The phenylglycines in Table I were prepared by this general method prior to resolution into L-(+) and D-(−) isomers. Resolution of the isomers was achieved by selective enzymatic degradation using hog kidney acylase.

L-(+)-2-(4-Hydroxyphenyl)glycine (25). DL-2-(4-Methoxyphenyl)glycine (93 g, 0.514 mol) was suspended in H_2O (1.3 L) and to the stirred suspension was added NaOH (21.3 g, 0.514 mol). Chloroacetic anhydride (177 g, 1.027 mol) was then slowly added over a period of 0.5 h, with cooling, followed by further addition of NaOH (42.6 g) in H_2O (200 mL). The pH was maintained at 9 by addition, if necessary, of more NaOH solution, and stirring at room temperature was continued for a 1.5 h period. The solution was then acidified to pH 2 by addition of concentrated HCl, and the resultant pale yellow precipitate of DL-*N*-(chloroacetyl)-2-(4-methoxyphenyl)glycine was filtered off, washed, and dried: yield 51 g; mp 174–178 °C (lit.[40] mp 182–183 °C).

The DL-*N*-(chloroacetyl)-2-(4-methoxyphenyl)glycine (51 g) was suspended in distilled H_2O (770 mL) and to this was added sufficient NH_4OH to maintain the pH at 7.8 and effect solution. Hog kidney acylase enzyme (2.8 g) (acylase-1, Sigma Chemical Co.) was added, and the solution was stirred at 37 °C for 22 h. A light brown precipitate of **27** was obtained and filtered off [the filtrate contains D-(−)-*N*-(chloroacetyl)-2-(4-methoxyphenyl)-glycine]. The crude **27** was added to hot 3 N HCl (100 mL) containing charcoal, and the mixture was warmed gently and filtered. The cooled filtrate was treated with 0.880 ammonia until pH 5–6 was obtained. A white crystalline solid of L-(+)-2-(4-methoxyphenyl)glycine (**27**) precipitated and was filtered off and recrystallized from water: yield 7.7 g (43%); mp 218 °C dec; $[\alpha]^{25}_D$ +137° (lit.[40] $[\alpha]^{25}_D$ +150.4°).

Compound **27** (10 g) was added to 48% HBr (100 mL), and the mixture was heated under reflux with stirring for 5 h. The resultant red solution was evaporated to dryness; the residue was then treated with H_2O (50 mL) and the mixture filtered. The filtrate was brought to pH 5 by addition of 0.880 ammonia, whereupon a solid precipitated after cooling. The solid was filtered off, washed, and recrystallized from H_2O to give **25**: yield 5.5 g (60%); mp 230 °C dec; $[\alpha]^{25}_D$ +124.5° (lit.[39] mp 225 °C dec).

D-(−)-2-(4-Methoxyphenyl)glycine (28). D-(−)-*N*-(chloroacetyl)-2-(4-methoxyphenyl)glycine (64 g) obtained as described above was added to 2 N HCl (680 mL), and the mixture was stirred and heated under reflux for 1.5 h. The solution was filtered while still hot and cooled, and the pH was adjusted to 5.5 using 0.880 ammonia. The resulting solution was cooled for a further 2 h, and then the precipitate was collected, washed, and recrystallized from H_2O to give **28**: yield 30 g (67%); mp 219–220 °C; $[\alpha]^{25}_D$ −140° (lit.[40] $[\alpha]^{25}_D$ −149.9°).

Acknowledgment. The authors thank D. V. J. Batchelor, R. F. Gammon, M. J. Pitcher, and D. J. Tims for their able technical assistance, and we are grateful to Dr. M. J. Sewell and his staff for analytical and spectral data. We also thank Drs. M. Morville, M. G. Page, A. J. Higgins, and Messrs. R. A. Burges, D. G. Gardiner, M. S. Robinson, S. Tickner, and A. P. Beresford for the biological results.

(41) A. H. Neims, D. C. DeLuca, and L. Hellerman, *Biochemistry*, 5, 203 (1966).

