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Synthesis of 2-Aminomethyl-3-benzyl-5,5-dimethylcyclohexanones[1)]

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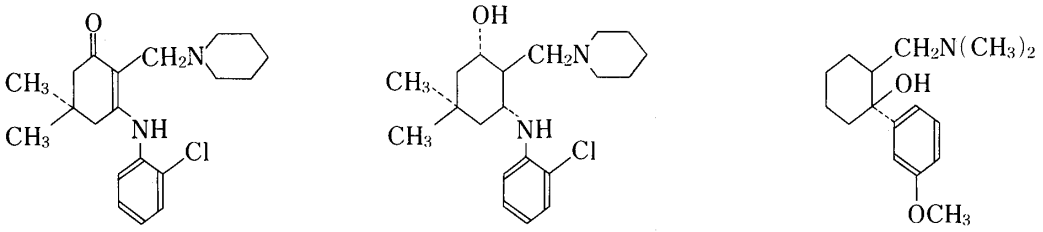
As part of our search for synthetic non-narcotic analgesics, 2-(substituted)aminomethyl-3-benzyl-5,5-dimethylcyclohexanones (**3**) were prepared by the Mannich reaction of 5,5-dimethylcyclohexanones (**2**) with secondary amine hydrochlorides. In this reaction, 6-(substituted)-aminomethylcyclohexanones (**4**) were also obtained as by-products. Reduction of **3** gave the corresponding 2-(substituted)aminomethyl-3-benzylcyclohexanols (**5** and **6**). The configurations of compounds **3**, **5** and **6** were determined to be 2,3-*trans*, 1,2-*cis*-2,3-*trans*, and 1,2-*trans*-2,3-*trans*, respectively, by analysis of the nuclear magnetic resonance spectral data. Among the tested compounds, 2,3-*trans*-3-benzyl- and 3-(3-methoxybenzyl)-2-dimethylaminomethyl-5,5-dimethylcyclohexanones (**3a** and **3c**) were almost as potent as codeine phosphate as regards analgesic activity determined by the phenylquinone writhing method.

Keywords——non-narcotic analgesic; Mannich reaction; configuration; aminomethylcyclohexanone; aminomethylcyclohexanol; analgesic activity; sodium borohydride; lithium aluminum hydride

In a previous paper,[1)] we reported that among the reduction products of 3-(2-chloroanilino)-5,5-dimethyl-2-piperidinomethyl-2-cyclohexen-1-one (A) and its analogues, 1,2-*trans*-2,3-*trans*-3-(2-chloroanilino)-5,5-dimethyl-2-piperidinomethylcyclohexanol (B) hydrochloride exhibited the most potent analgesic activity, comparable to that of codeine phosphate. We also showed in a structure–activity study that the basicity of the anilino group was not essential to the analgesic activity.

Tramadol (C), recently developed as a non-narcotic analgesic, also has a *trans* configuration of the dimethylaminomethyl and the phenyl groups.[2)] This structural similarity of compounds B an C prompted us to synthesize a series of compounds, in which the anilino group of compound B was replaced by a benzyl group, as new potential non-narcotic analgesics. This paper describes the synthesis of 2-aminomethyl-3-benzyl-5,5-dimethylcyclohexanones and 2-aminomethyl-3-benzyl-5,5-dimethylcyclohexanols in which the aminomethyl group is oriented *trans* to the benzyl group.



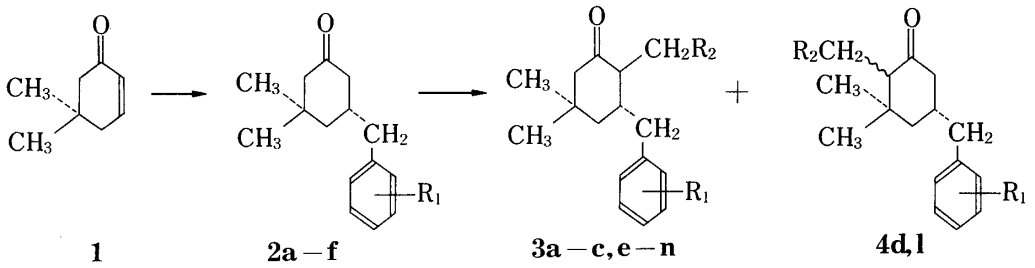
A B C

Chart 1

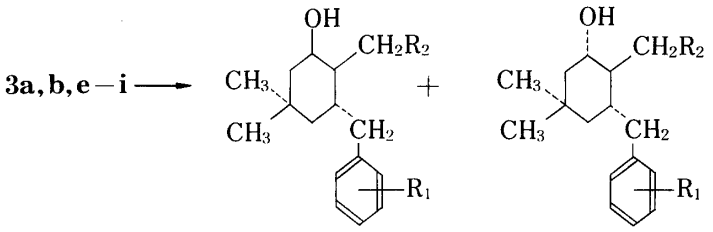
The introduction of an aminomethyl group into the benzylcyclohexanones (**2**) by means of the Mannich reaction was tried (Chart 2). Although compounds **2** have two possible

positions (2 and 6) at which the aminomethyl group could be introduced, 2-aminomethylcyclohexanones (**3**) might be preferentially formed because of the steric hindrance of the dimethyl groups at the 5-position. Furthermore, the 2-aminomethyl group might be oriented in the thermodynamically stable *trans*-equatorial manner with respect to the adjacent benzyl group, which seems to be oriented in an equatorial manner to avoid crowding the axial methyl group at C-5.[3] Consequently, we considered that compounds with the desired spatial structure would be obtained by this method.

