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Anticholinergic Agents.[1] Synthesis of 4-Diphenylmethylene-1,1,2,3-tetramethylpyrrolidinium Iodide

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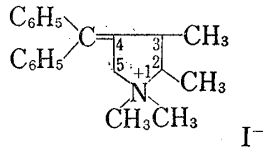
In order to examine the structure-activity relationship, *trans*- and *cis*-4-diphenylmethylene-1,1,2,3-tetramethylpyrrolidinium iodides (**1a, b**) were synthesized *via trans*-(**8a**) and *cis*-α,α-diphenyl-1,2,3-trimethyl-4-pyrrolidinemethanol (**8b**). These two intermediates were found to be derived readily from ethyl α-cyano-β-methyllevulinate. Although dehydration of **8a** by refluxing with sodium acetate in acetic anhydride resulted in the ring-opening to form N-methyl-N-(4,4-diphenyl-1,2-dimethyl-3-butenyl)acetamide, the treatment of **8a** and **8b** with 20% sulfuric acid in acetic acid gave smoothly *trans*- and *cis*-1,2,3-trimethyl-4-diphenylmethylenepyrrolidine (**10a, b**), respectively. Anticholinergic activity of the methiodides (**1a, b**) were tested.

In continuation of the preceding work,[1] synthesis of 4-diphenylmethylene-1,1,2,3-tetramethylpyrrolidinium iodide (**1**), which is expected to show an anticholinergic activity, is reported in this paper. Reductive ring-closure of ethyl α-cyano-β-methyllevulinate in the presence of Raney nickel produced ethyl 2,3-dimethyl-4-pyrrolidinecarboxylate[3] (**2**) and ethyl 2,3-dimethyl-4-pyrrolecarboxylate[3] (**3**) in 1:1 ratio. Ethoxycarbonylation of **2** afforded N-ethoxycarbonyl derivative (**6**). On the other hand, catalytic reduction of diethyl 2,3-dimethyl-1,4-pyrroledicarboxylate (**4**) obtained from **3** afforded diethyl 2,3-dimethyl-1,4-pyrrolidinedicarboxylate (**5**). In this reduction, formation of 2,3-*cis*-dimethyl compound is expected from the *cis* addition of hydrogen. In the gas–chromatographic spectrum (Shimadzu 4B-PF, column temperature 140°, N_2: 48 ml/min), retention time of **5** and **6** was 4.0 and 2.7 min, respectively. Attempted epimerization of **5** and **6** by heating in the presence of sodium ethoxide did not produce any new peak in the case of **6** but the mother peak of 4.0 min decreased accompanied by the appearance of a new peak at 3.5 min in the case of **5** but 2.7 min peak corresponding to **6** was not produced. These facts suggested that the configuration between C(2)–CH_3 and C(3)–CH_3 is *cis* in **5** and *trans* in **6** and that the configuration between C(3)–CH_3 and C(4)–COOEt in **5** is unstable *cis* form, while it is stable *trans* in **6**. Compound **5** was assumed to be in the all-*cis* form and **6**, in the all-*trans* form.



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The Grignard reaction of **7**, an N-methyl derivative of **2**, with 2 mol of phenylmagnesium bromide resulted in the formation of α,α-diphenyl-1,2,3-trimethyl-4-pyrrolidinemethanol (**8a**). In the infrared (IR) spectrum of **8a**, a weak but sharp absorption appeared at 3800 cm^{-1} (free OH) and another strong but broad absorption was present at 3300 cm^{-1} (N···H–O), whose intensity ratio was not altered by change of the concentration. From these facts, hydrogen bonding was assumed to be formed between the nitrogen lone-pair and hydroxyl group. Dehydration of **8a** by various methods was unsuccessful; the starting material was recovered unchanged when **8a** was allowed to stand overnight in ethanol saturated with dry hydrogen chlo-

1) This constitutes Part VIII of a series entitled "Synthesis of Pyrrolidine Derivatives with Pharmacological Activities." Part VII: S. Ohki, N. Ozawa, Y. Yabe, and H. Matsuda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1362 (1976).
2) Location: *1432-1, Horinouchi Hachioji, Tokyo 192-03, Japan.*
3) F. Korte and K. Trautner, *Chem. Ber.*, **95**, 307 (1962).

