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# Synthesis and Analgesic Activity of Cyclohexenylmethylamines and Related Compounds[1)]

TAKESHI KATO,* HARUMITSU ISHII, KIYOHISA KAWAI,
and YOICHI SAWA

*Central Research Division, Takeda Chemical Industries, Ltd.,
Jusohonmachi, Yodogawa-ku, Osaka 532, Japan*

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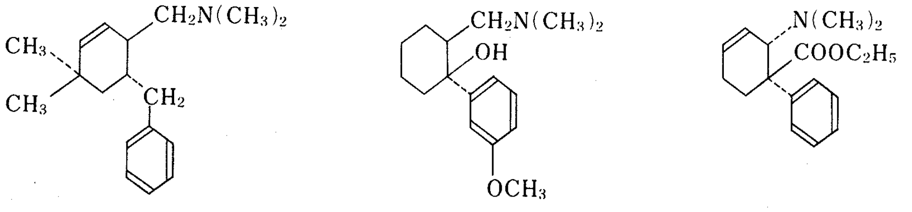
*N*,*N*-Dimethyl-(6-benzyl-2-cyclohexenyl)methylamine derivatives (I) were prepared by dehydrochlorination of the 1,2-*cis*-*N*,*N*-dimethyl-(6-benzyl-2-chlorocyclohexyl)methylamines (XII), which were obtained by the reaction of the 1,2-*trans*-cyclohexanol derivatives (X) with thionyl chloride. The cyclohexenylmethylamine derivatives and related compounds were examined for analgesic activity by using the phenylquinone writhing method. Some of them, in particular, 1,6-*trans*-*N*,*N*-dimethyl-(6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamine hydrochloride (**37**) showed pronounced pharmacological activities. Structure–activity relationships are discussed.

**Keywords**——Mannich reaction; thionyl chloride dehydration; cyclohexenylmethylamine derivative; dehydrochlorination; analgesic activity; structure–activity relationship

In a previous paper,[1)] we reported the synthesis of dimethylcyclohexenylmethylamine derivatives (*e.g.* **37** in Table IV) and related compounds as new potent analgesics. Since neither tramadol,[2)] recently developed as a non narcotic analgesic, nor tilidine,[3)] reported to be an analgesic without habituation, has a methyl substituent on the cyclohexane ring, it is thought that the dimethyl group in **37** is not essential for the analgesic activity. This paper describes the synthesis and biological activity of cyclohexenylmethylamine derivatives with or without a methyl substituent on the cyclohexene ring. Structure–activity relationships are also discussed and compared with those of the compounds reported previously.[1,4,5)]



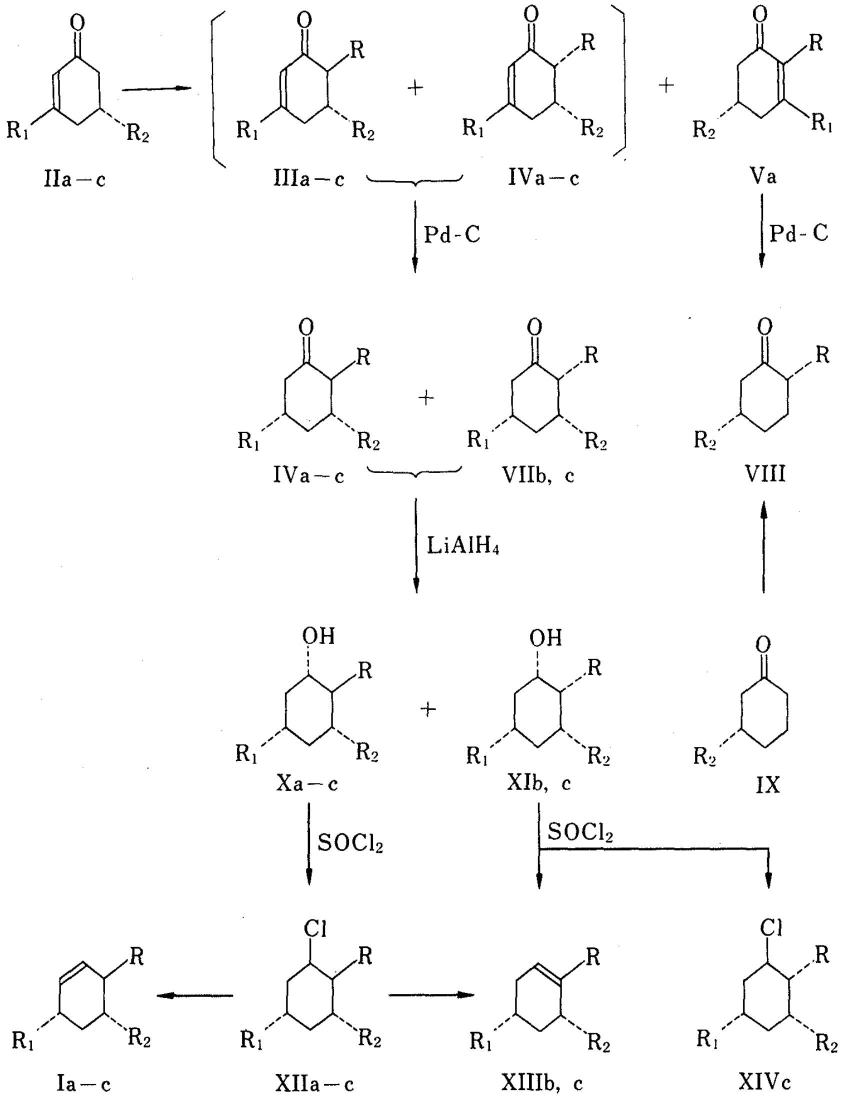
**37** tramadol tilidine

Chart 1

## Chemistry

Previously we reported[5)] that 2,3-*trans*-3-benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanone was obtained as the main product in the Mannich reaction of 3-benzyl-5,5-dimethylcyclohexanone with dimethylamine hydrochloride. However, it is anticipated that in the Mannich reaction of 3-benzylcyclohexanone (IXb), the aminomethyl group will be preferentially introduced at the 6-position that is sterically less hindered. 5-Benzyl-2-cyclohexenone (IIb), on the other hand, should preferentially give a 6-aminomethyl compound IIIb, because the more stable enol reacts with the iminium salt.[6)]

