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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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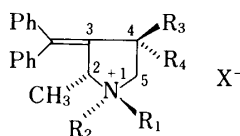
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Several new 3-diphenylmethylene-2,4-dimethylpyrrolidinium derivatives (**2**—**6**), structurally related to 3-diphenylmethylene-1,1-diethyl-2-methylpyrrolidinium bromide (**1**) (Prifinium Bromide, an antispasmodic agent), were synthesized so as to 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 | 4: R ₂ = Et, R ₁ = R ₄ = CH ₃ , R ₃ = H, X = I |
| 2: R ₁ = R ₂ = Et, R ₃ = H, R ₄ = CH ₃ , X = I | 5: R ₁ = R ₂ = R ₄ = CH ₃ , R ₃ = H, X = I |
| 3: R ₁ = Et, 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 (H₂, 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 ($N \cdots H-O$). 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-

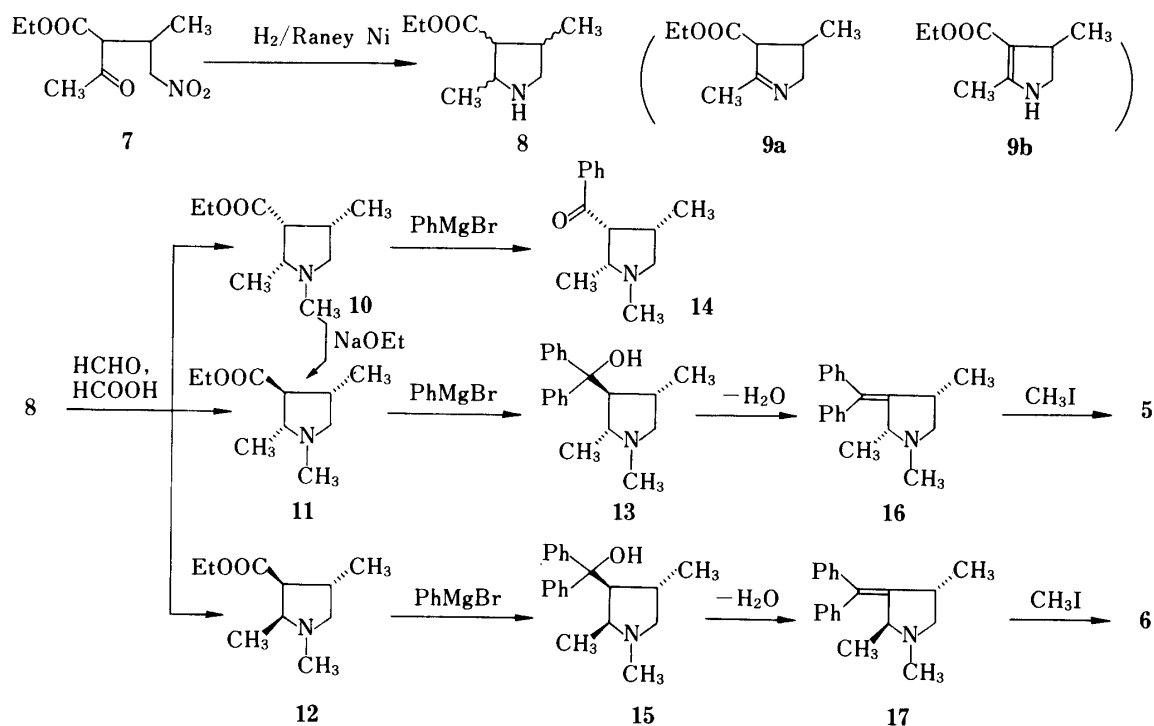


Chart 1

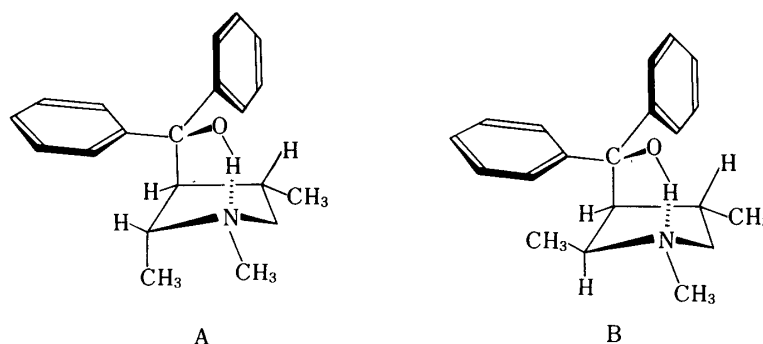


Fig. 1