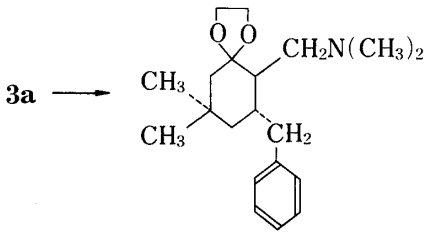
By the method of House and Fischer,[4] 5,5-dimethyl-2-cyclohexen-1-one (**1**) was allowed to react with benzylmagnesium chloride in the presence of cuprous chloride to give 3-benzyl-5,5-dimethylcyclohexanone (**2a**) in 72% yield. The structure was determined on the basis of its infrared (IR) and nuclear magnetic resonance (NMR) spectra. Similarly 3-(substituted)-



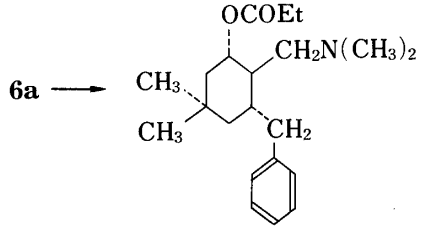
1 **2a–f** **3a–c,e–n** **4d,l**



5a,b,e–i **6a,e**



7a



9a

	R_1	R_2
a	H	$N(CH_3)_2$
b	4-CH_3	$N(CH_3)_2$
c	3-OCH_3	$N(CH_3)_2$
d	4-OCH_3	$N(CH_3)_2$
e	2-Cl	$N(CH_3)_2$
f	4-Cl	
g	H	
h	4-OCH_3	
i	2-Cl	
j	4-OH	
k	H	$N(C_2H_5)_2$
l	H	
m	H	
n	H	

Chart 2

benzyl-5,5-dimethylcyclohexanones (**2b**—**f**) were prepared by the reaction of **1** with the corresponding Grignard reagents (Table IV). Although these compounds were contaminated with small amounts of the by-products, they were used in the subsequent reaction without purification. 3-(4-Hydroxybenzyl)-5,5-dimethylcyclohexanone (**2j**) was prepared by hydrolysis of 3-(4-methoxybenzyl)-5,5-dimethylcyclohexanone (**2d**) with hydrobromic acid.

By the method of Boltze and Dell,[5] reaction of **2a** with dimethylamine hydrochloride and paraformaldehyde gave a crude basic oil that was purified as the hydrochloride to give 3-benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanone (**3a**) hydrochloride in 32% yield. In this Mannich reaction using paraformaldehyde, a few drops of hydrochloric acid are generally added to the reaction mixture as a catalyst;[6] however, in the present case, the addition of hydrochloric acid resulted in a rather low yield. Other 2-aminomethyl-5,5-dimethylcyclohexanones (**3**) were obtained by the reaction of 5,5-dimethylcyclohexanones (**2**) with secondary amine hydrochlorides and paraformaldehyde in a similar manner (Table I).

TABLE I. 2- and 6-Aminomethyl-5,5-dimethylcyclohexanones (**3** and **4**)

Compd. No.	mp (°C)	Recryst. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
3a	152—153	A	32	$C_{18}H_{27}NO \cdot HCl$	69.77	9.11	4.52
					(69.72	9.32	4.47)
3b	146—147	A	3.4	$C_{19}H_{29}NO \cdot HCl$	70.44	9.36	4.32
					(70.06	9.34	4.15)
3c	148—149	A	7.5	$C_{19}H_{29}NO_2 \cdot HCl$	67.12	8.92	4.12
					(67.09	9.06	4.11)
3e	158—160	A	34	$C_{18}H_{26}ClNO \cdot HCl$	62.79	7.90	4.07
					(62.84	8.05	3.91)
3f	166—167	B	15	$C_{21}H_{30}ClNO \cdot HCl$ H_2O	62.68	8.27	3.48
					(62.48	8.40	3.49)
3g	172—174[b]	A	16	$C_{21}H_{31}NO \cdot HCl$	72.08	9.22	4.00
					(71.97	9.45	3.81)
3h	164—165	A	13	$C_{22}H_{33}NO_2 \cdot HCl$	69.54	9.02	3.69
					(69.43	9.30	3.56)
3i	171—172	B	4.6	$C_{21}H_{30}ClNO \cdot HCl$	65.62	8.13	3.64
					(65.35	8.34	3.23)
3j	169—170	B	7.6	$C_{21}H_{31}NO_2 \cdot HCl$	68.93	8.81	3.83
					(68.43	9.14	3.75)
3k	139—141	A	11	$C_{20}H_{31}NO \cdot HCl$	71.09	9.54	4.14
					(71.27	9.82	3.97)
3l	172—173	A	14	$C_{20}H_{29}NO_2 \cdot HCl$	68.24	8.62	3.98
					(67.97	9.07	3.88)
3m	141—143	A	11	$C_{24}H_{31}NO \cdot HCl$	74.68	8.36	3.63
					(74.78	8.55	3.45)
3n	147—149	A	18	$C_{25}H_{33}NO \cdot HCl$	75.07	8.57	3.50
					(74.87	8.83	3.34)
3o	149—151	C	20	$C_{18}H_{27}NO_2 \cdot HCl$	66.34	8.66	4.30
					(66.44	8.67	4.20)
4d	177—179	B	13	$C_{19}H_{29}NO_2 \cdot HCl$ H_2O	63.76	9.01	3.91
					(63.52	8.61	3.86)
4l	202—204	D	4.3	$C_{20}H_{29}NO_2 \cdot HCl$	68.24	8.62	3.98
					(68.40	8.91	4.18)

a) A, AcOEt–MeOH; B, AcOEt–EtOH; C, AcOEt–Me_2CO; D, H_2O.
b) Decomposition.