The Mannich reaction of 5-phenyl-2-cyclohexenone (IIa) with dimethylamine hydrochloride and paraformaldehyde gave a basic oil, which had three main components in the proportions of *ca.* 9 : 8 : 3 on the basis of the nuclear magnetic resonance (NMR) spectrum. The major component was separated as the oxalate from the basic oil and determined to be Va on the basis of the NMR spectrum (the $C_2$–$CH_2$ signal appeared as a broad singlet at $\delta$ 3.12 and the $C_3$–H signal as a multiplet at $\delta$ 7.00). Hydrogenation on palladium carbon (Pd–C) of the hydrochloride of the crude basic oil (a mixture of IIIa, IVa and Va), followed by reduction with lithium aluminum hydride ($LiAlH_4$) and chromatographic separation gave Xa as an oil in 23% yield from IIa.



a: $R=CH_2N(CH_3)_2$, $R_1=H$, $R_2=C_6H_5$
b: $R=CH_2N(CH_3)_2$, $R_1=H$, $R_2=CH_2C_6H_5$
c: $R=CH_2N(CH_3)_2$, $R_1=CH_3$, $R_2=CH_2C_6H_5$

Chart 2

Similarly, the desired compounds, 3-benzyl-2-dimethylaminomethylcyclohexanols (Xb, c and XIb, c) were obtained by the catalytic hydrogenation of crude Mannich bases derived from 5-benzyl-2-cyclohexenone (IIb) and 5-benzyl-3-methyl-2-cyclohexenone (IIc), respectively, followed by $LiAlH_4$ reduction and chromatographic separation. In these reactions, only the cyclohexanols (X and XI) with an equatorial hydroxyl group were separated, probably because of the low yields of axial cyclohexanols formed by the $LiAlH_4$ reduction.[4]

Treatment of XIb with $SOCl_2$ did not give Ib[1] but *N*,*N*-dimethyl-(6-benzyl-1-cyclohexenyl)methylamine (XIIIb) as a hydrochloride in 72% yield. Under similar conditions, Xb afforded only *N*,*N*-dimethyl-(6-*t*-benzyl-2-*c*-chloro-1-*r*-cyclohexyl)methylamine (XIIb), whose configuration at the $C_1$-position was inverted.[1,7] When heated in alcoholic potassium hydroxide in the presence of sodium iodide, XIIb gave *N*,*N*-dimethyl-(6-benzyl-2-cyclohexenyl)methylamine (Ib) and XIIIb as the hydrochlorides in 36 and 19% yields, respectively. Formation of XIIIb from XIb in good yield (*via trans* elimination) suggests that the relation between the 1-hydroxyl and the 2-dimethylaminomethyl groups in XIb is *cis*. It is

TABLE I. *N*, *N*-Dimethyl-(cyclohexenyl)methylamines and Related Compounds

| Compd.[a] | mp (°C) | Yield | Formula[b] | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | NMR in $CDCl_3$[c] |
|---|---|---|---|---|---|
| Ia | 189—191 | 29 | $C_{15}H_{22}ClN$ | 1650 (C=C) | 2.03 (6H, s, $N(CH_3)_2$), 5.5—6.0 (2H, m, $C_2$–H, $C_3$–H), 6.9—7.4 (5H, m, $C_6H_5$)[d] |
| Ib | 120—122 | 40 | $C_{16}H_{24}ClN$ | 1650 (C=C) | 2.13 (6H, s, $N(CH_3)_2$), 5.69 (2H, s, $C_2$–H, $C_3$–H), 7.20 (5H, m, $C_6H_5$) |
| Ic | 141—143 | 44[e] | $C_{17}H_{26}ClN \cdot 1/2H_2O$ | 1645 (C=C) | 0.85 (3H, d, $J$=6 Hz, $C_4$–$CH_3$), 2.18 (6H, s, $N(CH_3)_2$), 3.07 (1H, complex d, $J$=14 Hz, $C_1\text{–}C{<}^{H}_{H}$), 5.46, 5.71 (each 1H, AB type q, $J_{AB}$=10 Hz, $C_2$–H, $C_3$–H), 6.9—7.4 (5H, m, $C_6H_5$) |
| Xa | 164—166 | 23[f] | $C_{15}H_{24}ClNO \cdot 1/2H_2O$ | 3200 (OH) | 2.13 (6H, s, $N(CH_3)_2$), 3.61 (1H, m, $C_1$–H), 7.1—7.4 (5H, m, $C_6H_5$) |
| Xb | 200—202 | 5.5[g] | $C_{16}H_{26}ClNO \cdot 1/2H_2O$ | 3250 (OH) | 2.28 (6H, s, $N(CH_3)_2$), 3.35 (1H, m, $C_1$–H), 6.10 (1H, m, OH), 6.8—7.4 (5H, m, $C_6H_5$)[d] |
| Xc | 198—200 | 4.7[g] | $C_{17}H_{28}ClNO$ | 3325 (OH) | 0.87 (3H, d, $J$=5 Hz, $C_5$–$CH_3$), 2.27 (6H, s, $N(CH_3)_2$), 3.50 (1H, m, $C_1$–H), 7.0—7.5 (5H, m, $C_6H_5$) |
| XIb | 234—237 | 5.4[g] | $C_{16}H_{26}ClNO$ | 3350 (OH) | 2.17 (6H, s, $N(CH_3)_2$), 3.63 (1H, m, $C_1$–H), 7.0—7.5 (5H, m, $C_6H_5$) |
| XIc | 265—268[h] | 0.8[g] | $C_{17}H_{28}ClNO$ | 3300 (OH) | 0.91 (3H, d, $J$=5 Hz, $C_5$–$CH_3$), 2.20 (6H, s, $N(CH_3)_2$), 3.67 (1H, m, $C_1$–H), 7.0—7.4 (5H, m, $C_6H_5$) |
| XIIa | Oil | 57 | $C_{15}H_{22}ClN$ | | 2.00 (6H, s, $N(CH_3)_2$), 4.75 (1H, s, $C_2$–H), 6.8—7.3 (5H, m, $C_6H_5$)[d] |
| XIIb | Oil | 90 | $C_{16}H_{24}ClN$ | | 2.18 (6H, s, $N(CH_3)_2$), 4.60 (1H, s, $C_2$–H), 6.8—7.4 (5H, m, $C_6H_5$)[d] |
| XIIIb | 215—217 | 72 | $C_{16}H_{24}ClN$ | 1660 (C=C) | 2.17 (6H, s, $N(CH_3)_2$), 3.20 (2H, complex d, $J$=12 Hz, $C_1$–$CH_2$), 5.60 (1H, m, $C_2$–H), 7.21 (5H, s, $C_6H_5$) |
| XIIIc | 236—239[h] | 35[e] | $C_{17}H_{26}ClN$ | 1650 (C=C) | 0.82 (3H, d, $J$=6 Hz, $C_4$–$CH_3$), 2.20 (6H, s, $N(CH_3)_2$), 3.30 (2H, complex d, $J$=12 Hz, $C_1$–$CH_2$), 5.64 (1H, m, $C_2$–H), 7.21 (5H, s, $C_6H_5$) |
| XIVc | 204—206 | 25 | $C_{17}H_{27}Cl_2N$ | | 0.86 (3H, d, $J$=6 Hz, $C_4$–$CH_3$), 2.19 (6H, s, $N(CH_3)_2$), 4.73 (1H, s, $C_2$–H), 7.1—7.5 (5H, m, $C_6H_5$) |