4-Amino-4-arylcyclohexanones and Their Derivatives: A Novel Class of Analgesics. 2. Modification of the Carbonyl Function

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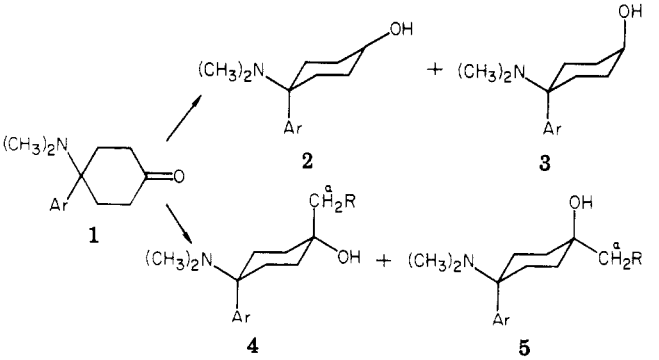
The effect on potency of modification of the carbonyl function of analgesics derived from 4-(dimethylamino)-4-arylcyclohexan-1-one was studied by reduction and by addition of nucleophiles. The resulting amino alcohols were separated and assigned structures on the basis of X-ray crystallography, NMR, and TLC mobility. The trans (OH and N) isomers were invariably more potent than the cis. Inclusion of flat lipophilic moieties (phenyl, cyclohexenyl) at a distance of at least two carbon atoms from the carbon bearing hydroxyl led to increases in potency by orders of magnitude. The possible significance of this on receptor interaction is discussed.

In the first report[2] in this series, we described the effect of substitution on the aromatic ring on the analgesic potency in a series of 4-(dimethylamino)-4-arylcyclohexanones and their ketals. The observation of marked differences in potency between these compounds and those lacking the oxygen indicated that the oxygen function at the 1 position has an important role in the activity of this series. In the present work, we describe the SAR of a series of derivatives in which nucleophiles have been added to the carbonyl function.

Chemistry. Reduction of ketones 1 (Ar = C_6H_5) by means of $NaBH_4$ afforded a pair of isomeric alcohols in the ratio of 4:1. The finding that these showed enhanced analgesic potency over the corresponding ketones and ketals[2] led us to extend this series to organometallic adducts of the carbonyl group. Condensations were all carried out with a large excess of reagents (RLi or RMgBr); though reactions were allowed to proceed as long as 3 days, considerable amounts of starting ketones were invariably recovered. In contrast to the stereoselectivity observed in the reduction, condensations afforded roughly equal amounts of isomeric amino alcohols. These, however, exhibited sufficiently different polarities on silica gel to make them easily separable.



Assignment of configuration of the reduction products (**2** and **3**) by NMR was relatively straightforward. Both chemical shift and multiplicity of the carbon-bearing oxygen confirmed our expectation that the predominant isomer bore an equatorial hydroxyl group. Some of our

(1) Adria Laboratories, Inc., Columbus, OH 43216.
(2) D. Lednicer, P. F. VonVoigtlander, and D. E. Emmert, *J. Med. Chem.*, 23, 424 (1980).

0022-2623/81/1824-0404$01.25/0

Table I. Chemical Shift of H[a] in Compounds 4 and 5[a]

Ar	R	more polar isomer	less polar isomer
p-$CH_3C_6H_4$	H	1.12	1.31
p-BrC_6H_4	$CH{=}CH_2$	2.1[b]	2.18
p-ClC_6H_4	C_6H_5	2.59	2.82

[a] Chemical shifts are reported in δ units relative to Me_4Si. [b] Estimated.

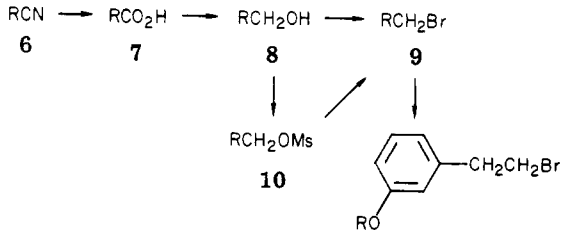
earlier work on a closely related system[3] indicated that the more stable solution conformations of 2 and 3 are those in which the aromatic ring is axially disposed. This then leads us to assign the trans (amine and hydroxyl) configuration to the major isomer. This assignment was confirmed by X-ray crystallographic structure determination.[4]

In the case of the condensation products, NMR could be used to assign stereochemistry only in those cases where the newly introduced groups showed resonances for H[a] (structures 4 and 5) as a simple pattern relatively well separated from the remaining resonances. NMR data on three isomeric pairs which fulfill this condition are listed in Table I; as will be noted, H[a] in that isomer which was less polar on silica gel consistently showed resonances downfield from the more polar isomer. It has been shown previously that axial methylene groups substituted on cyclohexane show a downfield shift relative to the equatorial isomer as a consequence of steric compression resulting from 1,3-diaxial interaction.[5,6] This led us to assign the newly added alkyl group in the less polar isomer to the axial configuration. The aromatic ring attached to cyclohexanes in each series was then assumed to be axially disposed. Putting these arguments together, the less polar isomer would carry hydroxyl and amino in a trans relationship, while the more polar isomers would have these grouped in a cis configuration.