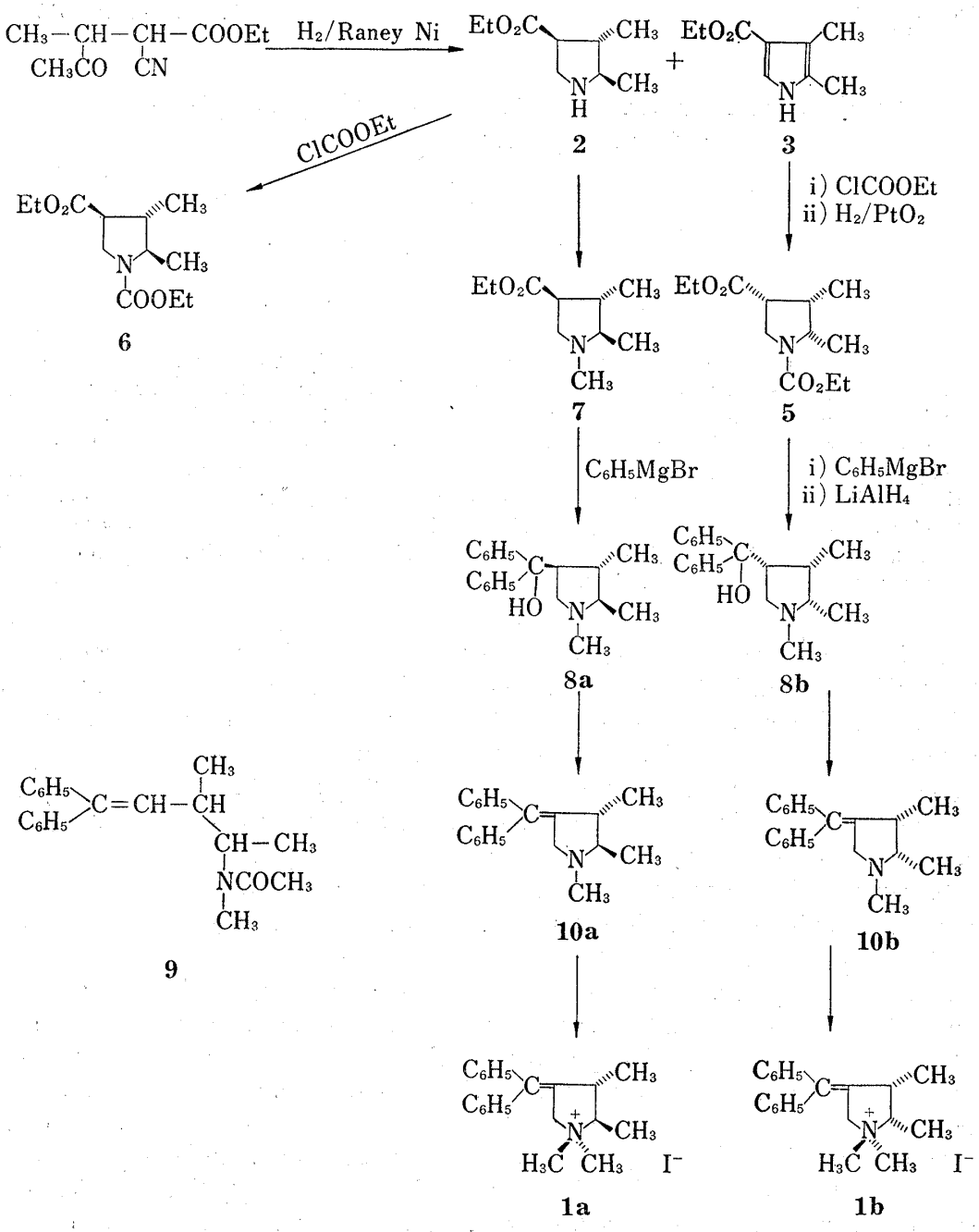

Chart 1

ride in the same way as in the successful dehydration of 1,2-dimethyl-α,α-diphenyl-4-pyrrolidinemethanol[1] or reacted with phosphoryl chloride in pyridine, or with dicyclohexylcarbodiimide in ether or tetrahydrofuran. A conc. sulfuric acid treatment yielded only a resinous product. Heating of **8a** with acetic anhydride in the presence of potassium acetate produced a new product. Its ultraviolet (UV) spectrum showed the absorption maximum at 248 nm which proved the presence of diphenylmethylene group. In the nuclear magnetic resonance (NMR) spectrum one proton singlet presumably due to $((C_6H_5)_2C{=}C\underline{H}{-})$ appeared at 5.95 ppm. In its IR spectrum carbonyl absorption appeared at 1650 cm^{-1} and in its mass spectrum, the parent peak appeared at *m/e* 307. These data suggested that the pyrrolidine ring was opened to produce **9**, whose reaction route is assumed as shown in Chart 2.