The relatively low yields of compounds **3** are assumed to be caused by the instability of **3**.[5] In general, the isomeric 6-aminomethylcyclohexanones (**4**) appeared to be formed as minor products but could not be isolated. The reaction of **2a** with morpholine hydrochloride, however, gave a mixture of two basic compounds **3l** and **4l**, which were separated from each other as their hydrochlorides by recrystallization.

The structure of compounds **3** was determined on the basis of the NMR spectra. The C_6–H_2 signals of **3** were observed as singlets or AB-type quartets in the region of δ 2.10—2.35 (Table II) as in the case of compounds **2** (δ 1.98—2.11) (Table IV). The difference of chemical shifts (δ 0.21—0.32) between the axial and the equatorial methyl groups at C-5 in compounds **3** was similar to that (δ 0.17—0.21) in the starting materials (**2**), but the difference of the chemical shifts (δ 0.48—0.68) in compounds **4** was larger than that in compounds **3**. The difference of chemical shifts between the two methyl groups seems to be a good criterion to decide whether the aminomethyl group was introduced at C-2 or C-6 of compounds **2**.

Ethylene acetal (**7a**) was also obtained by the reaction of **3a** with ethylene glycol.

Reduction of **3a** with sodium borohydride ($NaBH_4$) in aqueous methanol gave 1,2-*cis*-2,3-*trans*-3-benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanol (**5a**), mp 92—94 °C, and the 1,2-*trans* isomer (**6a**), mp 75—76 °C, which were separated in 48 and 10% yields, respectively, by column chromatography of the crude mixture. Other compounds **3** were also reduced with $NaBH_4$ in a similar manner to give **5b**, **f**, **h**—**j** (Table III). In general, the hydrochloride of the 1,2-*cis* isomer (**5**) was easily separated from the products mixture and purified because of its ready crystallizability. On the other hand, it was difficult to obtain pure 1,2-*trans* isomer (**6**) because of its low yield and poor crystallizability.

The conformations of **5a** and **6a** were examined by the analysis of NMR spectral data. The proton signals at C-1 (C_1–H) in **5a** and **6a** were observed as multiplets at δ 4.15 and 3.71, respectively, suggesting that the former was an equatorial and the latter an axial proton.[7] Furthermore, the multiplet of C_1–H of **6a** was converted into an octet (J=5, 8 and 11 Hz)

TABLE II. Physical Data for 2- and 6-Aminomethyl-5,5-dimethylcyclohexanones (**3** and **4**)

Compd. No.	IR ν_{max}^{KBr} cm^{-1} [a] (C=O)	NMR (δ)[b]			
		C_5–$(CH_3)_2$	$\Delta^{CH_3}_{ax.-eq.}$	C_6–H_2	Solvent[c]
3a	1715	0.73, 0.96	0.23	2.10	A
3b	1720	0.71, 0.94	0.23		B[a]
3c	1715	0.82, 1.03	0.21	2.25	B
3e	1710	0.70, 1.00	0.30	2.28[d]	B
3f	1705	0.67, 0.89	0.22	2.11	B
3g	1710	0.87, 1.10	0.23	2.34	B
3h	1710	0.72, 1.03	0.31		B[a]
3i	1720	0.70, 0.96	0.26	2.20	B
3j	1710	0.67, 0.95	0.28	2.15	B
3k	1710	0.77, 1.09	0.32	2.35	B
3l	1705	0.73, 0.96	0.23	2.23	B
3m	1715	0.72, 0.95	0.23	2.15	B
3n	1715	0.84, 1.05	0.21	2.29	B
3o	1715	1.02, 1.14	0.12	2.35[d]	B
4d	1720	0.62, 1.25	0.63		B
4l	1720	0.64, 1.12	0.48		B

a) Measured as the hydrochloride.
b) Measured as the free base.
c) A, CCl_4; B, $CDCl_3$.
d) Mean value of AB type quartet.

