₃, and brine and taken to dryness. The residue, when solid, was then recrystallized.

4-Acetoxyethyl-4-arylcyclohexanols (4) (Table VIII). To a solution of 0.037 mol of the appropriate 4-acetoxyethyl-4-arylcyclohexanone in 100 ml of 95% *i*-PrOH there was added 1.42 g of NaBH₄. Following 2 hr stirring at room temperature the bulk of the solvent was removed in vacuo. The residue was then taken up in H₂O and Et₂O. The organic layer was washed with H₂O 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	<i>p</i> -ClC ₆ H ₄	79	124–126.5	C ₆ H ₁₂	C ₁₅ H ₁₆ ClNO ₂
16c	<i>p</i> -FC ₆ H ₄	93	91–93.5	SSB	C ₁₅ H ₁₆ FNO ₂
16d	<i>p</i> -CH ₃ OC ₆ H ₄	92	101–103.5	CH ₂ Cl ₂ –SSB	C ₁₆ H ₁₉ NO ₃
16e	1-Naphthyl	92	166–167	EtOAc–C ₆ H ₁₂	C ₁₉ H ₁₉ NO ₂

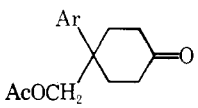
Table VI. 4-Aryl-4-carboxycyclohexanone Ethylene Ketals



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
17b	<i>p</i> -ClC ₆ H ₄	82	162.5–164.5	CH ₂ Cl ₂ -SSB	C ₁₅ H ₁₇ ClO ₄
17c	<i>p</i> -FC ₆ H ₄	93	117–122	^a	
17d	<i>p</i> -CH ₃ OC ₆ H ₄	83	154–155.5	CH ₂ Cl ₂ -SSB	C ₁₆ H ₂₀ O ₅
17e	1-Naphthyl	78	174–177	EtOAc-C ₆ H ₁₂	C ₁₉ H ₂₀ O ₄

^aCould not be satisfactorily recrystallized.

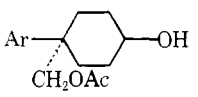
Table VII. 4-Acetoxyethyl-4-arylcyclohexanones



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
19b	<i>p</i> -ClC ₆ H ₄	66	^a		
19c	<i>p</i> -FC ₆ H ₄	54	80–84	Et ₂ O	C ₁₅ H ₁₇ FO ₃
19d	<i>p</i> -CH ₃ OC ₆ H ₄	68	86.5–88	Et ₂ O-SSB	C ₁₆ H ₂₀ O ₄
19e	1-Naphthyl	79	63–66	Et ₂ O ^b	C ₁₉ H ₂₀ O ₃ ^c

^aAmorphous gum, characterized by NMR. ^bWet Et₂O. ^cCalculated for C₁₉H₂₀O₃·0.5H₂O.

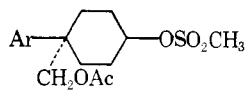
Table VIII. 4-Acetoxyethyl-4-phenylcyclohexanols



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
4b	<i>p</i> -ClC ₆ H ₄	39	105–107	Et ₂ O-SSB	C ₁₅ H ₁₉ ClO ₃
4c	<i>p</i> -FC ₆ H ₄	46	80–82.5	Et ₂ O-SSB	C ₁₅ H ₁₉ FO ₃
4d	<i>p</i> -CH ₃ OC ₆ H ₄	45	90–92.5	Et ₂ O-PE	C ₁₆ H ₂₂ O ₄
4e	1-Naphthyl	51	^a		

^a Amorphous gum, characterized by NMR.

Table IX. 4-Acetoxyethyl-4-arylcyclohexanol Methanesulfonates



Compd	Ar	Yield, %	Mp, °C	Recrystn solvent	Formula
5a	C ₆ H ₅	85	64–68.5	Et ₂ O-PE	C ₁₆ H ₂₂ O ₅ S
9a	C ₆ H ₅ (isomer)	94	^a		
5b	<i>p</i> -ClC ₆ H ₄	82	120–124	CH ₂ Cl ₂ -SSB	C ₁₆ H ₂₁ ClO ₅ S
5c	<i>p</i> -FC ₆ H ₄	86	95–97	Me ₂ CO-C ₆ H ₁₂	C ₁₆ H ₂₁ FO ₅ S
5d	<i>p</i> -CH ₃ OC ₆ H ₄	76	101–102	CH ₂ Cl ₂ -SSB	C ₁₇ H ₂₄ O ₆ S
5e	1-Naphthyl	90	^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.

