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Synthesis of Pyrrolidine Derivatives with Pharmacological Activity. XII.[1] Synthesis and Anticholinergic Activity of 1,1-Dialkyl-3-diphenylmethylene-2,4-dimethylpyrrolidinium Halides

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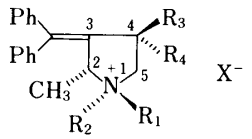
Several new 3-diphenylmethylene-2,4-dimethylpyrrolidinium derivatives (**2**—**6**), structurally related to 3-diphenylmethylene-1,1-diethyl-2-methylpyrrolidinium bromide (**1**) (Prifinium Bromide, an antispasmodic agent), were synthesized so as to examine the pharmacological effect of a methyl group at the 4-position of 3-diphenylmethylenepyrrolidinium salts. The stereochemistries of tertiary pyrrolidines (**10**—**20**) and quaternary pyrrolidinium salts (**2**—**6**) were confirmed on the basis of equilibrium reactions, Grignard reactions, and/or spectroscopic methods. The presence of a methyl group at the 4-position of 3-diphenylmethylenepyrrolidinium salts was found to reduce the anticholinergic activity.

Keywords——pyrrolidine; *N*-alkylation; Grignard reaction; equilibrium reaction; dehydration; 3-diphenylmethylene-2,4-dimethylpyrrolidine; anticholinergic activity; stereochemistry; structure–activity relationship

In the previous papers, we reported the synthesis and anticholinergic activities of 1,1-dialkyl-3-diphenylmethylenepyrrolidinium halides.[2a] Among these compounds, 3-diphenylmethylene-1,1-diethyl-2-methylpyrrolidinium bromide[2b] (Prifinium Bromide[2c]) (**1**) was found to be effective as a specific antispasmodic for spasms or hypermotility of the digestive and urinary tracts.[3,4] The intensity of the anticholinergic activity of these derivatives was found to depend greatly on the number, kind, position, and configuration of the alkyl groups substituted on the pyrrolidine ring.[2]



1: $R_1=R_2=Et$, $R_3=R_4=H$, $X=Br$
2: $R_1=R_2=Et$, $R_3=H$, $R_4=CH_3$, $X=I$
3: $R_1=Et$, $R_2=R_4=CH_3$, $R_3=H$, $X=I$
4: $R_2=Et$, $R_1=R_4=CH_3$, $R_3=H$, $X=I$
5: $R_1=R_2=R_4=CH_3$, $R_3=H$, $X=I$
6: $R_1=R_2=R_3=CH_3$, $R_4=H$, $X=I$

In this study, several new 3-diphenylmethylene-2,4-dimethylpyrrolidinium derivatives (**2**—**6**) were synthesized so as to examine the pharmacological effect of a methyl group at the 4-position of 3-diphenylmethylenepyrrolidinium salts.

Synthesis of 1,1-Dialkyl-3-diphenylmethylene-2,4-dimethylpyrrolidinium Iodides (2—6)

The Michael addition of ethyl acetoacetate to 1-nitro-1-propene afforded ethyl 2-acetyl-3-methyl-4-nitrobutyrate (**7**)[5] in high yield. Compound **7** was converted to ethyl 2,4-dimethylpyrrolidine-3-carboxylate (**8**) by reductive cyclization (H_2, 160 atm; Raney nickel). Compound **8** was assumed to be a mixture of stereoisomers on the basis of thin-layer chromatography (TLC) and spectral data. Hydrogenation of **7** at lower hydrogen pressure

(40 atm) resulted in the formation of the pyrroline (**9a** or **9b**) (major) and **8** (minor). Compound **9** was catalytically hydrogenated in the presence of platinum oxide to provide **8**. The Eschweiler–Clarke reaction of **8** gave a mixture of ethyl 1,2,4-trimethylpyrrolidine-3-carboxylates (**10** and **11** in the ratio of 1 : 3.6). Another possible stereoisomer (**12**) was expected but its formation could not be confirmed at this stage. Compound **10** was quantitatively epimerized to **11** by warming with sodium ethoxide. On the basis of this reaction, we assumed that **11** takes the most stable form in which all substituents on the pyrrolidine ring have the *trans*-form and **10** takes the comparatively unstable *cis*-form. This was concluded to be actually the case for the reasons stated later in this paper.

The Grignard reaction of the all-*trans* form (**11**) with phenylmagnesium bromide gave *t*-3-(1-hydroxy-1,1-diphenyl)methyl-1,*r*-2,*c*-4-trimethylpyrrolidine (**13**) in high yield. However, the all-*cis* form (**10**) did not readily undergo the Grignard reaction under the same conditions and only the ketone (**14**) was obtained in 33% yield with a 19% recovery of the starting material (**10**). The difficulty with which this reaction took place prompted us to consider that at least the 3-ethoxycarbonyl and 2-methyl (or 4-methyl) groups are *cis* in **10**.[6]

The stereoisomeric mixture of *N*-methyl derivatives, obtained by the Eschweiler–Clarke reaction of **8**, was, without purification, subjected to the Grignard reaction under the same conditions as mentioned above to afford **13** in 58% yield, the ketone (**14**) in 3.3% yield, and **15**, an epimeric isomer of **13**, in 6.5% yield. Apparently, **15** was derived from **12** which, though so far not isolated, must exist.