TABLE III. 2-Aminomethyl-5,5-dimethylcyclohexanols (**5** and **6**)

Compd. No.	Method[a]	mp (°C)	Recryst. solvent[b]	Yield (%)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
5a	A	92—94	A	48	$C_{18}H_{29}NO$	78.49	10.61	5.09
						(78.62	10.80	4.94)
5b	B	240—242	B	27	$C_{19}H_{31}NO \cdot HCl$	70.02	9.90	4.30
						(69.80	9.82	4.23)
5e	C	214—216	C	27	$C_{18}H_{28}ClNO \cdot HCl$	62.42	8.44	4.04
						(62.48	8.47	4.09)
5f	B	282—283[c]	E	25	$C_{21}H_{32}ClNO \cdot HCl$	65.28	8.61	3.62
						(65.25	8.67	3.48)
5g	C	277—280[c]	D	35	$C_{21}H_{33}NO \cdot HCl$	71.66	9.74	3.98
						(71.73	9.97	3.85)
5h	B	266—268	B	32	$C_{22}H_{35}NO_2 \cdot HCl$	69.18	9.50	3.67
						(68.87	9.71	3.56)
5i	B	264—265	E	45	$C_{21}H_{32}ClNO \cdot HCl$	65.28	8.61	3.62
						(65.56	9.01	3.58)
5j	B	283—284[c]	B	53	$C_{21}H_{33}NO_2 \cdot HCl$	68.55	9.31	3.81
						(68.34	9.52	3.86)
5o	C	85—87	A	14	$C_{18}H_{29}NO_2$	74.18	10.03	4.81
						(74.38	10.16	4.70)
6a	A	75—76	A	10	$C_{18}H_{29}NO$	78.49	10.61	5.09
						(78.35	10.84	4.99)
6e	C	216—218	C	37	$C_{18}H_{28}ClNO \cdot HCl$ $1/4H_2O$	61.62	8.47	3.99
						(61.25	8.66	3.95)
6o	C	Oil	—	59	$C_{18}H_{29}NO_2$	74.18	10.03	4.81
						(73.94	9.91	4.67)

a) A, B, reduction with $NaBH_4$ in MeOH (A) or EtOH (B); C, reduction with $LiAlH_4$ in ether.
b) A, hexane; B, AcOEt–MeOH; C, acetone; D, MeOH; E, EtOH.
c) Decomposition.

after treatment with deuterium oxide. The C_1–H signal in the *O*-propionate (**9a**), obtained by the reaction of **6a** with propionyl chloride, also appeared as a sextet (J=5, 11 and 11 Hz) at δ 4.86. The coupling constants of 5, 8, and 11 Hz correspond to $J_{ax.-eq.}$, $J_{ax.-ax.}$, and $J_{ax.-ax.}$, respectively,[8] and confirm C_1–H of **6a** to be an axial proton. Therefore, both the hydroxy and the dimethylaminomethyl groups in **6a** are oriented in a *trans*-equatorial manner, whereas the hydroxy group in **5a** is oriented in a *cis*-axial manner with respect to the dimethylaminomethyl group. On the other hand, an octet (J=4, 8 and 16 Hz) at δ 1.98 in **5a** was assigned to C_2–H, since irradiation at δ 1.98 converted the multiplet of C_1–H (δ 4.15) into a quartet (J=3 Hz) and the double doublet (J=5 and 13 Hz) of one of the methylene protons of the dimethylaminomethyl group (C_2–$C\overset{H}{\underset{\underline{H}}{<}}$–N) at δ 2.78 into a doublet (J=12 Hz). The octet of C_2–H at δ 1.98 was converted into a double doublet (J=4 and 9 Hz) by irradiation of C_2–$\underline{CH_2}$–N (δ 2.92). These coupling constants of 4 and 9 Hz correspond to $J_{ax.-eq.}$ and $J_{ax.-ax.}$, respectively. Since C_1–H in **5a** is equatorial, the value of 9 Hz corresponds to the coupling constant between C_2–H and C_3–H. Therefore, both C_2–H and C_3–H in **5a** are axial and thus the dimethylaminomethyl and the benzyl groups in **5a** are oriented in a *trans*-equatorial manner. The spatial structures of **5a** and **6a** are shown as 1,2-*cis*-2,3-*trans* and 1,2-*trans*-2,3-*trans*, respectively, in Fig. 1.

1,2-*cis*- and *trans*-2-dimethylaminomethyl-3-(3-methoxyphenyl)-5,5-dimethylcyclohexanols (**5o** and **6o**) were obtained by the lithium aluminum hydride ($LiAlH_4$) reduction

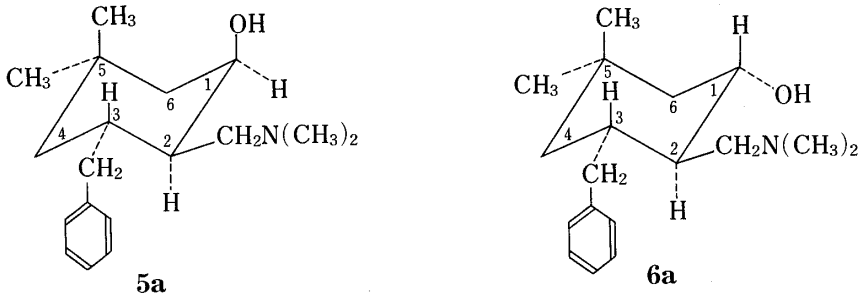


Fig. 1

of **3o**, which was prepared by the Grignard reaction of **1** with 3-methoxyphenylmagnesium bromide (Table IV), followed by the Mannich reaction (Chart 3).