The NMR spectra of the remaining isomeric pairs were sufficiently complex to preclude such assignments. Based on the observed consistency of the above NMR assignments with mobility on silica gel, this relative polarity was used to assign the relative configuration of the remaining compounds. Confirmation for the validity of this approach comes from the observation that X-ray crystallographic structure determination for one of the less polar isomers (4; Ar = p-BrC_6H_4; R = $CH_2C_6H_5$) unequivocally showed this isomer to carry trans amino and hydroxyl.[7]

The finding of the enormous enhancement of potency brought about by inclusion of the phenethyl group led us to study this effect in greater detail. Those β-phenethyl or β-cycloalkylethyl bromides which were not available commercially were prepared as shown in Scheme I. (The scheme was entered at whatever stage material could be purchased.) In the initial work, the alcohols were converted to the bromides by means of PBr_3. We subsequently found that consistently higher yields could be obtained by displacing the mesylate with bromide ion in the presence of HMPT. The m-methoxy compound (9, R = m-$CH_3OC_6H_4$) was demethylated to the corresponding phenol (11) by means of BBr_3, and this converted to the THP ether. Each of these bromides was then converted to the corresponding Grignard reagent, and this reacted

Scheme I[a]



11, R = H
12, R = THP

[a] R = aryl-CH_2, cycloalkyl-CH_2, cycloalkenyl-CH_2.

with the appropriate ketone.

Results

The analgesic (tail flick, tail pinch, and HCl writhing), sedative (inclined screen), and narcotic antagonist ED_{50} values for these compounds are listed in Tables II and III. As previously reported in the analogous ketone- and ketal-substituted compounds,[2] para-aromatic substitution greatly enhances the analgesic potency of these alcohols. In this regard, the potency order is Br $\simeq$ CH_3 > Cl $\gg$ H. Examination of the potency of the cis and trans isomers indicates that the trans compounds are more potent than the cis. This difference becomes extreme in the case of the more potent compounds. In fact, the potency-enhancing groups that are so effective in the trans configuration of the amino alcohols seem to have little, if any, effect in the cis configuration. Simple alkyl groups do not enhance potency; however, introduction of a double bond greatly enhances potency, particularly if it is located two or three carbons from the cyclohexyl ring. Double bonds provided by an additional aromatic system are even more effective. Again, the optimal placement is two carbons removed from the cyclohexyl ring. These phenylethyl-substituted compounds are the most potent analgesics of this series and are among the most potent opioids reported to date.[7] This huge jump in potency between the R = H and R = phenylethyl compounds suggests that this ring system may be providing an additional binding site for these molecules and, thus, greatly enhance their affinity for the opioid receptor. The compounds in Table III were synthesized to further examine the requirements for this ring system. From this series it appears that both a relatively flat ring and a double bond are necessary for optimal potency. In this regard, only the cyclohex-3-ene analogue was as potent as the phenylethyl.

Experimental Section

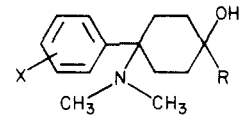
Melting points are uncorrected and are recorded as observed in a Thomas-Hoover capillary melting point apparatus. NMR spectra were obtained in $CDCl_3$ on a Varian A60D or T60 spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry Research at The Upjohn Company for IR spectra and elemental analyses. Where analyses are indicated by molecular formulas, compounds were analyzed for C, H, and N; results were within 0.4% of theory.

Cyclohex-1-eneacetic Acid. A mixture of 36.3 g (0.3 mol) of cyclohex-1-eneacetonitrile, 12.0 g of NaOH, and 120 mL of H_2O in 300 mL of EtOH was heated at reflux for 18 h. The bulk of the solvent was removed under vacuum, and the residue was partitioned between H_2O and Et_2O. The aqueous layer was acidified with concentrated HCl. The precipitated oil was taken up in Et_2O, washed with H_2O and brine, and taken to dryness. The product (31.2 g, 74%) was obtained as a viscous oil whose NMR spectrum is consistent with the structure.

Methyl 4-(*exo*-Methylene)cyclohexanecarboxylate. To a mechanically stirred suspension of 35.72 g (0.1 mol) of methyl triphenylphosphonium bromide in 250 mL of THF there was

(3) D. Lednicer and D. J. Duchamp, *J. Org. Chem.*, **39**, 2311 (1974).
(4) D. J. Duchamp, personal communication.
(5) B. V. Cheney, *J. Am. Chem. Soc.*, **90**, 5386 (1968).
(6) D. Lednicer and D. E. Emmert, *J. Org. Chem.*, **40**, 3844 (1975).
(7) D. Lednicer and P. F. VonVoigtlander, *J. Med. Chem.*, **22**, 1157 (1979).