The infrared (IR) spectra of **13** and **15** showed the presence of intramolecular hydrogen bonding (N···H–O). In the nuclear magnetic resonance (NMR) spectra ($CDCl_3$), the signal for C_2–CH_3 in **13** appeared at 0.98 ppm (3H, d, $J=7$ Hz), while that in **15** was shielded to a higher magnetic field (0.71 ppm; 3H, d, $J=7.5$ Hz),[7] presumably by the anisotropic effect of the benzene ring at the 3-position of **15**. Thus, the configuration of C_3–C(OH)Ph_2 and C_2–CH_3 in **15** may possibly be *cis* and that in **13**, *trans*.[8] Allowing for the intramolecular hydrogen bonding of both compounds, we derived the stereostructure (A) for **13** and (B) for **15** as follows (Fig. 1). The above findings confirmed **13** and **15** to have the *cis*- and *trans*-2,4-

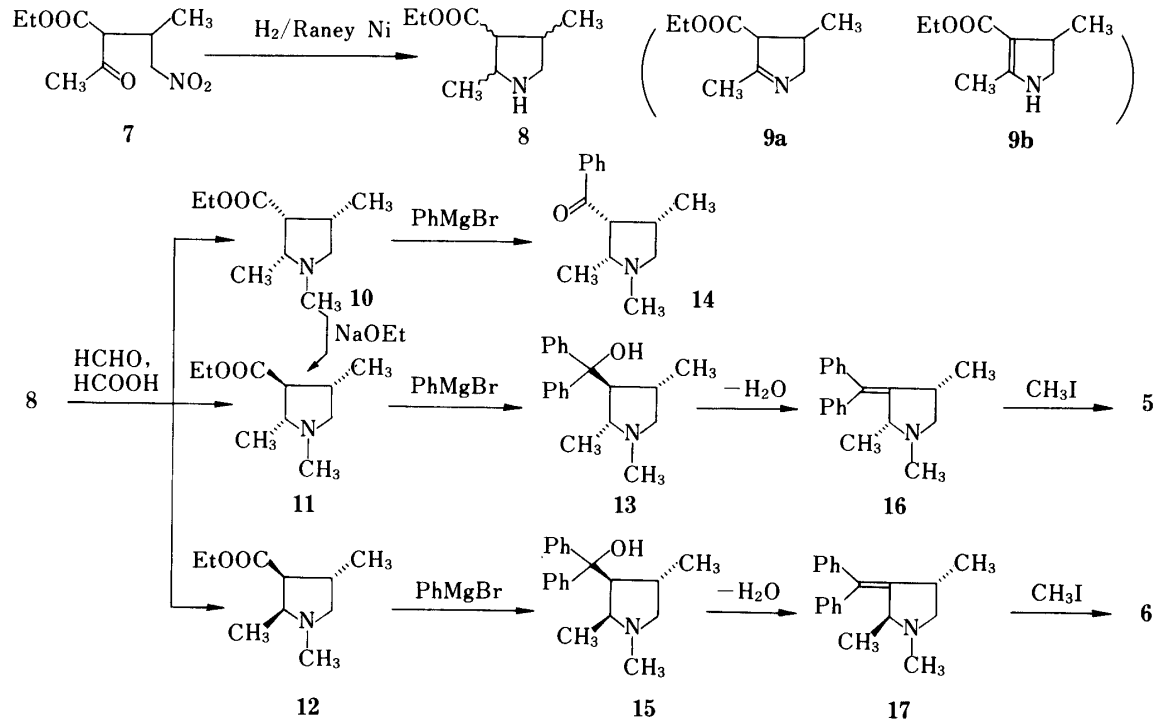
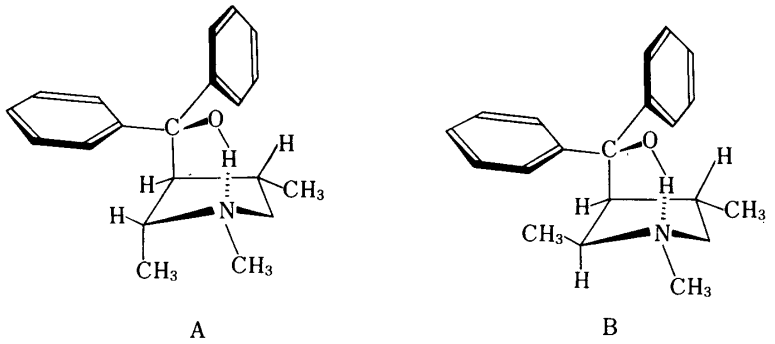


Chart 1



A B

Fig. 1

dimethyl groups, respectively, and the stereochemistry for **10**, **11**, and **12** to be that illustrated in Chart 1.

Dehydration of **13** and **15** under various conditions was carried out but was attended with considerable difficulty. Gentle refluxing of **13** and **15** in a mixture of 20% sulfuric acid and acetic acid (3:2, v/v) for 60 h produced *cis*- and *trans*-2,4-dimethyl-1-methyl-3-diphenylmethylenepyrrolidines (**16** and **17**), from which the methiodides **5** and **6** were derived, respectively.

