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Anticholinergic Agents. Synthesis of 1,1,4-Trimethyl- and 1,1,5-Trimethyl-3-diphenylmethylenepyrrolidinium Halides[1,2]

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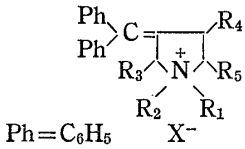
In connection with 1,1-diethyl-2-methyl-3-diphenylmethylenepyrrolidinium bromide (1) (anticholinergic agent), 1,1,4-trimethyl- (2) and 1,1,5-trimethyl-3-diphenylmethylenepyrrolidinium iodide (3) were synthesized. In the pharmacological examination of anticholinergic activity, the relative potencies of 2 and 3 were 0.01 and 0.27 respectively, in contrast to atropine which was defined as 1.00.

Synthesis of 1,1-dialkyl-3-diphenylmethylenepyrrolidinium halides was reported in our preceding paper.[4] Many of them have been proved later to have an anticholinergic activity. Among these, 1,1-diethyl-3-diphenylmethylene-2-methylpyrrolidinium bromide[4c] (Prifinium Bromide[4d]) (**1**) has a strong efficacy and is now being used clinically as a specific antispasmodic for spasm or hypermotility on the digestive and urinary tracts.

We have already reported[4] the correlation between the action of pyrrolidines and their anticholinergic activity, and have found that the intensity of pharmacological activity of these derivatives depends highly on the number, kind, position and configuration of the substituent alkyl groups on the pyrrolidine ring.

In this paper, we report the synthesis of 1,1,4-trimethyl- (**2**) and 1,1,5-trimethyl-3-di phenylmethylenepyrrolidinium iodide (**3**), both of which have one C-methyl group on the pyrrolidine ring, and they seem to be an interesting compound for examining the relation between the position of methyl substituent and intensity of anticholinergic activity.



1: $R_1=R_2=Et$, $R_3=Me$, $R_4=R_5=H$, X=Br
2: $R_1=R_2=R_4=Me$, $R_3=R_5=H$, X=I
3: $R_1=R_2=R_5=Me$, $R_3=R_4=H$, X=I

Synthesis of 1,1,4-Trimethyl-3-diphenylmethylenepyrrolidinium Iodide (2)

Synthesis of **2** was attempted by the route shown in Chart 1. As a preliminary experiment, 3-diphenylmethylenepyrrolidines (**7a—c**) were synthesized by the same route, although they have no methyl substituent at the 4-position of the pyrrolidine ring.

The reaction of 2-diphenylmethylenesuccinic acid[5] (**4a**) with an amine gave the ammonium salt (**5a**), which was converted to 2-diphenylmethylenesuccinimide[6] (**6a**) and its N-methyl (**6b**)

1) This constitutes Part VII of a series entitled "Synthesis of Pyrrolidine Derivatives with Pharmacological Activities." Part VI: S. Ohki, T. Azuma, and Y. Nagase, *Yakugaku Zasshi*, **89**, 633 (1969).
2) A part of this work was presented at the 4th International Congress of Heterocyclic Chemistry, Salt Lake City, July 1973.
3) Location: *1432-1, Horinouchi Hachioji, Tokyo, 192-03, Japan.*
4) *a*) S. Ohki, F. Hamaguchi, T. Yanagi, and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **14**, 187 (1966); *b*) S. Ohki and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **16**, 269 (1968); *c*) S. Ohki, M. Yoshino, and F. Hamaguchi, *Chem. Pharm. Bull.* (Tokyo), **16**, 320 (1968); *d*) This is the generic name [proposed by World Health Organization (WHO)] of Pyrodifenium bromide [described in lit. 4*c*) and Merck Index, 8th Ed., p. 894].
5) A.M. El-Abbady and H.H. Mousa, *Can. J. Chem.*, **43**, 928 (1968).
6) B. Harold and H.J. Schuemann, *Pharmazie*, **23**, 624 (1968).