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 ¹H-NMR spectra of 1-alkyl-1,2-dimethylpyrrolidinium iodides, the N⁺-CH₃ 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⁺-CH₃ group (3.21 ppm) is axial, while **4** is the *trans* isomer in which the N⁺-CH₃ 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

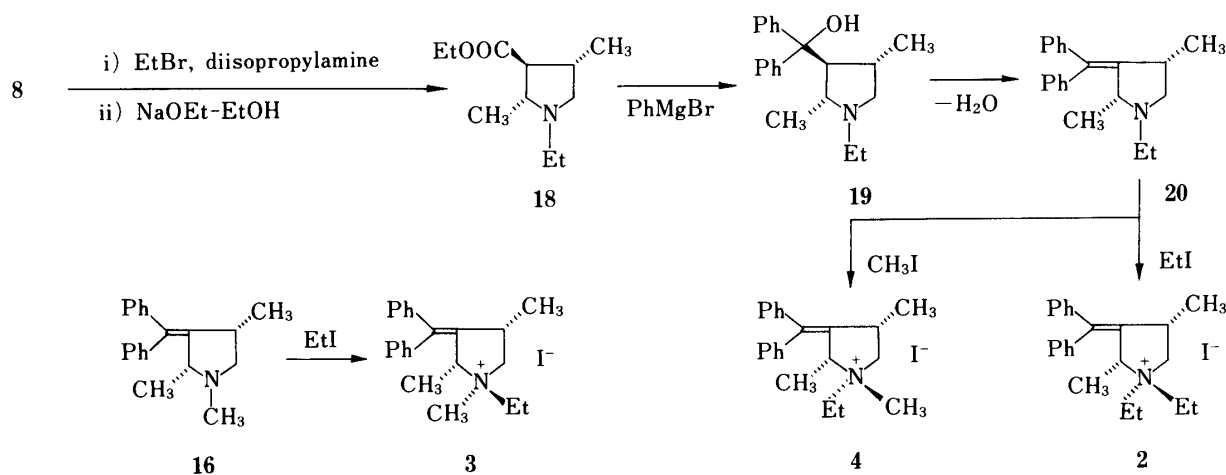


Chart 2

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 ^1H -NMR spectra was observed; that is, the N^+-CH_3 signal (49.12 ppm) of **4** and the CH_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; CH_2 of **4**, 55.50 ppm) *cis* to C_2-CH_3 .

Anticholinergic Activities¹²⁾

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	<i>n</i> -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	<i>n</i> -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. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ 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 $\times$ 2 m; carrier gas, N_2). TLC was performed on pre-coated silica gel plates (Kieselgel 60 F₂₅₄, Merck) and the spots were detected under UV irradiation.