Next, the synthesis of the 1,1-diethyl-(**2**) and 1-ethyl-1-methylpyrrolidinium salts (**3** and **4**) was carried out (Chart 2). *N*-Ethylation of **8** with ethyl bromide proceeded smoothly, using one molar equivalent of diisopropylamine as a base.[9] 1-Ethyl derivatives were obtained as a mixture of stereoisomers, and so their epimerization with sodium ethoxide in ethanol was carried out to afford only the 1-ethyl derivative (**18**) having the *trans* configuration similar to that of the corresponding 1-methyl derivative (**11**). The Grignard reaction of **18** with phenylmagnesium bromide afforded the diphenylmethanol (**19**), which was dehydrated to give 3-diphenylmethylene-1-ethyl-*cis*-2,4-dimethylpyrrolidine (**20**).

The methiodide (**4**) of **20** and the ethiodide (**3**) of **16** are diastereomers because of the epimeric *N*-ethyl-*N*-methylammonium bases, which were prepared taking into consideration their different pharmacological activities.[2b] McKenna *et al.*[10] reported that in the ^{1}H-NMR spectra of 1-alkyl-1,2-dimethylpyrrolidinium iodides, the N^+-CH_3 signal of the *trans*-1,2-dimethyl form appears at a lower magnetic field than that of the *cis*-1,2-dimethyl form. Thus, **3** is the *cis*-1,2-dimethyl isomer in which the N^+-CH_3 group (3.21 ppm) is axial, while **4** is the *trans* isomer in which the N^+-CH_3 group (3.36 ppm) is equatorial. This indicates that *N*-alkylation of tertiary bases (**16** and **20**) occurs at both equatorial sides. In the previous paper,[11] the *N*-alkylation of 1-alkyl-5-methyl-3-diphenylmethylenepyrrolidines was found to

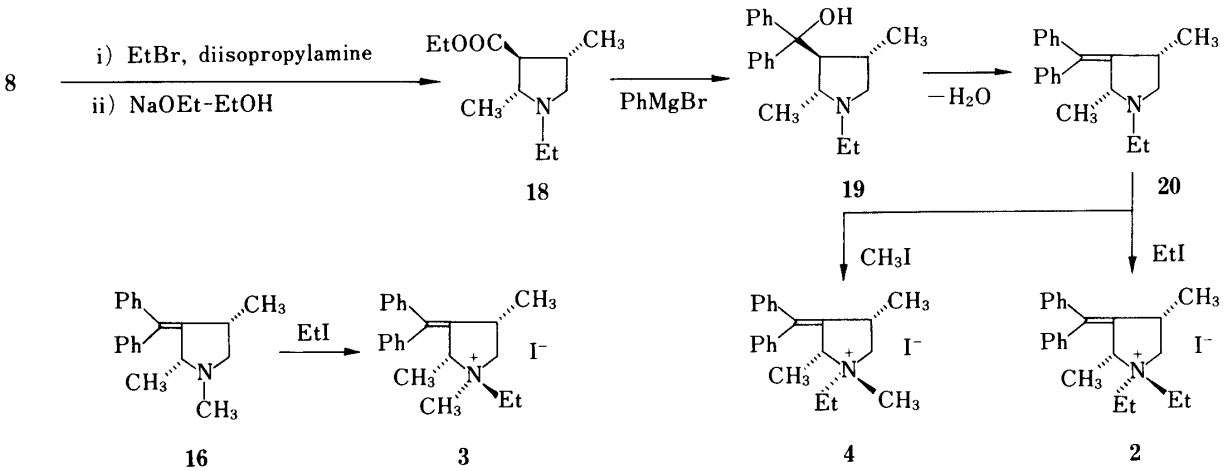


Chart 2

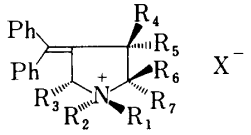
occur from the axial side according to the general tendency in quaternization, while the *N*-alkylation of 1-alkyl-3-diphenylmethylene-2-methylpyrrolidines occurred from the equatorial side. This difference seems to depend on the absence or presence of a methyl group at the 2-position of 1-alkyl-3-diphenylmethylenepyrrolidines.

In the ^{13}C-NMR spectra of **3** and **4** (see Experimental), the same chemical shift tendency as in the ^{1}H-NMR spectra was observed; that is, the N^{+}-$\underline{C}H_3$ signal (49.12 ppm) of **4** and the $\underline{C}H_2$ signal (59.11 ppm) of the *N*-ethyl moiety of **3**, both *trans* to C_2-CH_3, appeared at lower field than those (N^{+}-CH_3 of **3**, 45.22; $\underline{C}H_2$ of **4**, 55.50 ppm) *cis* to C_2-CH_3.

Anticholinergic Activities[12)]

The pharmacological activities in isolated guinea-pig ileum of the compounds (**2**—**6**) described in this paper, along with our previous results, are listed in Table I and compared with that of the reference standard, atropine. In general, the existence of a methyl group at the 4-position reduced the activity but a methyl group at the 2- or 5-position tended to increase it;