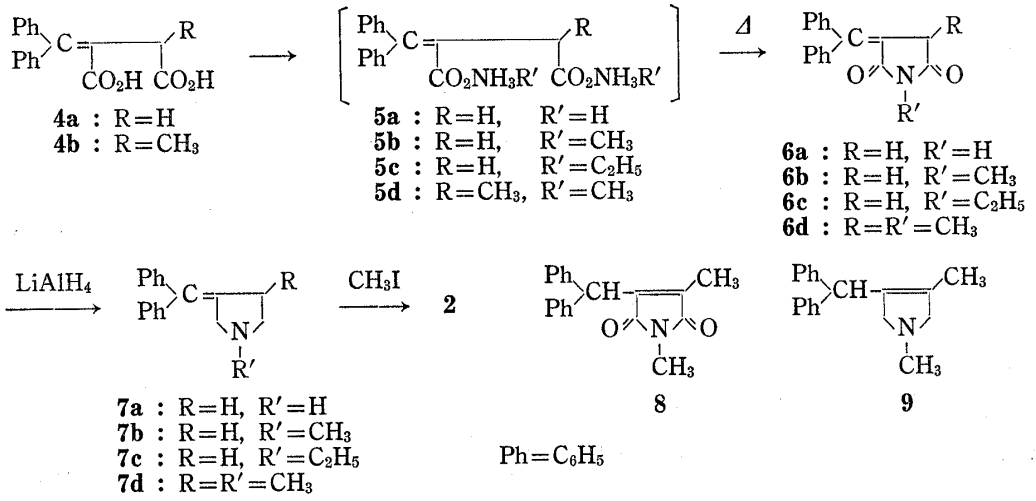


Chart 1

and N-ethyl derivative (**6c**). Infrared (IR) spectra of **6a**, **6b** and **6c** showed absorptions at 1775 and 1725 cm^{-1}, at 1775 and 1715 cm^{-1}, and at 1775 and 1715 cm^{-1}, respectively, which can be assigned to the imidocarbonyl function. In the nuclear magnetic resonance (NMR) spectra, the signals for C(3)-$\underline{H}_2$ in **6a**, **6b**, and **6c** appear at 3.41 ppm (2H, s), 3.42 ppm (2H, s), and 3.43 ppm (2H, s) respectively, and there is no signal for diphenylmethyl methine proton ($(C_6H_5)_2C\underline{H}$-). These data confirmed the structures of **6a**—**c**. Reduction of **6a**—**c** with lithium aluminum hydride ($LiAlH_4$) in ether gave 3-diphenylmethylenepyrrolidine (**7a**) and its N-methyl (**7b**) (methiodide, mp 223—224°) and N-ethyl derivative (**7c**) (methiodide, mp 179—180°). Compound **7b** was derived from **7a** by the Eschweiler-Clarke reaction. In NMR spectra of methiodides of **7b** and **7c**, the signal for C(4)-H_2 appear at 2.96 ppm (2H, t) and 3.0 ppm (2H, t), respectively, which confirm the chemical structures of **7a**—**c**, which has an *exo*-double bond. A great interest in **7c** has been recently taken owing to its anti-hypochondrial activity. On the basis of successful results mentioned above, synthesis of 4-methyl derivative (**2**) was undertaken. Pyrolysis of methylammonium salt (**5d**) of 2-diphenylmethylene-3-methylsuccinic acid[5] (**4b**) at 220° produced a crystalline mass, mp 78—92°, which contained two components. After purification, the major product of maleimide (**8**), mp 141—142°, and minor product of succinimide derivative (**6d**), mp 95—96°, were obtained in 5: 3 ratio. After examination of various reaction conditions, it was found that pyrolysis of **5d** at 180° produced **6d** in 89% yield, and at 240° produced **8** in 86% yield. Discrimination of **6d** from **8** depends on NMR spectra. Signal for $C_{(4)}$-CH_3 in **6d** is split into a doublet, while that in **8** appears as a singlet. Further, the methine proton signal of diphenylmethyl group is naturally lacking in the spectrum of **6d** but the signal exists in that of **8** (Fig. 1, 2, and 3). Reduction of **6d** with $LiAlH_4$ by refluxing in ether for 20 hr produced an oily liquid (bp 86—88° (0.8 mmHg)), which was separated by column chromatography into two components in 8.2: 1.8 ratio. The first elution gave the major product A and the second gave the minor product B. NMR spectrum of the methiodide (mp 185—186°) of the product A showed the presence of $C_{(4)}$-CH_3 signal at 2.05 ppm (3H) as a singlet, and methine proton ($(C_6H_5)_2C\underline{H}$-) signal at 5.65 ppm, and ultraviolet (UV) spectrum of the methiodide did not show the absorption maximum at 251 nm. On the other hand, NMR spectrum of the methiodide (mp 231—232°) of the product B showed the signal for $C_{(4)}$-CH_3 as a doublet at 0.98 ppm (3H) and UV spectrum of this methiodide showed the absorption maximum at 251 nm, which is characteristic for a diphenylmethylene group. From these spectral data as well as elemental analysis, product A was suggested to have a structure **9**, and product B was concluded as **7d** (methiodide (**2**)) which is the objective compound.

The *exo*-double bond in **6d** was assumed to have migrated to *endo* under reduction with $LiAlH_4$, and compared to **6a**, where such a migration was not observed, hyperconjugation of $C_{(4)}$-CH_3 group was suggested to have a large effect.