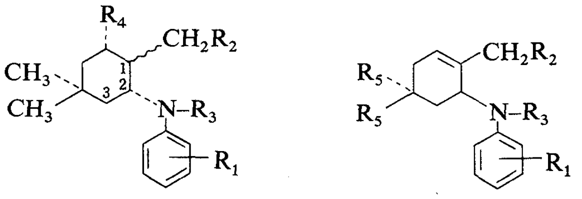
*a*) All compounds except XIIa and XIIb are hydrochlorides.
*b*) All compounds were analyzed for C, H and N: analytical results obtained for these elements were within ±0.4% of calculated values.
*c*) Measured as free base.
*d*) Measured as a solution in $CCl_4$.
*e*) Overall yield based on Xc.
*f*) Overall yield of a basic oil of Xa based on IIa.
*g*) Overall yield based on the corresponding II.
*h*) Decomposition.

also suggested that the stereochemistry between the two groups in Xb is 1,2-*trans* in view of the fact that XIIIb was not directly obtained from Xb[1] (1,2-*trans* elimination is impossible). Formation of XII is attributed to an $S_N2$ process.

Compounds Xa, c were treated with $SOCl_2$ to give 1,2-*cis* chlorides (XIIa, c), which were heated under the same conditions as in the case of XIIb to give Ia, c (as hydrochlorides) in 17 and 44% yields, respectively. XIIIc hydrochloride was also separated in 35% yield. Treatment of XIc with $SOCl_2$ gave XIIIc and the 1,2-*trans* chloride (XIVc) (as hydrochloride) in 27 and 25% yields, respectively. Compound XIIIc obtained from XIIc was identical with the product obtained from XIc, indicating that the methyl and the benzyl groups in both Xc and XIc have the same relative stereochemistry. Furthermore, the chemical shifts of the methyl group ($\delta$ 0.87 and 0.91, respectively) in Xc and XIc with an equatorial hydroxyl group were almost the same as those ($\delta$ 0.78 and 0.86) in XIIc and XIVc with the axial chlorine, suggesting that there is no 1,3-diaxial interaction between the methyl group and the chlorine atom. Consequently, the conformation of the methyl group is assumed to be equatorial.[8]

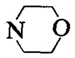
As mentioned above, both the 5,6-*trans* (III) and -*cis* forms (IV) were produced simultaneously in the Mannich reaction of 2-cyclohexenones (II), in contrast to the Mannich reaction of 3-benzyl-5,5-dimethylcyclohexanone, in which compounds with 2,3-*trans* con-

TABLE II. Biological Properties of Anilinocyclohexane Derivatives



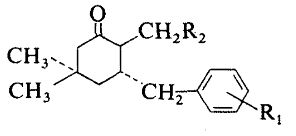
A: 1,2-*trans*
B: 1,2-*cis*

C

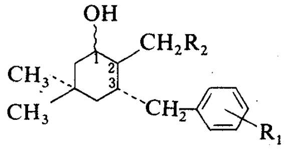
| No. | Type | $R_1$ | $R_2$ | $R_3$ | $R_4$ or $R_5$ | Analgesic activity[a] Oral dose (mg/kg) | Analgesic activity[a] Inhibition (%) | Toxicity in mice Oral dose (mg/kg) | Toxicity in mice Mortality |
|---|---|---|---|---|---|---|---|---|---|
| **1** | A | 2-Cl |  | H | OH | 25<br>12.5 | 45.1*[b]<br>43.6* | 200 | 0/4 |
| **2** | C | H | $N(CH_3)_2$ | H | H | 50 | 42.2[c] | 300 | 0/4 |
| **3** | C | 3-$OCH_3$ | $N(CH_3)(CH_2C_6H_5)$ | H | $CH_3$ | 50 | 31.3 | 500 | 0/4 |
| **4** | C | 3-$OCH_3$ | $N(CH_3)(CH_2C_6H_5)$ | $COCH_3$ | $CH_3$ | 50 | 47.5* | 500 | 2/4 |
| **5** | C | 3-Cl |  | H | $CH_3$ | 50 | −11.7 | 500 | 0/4 |
| **6** | B | H | $N(CH_3)_2$ | H | H | 50<br>25 | 66.7*<br>7.6 | 300<br>50 | 4/4<br>0/4 |
| **7** | B | H | $N(CH_3)_2$ | $COCH_3$ | H | 50 | 24.0 | —[d] | |
| **8** | B | H | $N(CH_3)_2$ | $C_2H_5$ | H | 25 | 24.0 | —[d] | |
| **9** | B | H | $N(CH_3)_2$ | $COC_2H_5$ | H | 50 | 27.4[c] | 300<br>50 | 1/4<br>0/4 |
| **10** | B | 2-Cl |  | H | H | 50 | 18.0 | 500 | 0/4 |

*a*) Measured by the phenylquinone writhing method in mice.
*b*) Statistically significant at $*p<0.05$, $**p<0.01$.
*c*) Measured by the acetic acid writhing method.
*d*) Not tested.