Ethyl 2-Acetyl-3-methyl-4-nitrobutyrate (7)—A modification of Grob's method⁵¹ 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 Et₂O (120 ml). A solution of 1-nitro-1-propene (17.4 g, 0.2 mol) in dry Et₂O (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 H₂O. The Et₂O layer was separated, washed with 5% NaHCO₃ and H₂O, and dried over MgSO₄. 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.⁵¹ bp 145–148 °C (10 mmHg)]. IR (neat) 1745 (COOEt), 1720 (C=O), 1560, 1380 cm⁻¹ (NO₂). GLC (column temp. 130 °C, N₂ 50 ml/min), t_R = 6.5 min. Anal. Calcd for C₉H₁₅NO₅: 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 H₂O (15 ml), washed with Et₂O and alkalified with K₂CO₃ powder. The oil, which was salted out with NaCl, was extracted with Et₂O and the extract was dried over MgSO₄. Evaporation of the Et₂O 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, N₂ 56 ml/min), t_R = 2.8 min (one peak). TLC (CHCl₃: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 (CDCl₃, Et $\times$ 2), and GLC [column temp. 120 °C, N₂ 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 PtO₂ (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 H₂O, 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 K₂CO₃ powder and the separated oil was extracted with Et₂O. The Et₂O extract was washed with saturated NaCl solution and dried over MgSO₄. 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). ¹H-NMR (CCl₄) δ: 2.18 and 2.26 (N-CH₃ × 2, ratio 4:1). GLC (column temp. 120 °C, N₂ 55 ml/min); *t*_R = 2.8 and 3.6 min (ratio 4:1). TLC (CHCl₃:MeOH = 3:1), *R*_f = 0.6 and 0.37. Chromatographic separation gave 4.15 g (66%) of pure **11** on elution with CHCl₃ and 1.15 g (18%) of pure **10** on further elution with CHCl₃-MeOH (10:1). **11**: bp 68–69 °C (4 mmHg). IR (neat): 1735 cm⁻¹ (COOEt). ¹H-NMR (CCl₄) δ: 2.18 (N-CH₃). ¹³C-NMR (CDCl₃) δ: 14.3 (CH₃-CH₂), 17.8, 21.4 (C₂-CH₃, C₄-CH₃), 34.5 (C₄), 39.9 (N-CH₃), 59.8, 60.3 (CH₃CH₂O, C₅), 63.5, 65.4 (C₂, C₃), 174.2 (C=O). GLC, *t*_R = 2.8 min. TLC, *R*_f = 0.6. *Anal.* Calcd for C₁₀H₁₉NO₂·C₆H₅N₃O₇, 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). ¹H-NMR (CCl₄) δ: 2.26 (N-CH₃). ¹³C-NMR (CDCl₃) δ: 14.5 (CH₃-CH₂), 15.3 (C₂- and C₄-CH₃), 33.5 (C₄), 41.2 (N-CH₃), 53.7 (C₃), 59.7 (CH₃CH₂O), 62.6 (C₅), 64.3 (C₂), 171.6 (C=O). GLC, *t*_R = 3.6 min. TLC, *R*_f = 0.37. High-resolution MS Calcd for C₁₀H₁₉NO₂: 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 H₂O, 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⁺). ¹H-NMR (*d*₆-DMSO) δ: 0.86 (3H, d, C₄-CH₃), 1.12 (3H, d, C₂-CH₃), 3.28 (3H, s, N-CH₃). K₂CO₃ powder was added to neutralize a suspension of this salt (4.76 g) in water and the salted-out solid was extracted with Et₂O. The extract was dried over K₂CO₃ 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 (CHCl₃): 3200 cm⁻¹ [br, no change on dilution (0.04–0.005 M solution), intramolecular hydrogen-bonding OH]. ¹H-NMR (CDCl₃) δ: 0.96 (3H, d, *J* = 7 Hz, C₄-CH₃), 0.98 (3H, d, *J* = 7 Hz, C₂-CH₃), 2.26 (3H, s, N-CH₃). *Anal.