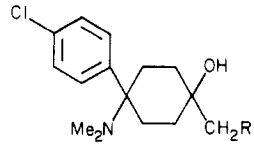
Table II. Analgesic, Sedative, and Narcotic Antagonist Activity

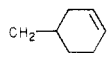
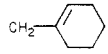
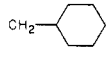
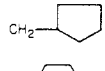
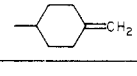


				ED_{50},[a] mg/kg[b]				
no.	X	R	isomer	flick	pinch	screen	writh	antag
3	H	H	cis	41	66	>100	19	>100
2a	H	H	trans	44	50	>100	17	>100
2b	*p*-Cl	H	trans	1.0	2.0	>6.3	1.8	>6.3
4a	*p*-Cl	CH_3	trans	2.0	2.2	>100	1.8	>100
5a	*p*-Cl	CH_3	cis	3.5	3.9	>100	3.5	>100
4b	*p*-CH_3	CH_3	trans	0.9	1.6	>25	0.9	>25
5b	*p*-CH_3	CH_3	cis	11	18	>100	10	>100
4c	*p*-Br	CH_3	trans	0.50	0.50	25	0.45	>25
5c	*p*-Br	CH_3	cis	3.1	3.1	>100	2.8	>50
4d	*p*-Cl	$CH_2CH_2CH_3$	trans	4.4	4.4	>25	3.9	>25
5d	*p*-Cl	$CH_2CH_2CH_3$	cis	35	35	>100	18	>100
4v	*p*-CH_3	C≡CH	trans	5.6	6.2	>100	5.6	>100
5v	*p*-CH_3	C≡CH	cis	>100	>100	>100	63	>100
5t	*p*-Cl	$CH_2CH{=}CH_2$	trans	0.45	0.45	>6.3	0.28	>6.3
5t	*p*-Cl	$CH_2CH{=}CH_3$	cis	2.8	3.5	>100	2.0	>100
4e	*p*-CH_3	$CH_2CH{=}CH_2$	trans	0.22	0.25	4.4	0.25	>25
5e	*p*-CH_3	$CH_2CH{=}CH_2$	cis	8.8	5.6	>100	3.9	>50
4f	*p*-Br	$CH_2CH{=}CH_2$	trans	0.22	0.25	5.0	0.22	>25
5f	*p*-Br	$CH_2CH{=}CH_2$	cis	3.1	3.1	79	2.2	>50
4g	*p*-Cl	$CH_2CH_2CH{=}CH_2$	trans	0.018	0.018	8	0.016	>25
5g	*p*-Cl	$CH_2CH_2CH{=}CH_2$	cis	6.0	6.0	>100	7.0	>100
4h	*p*-Cl	$CH_2CH_2CH_2CH{=}CH_2$	trans	0.018	0.018	0.90	0.018	>50
5h	*p*-Cl	$CH_2CH_2CH_2CH{=}CH_2$	cis	18	14	>100	16	>100
4i	*p*-Cl	$CH_2C_6H_5$	trans	0.0056	0.0056	1.0	0.0044	>50
5i	*p*-Cl	$CH_2C_6H_5$	cis	63	63	>100	32	>100
4j	*p*-Cl	$CH_2CH_2C_6H_5$	trans	0.0014	0.0014	0.10	0.0018	>100
5j	*p*-Cl	$CH_2CH_2C_6H_5$	cis	>100	>100	>100	56	>100
4k	*p*-Cl	$CH_2CH_2CH_2C_6H_5$	trans	0.11	0.11	2.2	0.11	>100
5k	*p*-Cl	$CH_2CH_2CH_2C_6H_5$	cis	32	32	>100	35	>100
4n	*p*-Br	$CH_2CH_2C_6H_5$	trans	0.0001	0.0001	0.09	0.0001	>100
5n	*p*-Br	$CH_2CH_2C_6H_5$	cis	7.9	7.9	>100	7.0	>100
4l	*p*-Cl	$CH_2CH_2(m\text{-}HOC_6H_4)$	trans	0.28	0.32	63	0.14	>100
4m	*p*-Cl	$CH_2CH_2(p\text{-}ClC_6H_4)$	trans	0.13	0.13	18	0.11	>100
5m	*p*-Cl	$CH_2CH_2(p\text{-}ClC_6H_4)$	cis	28	28	>100	22	>100

[a] See Experimental Section and ref 7 for description of methods. [b] The upper and lower 95% confidence intervals[5] were not more than 2 and 0.5 times the ED_{50}, respectively.