Finally, refluxing of **8a** in 20% sulfuric acid and half a volume (ml) of acetic acid for 6 to 8 hr successfully produced the desired 1-methyl-2,3-*trans*-dimethyl-4-diphenylmethylenepyrrolidine (**10a**). Its methiodide (**1a**) was obtained as crystals of mp 232—235° (decomp.).

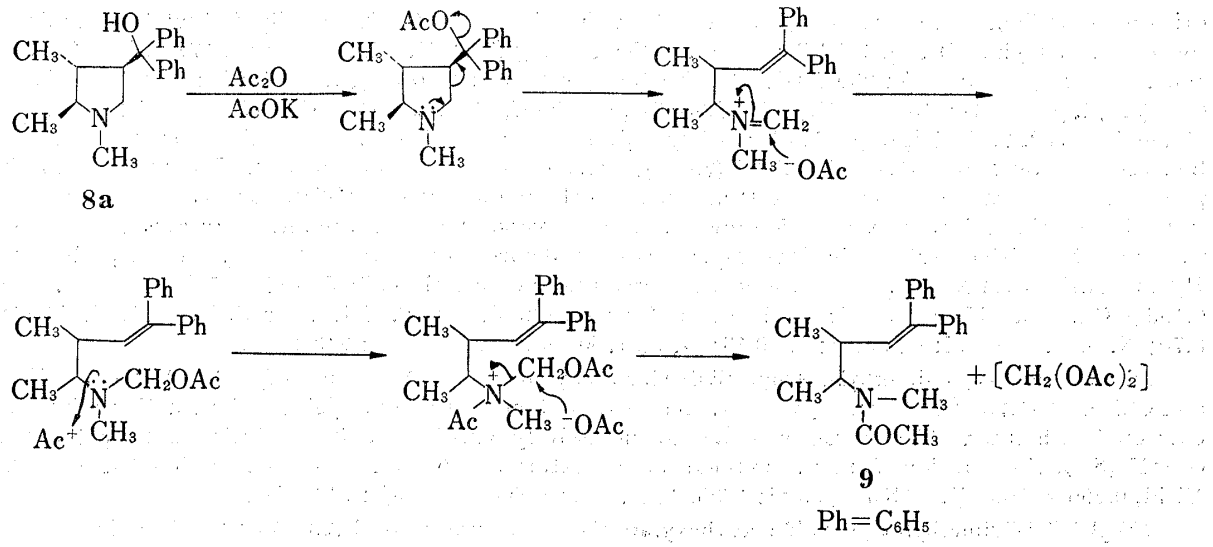

Chart 2

Similarly, reaction of **5** with phenylmagnesium bromide afforded the diphenylmethanol derivative, whose reduction with lithium aluminum hydride gave α,α-diphenyl-1,2,3-trimethylpyrrolidinemethanol (**8b**). Dehydration of **8b** under the same conditions used for **8a** resulted in the formation of 1-methyl-2,3-*cis*-dimethyl-4-diphenylmethylenepyrrolidine (**10b**), whose structure was supported by 248 nm absorption in its UV spectrum. The reaction of **10b** with methyl iodide afforded the corresponding methiodide (**1b**), needles, mp 274—277°. Stereostructure of **1b** was assigned to this 2,3-*cis*-dimethyl derivative considering the route of its formation and by comparing **5** with **6** on the gas- and thin-layer chromatography (TLC).