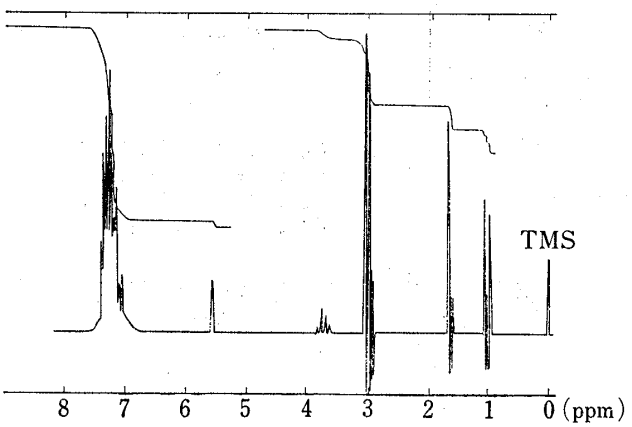


Fig. 1. NMR Spectrum of Mixture of **6d** and **8**

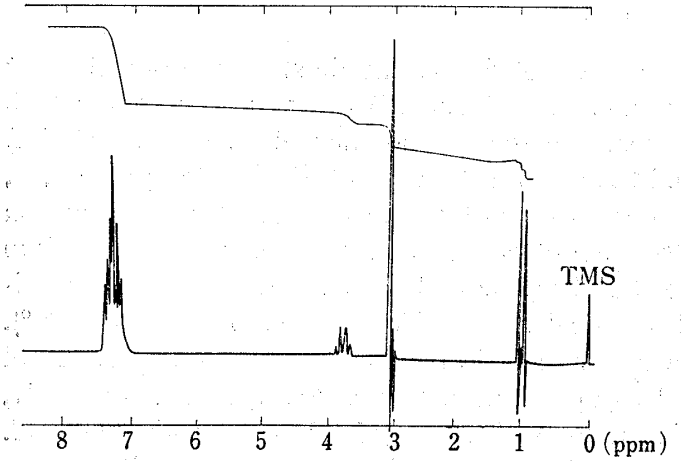


Fig. 2. NMR Spectrum of **6d**

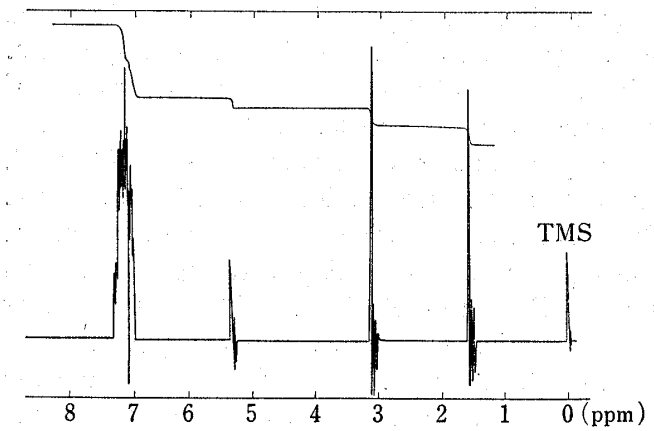


Fig. 3. NMR Spectrum of **8**

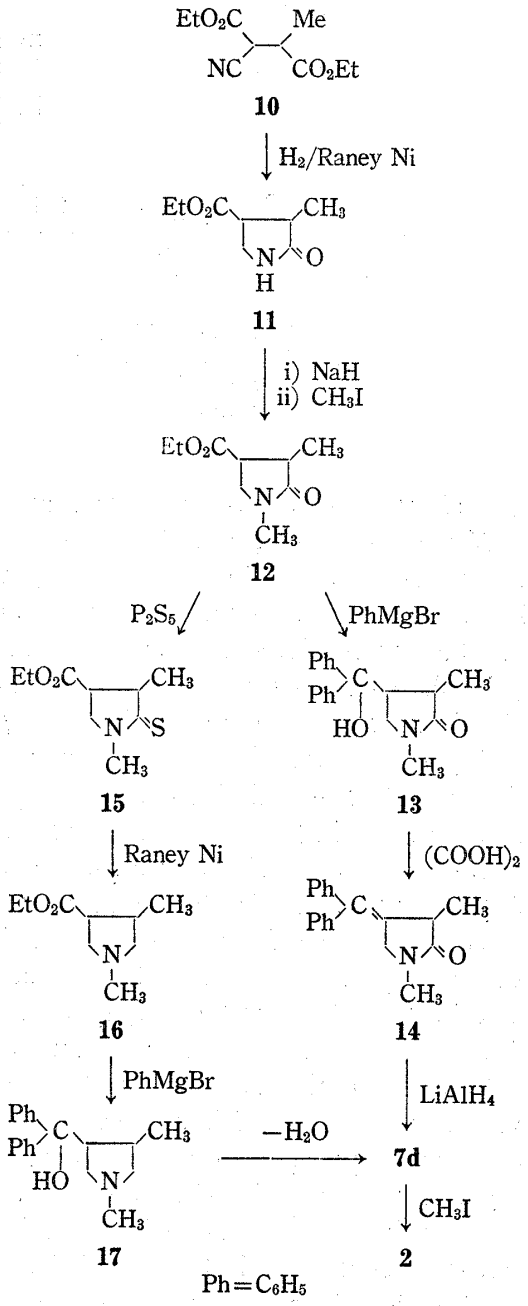


Chart 2

According to this method, the objective compound (2) was obtained only in a poor yield and an attempt was made to obtain **2** in a good yield through another route.