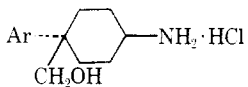
4-Acetoxyethyl-4-arylcyclohexanol Methanesulfonates (5 and 9) (Table IX). A solution of the appropriate 4-acetoxyethyl-4-arylcyclohexanol in 10 vol of pyridine was cooled in ice. There was then cautiously added 1 vol of CH₃SO₂Cl. Following 18 hr standing in the cold, the mixture was poured into ice-water. The gum was extracted with Et₂O. The organic layer was washed in turn with H₂O, 2.5 N HCl, H₂O, 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-acetoxyethyl-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 C₆H₆ and H₂O. The organic layer was washed with H₂O 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 LiAlH₄ 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 H₂O, 1.1 ml of 15% NaOH, and 3.3 ml of H₂O. The inorganic gel was collected on a filter and rinsed several times with Et₂O and CH₂Cl₂. 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 Et₂O and taken to dryness. The residue was recrystallized from MeOH-EtOAc.

4-Acetoxyethyl-4-phenylcyclohexylamine Hydrochloride (20a). A mixture of the crude azide obtained from 9.0 g of the crude 4-acetoxyethyl-4-phenylcyclohexanol methanesulfonate and 0.45 g of Pd/C was shaken under H₂ for 3 hr. The catalyst was then removed by filtration and the filtrate taken to dryness. The gummy residue was dissolved in Et₂O and this treated with 6 N HCl in Et₂O. The precipitated solid was recrystallized from MeOH-EtOAc to give 2.38 g of product, mp 195.5–198°. Anal. (C₁₅H₂₂ClNO₂·0.5H₂O) C, H, N.

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

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


Compd	Ar	Yield, %	Mp, °C	Formula
6a	C ₆ H ₅	80	260–262	C ₁₃ H ₂₀ ClNO
10a	C ₆ H ₅	60	215–218	C ₁₃ H ₂₀ ClNO
	(isomer)			
6b	<i>p</i> -ClC ₆ H ₄	66	303–304.5	C ₁₃ H ₁₉ Cl ₂ NO
6c	<i>p</i> -FC ₆ H ₄	84	288–290	C ₁₃ H ₁₉ ClFNO
6d	<i>p</i> -CH ₃ OC ₆ H ₄	27	267–269	C ₁₄ H ₂₂ ClNO ₂
6e	1-Naphthyl	33	268–269	C ₁₇ H ₂₂ ClNO

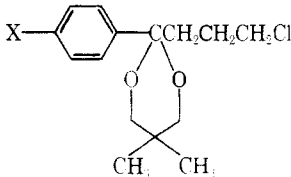
hexanol methanesulfonate and 0.32 g of 10% Pd/C in 150 ml of EtOAc was shaken under H₂ for 6 hr. The catalyst was then removed by filtration and the filtrate taken to dryness in vacuo. The residue was dissolved in Et₂O and this treated with 6 N HCl in Et₂O. The precipitate was recrystallized from MeOH-Et₂O to give

2.55 g (64%) of product, mp 191.5–193°. Anal. (C₁₆H₂₄ClNO₃) C, H, N.

Ethyl 4-[(ethoxycarbonyloxy)methyl]-4-phenylcyclohexylcarbamate (22). A suspension of 2.0 g (0.0083 mol) of 4-phenyl-4-hydroxymethylcyclohexylamine hydrochloride in CHCl₃ 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 ClCO₂C₂H₅. Following 18 hr of standing in the cold, the mixture was poured into ice-H₂O. The precipitated solid was recrystallized from Et₂O-petroleum ether to afford 2.32 g (77%) of solid, mp 69–72°. Anal. (C₁₉H₂₇NO₅) C, H, N.

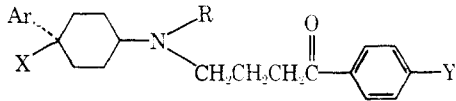
N-Methyl-4-(hydroxymethyl)-4-phenylcyclohexylamine Hydrochloride (23). A solution of 9.56 g (0.0274 mol) of ethyl 4-[(ethoxycarbonyloxy)methyl]-4-phenylcyclohexylcarbamate in 185 ml of THF was added to 2.78 g of LiAlH₄ in 50 ml of THF. Following 4 hr heating at reflux the mixture was cooled in ice. There was added, in turn, 2.8 ml of H₂O, 2.8 ml of 15% NaOH, and 8.4 ml of H₂O. 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 Et₂O, and taken to dryness. The residue was recrystallized from MeOH-EtOAc to give 5.10 g (73%) of product, mp 204–207°. Anal. (C₁₄H₂₂ClNO·0.5H₂O) C, H, N.

4-Formyl-4-phenylcyclohexanone Ethylene Ketal (25). To a well-stirred suspension of 2.74 g (0.072 mol) of LiAlH₄ 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)			<i>a</i>
32b	CH ₃	66.4		78.5–82	PE	C ₁₆ H ₂₃ ClO ₂
32c	CH ₃ O	30.9	174 (3)	51.5–53.5	PE	<i>b</i>
32d	Cl	73.5		87–92	SSB	C ₁₅ H ₂₀ Cl ₂ O ₂

^aCharacterized by ir and NMR. ^bUnstable. Characterized by ir and NMR.