TABLE I. Anticholinergic Activity



Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	X	Relative potency (Atropine = 1)
1[2b,6)]	Et	Et	Me	H	H	H	H	Br	0.45
2	Et	Et	Me	H	Me	H	H	I	0.04
3	Et	Me	Me	H	Me	H	H	I	0.09
4	Me	Et	Me	H	Me	H	H	I	0.04
5	Me	Me	Me	H	Me	H	H	I	0.07
6	Me	Me	Me	Me	H	H	H	I	0.14
21	Me	Me	Me	H	H	H	Me	I	0.31
22	Me	Me	Me	H	H	Me	H	I	0.31
23[13)]	Me	Me	H	H	H	H	H	I	0.02
24[3)]	Et	Et	H	H	H	H	H	I	0.13
25[13)]	Me	Me	Me	H	H	H	H	I	0.25
26[2b)]	Et	Me	Me	H	H	H	H	I	0.25
27[2b)]	Me	Et	Me	H	H	H	H	I	1.95
28[13)]	Me	Me	Et	H	H	H	H	I	0.02
29[13)]	Me	Me	*n*-Pr	H	H	H	H	I	0.03
30[8)]	Me	Me	H	H	Me	H	H	I	0.01
31[8)]	Me	Me	H	H	H	H	Me	I	0.27
32[8)]	Me	Me	H	Me	H	H	Me	I	0.13
33[8)]	Me	Me	H	Me	H	Me	H	I	0.27
34[14)]	Me	Me	Et	H	H	H	Me	I	0.09
35[14)]	Me	Me	Et	H	H	Me	H	I	0.17
36[14)]	Me	Me	Me	Me or H		H	Me	I	1.49
37[14)]	Me	Me	Me	H or Me		Me	H	I	0.82
38[14)]	Et or Me		Me	H	H	H	Me	I	0.50
39[15)]	Me	Me	Me	Me	Me	H	H	I	0.19
40[11)]	Me	Et	H	H	H	H	Me	I	0.13
41[11)]	Et	Me	H	H	H	H	Me	I	0.05
42[11)]	Et	Et	H	H	H	H	Me	I	0.13
43[13)]	Me	Me	iso-Pr	H	H	H	H	I	0.03
44[13)]	Me	Me	*n*-Bu	H	H	H	H	I	0.005

this tendency was also observed in 2,4- and 2,5-dimethylpyrrolidinium salts. For example, **25** (2-Me) and **31** (5-Me) are more potent than **23** (2- and 5-H), but **30** (4-Me) is less effective than **23**. A comparison of **31** with **21** and **22**, **30** with **5** and **6**, and **40** and **41** with **38** shows the latter compounds to be more effective as a result of methyl group substitution at the 2-position of the former compounds. Similarly, on comparing **25** with **21** and **22**, **30** with **32** and **33**, and **28** with **34** and **35**, the latter compounds were found to be more effective than the former compounds as a result of methyl group substitution at the 5-position of the former compounds. Such substitution at the 4-position diminished the activity of the dimethyl compounds, as is evident from a comparison of **1** with **2**, **26** and **27** with **3** and **4**, **25** with **5** and **6**, and **31** with **32**. However, the above hypothesis does not seem to be applicable to some 2,4,5- and 2,4,4-trimethyl compounds, and increased efficacy was observed on comparing **21** with **36**, **22** with **37**, and **5** and **6** with **39** in spite of the presence of a methyl group at the 4-position.

Thus, methyl group substitution at ring carbons (2- and 5-position) adjacent to quaternary nitrogen may be concluded generally to increase the activity in mono- and dimethyl compounds, possibly as a result of changes in the stereochemical and electronic character of the ammonium cation head which functions as an antagonist. The detailed structure–activity relationship among this series of compounds still requires further study.

Experimental

All melting points were determined with micro-melting point apparatus (Yanagimoto) and are uncorrected. IR, ultraviolet (UV) (in EtOH), and mass spectra (MS) were measured on a Hitachi EPI-G3 spectrophotometer, a Hitachi 200-10 spectrophotometer, and a Hitachi RMU-7L mass spectrometer, respectively. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL JNM-PS-100 (100 MHz) and JEOL FT-100X spectrometers, respectively. Chemical shifts were recorded in ppm downfield from an internal standard [tetramethylsilane (TMS)]. The following abbreviations are used: s = singlet, d = doublet, t = triplet, l = quartet, m = multiplet br = broad. Chromatographic separations were performed on silica gel (Wako-gel C-200) columns. Gas-liquid chromatography (GLC) was performed on a Shimadzu GC-4BPF instrument with a hydrogen flame ionization detector (column, 1.5% SE-30 on Chromosorb W, 3 mm × 2 m; carrier gas, N_2). TLC was performed on pre-coated silica gel plates (Kieselgel 60 F_{254}, Merck) and the spots were detected under UV irradiation.

Ethyl 2-Acetyl-3-methyl-4-nitrobutyrate (7)——A modification of Grob's method[5] increased the yield (31%) to 85—95% as described below.

A solution of EtONa (prepared with Na 135 mg) in EtOH (20 ml) was added to a solution of ethyl acetoacetate (52 g, 0.4 mol) in dry Et_2O (120 ml). A solution of 1-nitro-1-propene (17.4 g, 0.2 mol) in dry Et_2O (40 ml) was added dropwise to the above solution with stirring at 0 °C in ice-salt bath over a period of 1.5 h. After being stirred at room temperature for 2 d, the reaction mixture was neutralized with a small quantity of AcOH and diluted with H_2O. The Et_2O layer was separated, washed with 5% $NaHCO_3$ and H_2O, and dried over $MgSO_4$. The solvent was evaporated off under reduced pressure to afford a yellow oil, which, on fractional distillation, afforded 22 g of ethyl acetoacetate and 39.2 g (90%) of **7** as a yellow oil: bp 140—142 °C (4 mmHg) [lit.[5] bp 145—148 °C (10 mmHg)]. IR (neat) 1745 (COOEt), 1720 (C=O), 1560, 1380 cm^{-1} (NO_2). GLC (column temp. 130 °C, N_2 50 ml/min), t_R = 6.5 min. *Anal.* Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.80; H, 7.03; N, 6.45.