Reaction of ethyl cyanoacetate with ethyl α-bromopropionate in the presence of metallic sodium afforded ethyl 2-cyano-3-methylsuccinate[7] (**10**), and its high-pressure reductive cyclization catalyzed with Raney nickel produced a lactam (**11**) in 62% yield, which was treated with sodium hydride and then with methyl iodide to obtain N-methyl derivative (**12**). Compound **12** was allowed to react with phenylmagnesium bromide furnishing diphenylpyrrolidonemetha-

7) C.H. Gray and D.C. Nicholson, *J. Chem. Soc.*, **1958**, 3085.

nol (**13**), dehydration of which with oxalic acid under heating afforded diphenylmethylenepyrrolidone (**14**). The NMR spectrum of **14** indicated a three proton doublet (J=7.5 Hz) due to $C_{(4)}$-CH_3 at 0.75 ppm, and this fact also confirms the chemical structure of **14**. Reduction of **14** with $LiAlH_4$ resulted in an oily product (**7d**) (bp 86—88° (0.8 mmHg)) in 17.5% yield. Its methiodide, mp 231°, was identified with **2** obtained as mentioned above. In this method, yields from **13** to **14** and from **14** to **7d** are low, and this will be ascribed to the double bond migration from *exo*- to *endo*- with respect to the pyrrolidine ring, but this point was not examined further.

Finally, in order to avoid the double bond migration, another route to obtain **2** was attempted, deriving ethyl 1,3-dimethyl-4-pyrrolidinecarboxylate (**16**) from **12**, as shown in Chart 2 (see also footnote 8)). Namely, refluxing of **12** with phosphorus pentasulfide in benzene afforded the thioamide (**15**) in 60.4% yield, which was refluxed in ethanol with Raney nickel to produce **16** in 52% yield. The Grignard reaction of **16** with phenylmagnesium bromide afforded α,α-diphenyl-3-pyrrolidinemethanol (**17**) as a mixture of two diastereoisomers. Purification by column chromatography separated it into each isomer A (mp 112—113°) and B (mp 204—205°) in 11: 1 ratio. Dehydration of isomer A by refluxing in a mixture of 20% sulfuric acid and acetic acid produced **7d** in a comparatively good yield. Its methiodide, mp 231—232°, was identical with the sample of **7d** obtained through two methods mentioned above.

Synthesis of 1,1,5-Trimethyl-3-diphenylmethylenepyrrolidinium Iodide (3)

Condensation of ethyl N-ethoxycarbonylalaninate with ethyl acrylate in the presence of sodium hydride led to the formation of an oily product in 46% yield. It contained two components, diethyl 2-methyl-3-oxo-1,4-pyrrolidinedicarboxylate[11] (**18**) and diethyl 2-methyl-3-oxo-1,2-pyrrolidinedicarboxylate (**19**) in 2.3: 1 ratio. This is due to the fact that there are two kinds of possible orientations when ring-closure occurrs by the Dieckmann condensation in this case. Compound **18** was purified from 5% sodium hydroxide soluble portion as an oily product (bp 122° (0.6 mmHg)). The ferric chloride test was positive. Catalytic reduction of **18** with the Adams catalyst afforded 3-hydroxy derivative (**20**) (bp 138° (0.8 mmHg)), whose IR spectrum indicates a strong absorption due to the stretching vibration of OH at 3445 cm^{-1}. Compound **20** was readily dehydrated with phosphorus oxychloride-pyridine to form 3-pyrroline derivative (**21**) in 81% yield. It was presumed that *cis*-addition of hydrogen to the double bond of enol form in **18** favored the *cis*-configuration with respect to the ethoxycarbonyl and hydroxyl groups, and dehydration proceeded smoothly *via trans*-elimination. On the other hand, another 3-hydroxy derivative (**22**) (bp 106—107° (0.26 mmHg), IR: 3360 cm^{-1} (νOH, broad)) derived from **18** by reduction with sodium borohydride resisted dehydration under the same reaction conditions, because ethoxycarbonyl and hydroxyl groups are presumably oriented in the *trans*-configuration. It is concluded, concerning the two methods mentioned above, that these reductive methods possess a remarkably indifferent selectivity.