Table XII. Butyrophenones


Compd	Salt	Ar	X	Y	R	Yield, %	Mp, °C	Recrystn solvent	Formula
7a	HCl	C ₆ H ₅	CH ₂ OH	F	H	31.9	178–180	MeOH-EtOAc	C ₂₃ H ₂₉ ClFNO ₂
7b	HCl	<i>p</i> -ClC ₆ H ₄	CH ₂ OH	F	H	32.3	188–190	MeOH-EtOAc	C ₂₃ H ₂₈ Cl ₂ FNO ₂
7c	HCl	<i>p</i> -FC ₆ H ₄	CH ₂ OH	F	H	24.7	196–198	MeOH-EtOAc	C ₂₃ H ₂₈ ClF ₂ NO ₂
7d	HCl	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ OH	F	H	30.3	164–166	MeOH-EtOAc	C ₂₄ H ₃₁ ClFNO ₂
7e	HCl	1-Naphthyl	CH ₂ OH	F	H	19.5	202–203	MeOH-Me ₃ CO	C ₂₇ H ₃₁ ClFNO ₂
11 ^a	HCl	C ₆ H ₅	CH ₂ OH	F	H	22.8	<i>b</i>		
21a	HCl	C ₆ H ₅	CH ₂ OAc	F	H	20.5	138–139	EtOAc	C ₂₅ H ₃₁ ClFNO ₃ ^c
21b	HCl	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ OAc	F	H	46.0 ^d	<i>b</i>		
24		C ₆ H ₅	CH ₂ OH	F	CH ₃	56.2	91–94	MeOH	C ₂₄ H ₃₀ FNO ₂
30	HCl	C ₆ H ₅	CH ₃	F	H	40.5	194–197	MeOH-EtOAc	C ₂₃ H ₂₉ ClFNO
33a		C ₆ H ₅	CH ₂ OH	H	H	12.6 ^d	100–101	MeOH	C ₂₃ H ₂₉ NO ₂
33b		C ₆ H ₅	CH ₂ OH	CH ₃	H	13.7 ^d	123–125	MeOH	C ₂₄ H ₃₁ NO ₂
33c		C ₆ H ₅	CH ₂ OH	OCH ₃	H	19.7 ^d	98–99	MeOH	C ₂₄ H ₃₁ NO ₃
33d	HCl	C ₆ H ₅	CH ₂ OH	Cl	H	47.3	164–167	MeOH-EtOAc	C ₂₃ H ₂₉ Cl ₂ NO ₂

^aAromatic ring and N are cis. ^bAmorphous foam; characterized by ir and NMR. ^cAnal. Calcd for C₂₅H₃₁ClFNO₃: C, 67.02. Found: C, 66.46. ^dIsolated 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 H₂O, 2.8 ml of 15% NaOH, and 8.2 ml of H₂O. The inorganic gel was collected on a filter and rinsed with Et₂O. 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 NaHCO₃, and taken to near dryness. Et₂O 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. (C₁₅H₁₈O₃) 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 N₂H₄·H₂O, 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 H₂O, and extracted with Et₂O. The organic layer was washed with H₂O 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-H₂O. There was obtained 5.92 g (67%) of product, mp 48–50°. Anal. (C₁₅H₂₀O₂) 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 Me₂CO was stirred at room temperature for 20 hr. The solvent was removed in vacuo and the residue dissolved in Et₂O and H₂O. The organic layer was washed with NaHCO₃ 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 NaBH₄. 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% Me₂CO-CH₂Cl₂). 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 CH₃SO₂Cl in 30 ml of pyridine was allowed to stand in the cold overnight. The mixture was diluted with H₂O and then extracted with Et₂O. The organic layer was washed with H₂O, 2.5 N HCl, H₂O, and brine and taken to dryness.

A mixture of the gummy mesylate and 3.0 g of NaN₃ in 30 ml of DMF was stirred overnight at 90°. The solvent was removed in vacuo and the residue dissolved in C₆H₆ and H₂O. The organic layer was washed with H₂O and brine and taken to dryness.

The crude azide in 60 ml of THF was added to 0.70 g of LiAlH₄ in 10 ml of THF. At the end of 4 hr there was added in turn 0.7 ml of H₂O, 0.7 ml of 15% NaOH, and 2.1 ml of H₂O. The inorganic gel was collected on a filter and the filtrate taken to dryness. The residue was dissolved in Et₂O and treated with 5 N HCl in Et₂O. The resulting solid was recrystallized several times from MeOH-EtOAc to give 1.26 g (35%) of product, mp 313–315°. Anal. (C₁₃H₂₀ClN) 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 NaHCO₃, H₂O, 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 K₂CO₃, 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 C₆H₆ and water. The organic layer was washed with H₂O 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 Et₂O and then extracted with CH₂Cl₂. The CH₂Cl₂ extract was taken to dryness. If crystalline, this salt was then recrystallized.

Alternately, the residue was redissolved in CH₂Cl₂ 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.

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