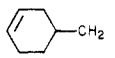
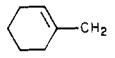
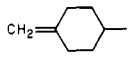
Table III. Biological Activities



			ED_{50}, mg/kg				
no.	isomer	R	flick	pinch	screen	writh	antag
4o	trans		0.001	0.0009	0.3	0.0009	>100
5o	cis		>100	>100	>100	>100	>100
4p	trans		0.006	0.006	0.5	0.005	>100
5p	cis		18	16	>100	14	>100
4q	trans		0.014	0.014	0.6	0.014	>100
5q	cis		71	71	>100	71	>100
4r	trans		0.004	0.003	0.1	0.003	>100
5r	cis		50	45	>100	56	>100
4s	trans		0.008	0.008	0.3	0.008	>100

added 62 mL of 1.6 N BuLi in pentane. This was followed by 15.6 g (0.1 mol) of 4-carbomethoxycyclohexanone. The mixture was stirred at room temperature for 3.5 h, allowed to cool, and treated with H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was allowed to stand under SSB overnight. The solid was collected on a filter and washed with SSB. The oil which remained when the filtrate was taken to dryness was distilled at 2.5 mm. There was obtained 5.62 g (36%) of product: bp δ 50–52 °C; NMR δ 4.85 (vinyl, s, 2 H, 3.85; (OCH, s, 3 H), remaining protons at about δ 2.2 (9 H).

Table IV. Alkyl Bromides (9)[a,b]

R	RCH$_2$Br % yield	bp (mmHg), °C
p-ClC$_6$H$_4$CH$_2$	76	95-97.5 (1.5)
m-CH$_3$OC$_6$H$_4$CH$_2$	32[c]	76-80 (0.1)
c-C$_5$H$_9$-CH$_2$	48	48-53 (7)
c-C$_6$H$_{11}$-CH$_2$	70	64-68 (8)
	55	65-68 (5)
	59	68-71 (5.5)
	28	65-66 (28)

[a] Method A unless stated otherwise. [b] All bromides characterized by NMR. [c] Method B.

Alkyl Bromides (9; Table IV). Method A. A solution of 0.12 mol of the appropriate acid in 200 mL of THF was added dropwise to a well-stirred suspension of 3.90 g of LiAlH$_4$ in 40 mL of THF. Following 4 h of heating at reflux, the mixture was cooled in ice and treated in turn with 3.9 mL of H$_2$O, 3.9 mL of 15% NaOH, and 11.7 mL of H$_2$O. The inorganic gel was collected on a filter, and the filtrate was taken to dryness under vacuum.

The residual oil was dissolved in 50 mL of pyridine, and the resulting solution was cooled in ice. There was then added dropwise 14 mL of methanesulfonyl chloride. Following 18 h of standing in cold, the mixture was poured onto ice–water. The precipitated gum was extracted with ether, and the extract was washed in turn with 2.5 N HCl, H$_2$O, and brine. The organic layer was taken to dryness to afford the mesylate as a viscous oil.

A mixture of the mesylate, 24 mL of HMPA, and 38 g of finely powdered NaBr in 270 mL of acetone was stirred at reflux for 6 h. The bulk of the solvent was removed under vacuum, and the residue was partitioned between benzene and H$_2$O. The organic layer was washed thoroughly with water and taken to dryness. The residual oil was then distilled under vacuum.

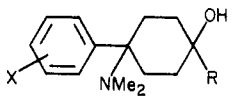
Method B. Phosphorus tribromide (1 equiv) was added to a cooled solution of the arylethyl alcohol in 10 volumes of C$_6$H$_6$. Following 30 min in the cold, the mixture was stirred at room temperature for 1 h and at reflux for 30 min. The mixture was allowed to cool and poured into NaHCO$_3$ solution. The organic layer was separated and taken to dryness, and the residue was distilled under vacuum.

4-(Dimethylamino)-4-phenylcyclohexanols (2 and 3, Ar = C$_6$H$_5$; R = H). To a solution of 7.76 g (0.036 mol) of 4-(dimethylamino)-4-phenylcyclohexanone in 150 mL of 95% ethanol there was added 1.35 g (0.036 g) of sodium borohydride. Following 5 h of stirring at room temperature, the bulk of the solvent was removed under vacuum. The residue was diluted with 60 mL of water, and this was extracted with 5 portions of 50 mL of methylene chloride. The extracts were taken to dryness, and the residue was dissolved in ether. This last solution was treated with an excess of 3 N hydrogen chloride in ether. The precipitated solid was recrystallized from methanol–ethyl acetate. There was obtained first 6.34 g (69%) of the equatorial alcohol (2, Ar = C$_6$H$_5$; R = H), mp 228–229 °C. Anal. Calcd. for C$_{14}$H$_{22}$ClNO: C, 65.73; H, 8.67; N, 5.48. Found: C, 65.25; H, 8.47; N, 5.70.