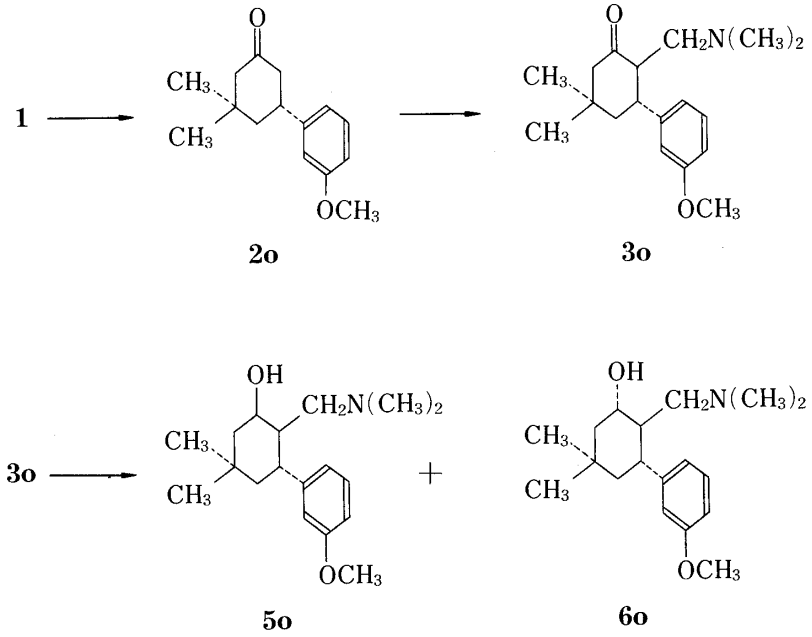


Chart 3

NMR spectra of **5o** and **6o** suggested the configuration of the 3-phenyl group to be equatorial. Although the C_3–H signal in **6o** was not identified because it was overlapped by other protons at higher magnetic field, the axial C_3–H of **5o** appeared as a sextet at lower field (δ 2.90) because of the 1,3-diaxial interaction[9] with the axial hydroxyl group at C_1–H. The sextet (J=4, 11 and 11 Hz) of C_3–H at δ 2.90 was converted to a doublet (J=11 Hz) by irradiation of C_4–H_2 (δ 1.42). This coupling constant corresponds to $J_{ax.\text{-}ax.}$. Therefore, both C_2–H and C_3–H in **5o** are axial and the dimethylaminomethyl and the 3-methoxyphenyl groups in **5o** and **6o** are oriented in a *trans*-equatorial manner as in **5a** and **6a**. Thus, compounds B, **6a** and **6o** all have the same configuration with respect to their substituents.

It is known that equatorial alcohol derivatives are preferentially produced in the reduction of cyclohexanones with $LiAlH_4$.[10] When **3a** was reduced with $LiAlH_4$, **5a** and **6a** were formed in a 2:7 ratio, in contrast to the 5:1 ratio in the $NaBH_4$ reduction of **3a** as mentioned above. This means that the 1,2-*trans* alcohol (**6a**), which has an equatorial hydroxyl group, was preferentially formed by the reduction with $LiAlH_4$, as was expected. Compounds **3e**, **g** were reduced with $LiAlH_4$ in a similar manner to give **5e**, **g** and **6e** (Table III).

The compounds synthesized in this report were tested for analgesic activities by using the

phenylquinone writhing method in mice. Compounds **3a** and **3c** showed activities almost equal to that of codeine phosphate. The pharmacological data will be reported in detail elsewhere.

Experimental

All melting points were taken in open capillaries and are uncorrected. IR and mass spectra (MS) were measured on Hitachi EPI-S2 and RWS-4 machines, respectively. NMR spectra were recorded on a Hitachi R-20 or a Varian Associates XL-100 spectrometer using tetramethylsilane as an internal standard.

3-Benzyl-5,5-dimethylcyclohexanone (2a)——Anhydrous CuCl (0.4 g) was added at −20 °C to the Grignard reagent prepared from Mg turnings (4.8 g, 0.20 mol) and benzyl chloride (25.3 g, 0.20 mol) in dry ether (140 ml), and the mixture was stirred for 15 min; a black reaction mixture resulted. A solution of 5,5-dimethyl-2-cyclohexen-1-one (**1**) (24.8 g, 0.20 mol) in dry ether (60 ml) was added dropwise at −40 °C with stirring. One hour after completion of the addition, the cooling bath was removed and the mixture was allowed to stand at room temperature for 5.5 h. Then a saturated NH_4Cl solution was added dropwise, and the ethereal layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residual oil was distilled *in vacuo* to give a pale yellowish oil (31.1 g, 72%), bp 105—120 °C (0.2 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1710 (C=O). NMR (CCl_4) δ: 0.82, 1.00 (each 3H, s, C_5–CH_3), 2.00 (2H, s, C_6–H_2), *ca.* 2.5 (2H, m, C_3–H_2), 7.15 (5H, m, C_6H_5). *Anal.* Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.40; H, 9.46.

The compounds shown in Table IV were synthesized similarly by this procedure.

3-(4-Hydroxybenzyl)-5,5-dimethylcyclohexanone (2j)——A mixture of 3-(4-methoxybenzyl)-5,5-dimethylcyclohexanone (**2d**) (6.5 g, 26 mmol) and 47% aqueous HBr (80 ml) was stirred for 2 h at 120—130 °C. H_2O was added to the mixture and the separated oil was extracted with C_6H_6. The C_6H_6 layer was washed with H_2O and then extracted with 5% NaOH solution (40 ml). The alkaline aqueous solution was acidified with conc. HCl and extracted with C_6H_6. The extract was washed with H_2O and concentrated *in vacuo*. The resulting residue (6.0 g) was chromatographed on a silica gel (100 g) column using C_6H_6–AcOEt (10:1) as an eluent to give yellowish prisms (4.2 g, 70%), mp 124—126 °C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1690 (C=O). NMR ($CDCl_3$) δ: 0.83, 1.01 (each 3H, s, C_5–CH_3), 2.11 (2H, s, C_6–H_2). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.32; H, 8.75.