* Calcd for C₂₀H₂₅NO: 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 Et₂O, alkalified with K₂CO₃ powder, and extracted with Et₂O. The extract was washed with saturated NaCl solution, dried over MgSO₄, and evaporated to a residual oil (490 mg). A careful chromatographic separation of this oil by elution with CHCl₃ 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). ¹H-NMR (CDCl₃) δ: 1.10 (3H, d, C₄-CH₃), 1.20 (3H, d, C₂-CH₃), 2.30 (3H, s, N-CH₃), 7.33, 7.93 (3H, 2H, each m, aromatic-H). MS *m/z* 217 (M⁺). *Anal.* Calcd for C₁₄H₁₉NO: 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 CHCl₃ in this order from silica gel. **15**: mp 107–108 °C, colorless needles from hexane. IR (CHCl₃): 3200 cm⁻¹ [br, no change on dilution (0.04–0.005 M solution), intramolecular hydrogen-bonding OH]. ¹H-NMR (CDCl₃) δ: 0.71 (3H, d, *J* = 7.5 Hz, C₂-CH₃), 0.93 (3H, d, *J* = 7 Hz, C₄-CH₃), 1.64 (1H, dd, *J* = 8, 7 Hz, C₃-H), 2.05 (1H, m, C₄-H), 2.17 (3H, s, N-CH₃), 2.50 (1H, m, C₂-H), 2.95 (1H, dd, *J* = 5, 3 Hz, C₅-H), 3.30 (1H, t, *J* = 8 Hz, C₅-H), 6.50 (1H, br, OH), 7.1–7.8 (10H, m, aromatic H). High-resolution MS Calcd for C₂₀H₂₅NO: 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. Et₂O 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 (CHCl₃:EtOH = 3:1, two spots) and GLC [column temp. 120 °C, N₂ 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). $^1\text{H-NMR}$ (CDCl_3) δ : 0.9—1.4 (12H, m, $\text{CH}_2\text{CH}_3 \times 2$, $\text{CH}_3 \times 2$). MS m/z : 199 (M^+). GLC, $t_R = 3.2$ min (one peak). TLC, one spot. Picrate, mp 111—113 $^\circ\text{C}$. Anal. Calcd for $\text{C}_{11}\text{H}_{21}\text{NO}_2 \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: 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 $> 300^\circ\text{C}$. IR (KBr): 3350 (OH), 2750—2500 cm^{-1} ($\text{N}^+\text{-H}$). $^1\text{H-NMR}$ (d_6 -DMSO) δ : 0.96 (3H, d, $J = 7.5$ Hz, $\text{C}_4\text{-CH}_3$), 1.15 (3H, d, $J = 8$ Hz, $\text{C}_2\text{-CH}_3$), 1.22 (3H, t, $J = 7$ Hz, CH_2CH_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 $^\circ\text{C}$. IR (CHCl_3): 3200 cm^{-1} (hydrogen-bonding OH). $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (6H, d, $J = 7$ Hz, $\text{C}_2\text{-}$ and $\text{C}_4\text{-CH}_3$), 0.98 (3H, t, $J = 7$ Hz, CH_2CH_3). MS m/z : 309 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{27}\text{NO}$: 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-Diphenylmethylen-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (3H, d, $J = 7$ Hz, $\text{C}_2\text{-CH}_3$), 1.18 (3H, d, $J = 6$ Hz, $\text{C}_4\text{-CH}_3$), 3.20 (1H, q, $J = 7$ Hz, $\text{C}_2\text{-H}$), 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.62 (3H, d, $J = 7$ Hz, $\text{C}_2\text{-CH}_3$), 0.74 (3H, d, $J = 6$ Hz, $\text{C}_4\text{-CH}_3$), 2.34 (3H, s, N-CH_3), MS m/z : 277 (M^+). **20**: mp 63—64 $^\circ\text{C}$, colorless needles from benzene (yield, 77%). IR (KBr): 1590, 1485, 760, 700 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.8—1.2 (9H, m, $\text{CH}_3 \times 3$), 3.34 (2H, q, $J = 6$ Hz, NCH_2CH_3), 7.20 (10H, s, $\text{Ph} \times 2$). MS m/z : 291 (M^+). UV: 210 nm. Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{N}$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.47; H, 8.88; N, 4.61.