Ethyl 2,4-Dimethyl-3-pyrrolidinecarboxylate (8)——A) A mixture of **7** (13.0 g, 0.06 mol) and Raney Ni (*ca.* 2 g) in EtOH (50 ml) was subjected to catalytic hydrogenation at 90 °C for 8 h under high hydrogen pressure (160 atm), then allowed to cool. The catalyst was removed by filtration and the filtrate was acidified with conc. HCl (10 ml) and concentrated at 50 °C to give an oil. This residual oil was diluted with H_2O (15 ml), washed with Et_2O and alkalified with K_2CO_3 powder. The oil, which was salted out with NaCl, was extracted with Et_2O and the extract was dried over $MgSO_4$. Evaporation of the Et_2O gave 7.75 g of a yellow oil, which on distillation afforded 6.5 g (63%) of **8** as a colorless oil: bp 86 °C (8 mmHg). IR (neat): 1720 cm^{-1} (COOEt). GLC (column temp. 120 °C, N_2 56 ml/min), t_R = 2.8 min (one peak). TLC ($CHCl_3$: EtOH = 3 : 1), two spots.

B) Catalytic hydrogenation of **7** (13 g) with Raney Ni at 90 °C for 6 h at relatively low hydrogen pressure (40 atm) followed by fractional distillation gave 7.3 g of a colorless oil, bp 76—96 °C (5 mmHg), which was found to be a mixture of **8** and **9** (**9a** or **9b**) by IR (neat, 1720, 1640 cm^{-1}), NMR ($CDCl_3$, Et × 2), and GLC [colum temp. 120 °C, N_2 56 ml/min, t_R = 2.8 (**8**) and 3.0 min (**9**) (1 : 2)]. This oily mixture was reduced to give 3 g (29%) of pure **8** by catalytic hydrogenation with PtO_2 (0.2 g) in a solution (40 ml) of AcOH–EtOH (1 : 1) at 2 atm hydrogen pressure.

Ethyl 1,2,4-Trimethylpyrrolidine-3-carboxylate (10 and 11)——Formic acid (9.47 g, 206 mmol) and formaldehyde

(35% solution in H_2O, 8.83 g, 103 mmol) were added to **8** (5.82 g, 34 mmol) with caution under ice cooling. The mixture was warmed with stirring at 80—90 °C for 12 h, then allowed to cool. Concentrated HCl (5 ml, 50 mmol) was added, and the whole was concentrated under reduced pressure at 60 °C (bath temp.). The residual oil was alkalified with K_2CO_3 powder and the separated oil was extracted with Et_2O. The Et_2O extract was washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation of the solvent gave 7.07 g of a yellow oil, which was distilled to afford 6.26 g (99%) of amines (**10** and **11**) as a colorless oil: bp 87—88 °C (12 mmHg). ^{1}H-NMR (CCl_4) δ: 2.18 and 2.26 (N-CH_3 × 2, ratio 4:1). GLC (column temp. 120 °C, N_2 55 ml/min), t_R = 2.8 and 3.6 min (ratio 4:1). TLC ($CHCl_3$: MeOH = 3:1), Rf = 0.6 and 0.37. Chromatographic separation gave 4.15 g (66%) of pure **11** on elution with $CHCl_3$ and 1.15 g (18%) of pure **10** on furter elution with $CHCl_3$–MeOH (10:1). **11**: bp 68—69 °C (4 mmHg). IR (neat): 1735 cm^{-1} (COOEt). ^{1}H-NMR (CCl_4) δ: 2.18 (N-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 14.3 ($\underline{C}H_3$-CH_2), 17.8, 21.4 (C_2-$\underline{C}H_3$, C_4-$\underline{C}H_3$), 34.5 (C_4), 39.9 (N-$\underline{C}H_3$), 59.8, 60.3 ($CH_3\underline{C}H_2O$, C_5), 63.5, 65.4 (C_2, C_3), 174.2 (C=O). GLC, t_R = 2.8 min. TLC, Rf = 0.6. *Anal.* Calcd for $C_{10}H_{19}NO_2 \cdot C_6H_3N_3O_7$, mp 111 °C) C, 46.37; H, 5.35; N, 13.52. Found: C, 46.20; H, 5.47; N, 13.85. **10**: bp 73 °C (5 mmHg). ^{1}H-NMR (CCl_4) δ: 2.26 (N-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 14.5 ($\underline{C}H_3$-CH_2), 15.3 (C_2- and C_4-$\underline{C}H_3$), 33.5 (C_4), 41.2 (N-$\underline{C}H_3$), 53.7 (C_3), 59.7 ($CH_3\underline{C}H_2O$), 62.6 (C_5), 64.3 (C_2), 171.6 (C=O). GLC, t_R = 3.6 min. TLC, Rf = 0.37. High-resolution MS Calcd for $C_{10}H_{19}NO_2$: 185.1414. Obsd: 185.1391.