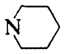
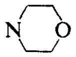
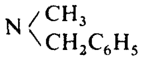
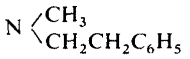
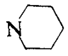
Table III. Biological Properties of Cyclohexanone and Cyclohexanol Derivatives



D



E: 1,2-*cis*
F: 1,2-*trans*

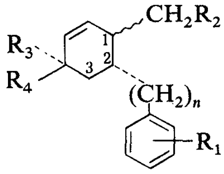
| No. | Type | $R_1$ | $R_2$ | Analgesic activity[a] |  | Toxicity in mice |  |
|---|---|---|---|---|---|---|---|
|  |  |  |  | Oral dose (mg/kg) | Inhibition (%) | Oral dose (mg/kg) | Mortality |
| **11** | D | H | $N(CH_3)_2$ | 12.5 | 51.7**[b] | 300 | 2/4 |
|  |  |  |  | 6.25 | 49.1* | 50 | 0/4 |
| **12**[d] | D | H | $N(CH_3)_2$ | 50 | 83.1** | 300 | 4/4 |
|  |  |  |  | 12.5 | 6.0 | 50 | 0/4 |
| **13** | D | H | $N(C_2H_5)_2$ | 50 | 64.4* | 500 | 4/4 |
|  |  |  |  |  |  | 125 | 0/4 |
| **14** | D | H |  | 50 | 27.6 | 500 | 4/4 |
|  |  |  |  |  |  | 125 | 0/4 |
| **15** | D | H |  | 50 | 32.7 | 500 | 0/4 |
| **16** | D | H |  $\mathrm{N}\genfrac{}{}{0pt}{}{\mathrm{CH_3}}{\mathrm{CH_2C_6H_5}}$ | 50 | 62.5* | 500 | 0/4 |
|  |  |  |  | 25 | 39.4 |  |  |
| **17** | D | H |  $\mathrm{N}\genfrac{}{}{0pt}{}{\mathrm{CH_3}}{\mathrm{CH_2CH_2C_6H_5}}$ | 50 | 50.4* | 500 | 0/4 |
|  |  |  |  | 25 | 18.2 |  |  |
| **18** | D | 4-$CH_3$ | $N(CH_3)_2$ | 25 | 59.3* | 300 | 0/4 |
|  |  |  |  | 12.5 | 34.2 |  |  |
| **19**[e] | D | 3-$OCH_3$ | $N(CH_3)_2$ | 25 | 71.2** | 300 | 1/4 |
|  |  |  |  | 12.5 | 32.4 | 50 | 0/4 |
| **20** | D | 3-$OCH_3$ | $N(CH_3)_2$ | 25 | 74.3** | 300 | 1/4 |
|  |  |  |  | 12.5 | 39.6* | 50 | 0/4 |
|  |  |  |  | 6.25 | 29.4 |  |  |
| **21** | D | 4-$OCH_3$ |  | 50 | −12.6 | 500 | 3/4 |
| **22** | D | 4-OH |  | 50 | 22.9 | 500 | 1/4 |
| **23** | D | 2-Cl |  | 25 | 5.5 | 300 | 0/4 |
| **24** | D | 4-Cl |  | 25 | 3.4 | 300 | 0/4 |
| **25** | E | H | $N(CH_3)_2$ | 50 | 62.0*[c] | 300 | 3/4 |
|  |  |  |  |  |  | 50 | 0/4 |
| **26** | F | H | $N(CH_3)_2$ | 25 | 54.7* | 300 | 1/4 |
|  |  |  |  | 12.5 | 17.2 |  |  |
| **27**[f] | F | H | $N(CH_3)_2$ | 25 | 54.9* | 500 | 2/5 |
| **28** | E | 4-$CH_3$ | $N(CH_3)_2$ | 25 | 40.9 | 300 | 0/4 |
|  |  |  |  | 12.5 | −16.0 |  |  |
| **29** | E | 4-$OCH_3$ |  | 25 | 8.2 | 300 | 0/4 |
| **30** | E | 4-OH |  | 50 | 13.4 | 500 | 0/4 |
| **31** | F | 2-Cl | $N(CH_3)_2$ | 25 | 57.1* | 500 | 3/5 |
|  |  |  |  |  |  | 200 | 0/5 |
| **32** | E | 2-Cl |  | 25 | 58.9** | 300 | 0/4 |
|  |  |  |  | 12.5 | 40.1* |  |  |
|  |  |  |  | 6.25 | 17.5 |  |  |
| **33** | E | 4-Cl |  | 25 | −20.5 | 300 | 0/4 |

*a)*—*c)* See the corresponding footnote in Table II.
*d)* 3-Benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanone ethylene acetal.
*e)* 2-Dimethylaminomethyl-3-(3-methoxyphenyl)-5,5-dimethylcyclohexanone.
*f)* 3-Benzyl-2-dimethylaminomethyl-5,5-dimethyl-1-cyclohexyl propionate.

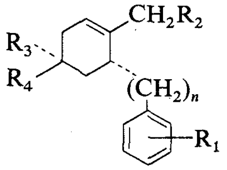
figuration were mainly produced.[5] This difference may be explained by the tendency of cyclohexenone to be a flatter molecule than cyclohexanone.

Physical data for Ia—c and related compounds are listed in Table I.