Anticholinergic activity expressed by the relative potency was 0.13 for **1a** and 0.27 for **1b**, respectively, when the potency of atropine was defined as 1.00. It is interesting that the difference of stereostructure at C(2)–CH_3 and C(3)–CH_3 resulted in about 2-fold efficacy of anticholinergic activity in **1b** over that of **1a**. Compared with 3-(diphenylmethylene)-1,1-diethyl-2-methylpyrrolidinium bromide (Prifinium Bromide[1,4]) (0.50) and 3-diphenylmethylene-1,1,2-trimethylpyrrolidinium iodide[4] (0.25), **1a** and **1b** showed a fairly strong efficacy.

Experimental

All melting points were determined on a Yanagimoto micro melting apparatus and uncorrected. Boiling points were also uncorrected. IR spectra were determined on a Hitachi EPI-G2 spectrometer in liquid films unless otherwise noted. UV spectra were measured in EtOH solutions with a Hitachi EPS-II spectrometer. NMR spectra were recorded at 100 MHz with JEOL Model JNM-MH-100 or JEOL Model PS-100. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were determined with a Hitachi RMU-7L spectrometer with the direct sample inlet system (ionizing potential at 75 eV).

Ethyl 2,3-Dimethyl-4-pyrrolidinecarboxylate (2) and Ethyl 2,3-Dimethyl-4-pyrrolecarboxylate (3)——Ethyl α-cyano-β-methyllevulinate[3] (12 g) was hydrogenated over Raney Ni (2.0 g) in EtOH (50 ml) under 150 atm of H_2 at 150° for 2 hr. The reaction mixture was filtered and EtOH was evaporated from the filtrate under reduced pressure to give an oil. **2**, bp 84—86° (6 mmHg) (reported[3] bp 90—92.5° (8 mmHg)). IR ν_{max}^{film} cm^{-1}: 3300 (NH), 1730 (CO). Yield, 4.43 g (39.4%). **3**, bp 114—119° (0.02 mmHg), (reported[3] bp 100—115° (0.01 mmHg)), mp, 110—111° (from benzene), (reported[3,5] mp 110—111°). Yield, 4.05 g (37.2%). IR ν_{max}^{film} cm^{-1}: 3275 (NH), 1675 (CO).

Diethyl *cis*-2,3-Dimethyl-1,4-pyrrolidinedicarboxylate (5)——A mixture of **3** (2.15 g) and metallic K (0.52 g) in xylene (15 ml) was refluxed for 24 hr. After being cooled, ClCOOEt (1.38 g) was added dropwise to the reaction mixture and the solution was stirred for 2 hr and evaporated under reduced pressure. The residue was extracted with ether and the ether layer was washed successively with dil. HCl and H_2O, and

4) S. Ohki, M. Yoshino, and F. Hamaguchi, *Chem. Pharm. Bull.* (Tokyo), **16**, 320 (1968).
5) O. Piloty and K. Wilke, *Chem. Ber.*, **45**, 2588 (1912).

dried over Na_2SO_4. Ether was evaporated under reduced pressure to give an oily diethyl 2,3-dimethyl-1,4-pyrroledicarboxylate (**4**), bp 127° (5 mmHg). Yield, 1.55 g (50.4%). IR ν_{max}^{film} cm^{-1}: 1775 (CO), 1720 (CO), 1600. Mass Spectrum *m/e*: 239 (M^+). NMR ($CDCl_3$) δ (ppm): 0.80 (3H, t, J=7.5 Hz, C(4)-$COOCH_2C\underline{H}_3$), 0.85 (3H, t, J=7.5 Hz, N-$COOCH_2C\underline{H}_3$), 1.30 (3H, s, C(3)-$C\underline{H}_3$), 1.42 (3H, s, C(2)-$C\underline{H}_3$), 2.55 (2H, q, J=7.5 Hz, -$C\underline{H}_2$-CH_3), 2.65 (2H, q, J=7.5 Hz, -$C\underline{H}_2CH_3$), 4.70 (1H, s, C(5)-$\underline{H}$). This oily substance (0.25 g) was hydrogenated over PtO_2 (0.1 g) in EtOH (20 ml), which contained 2 drops of conc. HCl, under atmospheric pressure. The hydrogen up-take was 94 ml (theoretical amount: 69.3 ml (18°)). The catalyst was removed from the reaction mixture by filtration and EtOH was evaporated from the filtrate *in vacuo*. The residue was extracted with ether and the ether layer was washed successively with saturated $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. Ether was evaporated to leave a colorless oily **5**, bp 76—78° (5 mmHg). Yield, 0.133 g (52.3%). IR ν_{max}^{film} cm^{-1}: 1730 (ester), 1700 (urethan). *Anal.* Calcd. for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.93; H, 9.13; N, 5.81. Mass Spectrum *m/e*: 243 (M^+).