Isomerization of 10 to 11——A mixture of crude reaction products (**10** and **11**, 5.88 g) and EtONa (prepared from Na 32 mg) in dry EtOH (10 ml) was warmed at 70—80 °C for 3 h. Evaporation of the EtOH afforded a residual oil, which was distilled to give 5.1 g (87%) of pure **11**. This compound was identical with an authentic sample on the basis of comparisons of IR and NMR spectra, and TLC and GLC behavior.

Pure **10** was also transformed into pure **11** by the same method.

***t*-3-(1-Hydroxy-1,1-diphenyl)methyl-1,*r*-2,*c*-4-trimethylpyrrolidine (13)**——A solution of **11** (2.63 g, 14.2 mmol) in dry THF (4 ml) was added dropwise to a solution of PhMgBr (44 mmol) in dry THF (10 ml) (prepared from 1.07 g of Mg and 6.9 g of PhBr). The reaction mixture was stirred at room temperature for 2 d and then refluxed for 5 h. After evaporation of the solvent, 5% HCl (40 ml) was carefully added to the residual white solid, and the mixture was then warmed for 30 min in a water bath with swirling. The insoluble crystals were filtered off, washed with H_2O, and dried. This solid (4.76 g) apparently consisted of the HCl and HBr salts of **13** on the basis of elemental analysis and the qualitative reactions for Cl^- and Br^-: mp > 300 °C (prisms from EtOH). IR (KBr): 3380 (OH), 2700—2500 cm^{-1} (NH^+). ^{1}H-NMR (d_6-DMSO) δ: 0.86 (3H, d, C_4-CH_3), 1.12 (3H, d, C_2-CH_3), 3.28 (3H, s, N-CH_3). K_2CO_3 powder was added to neutralize a suspension of this salt (4.76 g) in water and the salted-out solid was extracted with Et_2O. The extract was dried over K_2CO_3 and evaporated to give a residual solid mass, which was recrystallized from hexane to give 3.5 g (84%) of **13** as colorless needles: mp 136—138 °C. IR ($CHCl_3$): 3200 cm^{-1} [br, no change on dilution (0.04—0.005 M solution), intramolecular hydrogen-bonding OH]. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J = 7 Hz, C_4-CH_3),[7] 0.98 (3H, d, J = 7 Hz, C_2-CH_3), 2.26 (3H, s, N-CH_3). *Anal.* Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.70; H, 8.77; N, 4.78.

Grignard Reaction of 10——The Grignard reaction of **10** (525 mg) was carried out under the same conditions as described above. When the resulting reaction mixture was treated with 5% HCl (12 ml), however, no insoluble solid was observed, but an oil (benzene derived from the unreacted Grignard reagent) separated out. The aqueous layer was washed with Et_2O, alkalified with K_2CO_3 powder, and extracted with Et_2O. The extract was washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated to a residual oil (490 mg). A careful chromatographic separation of this oil by elution with $CHCl_3$ gave 201 mg (33%) of the ketone (**14**) as a colorless oil along with 100 mg (19%) of the starting material (**10**). **14**: bp 150 °C (bath temp.) (4 mmHg). IR (neat): 1670 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, C_4-CH_3), 1.20 (3H, d, C_2-CH_3), 2.30 (3H, s, N-CH_3), 7.33, 7.93 (3H, 2H, each m, aromatic-H). MS *m/z* 217 (M^+). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.04; H, 9.07; N, 6.54.

***c*-3-(1-Hydroxy-1,1-diphenyl)methyl-1,*r*-2,*t*-4-trimethylpyrrolidine (15)**——The Grignard reaction of crude amines (2.59 g) obtained from the Eschweiler–Clarke reaction of **8** was carried out by the same procedure as described above and afforded 267 mg (6.5%) of **15**, 2.4 g (58%) of **13**, and 100 mg (3.3%) of the ketone (**14**). These products were eluted with $CHCl_3$ in this order from silica gel. **15**: mp 107—108 °C, colorless needles from hexane. IR ($CHCl_3$): 3200 cm^{-1} [br, no change on dilution (0.04—0.005 M solution), intramolecular hydrogen-bonding OH]. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, d, J = 7.5 Hz, C_2-CH_3),[7] 0.93 (3H, d, J = 7 Hz, C_4-CH_3), 1.64 (1H, dd, J = 8, 7 Hz, C_3-H), 2.05 (1H, m, C_4-H), 2.17 (3H, s, N-CH_3), 2.50 (1H, m, C_2-H), 2.95 (1H, dd, J = 5, 3 Hz, C_5-H), 3.30 (1H, t, J = 8 Hz, C_5-H), 6.50 (1H, br, OH), 7.1—7.8 (10H, m, aromatic H). High-resolution MS Calcd for $C_{20}H_{25}NO$: 295.1935. Obsd: 295.1957.