General Procedure for Preparing Mannich Bases (3)——A mixture of **2** (0.1 mol), a secondary amine hydrochloride (0.1 mol), paraformaldehyde (4.0 g), and EtOH (30 ml) was stirred for 20 h at 70—80 °C. The solvent was evaporated off, H_2O was added to the resulting residue and the separated oil was extracted with ether. The aqueous solution was basified with ammonia water and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and concentrated *in vacuo* to give a residual oil. Conc. HCl (2.0 × the calculated amount) was added to a solution of this oil in EtOH under cooling and the solution was concentrated to dryness *in vacuo*. AcOEt was added to the resulting residue. The precipitated solid was collected by filtration and recrystallized to give colorless crystals (Tables I and II).

3-Benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanone (3a)——A mixture of **2a** (27.9 g, 0.13 mol), $NH(CH_3)_2 \cdot HCl$ (10.6 g, 0.13 mol), paraformaldehyde (5.3 g) and EtOH (40 ml) was stirred for 20 h at 70—80 °C. The solvent was evaporated off, H_2O was added to the residue and the separated oil (15.7 g) was extracted with ether. The aqueous solution was treated as described in the general procedure to give a yellowish oil (16.1 g). NMR (CCl_4) δ: 0.73, 0.96 (each 3H, s, C_5–CH_3), 2.10 (2H, s, C_6–H_2), 2.19 (6H, s, $N(CH_3)_2$), 2.7—3.4 (2H, m, C_2–CH_2), 7.15 (5H, m, C_6H_5). Conc. HCl (12.3 g) was added to a solution of this oil in EtOH (60 ml) under cooling and the solution was concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from AcOEt–MeOH to give **3a**·HCl as colorless plates (12.8 g, 32%), mp 152—153 °C.

TABLE IV. 3-Benzyl (and Phenyl)-5,5-dimethylcyclohexanones (**2**)

Compd. No.	bp °C (mmHg)	Yield (%)	IR ν_{max}^{film} cm^{-1} (C=O)	NMR (δ)[a]		
				C_5–$(CH_3)_2$	C_6–H_2	Solvent[b]
2b	125—140 (0.7)	40	1720	0.88, 1.08	2.11	A
2c	130—140 (0.2)	37	1710	0.83, 1.00	1.98	B
2d	155—165 (0.2)	30	1715	0.81, 1.01	2.10	A
2e	140—170 (0.2)	75	1710	0.80, 1.01	2.10	A
2f	160—190 (0.2)	60	1710	0.80, 1.00	2.11	A
2o	135—145 (0.1)	44	1710	1.02, 1.11	2.09	B

a) All signals are singlets.
b) A, $CDCl_3$; B, CCl_4.

3-Benzyl-5,5-dimethyl-2-morpholinomethylcyclohexanone (31) and 5-Benzyl-3,3-dimethyl-2-morpholinomethylcyclohexanone (41)——A mixture of **2a** (12.8 g, 59 mmol), morpholine·HCl (7.3 g, 59 mmol), paraformaldehyde (2.7 g), and EtOH (20 ml) was stirred for 20 h at 70—80 °C and treated as described in the general procedure to give crude crystals of the hydrochloride (7.5 g). The part insoluble in AcOEt–MeOH was collected by filtration and recrystallized from H_2O to give **41**·HCl as colorless needles (0.9 g, 4.3%), mp 202—204 °C. MS *m/e*: 315 (M^+), 229, 223, 187, 171. The filtrates were combined and concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from AcOEt–MeOH to give **31**·HCl as colorless needles (3.0 g, 14%), mp 172—174 °C. MS *m/e*: 315 (M^+), 228, 213, 172.

3-Benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanone Ethylene Acetal (7a)——A mixture of **3a**·HCl (4.3 g, 13 mmol), ethylene glycol (20 ml), *p*-toluenesulfonic acid monohydrate (0.25 g), EtOH (15 ml), and C_6H_6 (15 ml) was distilled very slowly for 4 h; a mixture of EtOH and C_6H_6 (1 : 1) was added at intervals to maintain the starting volume. H_2O was added to the solution and the C_6H_6 layer was separated. The aqueous solution was basified with ammonia water and extracted with C_6H_6. The extract was washed with H_2O and concentrated to dryness *in vacuo* to give a pale yellowish oil (4.5 g). NMR ($CDCl_3$) δ: 0.81, 0.83 (each 3H, s, C_5–CH_3), 2.16 (6H, s, $N(CH_3)_2$), 3.92 (4H, s, O–$(CH_2)_2$–O), 7.1—7.5 (5H, m, C_6H_5). This oil was converted to its hydrochloride by the procedure described above and the solid hydrochloride was recrystallized from AcOEt–EtOH to give **7a**·HCl as colorless needles (1.5 g, 37%), mp 216—218 °C. *Anal.* Calcd for $C_{20}H_{31}NO_2$·HCl: C, 67.87; H, 9.11; N, 3.96. Found: C, 67.87; H, 9.23; N, 3.95.