Diethyl *trans*-2,3-Dimethyl-1,4-pyrrolidinedicarboxylate (6)——A mixture of **2** (1.0 g), Na_2CO_3 (1.22 g), and ClCOOEt (1.26 g) in 10 ml H_2O was stirred at room temperature overnight. The reaction mixture was extracted with ether. The extract was washed successively with 5% $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. Evaporation of ether from the reaction mixture gave **6** as a colorless oil, bp 130—132° (4 mmHg). Yield, 0.796 g (56.0%). IR ν_{max}^{film} cm^{-1}: 1735, 1700. Mass Spectrum *m/e*: 243 (M^+).

Ethyl 1,2,3-Trimethyl-4-pyrrolidinecarboxylate (7)——A mixture of **2** (2.0 g) and 37% HCHO (3 ml) in HCOOH (3.5 g) was heated on a steam bath till evolution of CO_2 ceased in about 6 hr. After being cooled, the reaction mixture was made alkaline with K_2CO_3, extracted with ether, and the ether layer was dried over Na_2SO_4. Evaporation of ether gave **7** as an oil, bp 69—72° (9 mmHg). Yield, 0.75 g (34.7%). IR ν_{max}^{film} cm^{-1}: 2770 (N-CH_3), 1735 (ester). Mass Spectrum *m/e*: 185 (M^+). Picrate, yellow needles from EtOH, mp 105—106°. *Anal.* Calcd. for $C_{10}H_{19}O_2N \cdot C_6H_3O_7N_3$: C, 46.37; H, 5.35; N, 13.52. Found: C, 46.72; H, 5.51; N, 13.53.

***trans*-α,α-Diphenyl-1,2,3-trimethyl-4-pyrrolidinemethanol (8a)**——To the Grignard reagent (prepared from Mg (0.3 g) and bromobenzene (2.0 g) in anhyd. ether (20 ml)), **7** (0.78 g) was added dropwise and the solution was stirred for 30 min at room temperature and then refluxed for 2 hr. After being cooled, ether was evaporated *in vacuo*, and 5% HCl was added to the residue under ice-cooling. The acidic solution was made alkaline with solid K_2CO_3, and it was extracted with ether. The ether extract was dried over Na_2SO_4, and evaporated *in vacuo* to give colorless powder, which was recrystallized from (iso-Pr)$_2$O to give **8a** as colorless needles, mp 113—115°. Yield, 0.563 g (57.0%). Calcd. for $C_{20}H_{25}ON$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.21; H, 8.36; N, 4.62. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3800 (free OH), 3300 (N····H-O). The ratio of intensity of 3800 and 3300 cm^{-1} was not changed although the concentration of the sample was altered as following: 5 mg/0.5 ml, 10 mg/0.5 ml, 20 mg/0.5 ml. NMR ($CDCl_3$) δ (ppm): 0.83 (3H, d, J=7 Hz, C(3)-$C\underline{H}_3$), 1.07 (3H, d, J=7 Hz, C(2)-$C\underline{H}_3$), 1.7 (2H, m, C(2)-$\underline{H}$ and C(3)-$\underline{H}$), 2.14 (3H, s, N-CH_3), 2.42, 2.88 (1H each, d, J=15 Hz, C(5)-$\underline{H}_2$).