Catalytic reduction of **21** led to the formation of pyrrolidinecarboxylate (**23**) and its Grignard reaction with 2 molar equivalents of phenylmagnesium bromide produced α,α-diphenyl-1-ethoxycarbonyl-2-methyl-4-pyrrolidinemethanol (**24**). Dehydration of **24** by standing overnight in ethanol saturated with hydrogen chloride (gas) gave diphenylmethylenepyrrolidine (**25**), whose UV absorption maximum appeared at 248 nm which is assigned to diphenylmethy-

8) As a preliminary experiment, ethyl 1-methyl-2-oxo-4-pyrrolidinecarboxylate[9] was successfully converted to 2-thio derivative, followed by Raney nickel treatment to form ethyl 1-methyl-3-pyrrolidinecarboxylate[10] in good yield.

9) Y-H. Wu and R.F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).; F.C. Uhle, *J. Org. Chem.*, **27**, 4081 (1962).

10) J.F. Cavalla, *J. Chem. Soc.*, **1959**, 851.

11) Y-H. Wu, W.A. Gould, W.G. Lobeck, Jr., H.R. Roth, and R.F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 752 (1962).

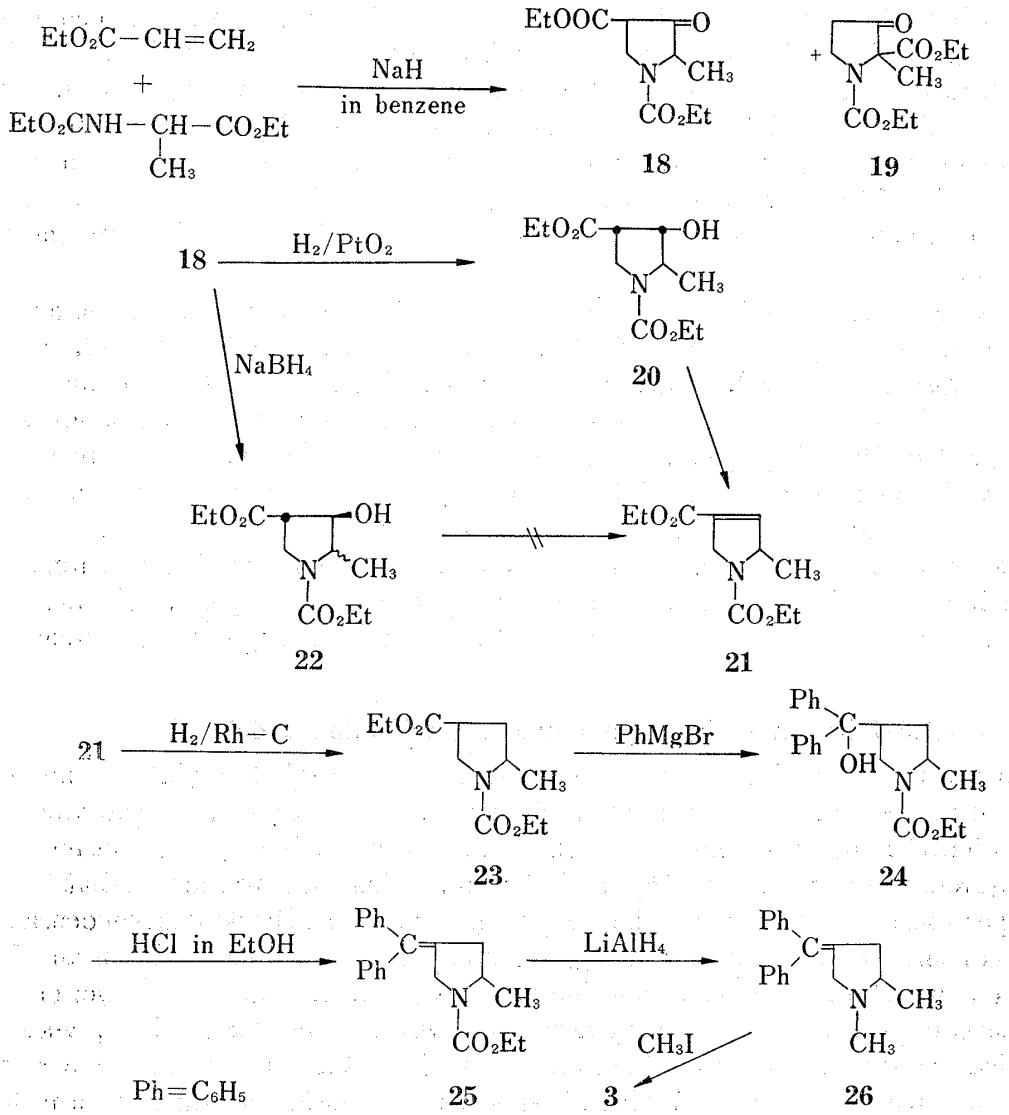


Chart 3

lene group. Reduction of **25** with $LiAlH_4$ afforded 1,5-dimethyl-3-diphenylmethylenepyrrolidine (**26**) as its methiodide (**3**) (mp 224—225°).