1,2-*cis*- and 1,2-*trans*-3-Benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanols (5a and 6a)——i) A 20% NaOH solution (6 g) and then $NaBH_4$ (1.1 g) were added with stirring to a solution of **3a**·HCl (9.1 g, 29 mmol) in MeOH (50 ml); the stirring was continued for 1 h at room temperature. The solvent was evaporated off, H_2O was added to the residue and the mixture was extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and concentrated *in vacuo* to give a solid (7.6 g). This solid was recrystallized from hexane to give **5a** as colorless prisms (3.2 g, 40%), mp 92—94 °C. IR ν_{max}^{KBr} cm^{-1}: 3250 (OH). NMR ($CDCl_3$) δ: 0.89, 0.98 (each 3H, s, C_5–CH_3), 1.98 (1H, octet, J=4, 8 and 16 Hz, C_2–H), 2.26 (6H, s, $N(CH_3)_2$), 2.78 (1H, dd, J=9, 13 Hz, C_3–$C\underset{H}{<}^{H}$), 2.96 (1H, dd, J=5, 13 Hz, C_2–$C\underset{H}{<}^{H}$–N), 4.15 (1H, m, C_1–H), 4.95 (1H, m, OH), 7.0—7.4 (5H, m, C_6H_5). The filtrate was concentrated *in vacuo*. Chromatography of the resulting solid on a silica gel (40 g) column using AcOEt and AcOEt–MeOH (10 : 1) as eluents yielded **6a** as a solid and additional **5a** (0.6 g, 8%), respectively. The solid **6a** was recrystallized from hexane to give colorless prisms (0.8 g, 10%), mp 75—76 °C. IR ν_{max}^{KBr} cm^{-1}: 3170 (OH). NMR ($CDCl_3$) δ: 0.80, 0.86 (each 3H, s, C_5–CH_3), 2.29 (6H, s, $N(CH_3)_2$), 2.7—3.2 (2H, m, C_2–CH_2), 3.71 (1H, m, C_1–H, treated with D_2O, octet, J=5, 8 and 11 Hz).

ii) $LiAlH_4$ (0.7 g) was added to a solution of **3a** (2.2 g, 8.1 mmol) in dry ether (30 ml) and the mixture was refluxed for 2 h with stirring. Hydrolysis was effected by the dropwise addition of a saturated NH_4Cl solution under cooling. The ethereal layer was separated and the aqueous mixture was extracted with ether. The combined ethereal solutions were washed with H_2O, dried over K_2CO_3, and concentrated *in vacuo* to give a solid. This solid was chromatographed on silica gel (25 g) as described above to give **6a** (1.55 g, 70%) and **5a** (0.50 g, 22%), both as colorless prisms. The products were identical with corresponding authentic samples.

1,2-*cis*- and 1,2-*trans*-2-Dimethylaminomethyl-3-(2-chlorobenzyl)-5,5-dimethylcyclohexanols (5e and 6e)——$LiAlH_4$ (2.0 g) was added to a solution of **3e** (10 g, 34 mmol) in dry ether (90 ml) with stirring and cooling. The mixture was refluxed for 3 h and treated as described in the preceding paragraph to give **6e** (4.2 g, 42%), mp 63—65 °C and **5e** (3.0 g, 30%), mp 87—90 °C. **6e**, NMR ($CDCl_3$) δ: 0.74, 0.84 (each 3H, s, C_5–CH_3), 2.43 (6H, s, $N(CH_3)_2$), 3.75 (1H, m, C_1–H), 6.97—7.35 (4H, m, C_6H_4). **5e**, NMR ($CDCl_3$) δ: 0.83, 0.94 (each 3H, s, C_5–CH_3), 2.22 (6H, s, $N(CH_3)_2$), 4.10 (1H, m, C_1–H), 6.29—7.42 (4H, m, C_6H_4). Conc. HCl (1.5 g) was added to a solution of **6e** (4.2 g) in EtOH (15 ml) and the solution was concentrated to dryness *in vacuo*. The resulting residue was recrystallized from acetone to give **6e**·HCl (4.2 g, 37%) as colorless plates, mp 216—218 °C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH). The crystals of **5e** (3.0 g) were similarly treated to give **5e**·HCl (3.0 g, 27%) as colorless needles, mp 214—216 °C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH).

3-(2-Chlorobenzyl)-5,5-dimethyl-2-piperidinomethylcyclohexanol (5i)——$NaBH_4$ (2.0 g) was added to a solution of **3i** (6.0 g, 17 mmol) in EtOH (50 ml) with stirring and cooling and the mixture was further stirred for 2 h at room temperature. The solvent was evaporated off, H_2O was added to the residue and the separated oil was extracted with C_6H_6. The extract was washed with H_2O and concentrated *in vacuo* to give a pale yellowish oil (6.0 g). By the procedure described above, this oil was converted to its hydrochloride, which was recrystallized from EtOH to give **5i**·HCl as colorless needles (3.0 g, 45%), mp 264—265 °C (Table III). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH). **5i**, NMR ($CDCl_3$) δ: 0.85, 0.90 (each 3H, s, C_5–CH_3), 4.09 (1H, m, C_1–H).