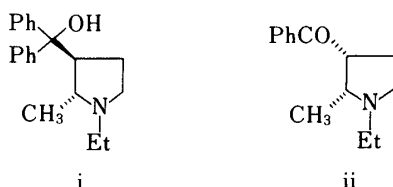
Quaternization of 16, 17, and 20—The methiodides (**5**, **6**, and **4**) and ethiodides (**3** and **2**) were obtained by the reaction of **16**, **17**, and **20** with CH_3I and the reaction of **16** and **20** with EtI , respectively. This quaternization was carried out at room temperature in 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 $^\circ\text{C}$, 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. $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (3H, d, $J = 7$ Hz, $\text{C}_4\text{-CH}_3$), 1.59 (3H, d, $J = 8$ Hz, $\text{C}_2\text{-CH}_3$), 3.42 (3H, s, N-CH_3), 3.50 (3H, s, N-CH_3). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{IN}$: C, 60.15; H, 6.25; N, 3.34. Found: C, 60.32; H, 6.12; N, 3.34. **6**: mp 231—234 $^\circ\text{C}$, colorless prisms from acetone. Yield, 51% from **17**. IR (KBr): 1590, 1460, 780, 768, 707 cm^{-1} . UV: 208, 218, 250 nm. $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, d, $J = 7$ Hz, $\text{C}_4\text{-CH}_3$), 1.04 (3H, d, $J = 7$ Hz, $\text{C}_2\text{-CH}_3$), 3.19 (3H, s, N-CH_3), 3.59 (3H, s, N-CH_3). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{IN}$: C, 60.15; H, 6.25; N, 3.34. Found: C, 60.13; H, 6.34; N, 3.45. **4**: mp 231—232 $^\circ\text{C}$, colorless prisms from acetone. Yield, 95% from **20**. IR (KBr): 760, 708, 700 cm^{-1} . UV: 208, 218 (sh) nm. $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (3H, d, $J = 6$ Hz, $\text{C}_4\text{-CH}_3$), 1.36 (3H, t, $J = 6$ Hz, NCH_2CH_3), 1.60 (3H, d, $J = 7$ Hz, $\text{C}_2\text{-CH}_3$), 3.36 (3H, s, N-CH_3), 4.55 (1H, q, $\text{C}_2\text{-H}$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 9.5 ($\text{CH}_3\text{CH}_2\text{N}$), 17.5, 18.8 ($\text{C}_2\text{-}$ and $\text{C}_4\text{-CH}_3$), 32.4 (C_4), 49.1 (N-CH_3), 55.5, 66.4 (NCH_2CH_3 and C_5), 72.7 (C_2). Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{IN}$: C, 60.97; H, 6.51; N, 3.23. Found: C, 60.95; H, 6.77; N, 3.18. **3**: mp 231—232 $^\circ\text{C}$, colorless prisms from acetone. Yield, 65% from **16**. IR (KBr): 770, 760, 710 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (3H, d, $J = 6$ Hz, $\text{C}_4\text{-CH}_3$), 1.36 (3H, t, $J = 6$ Hz, NCH_2CH_3), 1.60 (3H, d, $J = 7$ Hz, $\text{C}_2\text{-CH}_3$), 3.21 (3H, s, N-CH_3), 4.44 (1H, q, $\text{C}_2\text{-H}$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 9.4 (NCH_2CH_3), 17.7, 18.7 ($\text{C}_2\text{-}$ and $\text{C}_4\text{-CH}_3$), 32.7 (C_4), 45.2 (N-CH_3), 59.1, 66.8 (NCH_2CH_3 and C_5), 70.4 (C_2). Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{IN}$: C, 60.97; H, 6.51; N, 3.23. Found: C, 61.16; H, 6.68; N, 3.15. **2**: mp 162—164 $^\circ\text{C}$, colorless prisms from isopropanol. Yield, 30% from **20**. IR (KBr): 765, 710 cm^{-1} . UV: 208, 220 (sh) nm. $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (3H, d, $J = 7$ Hz, $\text{C}_4\text{-CH}_3$), 1.32 (6H, m, $\text{NCH}_2\text{CH}_3 \times 2$), 1.64 (3H, d, $J = 7$ Hz, $\text{C}_2\text{-CH}_3$), 4.24 (1H, m, $\text{C}_2\text{-H}$). Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{IN}$: C, 61.75; H, 6.76; N, 3.13. Found: C, 61.47; H, 6.74; N, 2.93.

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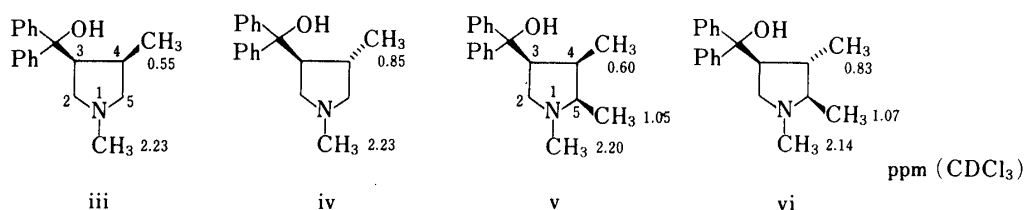
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