Concentration of the mother liquors afforded the crude axial alcohol. This in turn was recrystallized from the same solvent to afford 1.27 g (14%) of axial alcohol (Ar = C$_6$H$_5$; R = H), mp 211–213 °C. Anal. (C$_{14}$H$_{22}$ClNO) C, H, N.

4-(Dimethylamino)-4-(p-chlorophenyl)cyclohexanol (2b). A suspension of 4.0 g (0.016 mol) of 4-(dimethylamino)-4-(p-chlorophenyl)cyclohexanone in 60 mL of 95% 2-propanol was warmed to dissolve the solid. Sodium borohydride (0.61 g) was then added, and the mixture was stirred at room temperature for 6 h. The bulk of the solvent was then removed under vacuum.

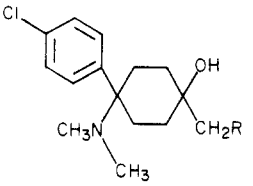
Table V. 1-Alkyl-4-aryl-4-dimethylcyclohexan-1-ols

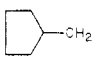
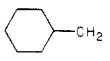
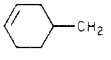
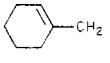
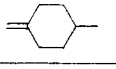


no.	X	R	isomer	chromat solv[c]	recrystn solv	mp, °C	% yield	formula
4a	p-Cl	CH$_3$	t[a]	3[d]	CH$_3$CN-H$_2$O	119-120	15	C$_{15}$H$_{22}$ClNO
4t	p-Cl	CH$_2$CH=CH$_2$	t	5	CHCl$_3$-EtOAc	227-229	39	C$_{17}$H$_{25}$Cl$_2$NO
5t	p-Cl	CH$_2$CH=CH$_2$	c[b]	15	MeOH-EtOAc	231.5-232	30	C$_{17}$H$_{25}$Cl$_2$NO·H$_2$O
4d	p-Cl	CH$_2$CH$_2$CH$_3$	t	10[d]	MeOH-EtOAc	226-227	13	C$_{17}$H$_{27}$Cl$_2$NO·0.5H$_2$O
5d	p-Cl	CH$_2$CH$_2$CH$_3$	c	20[d]	CHCl$_3$-EtOAc	221-223	18	C$_{17}$H$_{27}$Cl$_2$NO·1.5H$_2$O
4i	p-Cl	CH$_2$C$_6$H$_5$	t	5	MeOH-EtOAc	232-233	28	C$_{21}$H$_{27}$Cl$_2$NO·$^1/_3$H$_2$O
5i	p-Cl	CH$_2$C$_6$H$_5$	c	20	CHCl$_3$-EtOAc	247-248	37	C$_{21}$H$_{27}$Cl$_2$NO·$^2/_3$H$_2$O
4k	p-Cl	(CH$_2$)$_3$C$_6$H$_5$	t	7.5[d]	MeOH-H$_2$O	150-151	14	C$_{23}$H$_{30}$ClNO[g]
5k	p-Cl	(CH$_2$)$_3$C$_6$H$_5$	c	7.5[d]	CH$_2$Cl$_2$-EtOAc	222-224	11	C$_{23}$H$_{31}$Cl$_2$NO·0.5H$_2$O
4j	p-Cl	(CH$_2$)$_2$C$_6$H$_5$	t	5	MeOH-EtOAc	240-241	19	C$_{22}$H$_{29}$Cl$_2$NO·$^1/_3$H$_2$O
5j	p-Cl	(CH$_2$)$_2$C$_6$H$_5$	c	20	CH$_2$Cl$_2$-EtOAc	224-224.5	15	C$_{22}$H$_{29}$Cl$_2$NO·2H$_2$O
4l	p-Cl	(CH$_2$)$_2$(m-HOC$_6$H$_4$)	t	5[e]	Me$_2$CO-SSB	195-198	11	C$_{22}$H$_{28}$ClNO$_2$
4m	p-Cl	(CH$_2$)$_2$-p-ClC$_6$H$_4$	t	2	MeOH-EtOAc	249-250	24	C$_{22}$H$_{28}$Cl$_3$NO
5m	p-Cl	(CH$_2$)$_2$-p-ClC$_6$H$_4$	c	5	CHCl$_3$-EtOAc	188-192	47	C$_{22}$H$_{28}$Cl$_3$NO·1.5H$_2$O
4g	p-Cl	(CH$_2$)$_2$CH=CH$_2$	t	5	CHCl$_3$-EtOAc	220-221.5	21	C$_{18}$H$_{27}$Cl$_2$NO·H$_2$O
5g	p-Cl	(CH$_2$)$_2$CH=CH$_2$	c	20	CHCl$_3$-EtOAc	205-207	14	C$_{18}$H$_{27}$Cl$_2$NO·1.5H$_2$O
4h	p-Cl	(CH$_2$)$_3$CH=CH$_2$	t	5	MeOH-EtOAc	236-237	27	C$_{19}$H$_{29}$Cl$_2$NO
5h	p-Cl	(CH$_2$)$_3$CH=CH$_2$	c	20	MeOH-EtOAc	185-188	34	C$_{19}$H$_{29}$Cl$_2$NO·1.5H$_2$O
4f	p-Br	CH$_2$CH=CH$_2$	t	10[d]	MeOH-EtOAc	229-230	14	C$_{17}$H$_{25}$BrClNO·$^1/_3$H$_2$O
5f	p-Br	CH$_2$CH=CH$_2$	c	20[d]	CHCl$_3$-EtOAc	235-236.5	20	C$_{17}$H$_{25}$BrClNO·0.5H$_2$O
4c	p-Br	CH$_3$	t	10	MeOH-H$_2$O	119.5-120	21	C$_{15}$H$_{22}$BrNO
5c	p-Br	CH$_3$	c	20	Me$_2$CO-SSB	124.5-126	31	C$_{15}$H$_{22}$BrNO
4n	p-Br	(CH$_2$)$_2$C$_6$H$_5$	t	5	MeOH-EtOAc	242-243	13	C$_{22}$H$_{29}$BrClNO·0.5H$_2$O
5n	p-Br	(CH$_2$)$_2$C$_6$H$_5$	c	20	CH$_2$Cl$_2$-Me$_2$CO	208-210	16	C$_{22}$H$_{29}$BrClNO·2H$_2$O
4b	p-CH$_3$	CH$_3$	t	10[f]	CH$_2$Cl$_2$-EtOAc	226-227	9.5	C$_{16}$H$_{26}$ClNO·$^1/_3$H$_2$O
5b	p-CH$_3$	CH$_3$	c	10[f]	CH$_2$Cl$_2$-EtOAc	221-223	34	C$_{16}$H$_{26}$ClNO·$^2/_3$H$_2$O
4v	p-CH$_3$	CH≡CH	t	7.5[d]	MeOH-H$_2$O	148-151	7.8	C$_{17}$H$_{23}$NO·$^1/_3$H$_2$O
5v	p-CH$_3$	CH≡CH	c	7.5[d]	Me$_2$CO-SSB	175-176	29	C$_{17}$H$_{23}$NO
4e	p-CH$_3$	CH$_2$CH=CH$_2$	t	10[d]	MeOH-EtOAc	220-222	24	C$_{18}$H$_{28}$ClNO
5e	p-CH$_3$	CH$_2$CH=CH$_2$	c	20[d]	CHCl$_3$-EtOAc	212-212.5	22	C$_{18}$H$_{28}$ClNO·H$_2$O