In the pharmacological examination of anticholinergic activity by the Magnus method, the relative potencies of **2** and **3** were 0.01 and 0.27 respectively, in contrast to atropine which was defined as 1.00. The relative potencies of **1** and 1,1-dimethyl-3-diphenylmethylene-2-methylpyrrolidinium iodide were 0.5 and 0.12, respectively.[12]

Experimental[13]

2-Diphenylmethylenesuccinimide (6a)——A clear mixture of 2-diphenylmethylenesuccinic acid[5] (**4a**) (4.2 g) and 10% aq. NH_3 (15 ml) was evaporated to dryness under reduced pressure and the residual white powder was transferred to a Claisen flask. This was pyrolyzed at 295° for 20 min and distilled under reduced

12) M. Hitomi, H. Nojima, and S. Uchida, *Folia Pharmacol. Jap.*, **62**, 427 (1966).

13) 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 spectrophotometer. UV spectra were measured in EtOH solutions with a Hitachi EPS-II spectrophotometer. NMR spectra were recorded at 100 MHz with JEOL Model JNM-MH-100 using tetramethylsilane (TMS) as the internal standard. 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).

pressure after NH_3 gas evolution ceased, to obtain an oily liquid, bp 181—182° (1 mmHg). It solidified on standing for several minutes (1.66 g), and was recrystallized from EtOH to form pale yellow needles, (**6a**) mp 247° (reported[6] mp 247—248°). IR ν_{max}^{KBr} cm^{-1}: 3535 (ν_{NH}), 1775, 1725 (ν_{CO}, imide), 748, 705 ($\delta_{=CH}$, five-adjacent ring hydrogen atoms). Mass Spectrum *m/e*: 263 (M^+). NMR ($CDCl_3$) δ (ppm): 3.41 (2H, s, $C_{(3)}$-$\underline{H}_2$), 4.43 (1H, s, N-$\underline{H}$).

N-Methyl-2-diphenylmethylenesuccinimide (**6b**)——A mixture of **4a** (3 g) and 40% aq. $MeNH_2$ (25 ml) was similarly worked up to produce pale yellow needles (**6b**) (bp 181—184° (1 mmHg), mp 174° from EtOH). Yield, 1.88 g (77.3%). *Anal.* Calcd. for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.03; H, 5.68; N, 4.99. IR ν_{max}^{KBr} cm^{-1}: 1775, 1715, 745, 705. NMR ($CDCl_3$) δ (ppm): 3.02 (3H, s, N-CH_3), 3.42 (2H, s, $C_{(3)}$-$\underline{H}_2$), 7.1—7.5 (10H, m, $(C_6\underline{H}_5)_2C$). Mass Spectrum *m/e*: 277 (M^+).

N-Ethyl-2-diphenylmethylenesuccinimide (**6c**)——A mixture of **4a** (4 g) and 40% aq. $EtNH_2$ (20 ml) was worked up similarly to produce pale yellow needles (**6c**) (bp 181—183° (1 mmHg), mp 112—113°). Yield, 2.063 g (70.3%). IR ν_{max}^{KBr} cm^{-1}: 1775, 1715, 1600, 756, 702. *Anal.* Calcd. for $C_{19}H_{17}O_2N$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.32; H, 5.89; N, 4.87. NMR ($CDCl_3$) δ (ppm): 1.20 (3H, t, J=7.5 Hz, N-$CH_2C\underline{H}_3$), 3.43 (2H, q, J=7.5 Hz, N-$C\underline{H}_2CH_3$), 7.0—7.40 (10H, m, $(C_6\underline{H}_5)_2C$). Mass Spectrum *m/e*: 291 (M^+).

3-Diphenylmethylenepyrrolidine (**7a**)——A mixture of **6a** (0.6 g) and $LiAlH_4$ (0.5 g) in anhyd. ether (40 ml) was refluxed for 24 hr, and the solvent was evaporated under reduced pressure. Ice-water (10 ml) was added to the residue, which was extracted with ether. The ether layer was extracted with 5% HCl, which was neutralized with solid K_2CO_3 under ice-cooling to afford a pale yellow oily product. This was purified by distillation, bp 99—101° (2 mmHg). Yield, 0.21 g (39.3%). UV λ_{max}^{EtOH} nm: 248. Mass Spectrum *m/e*: 235 (M^+). IR ν_{max}^{film} cm^{-1}: 3379 (ν_{NH}), 748, 705.