N-Methyl-N-(4,4-diphenyl-1,2-dimethyl-3-butenyl)acetamide (9)——A mixture of **8a** (0.1 g) and AcONa (0.05 g) in Ac_2O (5 ml) was refluxed for 2 hr, and the reaction mixture was evaporated under reduced pressure. The residue was dissolved in ether (10 ml) and the solution was washed with 5% $NaHCO_3$ and H_2O, and dried over Na_2SO_4. Evaporation of ether and distillation of the residual oil gave **9** as a colorless oil, bp 108—109° (0.1 mmHg). Yield, 0.032 g (34%). IR ν_{max}^{film} cm^{-1}: 1650 (N-CO), 747, 695. UV λ_{max}^{EtOH} nm: 248. Mass Spectrum *m/e*: 307 (M^+). NMR ($CDCl_3$) δ (ppm): 1.05 (3H, d, J=7.5 Hz, C(1)-$C\underline{H}_3$), 1.10 (3H, d, J=7.5 Hz, C(2)-$C\underline{H}_3$), 1.35 (1H, m, C(2)-$\underline{H}$), 1.40 (1H, m, C(2)-$\underline{H}$), 2.26 (1H, m, C(1)-$\underline{H}$), 2.30 (3H, s, N-$COC\underline{H}_3$), 2.80 (3H, s, N-$C\underline{H}_3$), 5.95 (1H, s, =CH), 7.2—7.4 (10H, m, $(C_6\underline{H}_5)_2C$=).

***trans*-1,2,3-Trimethyl-4-diphenylmethylenepyrrolidine (10a) and *trans*-1,1,2,3-Tetramethylpyrrolidinium Iodide (1a)**——A mixture of **8a** (0.5 g), AcOH (8.3 ml), and 20% H_2SO_4 (17 ml) was refluxed for 7 hr. After being cooled, the reaction mixture was made alkaline with solid K_2CO_3 under ice-cooling, extracted with ether, and the ether layer was extracted with 5% HCl. The acidic layer was washed with ether, made alkaline with K_2CO_3, and extracted with ether. The extract was dried over Na_2SO_4 and evaporated. The residue was distilled to give **10a** as an oil, bp 108—111° (2 mmHg). Yield, 0.371 g (79.0%). IR ν_{max}^{film} cm^{-1}: 2770 (N-CH_3), 1600, 1500, 760, 703. NMR ($CDCl_3$) δ (ppm): 0.64 (3H, d, J=7.5 Hz, C(3)-$C\underline{H}_3$), 1.15 (3H, d, J=7.5 Hz, C(2)-$C\underline{H}_3$), 1.85 (1H, m, C(2)-$\underline{H}$), 2.25 (3H, s, N-$C\underline{H}_3$), 2.65 (1H, m, C(3)-$\underline{H}$), 3.08, 3.48 (1H each, d, J=15 Hz, C(5)-$\underline{H}_2$), 7.00—7.40 (10H, m, $(C_6\underline{H}_5)_2C$-). UV λ_{max}^{EtOH} nm: 250. A solution of **10a** (0.37 g) and MeI (0.5 ml) in anhyd. benzene (1 ml) was refluxed on a steam bath for 10 min to give a colorless precipitate, which was collected on a suction filter. Recrystallization from acetone gave **1a**, as colorless needles, mp 232—235° (decomp.). Yield, 0.484 g (92%). IR ν_{max}^{KBr} cm^{-1}: 765, 700. UV λ_{max}^{EtOH} nm: 250. *Anal.* Calcd. for $C_{21}H_{26}NI$: C, 60.15; H, 6.25; N, 3.34. Found: C, 60.07; H, 6.19; N, 3.19. NMR ($CDCl_3$) δ (ppm): 0.95 (3H, d, J=7.5 Hz, C(3)-$C\underline{H}_3$), 1.50 (3H, d, J=7.5 Hz, C(2)-$C\underline{H}_3$), 3.00, 3.50 (3H each, s, $\overset{+}{N}(CH_3)_2$), 3.20 (1H, m, C(3)-$\underline{H}$), 4.30 (1H, m, C(2)-$\underline{H}$), 3.96, 5.62 (1H each, d, J=13 Hz, C(5)-$\underline{H}_2$), 7.1—7.55 (10H, m, $(C_6H_5)_2C$).