Compounds **5b**, **f**—**h** were obtained by the procedure employed for the preparation of **5e** or **5i** (Table III).

3-Benzyl-2-dimethylaminomethyl-5,5-dimethyl-1-cyclohexyl Propionate (9a)——Propionyl chloride (0.5 g, 5.4 mmol) was added to a solution of **6a** (0.68 g, 2.5 mmol) in pyridine (10 ml) with stirring and cooling; the mixture was stirred for 3 h at room temperature. H_2O was added to the mixture. The solution was basified with ammonia

water and extracted with C_6H_6. The extract was wahsed with H_2O and concentrated *in vacuo* to give a pale yellowish oil (0.8 g). NMR ($CDCl_3$) δ: 0.85 (6H, s, $C_5(CH_3)_2$), 1.13 (3H, t, J=8 Hz, $CH_2\underline{CH_3}$), 2.23 (6H, s, $N(CH_3)_2$), 3.36 (1H, dd, J=3 and 14 Hz, $C_2-C\lesssim^{H}_{\underline{H}}$), 4.86 (1H, sextet, J=5, 11 and 11 Hz, C_1–H), 7.0—7.4 (5H, m, C_6H_5). Next, 1 N HCl (2.5 ml) was added to a solution of this oil in EtOH (5 ml) and the solution was concentrated to dryness *in vacuo*. The resulting residue was recrystallized from AcOEt–MeOH to give **9a**·HCl as colorless needles (0.45 g, 49%), mp 229—230 °C. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). *Anal.* Calcd for $C_{21}H_{33}NO_2$·HCl: C, 68.55; H, 9.31; N, 3.81. Found: C, 68.34; H, 9.48; N, 3.97.

2-Dimethylaminomethyl-3-(3-methoxyphenyl)-5,5-dimethylcyclohexanone (3o)——A mixture of **2o** (23.2 g), $NH(CH_3)_2$·HCl (8.2 g), paraformaldehyde (4.0 g), and EtOH (40 ml) was stirred for 10 h at 70—80 °C. The solvent was evaporated off, and the resulting residue was treated as described in the general procedure for preparing **3** to give a yellowish oil (10.5 g). This oil was similarly treated with conc. HCl (5.0 g) to give a solid hydrochloride, which was recrystallized from AcOEt–acetone (1 : 1) to give **3o**·HCl as colorless needles (6.6 g, 20%), mp 149—151 °C (Tables I and II).

1,2-*cis*- and 1,2-*trans*-2-Dimethylaminomethyl-3-(3-methoxyphenyl)-5,5-dimethylcyclohexanol (5o and 6o)—— $LiAlH_4$ (1.0 g) was added to a solution of **3o** (4.8 g, 17 mmol) in dry ether (40 ml) with stirring and cooling. The mixture was refluxed for 3 h and treated as described for preparing **6a** to give a pale yellowish oil (4.4 g), which was chromatographed on a silica gel (50 g) column using AcOEt and AcOEt–MeOH (10 : 1) as eluents to give **6o** (2.9 g, 59%) as a faintly pale yellowish oil and **5o** (0.7 g, 14%) as pale yellowish crystals, respectively. **6o**, IR $\nu_{max}^{liq.}$ cm^{-1}: 3200 (OH). NMR ($CDCl_3$) δ: 0.90, 0.95 (each 3H, s, C_5–CH_3), 2.19 (6H, s, $N(CH_3)_2$), 3.60 (1H, m, C_1–H), 3.72 (3H, s, OCH_3), 5.90 (1H, m, OH), 6.4—7.2 (4H, m, C_6H_4). The pale yellowish crystals of **5o** were recrystallized from hexane to give colorless needles, mp 85—87 °C. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH). NMR ($CDCl_3$) δ: 0.91, 1.22 (each 3H, s, C_5–CH_3), 2.14 (6H, s, $N(CH_3)_2$), 2.90 (1H, sextet, J=4, 11 and 11 Hz, C_3–H), 3.80 (3H, s, OCH_3), 4.26 (1H, m, C_1–H), 6.6—7.4 (4H, m, C_6H_4).

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References and Notes

1) Previous paper: T. Kato, K. Kawai, and Y. Sawa, *Yakugaku Zasshi*, **100**, 280 (1980).
2) *a*) T. Hayano, *Nippon Yakurigaku Zasshi*, **65**, 604 (1969); *b*) Y. Kawahara, A. Nakamura, Y. Kato, H. Suzuki, and M. Matsukuma, *Clinical Reports*, **6**, 1427 (1972).
3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, 1965, pp. 50—53.
4) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).
5) K. H. Boltze and H. D. Dell, *Arzneim.-Forsch.*, **17**, 731 (1967).
6) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, 1972, p. 655.
7) W. C. Neikam and B. P. Daily, *J. Chem. Phys.*, **38**, 445 (1963).
8) A. Gaudemer, "Spectrochemistry Fundamentals and Methods, Vol. 1, Determination of Configurations by Spectrometric Methods," ed. by H. B. Kagan, George Thieme Publishers, Stuttgart, 1977, p. 94.
9) A. Gaudemer, "Spectrochemistry Fundamentals and Methods, Vol. 1, Determination of Configurations by Spectrometric Methods," ed. by H. B. Kagan, George Thieme Publishers, Stuttgart, 1977, p. 100.
10) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).