Ethyl 1-Ethyl-*r*-2,*c*-4-dimethylpyrrolidine-*t*-3-carboxylate (18)——A solution of 3.4 g (32 mmol) of EtBr in EtOH (5 ml) was added dropwise to a solution of 5.4 g (32 mmol) of **8** and 3.2 g (32 mmol) of diisopropylamine (DIPA) in dry EtOH (10 ml) over a period of 10 min. The reaction mixture was stirred at room temperature for 30 h, then refluxed for 1 h, and allowed to cool. Et_2O was added to the mixture, and a white precipitate (DIPA · HBr, 5.48 g) was filtered off. Evaporation of the filtrate gave an oil (4.86 g), which, on distillation, gave an oil with a bp of 94—95 °C (10 mmHg). This oil was found to be a mixture (all-*cis* and all-*trans*) by TLC ($CHCl_3$: EtOH = 3:1, two spots) and GLC [column temp. 120 °C, N_2 54 ml/min; t_R = 3.2 and 3.8 min (ratio 5:1)]. An equilibration reaction was carried out by the same method as used for the synthesis of **11** to give 4.87 g (78%) of pure **18** as a colorless oil: bp 95 °C

(10 mmHg). IR (neat): 1730 cm^{-1} (COOEt). ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.4 (12H, m, $CH_2CH_3 \times 2$, $CH_3 \times 2$). MS *m/z*: 199 (M^+). GLC, t_R = 3.2 min (one peak). TLC, one spot. Picrate, mp 111—113 °C. *Anal.* Calcd for $C_{11}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 47.66; H, 5.64; N, 13.08. Found: C, 47.96; H, 5.91; N, 13.20.

***t*-3-(1-Hydroxy-1,1-diphenyl)methyl-1-ethyl-*r*-2,*c*-4-dimethylpyrrolidine (19)**——The Grignard reaction of **18** (2.83 g) as described for the synthesis of **13** afforded 4.87 g of the salt of **19** as an insoluble solid mass in HCl solution: mp > 300 °C. IR (KBr): 3350 (OH), 2750—2500 cm^{-1} (N^+-H). ^{1}H-NMR (d_6-DMSO) δ: 0.96 (3H, d, J = 7.5 Hz, C_4-CH_3), 1.15 (3H, d, J = 8 Hz, C_2-CH_3), 1.22 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$). By the same method as used for the isolation of **13**, the salt of **19** was converted to crude **19**, which, on recrystallization from petroleum ether, gave 3.2 g (73%) of pure **19** as colorless needles: mp 78—79 °C. IR ($CHCl_3$): 3200 cm^{-1} (hydrogen-bonding OH). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d, J = 7 Hz, C_2- and C_4-CH_3), 0.98 (3H; t, J = 7 Hz, $CH_2C\underline{H}_3$). MS *m/z*: 309 (M^+). *Anal.* Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.39; H, 8.95; N, 4.23.

***cis*- and *trans*-1,2,4-Trimethyl-3-diphenylmethylenepyrrolidines (16 and 17) and 3-Diphenylmethylene-1-ethyl-*cis*-2,4-dimethylpyrrolidine (20)**——The dehydration reaction of the diphenylmethanols (**13**, **15**, and **19**) to diphenylmethylenes (**16**, **17**, and **20**, respectively) was performed by refluxing them for 60 h in a mixture of AcOH–20% aq. H_2SO_4 (2 : 3, v/v). The following procedure for the synthesis of **16** is typical. A mixture of **13** (1.5 g), AcOH (20 ml), and 20% aq. H_2SO_4 (30 ml) was gently refluxed for 60 h, then allowed to cool. K_2CO_3 powder was added to the reaction mixture and the separated oil was extracted with $CHCl_3$. The extract was washed with NaCl solution and dried over $MgSO_4$. Evaporation of the solvent gave a yellow syrup, which was purified on a short column by elution with $CHCl_3$ to give pure **16** in a quantitative yield: IR (neat): 1595, 1490, 760, 705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J = 7 Hz, C_2-CH_3), 1.18 (3H, d, J = 6 Hz, C_4-CH_3), 3.20 (1H, q, J = 7 Hz, C_2-H), 2.30 (3H, s, N–CH_3). MS *m/z*: 277 (M^+). **17**: yellow syrup (yield, 89%). IR (neat): 1595, 1490, 760, 705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.62 (3H, d, J = 7 Hz, C_2-CH_3), 0.74 (3H, d, J = 6 Hz, C_4-CH_3), 2.34 (3H, s, N–CH_3), MS *m/z*: 277 (M^+). **20**: mp 63—64 °C, colorless needles from benzene (yield, 77%). IR (KBr): 1590, 1485, 760, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.2 (9H, m, $CH_3 \times 3$), 3.34 (2H, q, J = 6 Hz, $NC\underline{H}_2CH_3$), 7.20 (10H, s, Ph × 2). MS *m/z*: 291 (M^+). UV: 210 nm. *Anal.* Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.47; H, 8.88; N, 4.61.