[a] Hydroxyl and amine trans. [b] Hydroxyl and amine cis. [c] Percent MeOH in CH$_2$Cl$_2$. [d] Chromatographed by HPLC, percent MeOH in CHCl$_3$. [e] Percent MeOH in CHCl$_3$. [f] Solvent contains 1% NH$_4$OH. [g] No satisfactory elemental analysis could be obtained.

Table VI. *N,N*-Dimethyl-1-(*p*-chlorophenyl)-4-(cycloalkylalkyl)-4-hydroxycyclohexylamines



no.	R	isomer	salt	mp, °C	recrystn solv	% yield	formula
4r		trans	HCl	243.0-244.5	MeOH-$CHCl_3$	28	$C_{21}H_{33}Cl_2NO$
5r		cis		134.5-135.5	MeOH-H_2O	19	$C_{21}H_{32}ClNO \cdot {}^1/_3H_2O$
4q		trans	HCl	243.0-244.0	MeOH-EtOAc	30	$C_{22}H_{35}Cl_2NO$
5q		cis	HCl	245.0-246.0	MeOH-EtOAc	32	$C_{22}H_{35}Cl_2NO \cdot {}^2/_3H_2O$
4o		trans	HCl	240.0-241.0	MeOH-EtOAc	25	$C_{22}H_{33}Cl_2NO$
5o		cis	HCl	235.0-236.0	$CHCl_3$-EtOAc	32	$C_{22}H_{33}Cl_2NO \cdot {}^1/_3H_2O$
4p		trans	HCl	236.0-236.5	MeOH-EtOAc	20	$C_{22}H_{33}Cl_2NO \cdot 0.5H_2O$
5p		cis	HCl	210.0-214.0	$CHCl_3$-EtOAc	13	$C_{22}H_{33}Cl_2NO \cdot 1.5H_2O$
4s		trans	HCl	213.0-215.0	CH_2Cl_2-EtOAc	5	$C_{22}H_{33}Cl_2NO \cdot {}^2/_3H_2O$