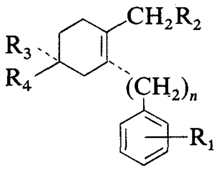
TABLE IV. Biological Properties of Cyclohexenylmethylamine Derivatives



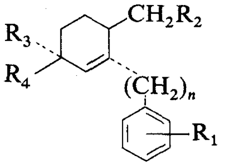
G: 1,2-*trans*
H: 1,2-*cis*



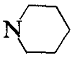
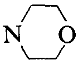
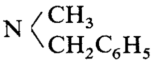
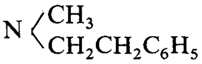
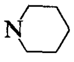
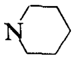
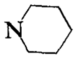
I



J

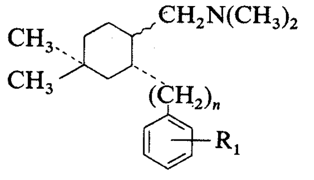


K

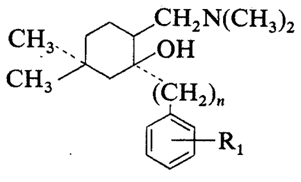
| No. | Type | $R_1$ | $R_2$ | $R_3$ | $R_4$ | *n* | Analgesic activity[a] |  | Toxicity in mice |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  | Oral dose (mg/kg) | Inhibition (%) | Oral dose (mg/kg) | Mortality |
| **34** | G | H | $N(CH_3)_2$ | H | H | 0 | 25 | 69.8**[b] | 200 | 3/5 |
|  |  |  |  |  |  |  |  |  | 100 | 0/5 |
| **35** | G | H | $N(CH_3)_2$ | H | H | 1 | 12.5 | 49.1* | 500 | 5/5 |
|  |  |  |  |  |  |  | 6.25 | 45.1 | 200 | 0/5 |
| **36** | G | H | $N(CH_3)_2$ | $CH_3$ | H | 1 | 12.5 | 68.1** | 500 | 3/5 |
|  |  |  |  |  |  |  | 6.25 | 58.2** | 200 | 0/5 |
|  |  |  |  |  |  |  | 3.125 | 53.9* |  |  |
| **37** | G | H | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 12.5 | 65.1** | 300 | 0/4 |
|  |  |  |  |  |  |  | 6.25 | 47.9* |  |  |
| **38** | H | H | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 12.5 | 58.0** | 300 | 1/4 |
|  |  |  |  |  |  |  | 6.25 | 55.9* | 50 | 0/4 |
| **39** | G | H |  | $CH_3$ | $CH_3$ | 1 | 25 | 3.1 | 300 | 0/4 |
| **40** | G | H |  | $CH_3$ | $CH_3$ | 1 | 25 | 29.2 | 300 | 0/4 |
| **41**[d] | G | H |  $N\langle^{CH_3}_{CH_2C_6H_5}$ | $CH_3$ | $CH_3$ | 1 | 25 | 20.8 | 300 | 0/4 |
| **42** | G | H |  $N\langle^{CH_3}_{CH_2CH_2C_6H_5}$ | $CH_3$ | $CH_3$ | 1 | 25 | 12.3 | 300 | 0/4 |
| **43** | G | 4-$CH_3$ | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 25 | 44.7 | 300 | 0/4 |
| **44** | G | 3-$OCH_3$ | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 0 | 12.5 | 69.7** | 300 | 3/4 |
|  |  |  |  |  |  |  | 6.25 | 32.0 | 50 | 0/4 |
| **45** | G | 3-$OCH_3$ | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 25 | 58.2* | 300 | 0/4 |
|  |  |  |  |  |  |  | 12.5 | 22.5 |  |  |
| **46** | G | 2-Cl | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 25 | 57.7* | 500 | 4/5 |
| **47** | G | 2-Cl |  | $CH_3$ | $CH_3$ | 1 | 25 | 25.7 | 500 | 0/5 |
| **48** | G | 4-Cl |  | $CH_3$ | $CH_3$ | 1 | 25 | −28.5 | 300 | 0/4 |
| **49** | G | 4-$OCH_3$ |  | $CH_3$ | $CH_3$ | 1 | 25 | 16.0 | 300 | 0/4 |
| **50** | I | H | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 25 | 76.8** | 300 | 1/4 |
|  |  |  |  |  |  |  | 12.5 | 15.2 | 50 | 0/4 |
| **51** | J | H | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 12.5 | 60.7** | 250 | 4/5 |
|  |  |  |  |  |  |  | 6.25 | 48.0* | 125 | 1/5 |
| **52** | K | H | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 1 | 25 | 48.6* | 500 | 3/5 |
| **53** | K | H | $N(CH_3)_2$ | $CH_3$ | $CH_3$ | 0 | 25 | 63.2** | 500 | 5/5 |
|  |  |  |  |  |  |  | 12.5 | 9.1 | 200 | 1/5 |

*a)*—*c)* See the corresponding footnote in Table II.
*d)* Hydrobromide.

Table V. Biological Properties of Cyclohexylmethylamine Derivatives and Related Compounds



L : 1,2-*trans*
M: 1,2-*cis*



N

| No. | Type | $R_1$ | *n* | Analgesic activity[a)] | | Toxicity in mice | |
|---|---|---|---|---|---|---|---|
| | | | | Oral dose (mg/kg) | Inhibition (%) | Oral dose (mg/kg) | Mortality |
| **54** | L | H | 1 | 12.5 | 71.8**[b)] | 300 | 3/4 |
| | | | | 6.25 | 60.9* | 50 | 0/4 |
| | | | | 3.125 | 12.0 | | |
| **55** | M | H | 1 | 25 | 52.3* | 250 | 4/5 |
| | | | | 12.5 | −0.7 | 125 | 0/5 |
| **56** | L | 3-$OCH_3$ | 0 | 25 | 36.1 | 200 | 2/5 |
| **57** | L | 3-$OCH_3$ | 1 | 25 | 22.5 | 500 | 1/5 |
| **58** | M | 3-$OCH_3$ | 1 | 25 | −7.2 | 500 | 4/5 |
| **59** | L | 3-OH | 1 | 25 | 7.2 | 500 | 1/5 |
| **60** | M | 3-OH | 1 | 25 | −1.8 | 500 | 4/5 |
| **61** | N | H | 1 | 25 | 49.2* | 500 | 5/5 |
| **62** | N | 3-$OCH_3$ | 0 | 12.5 | 59.5* | 200 | 2/5 |
| **63** | N | 3-$OCH_3$ | 1 | 25 | 13.8 | 300 | 0/4 |
| | Tramadol | | | 12.5 | 89.1** | | |
| | | | | 6.25 | 67.8** | | |
| | | | | 3.125 | 28.8 | | |
| | Codeine phosphate | | | 25 | 75.0** | | |
| | | | | 12.5 | 50.9* | | |

*a, b*) See the corresponding footnote in Table II.

## Biological Methods

**Phenylquinone Writhing**[9)]——Male mice weighing 17—24 g were given an aqueous solution of 0.02% phenylquinone (dissolved by adding 5% ethanol) *i.p.* in the volume of 0.1 ml/10 g b.w. at 30 min after the oral administration of test compounds. For 20 min after the phenylquinone injection, the frequency of writhing and stretching was counted. The analgesic activity was assessed in terms of the inhibition of these responses.