Quaternization of 16, 17, and 20——The methiodides (**5**, **6**, and **4**) and ethiodides (**3** and **2**) were obtained by the reaction of **16**, **17**, and **20** with CH_3I and the reaction of **16** and **20** with EtI, respectively. This quaternization was carried out at room temperature in Et_2O or by refluxing in benzene. The ethylation of **20** was slower than that of **16** and the methylation of both the *cis*- and *trans*-2,4-dimethyl-1-alkylpyrrolidines (**16**, **20**, and **17**) proceeded faster than their ethylation. **5**: mp 242—244 °C, colorless prisms from acetone. Yield, 78% from **16**. IR (KBr): 1595, 1570, 1490, 1470, 780, 770, 715, 700 cm^{-1}. UV: 206, 220 (sh) nm. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J = 7 Hz, C_4-CH_3), 1.59 (3H, d, J = 8 Hz, C_2-CH_3), 3.42 (3H, s, N–CH_3), 3.50 (3H, s, N–CH_3). *Anal.* Calcd for $C_{21}H_{26}IN$: C, 60.15; H, 6.25; N, 3.34. Found: C, 60.32; H, 6.12; N, 3.34. **6**: mp 231—234 °C, colorless prisms from acetone. Yield, 51% from **17**. IR (KBr): 1590, 1460, 780, 768, 707 cm^{-1}. UV: 208, 218, 250 nm. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J = 7 Hz, C_4-CH_3), 1.04 (3H, d, J = 7 Hz, C_2-CH_3), 3.19 (3H, s, N–CH_3), 3.59 (3H, s, N–CH_3). *Anal.* Calcd for $C_{21}H_{26}IN$: C, 60.15; H, 6.25; N, 3.34. Found: C, 60.13; H, 6.34; N, 3.45. **4**: mp 231—232 °C, colorless prisms from acetone. Yield, 95% from **20**. IR (KBr): 760, 708, 700 cm^{-1}. UV: 208, 218 (sh) nm. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J = 6 Hz, C_4-CH_3), 1.36 (3H, t, J = 6 Hz, $NCH_2C\underline{H}_3$), 1.60 (3H, d, J = 7 Hz, C_2-CH_3), 3.36 (3H, s, N–CH_3), 4.55 (1H, q, C_2-H). ^{13}C-NMR ($CDCl_3$) δ: 9.5 ($\underline{C}H_3CH_2N$), 17.5, 18.8 (C_2- and C_4-$\underline{C}H_3$), 32.4 (C_4), 49.1 (N-$\underline{C}H_3$), 55.5, 66.4 ($N\underline{C}H_2CH_3$ and C_5), 72.7 (C_2). *Anal.* Calcd for $C_{22}H_{28}IN$: C, 60.97; H, 6.51; N, 3.23. Found: C, 60.95; H, 6.77; N, 3.18. **3**: mp 231—232 °C, colorless prisms from acetone. Yield, 65% from **16**. IR (KBr): 770, 760, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J = 6 Hz, C_4-CH_3), 1.36 (3H, t, J = 6 Hz, $NCH_2C\underline{H}_3$), 1.60 (3H, d, J = 7 Hz, C_2-CH_3), 3.21 (3H, s, N–CH_3), 4.44 (1H, q, C_2-H). ^{13}C-NMR ($CDCl_3$) δ: 9.4 ($NCH_2\underline{C}H_3$), 17.7, 18.7 (C_2- and C_4-$\underline{C}H_3$), 32.7 (C_4), 45.2 (N-$\underline{C}H_3$), 59.1, 66.8 ($N\underline{C}H_2CH_3$ and C_5), 70.4 (C_2). *Anal.* Calcd for $C_{22}H_{28}IN$: C, 60.97; H, 6.51; N, 3.23. Found: C, 61.16; H, 6.68; N, 3.15. **2**: mp 162—164 °C, colorless prisms from isopropanol. Yield, 30% from **20**. IR (KBr): 765, 710 cm^{-1}. UV: 208, 220 (sh) nm. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J = 7 Hz, C_4-CH_3), 1.32 (6H, m, $NCH_2C\underline{H}_3 \times 2$), 1.64 (3H, d, J = 7 Hz, C_2-CH_3), 4.24 (1H, m, C_2-H). *Anal.* Calcd for $C_{23}H_{30}IN$: C, 61.75; H, 6.76; N, 3.13. Found: C, 61.47; H, 6.74; N, 2.93.

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References and Notes

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2) *a*) See Part I—XI of this series and references cited therein; *b*) S. Ohki, M. Yoshino, and F. Hamaguchi, *Chem. Pharm. Bull.*, **16**, 320 (1968); *c*) This is the generic name [Padrin®, Riabal®, *cf.* The Merck Index, 10th ed., p.

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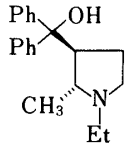
6) The Grignard reaction of 3-ethoxycarbonyl-1-ethyl-2-methylpyrrolidine (*trans* and *cis* mixture) with PhMgBr gave 1-ethyl-*trans*-3-(1-hydroxy-1,1-diphenyl)methyl-2-methylpyrrolidine (i) in 34% yield with a trace of the ketone (ii). [F. Hamaguchi and S. Ohki, *Yakugaku Zasshi*, **86**, 148 (1966)].



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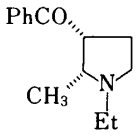
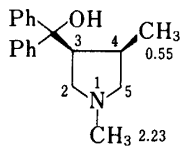


ii

7) The chemical shifts assigned to C_2- and C_4-CH_3 in **13** and **15** were confirmed by a double resonance experiment.

8) Signals for the CH_3 in the *cis* configuration to the diphenylmethanol (iii and v) appear at a higher magnetic field than those in the *trans*-form (iv and vi) as shown below. S. Ohki, N. Ozawa, Y. Yabe, and H. Matsuda, *Chem. Pharm. Bull.*, **24**, 1362 (1976); N. Ozawa, H. Matsuda, Y. Yabe, and S. Ohki, *ibid.*, **24**, 1371 (1976).



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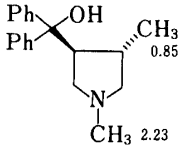

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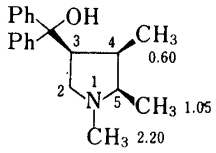

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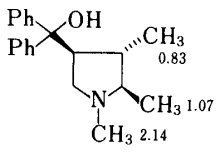

vi

ppm ($CDCl_3$)

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