The residue was taken up in water and methylene chloride. The organic layer was washed with water and brine and taken to dryness. The residual solid was recrystallized twice from acetone to afford 1.21 g (30%) of product, mp 148–150.5 °C. Anal. ($C_{14}H_{20}ClNO$) C, H, N.

1-Alkyl-4-Aryl-4-(dimethylamino)cyclohexan-1-ols (2 and 3; Table V). In a typical experiment, a solution of 6 mmol of the 4-aryl-4-(dimethylamino)cyclohexanone was added to a solution of 30 mmol of the appropriate Grignard reagent in 40 mL of THF. Following 40 h of standing at room temperature under nitrogen, the mixture was cooled in ice and treated with 25 mL of saturated aqueous $NaHCO_3$ and benzene. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was then chromatographed on 250 mL of silica gel. The appropriate fractions were combined and recrystallized either as the free base or the hydrochloride salt.

***N,N*-Dimethyl-1-(*p*-chlorophenyl)-4-(cycloalkylalkyl)-4-hydroxycyclohexylamines (4 and 5; Table VI).** To a nitrogen-covered, ice-cooled solution of the Grignard reagent prepared from 0.03 mol of the appropriate cycloalkyl bromide and 0.73 g of Mg in 40 mL of THF there was added 1.50 g (6 mmol) of 4-(*p*-chlorophenyl)-4-(dimethylamino)cyclohexanone. The mixture was stirred overnight at room temperature, again cooled in ice, and treated with 25 mL of saturated NH_4Cl and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 250 mL of silica gel. Elution with 5% MeOH in CH_2Cl_2 afforded the amino alcohol, which on the basis of the earlier work was assigned the trans configuration. The cis isomer was obtained by elution of the column with 20% MeOH–CH_2Cl_2. Each of the amino alcohols was then recrystallized either as the free base or as the appropriate salt.

Biology. Methods. The biological testing consisted of a battery of standard assays.[7] Briefly, CF-1 female mice were dosed sc with a suspension (or solution) of the test compound in 0.25% aqueous methylcellulose and 15 min later subjected to a series of procedures to detect analgesia, sedation, and narcotic antagonism. The tail-flick, tail-pinch, and HCl writhing procedures were used to detect analgesia, whereas the inclined screen test was used to measure sedation. After the completion of the tests (about 45 min postinjection), 6.3 mg/kg morphine sulfate was given subcutaneously, and 15 min later the mice were retested on the tail-flick procedure to determine if the compound might have narcotic antagonist properties. Blockade of morphine-induced elevation of tail-flick latency was scored as antagonism. Six mice were tested at each dose in this battery of assays. When multiple doses were examined, the ED_{50} values were calculated by the method of Spearman and Karber.[8]

Acknowledgment. The authors acknowledge the technical assistance of R. A. Lewis. Special thanks are due to Dr. David J. Duchamp for making available for publication the results of the X-ray crystallographic determination on compounds **2b** and **4n**.

(8) D. J. Finney, "Statistical Method in Biological Assay", Hafner, New York, 1952.
(9) Skellysolve B, a petroleum fraction of bp 60 °C sold by The Skelly Oil Co.

Dihydrochalcone Sweeteners. A Study of the Atypical Temporal Phenomena

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Neohesperidin dihydrochalcone (NHDHC), known since 1963 as an intensely sweet compound, is determined to be 340 ± 60 ($p < 0.05$) times more potent than sucrose. The unusual temporal properties of this material are hypothesized as being due to the effects of metabolism, conformation, chelation, or hydrophobicity. Forty-four analogues are synthesized to test the four hypotheses, none of which are strongly supported. A method of quantitation of temporal characteristics of tastant molecules is developed so as to allow comparison of taste appearance time (AT) and extinction time (ET) of experimental compounds. Four of the new compounds, **40** and **43–45**, exhibit high sweetness potencies, ranging from 280 to 440 times sucrose, and may be useful in selected food systems. The temporal taste characteristics remain unimproved over NHDHC, however.

In 1963, Horowitz and Gentili reported the discovery of a new nonnutritive sweetener called neohesperidin dihydrochalcone (NHDHC; **1**), which was derived from a natural flavonoid found in the rinds of the Seville orange.[1]

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