**Acetic Acid Writhing**[10)]——Male mice weighing 17—24 g were given *i.p.* 0.6% acetic acid solution in the volume of 0.1 ml/10 g b.w. Other procedures were the same as for the phenylquinone writhing test.

## Results and Discussion

The biological data for compounds reported in earlier papers[1,4,5)] are shown in Tables II—V.

Table II shows the activities of anilinocyclohexylmethylamine derivatives.[4)] Among these compounds, compound **1** showed the most potent analgesic activity. Compound **10**, which is a more reduced form of **1**, was less active than **1**. The difference of activity may be due to the different stereochemistry between anilino and piperidinomethyl groups rather than the loss of the hydroxyl group. The analgesic activity was increased (**3**<**4**) or decreased (**6**>**7**, **9**) by acylation of the NH group, suggesting that the basicity of the anilino group is not critical for the activity. This was confirmed by the fact that the benzylcyclohexanol (**32**), a carba isostere of **1**, showed activity comparable with that of **1**, as can be seen in Table III.

Table III shows the analgesic activities of cyclohexanone and cyclohexanol derivatives,[5] which have benzyl substituents instead of the anilino group. Compounds **11**, **19**, **20**, **31** and **32** showed potent analgesic activities. Among these compounds, **11** showed the most potent activity, but had high toxicity. In general, introduction of a substituent on the phenyl ring resulted in reduction of the activity (**11** > **20** > **18**). The compounds with a dimethylaminomethyl group showed potent analgesic activity. Substitution of the methyl groups of the dimethylaminomethyl group with ethyl groups (**13**) or of one methyl group with a benzyl or phenethyl group (**16** or **17**) resulted in reduction of the activity (**11** > **13**, **16**, **17**). The compounds (*e.g.*, **14** and **15**) having piperidinomethyl and morpholinomethyl groups did not show analgesic activity, but only **32**, which has the combination of piperidinomethyl and 2-chlorobenzyl groups, showed potent analgesic activity as mentioned above.

Table IV shows the analgesic activities of cyclohexenylmethylamine derivatives.[1] The relationship between the position of the double bond on the cyclohexene ring and analgesic activity was investigated. Among these compounds, the compounds of G and H types, in which the relationships between the positions of the $CH_2R_2$ group and a double bond are the same as in tilidine,[3] seem to have favorable activities, *i.e.* potent analgesic activity with low toxicity (activity, **36** > **37**, **38**, **51** > **52**; toxicity, **37** < **36**, **38**, **52** < **51**). Although the relationship between analgesic activity and the orientation of the benzyl and dimethylaminomethyl groups is not clear from the data in Tables IV and V, the compounds which have *trans* orientation seem to have high activity and low toxicity (activity, **54** > **55**; toxicity, **37** < **38**; **54** < **55**; **57** < **58**; **59** < **60**).

Although the difference of analgesic activity between the compounds which have benzyl and phenyl groups is not clear (**34** ≑ **35**; **44** < **45**; **52** < **53**; **62** > **63**), the toxicity of the compounds with a phenyl group seems to be higher than that of the corresponding benzyl analogues (**34**, **44**, **53**, **56**, **62** > **35**, **45**, **52**, **57**, **63**).

Regarding the functional groups on the cyclohexane ring, all compounds which have dimethylaminomethyl, benzyl and dimethyl groups on the cyclohexane ring, especially **11**, **37**, **38**, **51** and **54**, showed pronounced activity, but also had high toxicity except for **37** and **38**, as can be seen in Tables II—V.

Although **35**, **36**, **37** and **38** showed potent analgesic activities, compound **62**, which is a dimethyl derivative of tramadol showed only weak analgesic activity. The dimethyl groups of the N type compounds seem to adversely affect the analgesic activity. On the other hand, in our compounds (G) the methyl group on the cyclohexene ring did not influence the analgesic activity. This finding suggests that the conformational requirement is different between the G and N type compounds.

In conclusion, compounds **11**, **35**, **36**, **37**, **38**, **44**, **51** and **54** showed potent analgesic activity. 1,6-*trans*-*N*,*N*-Dimethyl-(6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamine hydrochloride (**37**) in particular showed potent analgesic activity and low toxicity, and therefore seems worthy of further pharmacological evaluation.

## Experimental

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

**2-*t*-Dimethylaminomethyl-3-*c*-phenyl-1-*r*-cyclohexanol (Xa)**——A mixture of 5-phenyl-2-cyclohexen-1-one[11] (IIa) (15.7 g, 91 mmol), $HN(CH_3)_2 \cdot HCl$ (7.4 g), paraformaldehyde (3.5 g) and EtOH (30 ml) was stirred for 6 h at 75—80 °C. The solvent was evaporated off, then $H_2O$ was added to the residue and a separated oil was extracted with

AcOEt. The aqueous solution was basified with ammonia water and extracted with AcOEt. The extract was washed with $H_2O$ and concentrated *in vacuo* to give a pale yellowish oil (13.3 g). Conc. HCl (6.8 g) was added to a solution of this oil in EtOH (60 ml) and the mixture was concentrated to dryness *in vacuo*. A suspension of the resulting residue and 5% Pd–C (50% wet) (3.5 g) in MeOH (100 ml) was shaken under a hydrogen atmosphere at room temperature. When the absorption of $H_2$ had ceased, the catalyst was filtered off and the filtrate was concentrated to dryness *in vacuo* to give a solid, which was converted to a free basic oil (11.9 g) in the usual manner. IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 1705 (C=O). A solution of this oil in dry ether (30 ml) was added dropwise to a suspension of $LiAlH_4$ (2.0 g) in dry ether (70 ml) and the mixture was refluxed for 4 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 mixture was extracted with ether. The combined ethereal solutions were washed with $H_2O$, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellowish oil (10.2 g), which was chromatographed on an alumina (150 g) column using $C_6H_6$ as an eluent to yield Xa as a pale yellowish oil (4.9 g, 23%). A part of this oil was converted to the hydrochloride and recrystallized from AcOEt–MeOH to give Xa·HCl as colorless needles, mp 164—166 °C.