1-Methyl-3-diphenylmethylenepyrrolidine (**7b**)——(i) To a stirred solution of **6b** (0.4 g) in anhyd. ether (40 ml), $LiAlH_4$ (0.4 g) was added in small portions at room temperature and the reaction mixture was refluxed for 24 hr. This was worked up similarly as mentioned above to afford **7b**, bp 116—118° (2 mmHg). Yield, 0.22 g (65.0%). IR ν_{max}^{film} cm^{-1}: 2810 (N-CH_3), 1600, 756, 700. UV λ_{max}^{EtOH} nm: 248. Picrate, mp 180—181° (from EtOH). *Anal.* Calcd. for $C_{18}H_{19}N \cdot C_6H_3O_7N_3$: C, 60.24; H, 4.63; N, 11.71. Found: C, 60.48; H, 4.80; N, 11.69. Methiodide, colorless needles from $CHCl_3$, mp 223—224°. *Anal.* Calcd. for $C_{19}H_{22}NI$: C, 58.32; H, 5.67; N, 3.58. Found: C, 58.63; H, 5.90; N, 3.44. NMR ($CDCl_3$) δ (ppm): 2.96 (2H, t, J=7.5 Hz, $C_{(4)}$-$\underline{H}_2$), 3.49 (6H, s, $\overset{+}{N}(CH_3)_2$), 4.18 (2H, t, J=7.5 Hz, $C_{(5)}$-$\underline{H}_2$) 4.50 (2H, s, $C_{(2)}$-$\underline{H}_2$), 7.10—7.40 (10H, m, $(C_6H_5)_2$-C=).

(ii) Eschweiler-Clarke Reaction of 7a. A mixture of **7a** (0.21 g), 37% HCHO (2 ml), and 99% HCOOH (1 ml) was heated on a steam bath until gas evolution ceased in 15 min. After evaporation of the solvent, the mixture was made alkaline with 5% NaOH to give a thick syrup. The product was extracted with ether. Usual work-up of the extract gave 0.065 g of a pale yellow liquid (**7b**), bp 67—69° (2 mmHg). Yield, 30.3%. The methiodide of this product was identified with the sample obtained by the method (i) by comparison of IR and NMR spectra.

1-Ethyl-3-diphenylmethylenepyrrolidine (**7c**)——A mixture of **6c** (0.6 g) and $LiAlH_4$ (0.5 g) in anhyd. ether (10 ml) was refluxed for 20 hr. The same treatment as noted above gave a basic oily product (**7c**), bp 112—118° (0.8 mmHg). Yield, 0.38 g (70%). IR ν_{max}^{film} cm^{-1}: 3072, 3045 (phenyl), 1603, 751, 705. UV λ_{max}^{EtOH} nm: 248. Picrate, yellow needles from EtOH, mp 153°. *Anal.* Calcd. for $C_{19}H_{21}N \cdot C_6H_3O_7N_3$: C, 46.21; H, 5.25; N, 12.15. Found: C, 46.21; H, 5.21; N, 12.09. Methiodide: Colorless needles from $CHCl_3$, mp 179—180°. *Anal.* Calcd. for $C_{20}H_{24}NI$: C, 59.26; H, 5.08; N, 3.45. Found: C, 59.32; H, 5.14; N, 3.39. IR ν_{max}^{KBr} cm^{-1}: 3065, 3050, 1603, 750, 700. NMR ($CDCl_3$) δ (ppm): 1.40 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.0 (2H, t, J=7.5 Hz, $C_{(4)}$-$\underline{H}_2$), 3.25 (3H, s, $\overset{+}{N}$-$C\underline{H}_3$), 3.75 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.15 (2H, t, J=7.5 Hz, $C_{(5)}$-$\underline{H}_2$), 4.2 and 4.7 (1H each, d, J=15 Hz, $C_{(2)}$-$\underline{H}_2$), 7.0—7.4 (10H, m, $(C_6\underline{H}_5)_2C$).

N-Methyl-2-diphenylmethylene-3-methylsuccinimide (**6d**)——A solution of 2-diphenylmethylene-3-methylsuccinic acid[5] (4 g) and 40% aq. $MeNH_2$ (20 ml) was evaporated to dryness *in vacuo*, to give colorless needles (**5d**), mp 169—171°. Yield, 4.46 g (92%).