***cis*-α,α-Diphenyl-1,2,3-trimethylpyrrolidinemethanol (8b)**——A solution of **5** (1.20 g, 0.0049 mol) in anhyd. ether (10 ml) was added to a solution of the Grignard reagent (prepared from Mg (0.48 g, 0.02 mol) in

anhyd. ether (10 ml) and bromobenzene (3.20 g, 0.02 mol)) and the reaction mixture was stirred overnight at room temperature. The same work-up as for **8a** gave a crystalline mass. Recrystallization from (iso-Pr)$_2$O gave a hydroxy compound as needles, mp 166—168°. *Anal.* Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.32; H, 7.79; N, 3.75. $LiAlH_4$ (0.5 g) was added in small portions to a solution of this substance (0.214 g) in tetrahydrofuran (THF) (10 ml) under ice-cooling and the reaction mixture was stirred overnight and refluxed for 2 hr. THF was evaporated under reduced pressure and the residue was washed with 5% HCl. The acidic layer was filtered and the filtrate was made alkaline with solid K_2CO_3 and extracted with ether. The extract was dried over Na_2SO_4 and concentrated to dryness. The residual crystalline mass was applied to a column of Al_2O_3 (10 g) (Grade II—III (Merck)). Elution of the column with benzene: MeOH (1: 1, v/v) and recrystallization from $CHCl_3$ gave **8b**, mp 88—90°. Yield, 0.142 g (80.2%). *Anal.* Calcd. for $C_{20}H_{25}ON$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.54; H, 8.75; N, 4.39. Mass Spectrum *m/e*: 295 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2800 (N-CH_3), 749, 710. NMR ($CDCl_3$) δ (ppm): 0.60 (3H, d, J=7.5 Hz, C(3)-C$\underline{H}_3$), 1.05 (3H, d, J=7.5 Hz, C(2)-C$\underline{H}_3$), 2.20 (3H, s, N-C$\underline{H}_3$), 2.2—2.99 (5H, m, C(2)-$\underline{H}$, C(3)-$\underline{H}$, C(4)-$\underline{H}$, and C(5)-$\underline{H}_2$), 6.15 (1H, broad s, O$\underline{H}$), 7.0—7.40, 7.50—7.70 (10H, m, $(C_6\underline{H}_5)_2C$).

***cis*-1,2,3-Trimethyl-4-diphenylmethylenepyrrolidine (10b) and *cis*-1,1,2,3-Tetramethyl-4-diphenylmethylenepyrrolidinium Iodide (1b)**——A solution of **8b** (141 mg) and 20% H_2SO_4 (6 ml) in AcOH (3 ml) was refluxed for 6 hr. The same work-up as above gave **10b** as a colorless oil, bp 114—115° (2 mmHg). Yield, 0.098 g (63%). IR ν_{max}^{film} cm^{-1}: 2780 (N-CH_3), 1600, 760, 705. Mass Spectrum *m/e*: 277 (M^+). UV λ_{max}^{EtOH} nm: 248. Methiodide (**1b**), mp 274—277° (from acetone: MeOH, 1: 1, v/v). Yield, 116 mg (100%). *Anal.* Calcd. for $C_{21}H_{26}NI$: C, 60.15; H, 6.25; N, 3.34. Found: C, 60.32; H, 6.32; N, 2.94. IR ν_{max}^{KBr} cm^{-1}: 1595, 775, 765, 740, 710, 705. NMR (CD_3OD) δ (ppm): 0.85 (3H, d, J=7.5 Hz, C(3)-C$\underline{H}_3$), 1.45 (3H, d, J=7.5 Hz, C(2)-C$\underline{H}_3$), 3.10, 3.20 (3H each, s, $\overset{+}{N}(C\underline{H}_3)_2$), 3.60—4.20 (2H, m, C(2)-$\underline{H}$ and C(3)-$\underline{H}$), 4.10, 4.62 (1H each, d, J=14.0 Hz, C(5)-$\underline{H}_2$), 7.15—7.40 (10H, m, $(C_6\underline{H}_5)_2C$-).

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