**2-Dimethylaminomethyl-5-phenyl-2-cyclohexen-1-one (Va)**——A mixture of IIa (10.0 g), $HN(CH_3)_2 \cdot HCl$ (4.7 g), paraformaldehyde (2.2 g) and EtOH (20 ml) was stirred for 6 h at 75—80 °C. The mixture was treated as above to give a yellowish basic oil (8.0 g). The NMR ($CDCl_3$) spectrum showed that the proportion of Mannich bases produced is *ca.* 9 : 8 : 3 based on the peak areas of $N(CH_3)_2$ signals (*ca.* $\delta$ 2.3). Anhydrous oxalic acid (3.1 g) was added to a solution of this oil in EtOH (20 ml) and the mixture was concentrated to dryness *in vacuo*. AcOEt was added to a solution of the residue in acetone–MeOH and the solution was allowed to stand at room temperature to give crystals (1.3 g), which were recrystallized from acetone–MeOH to give Va oxalate as pale brownish crystals (0.7 g, 3.8%), mp 114—117 °C. Va oxalate was converted to a free basic oil. Then 1 N HCl (12 ml) was added to a solution of this oil in EtOH (15 ml) and the solution was concentrated to dryness *in vacuo*. The residue was recrystallized from acetone to give Va·HCl as colorless needles (0.45 g), mp 153—155 °C. IR $\nu_{\max}^{\text{KBr}}$ cm$^{-1}$: 1675 (C=O), 1635 (C=C). Va, NMR ($CDCl_3$) $\delta$: 2.26 (6H, s, $N(CH_3)_2$), 3.12 (2H, br s, $C_2$–$CH_2$), 3.0—3.5 (1H, m, $C_5$–H), 7.00 (1H, m, $C_3$–H), 7.2—7.4 (5H, m, $C_6H_5$). *Anal.* Calcd for $C_{15}H_{20}ClNO$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.51; H, 7.50; N, 5.30.

**3-*c*-Benzyl-2-*t*- and *c*-dimethylaminomethyl-1-*r*-cyclohexanols (Xb and XIb)**——A mixture of 5-benzyl-2-cyclohexen-1-one (IIb)[11,12] (15.0 g, 81 mmol), $HN(CH_3)_2 \cdot HCl$ (6.6 g), paraformaldehyde (3.1 g) and EtOH (20 ml) was worked up as described for the preparation of Xa to give a crude basic oil (15.5 g), which was hydrogenated as described in the case of Xa to give a yellowish oil (14.5 g), IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 1710 (C=O). This oil was further reduced with $LiAlH_4$ (2.5 g) in dry ether (70 ml) to give a pale yellowish oil (13.0 g), IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 3400 (OH). Chromatography of this oil on an alumina (150 g) column using $C_6H_6$ as an eluent yielded an oil (9.0 g). This oil was converted in the usual manner to crude crystals (3.0 g) of the hydrochloride, which were recrystallized from EtOH to give XIb·HCl as colorless needles (1.2 g, 5.4%), mp 234—237 °C. The combined filtrates were concentrated to dryness *in vacuo*. A solution of the residue in acetone was allowed to stand at room temperature and a separated solid (1.5 g, mp 196—198 °C) was filtered off. The filtrate was concentrated *in vacuo* and converted to a free basic oil (5.8 g) in the usual manner. Chromatography of this oil on a silica gel (170 g) column using AcOEt–MeOH (10 : 1) as an eluent yielded a pale yellowish oil (3.0 g). This oil was converted to the hydrochloride (crude solid) in the usual manner. The solid was recrystallized from AcOEt–MeOH to give Xb·HCl as colorless plates (1.3 g, 5.5%), mp 200—202 °C.

**5-Benzyl-3-methyl-2-cyclohexen-1-one (IIc)**——According to the literature,[13] the preparation of 3-methyl-5-phenyl-2-cyclohexen-1-one, 40% phenylacetoaldehyde solution in diethyl phthalate (25 g, 83 mmol) was worked up to give IIc as a pale yellowish oil (13 g, 78%). IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 1670 (C=O). NMR ($CDCl_3$) $\delta$: 1.90 (3H, s, $C_3$–$CH_3$), 5.88 (1H, s, $C_2$–H). *Anal.* Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.83; H, 8.21.

**3-*c*-Benzyl-2-*t*- and *c*-dimethylaminomethyl-5-*c*-methyl-1-*r*-cyclohexanols (Xc and XIc)**——A mixture of IIc (18.5 g, 93 mmol), $HN(CH_3)_2 \cdot HCl$ (7.6 g), paraformaldehyde (4.1 g) and EtOH (26 ml) was worked up as described for the preparation of Xa to give a crude basic oil (12.5 g). The oil was purified as the oxalate, as described for the preparation of Va to give a yellowish oil (8.3 g). This oil was hydrogenated as described above to give a yellowish oil (7.6 g), IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 1710 (C=O), which was reduced with $LiAlH_4$ (1.0 g) in dry ether (40 ml) to give a yellowish oil (7.2 g). Chromatography of this oil on an alumina (105 g) column using $C_6H_6$ as an eluent yielded a mixture of Xc and XIc as a yellowish oil (4.6 g). The oil was converted to crude crystals of hydrochloride in the usual manner, and these were recrystallized from AcOEt–MeOH to give XIc·HCl as colorless needles (0.2 g, 0.8%), mp 265—268 °C (dec.). The combined filtrates were concentrated *in vacuo* and converted to a free basic oil (4.4 g). Chromatography of this oil on an alumina (105 g) column using $C_6H_6$–hexane as an eluent yielded an Xc-rich oil, which was again chromatographed on a silica gel (40 g) column using AcOEt–$C_6H_6$ (10 : 1) to give Xc as a pale yellowish oil (1.4 g). The oil was converted to a solid hydrochloride, which was recrystallized from AcOEt–MeOH to give Xc·HCl as colorless needles (1.3 g, 4.7%), mp 198—200 °C.

***N*,*N*-Dimethyl-(6-benzyl-1-cyclohexenyl)methylamine (XIIIb)**——$SOCl_2$ (0.32 g) was added to a solution of XIb·HCl (0.38 g, 1.3 mmol) in $CH_2Cl_2$ (5 ml) and the mixture was refluxed for 3 h. The solvent was evaporated off, and the residue was recrystallized from AcOEt–MeOH to give XIIIb·HCl as colorless plates (0.25 g, 72%), mp 215—217 °C.

**1,6-*trans*-*N*,*N*-Dimethyl-(6-benzyl-2-cyclohexenyl)methylamine (Ib)**——$SOCl_2$ (1.5 g) was added to a solution of

Xb·HCl (1.2 g, 4.2 mmol) in $CH_2Cl_2$ (13 ml) and the mixture was refluxed for 2 h. The solvent was evaporated off, and $H_2O$ was added to the residue. 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 yellowish oil (1.1 g). The oil was chromatographed on an alumina (20 g) column using $C_6H_6$–hexane (1 : 2) as an eluent to yield *N*,*N*-dimethyl-(6-*t*-benzyl-2-*c*-chloro-1-*r*-cyclohexyl)methylamine (XIIb) as a pale yellowish oil (1.0 g, 90%) (Table I). A mixture of XIIb (0.90 g, 3.4 mmol), NaI (0.64 g) and 10% alcoholic KOH (12 ml) was refluxed for 21 h with stirring. $H_2O$ was added to the reaction mixture and the separated oil was extracted with ether. The extract was washed with $H_2O$, dried over $K_2CO_3$, and concentrated *in vacuo* to give a yellowish oil (0.80 g). Then 1 N HCl (5 ml) was added to a solution of this oil in EtOH (10 ml) and the solution was concentrated to dryness *in vacuo*. The residue was recrystallized from AcOEt–MeOH to give XIIIb·HCl as colorless plates (0.19 g, 21%), mp 215—217 °C. The filtrate was concentrated to dryness *in vacuo* and AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from acetone–AcOEt to give Ib·HCl as colorless needles (0.36 g, 40%), mp 120—122 °C.

**1,6-*trans*-*N*,*N*-Dimethyl-(6-phenyl-2-cyclohexenyl)methylamine (Ia)**——$SOCl_2$ (0.4 g) was added to a solution of Xa (4.6 g, 20 mmol) in $CH_2Cl_2$ (20 ml) and the mixture was refluxed for 3 h. The reaction mixture was treated as described for the preparation of Ib to give a yellowish oil, which was chromatographed on an alumina (50 g) column using $C_6H_6$–hexane (1 : 2) as an eluent to yield *N*,*N*-dimethyl-(2-*c*-chloro-6-*t*-phenyl-1-*r*-cyclohexyl)methylamine (XIIa) as a pale yellowish oil (2.8 g, 57%) (Table I). A mixture of XIIa (2.8 g, 11 mmol), NaI (0.3 g), and 10% alcoholic KOH (20 ml) was refluxed for 13 h and treated as described above to give a pale yellowish oil (2.3 g). Chromatography of this oil on a silica gel (30 g) column using $C_6H_6$–AcOEt (1 : 1) as an eluent yielded Ia as a pale yellowish oil (1.2 g). Ia was converted in the usual manner to crystals of Ia·HCl, which were recrystallized from AcOEt–MeOH to give colorless needles (0.80 g, 29%), mp 189—191 °C.

***N*,*N*-Dimethyl-(6-*t*-benzyl-4-*t*-methyl-2-cyclohexen-1-*r*-yl)methylamine (Ic) and 4,6-*cis*-*N*,*N*-Dimethyl-(6-benzyl-4-methyl-1-cyclohexenyl)methylamine (XIIIc)**——$SOCl_2$ (1.3 g) was added to a solution of Xc·HCl (0.795 g, 2.66 mmol) in $CH_2Cl_2$ (12 ml) and the mixture was refluxed for 2.5 h and treated as described for the preparation of Ib to give *N*,*N*-dimethyl-(6-*t*-benzyl-2-*c*-chloro-4-*t*-methyl-1-*r*-cyclohexyl)methylamine (XIIc) as a yellowish oil (0.8 g). NMR ($CCl_4$) $\delta$: 0.78 (3H, d, $J=6$ Hz, $C_4$–$CH_3$), 2.20 (6H, s, $N(CH_3)_2$), 4.60 (1H, m, $C_2$–H), 6.9—7.3 (5H, m, $C_6H_5$). A mixture of XIIc (0.8 g), NaI (0.4 g), and 10% alcoholic KOH (9 ml) was refluxed for 32 h and treated as described above to give a mixture of Ic and XIIIc as a yellowish oil (0.8 g). Conc. HCl (0.3 g) was added to a solution of this oil in EtOH (20 ml) and the mixture was concentrated to dryness *in vacuo*. The resulting residue was recrystallized from MeOH–acetone to give XIIIc·HCl as colorless needles (0.175 g, 24%), mp 236—239 °C (dec.). The filtrate was concentrated to dryness *in vacuo* and AcOEt was added to the resulting residue. A hot solution of the precipitated solid collected by filtration in acetone was allowed to stand at room temperature to give additional XIIIc·HCl (84 mg, 11%). The filtrate was concentrated to dryness *in vacuo* and the residue was recrystallized from acetone to give Ic·HCl as colorless needles (0.339 g, 44%), mp 141—143 °C.

***N*,*N*-Dimethyl-(6-*c*-benzyl-2-*t*-chloro-4-*c*-methyl-1-*r*-cyclohexyl)methylamine (XIVc)**——A solution of XIc·HCl (0.23 g, 0.77 mmol) and $SOCl_2$ (0.12 ml) in $CH_2Cl_2$ (10 ml) was refluxed for 5 h and treated as described for the preparation of Ib to give a yellowish oil (0.21 g). Chromatography of this oil on an alumina (5 g) column using hexane as an eluent yielded a mixture of XIIIc and XIVc as an oil (0.147 g). Then 1 N HCl (1 ml) was added to a solution of this oil and the mixture was concentrated to dryness *in vacuo*. The resulting residue was recrystallized twice from acetone to give XIIIc·HCl (59 mg, 27%), mp 236—239 °C (dec.). The combined filtrates were concentrated to dryness *in vacuo* and the residue was recrystallized twice from acetone to give XIVc·HCl as colorless needles (61 mg, 25%), mp 204—206 °C.

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## References and Notes

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