(i) Four grams of the product (**5d**) was heated at 220° for 15 min, when gas evolution ceased, and distilled under reduced pressure to produce a pale yellow oily liquid, bp 174° (0.3 mmHg), which solidified in several minutes. Yield, 2.98 g (92%). The product was dissolved in *n*-hexane (32 ml) and applied to an Al_2O_3 column (alumina, 50 g, Brockman grade II—III (Merck)) using *n*-hexane as an eluent. The first effluent was concentrated to dryness giving a crystalline mass (**8**) (1.64 g, 50.4%). Recrystallization from EtOH afforded N-methyl-2-diphenylmethyl-3-methylmaleimide (**8**) as colorless plates, mp 98°. IR ν_{max}^{KBr} cm^{-1}: 1765, 1705 (ν_{CO}, five-membered imide), 785, 705. NMR ($CDCl_3$) δ (ppm): 1.05 (3H, s, $C_{(3)}$-$C\underline{H}_3$), 3.10 (3H, s, N-$C\underline{H}_3$), 5.15 (1H, s, $(C_6H_5)_2C\underline{H}$-), 7.05—7.45 (10H, m, $(C_6\underline{H}_5)_2C$). Mass Spectrum *m/e*: 291 (M^+). *Anal.* Calcd. for $C_{19}H_{17}O_2N$: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.79; H, 5.54; N, 4.33. The second effluent was also concentrated to dryness giving a crystalline mass (**6d**) (0.988 g, 30.3%). Recrystallization from EtOH afforded N-methyl-2-diphenylmethylene-3-methylsuccinimide (**6d**) as pale yellow needles, mp 141—142°. *Anal.* Calcd. for $C_{19}H_{17}O_2N$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.21; H, 5.39; N, 4.30. IR ν_{max}^{KBr} cm^{-1}: 1775, 1705 (ν_{CO}, five-membered cyclic imide), 751, 706. NMR ($CDCl_3$) δ (ppm): 0.95 (3H, d, J=7.5 Hz, $C_{(3)}$-$C\underline{H}_3$), 3.05 (3H, s, N-$C\underline{H}_3$), 7.10—7.55 (10H, m, $(C_6\underline{H}_5)_2C$). Mass Spectrum *m/e*: 291 (M^+).

(ii) When pyrolysis was done at 180°, the same work-up as above afforded only one product (**6d**) in 89% yield.

(iii) When pyrolysis was done at 240°, the same work-up as above afforded **8** as a single product in 86% yield.

1,1,4-Trimethyl-3-diphenylmethylenepyrrolidinium Iodide (2)——To a solution of **6d** (1.5 g) in anhyd. Et_2O (25 ml) $LiAlH_4$ (1.5 g) was added with ice-cooling and stirring. After stirring at room temperature for 1 hr, followed by gentle refluxing for 20 hr, the reaction mixture was diluted with H_2O (5 ml) and the ether layer was separated. The ether layer was extracted with 10% HCl. The acidic layer was made alkaline by adding solid K_2CO_3 and extracted with ether. Usual work-up of the extract gave a residual oil, which was chromatographed over silica gel (5 g). Elution with benzene–acetone (3: 1, v/v), followed by evaporation gave 0.32 g (23%) of a syrup, which was suggested as 3-diphenylmethyl-1,4-dimethyl-Δ^3-pyrroline (**9**), bp 142—143° (0.3 mmHg). IR ν_{max}^{film} cm^{-1}: 2810, 745, 700. Mass Spectrum *m/e*: 263 (M^+). Methiodide: Colorless needles from Me_2CO, mp 185—186°. NMR ($CDCl_3$) δ (ppm): 1.80 (2H, s, $C_{(2)}$–$\underline{H}_2$), 2.05 (3H, s, $C_{(4)}$–$C\underline{H}_3$), 3.25 (2H, s, $C_{(5)}$–$\underline{H}_2$), 3.40, 3.55 (3H each, s, $\overset{+}{N}(C\underline{H}_3)_2$), 5.65 (1H, s, $(C_6H_5)_2C\underline{H}$–), 7.02—7.45 (10H, m, $(C_6\underline{H}_5)_2C$). Successively, elution with the same solvent as above followed by evaporation gave 0.062 g (4.73%) of **7d** as an oil. IR ν_{max}^{film} cm^{-1}: 2810, 1603, 751, 704. UV λ_{max}^{EtOH} nm: 246. Methiodide, colorless needles from acetone, mp 231—232°. *Anal.* Calcd. for $C_{20}H_{24}NI$: C, 59.26; H, 5.96; N, 3.45. Found: C, 59.00; H, 6.52; N, 3.41. IR ν_{max}^{KBr} cm^{-1}: 3060, 3040, 2975, 1595, 765, 710. UV λ_{max}^{EtOH} nm: 251. NMR ($CDCl_3$) δ (ppm): 0.98 (3H, d, J=7.5 Hz, $C_{(4)}$–$C\underline{H}_3$), 3.28, 3.70 (3H, each, s, $\overset{+}{N}(C\underline{H}_3)_2$), 3.80—4.45 (3H, m, $C_{(5)}$–$\underline{H}_2$, $C_{(4)}$–$\underline{H}$), 3.93, 5.28 (1H each, d, J=15 Hz, $C_{(2)}$–$\underline{H}_2$) 7.0—7.45 (10H, m, $(C_6\underline{H}_5)_2C$).

Ethyl 1,3-Dimethyl-2-oxo-4-pyrrolidinecarboxylate (12)——To a solution of ethyl α-bromopropionate (35.32 g, 0.2 mol) in EtOH (100 ml) sodium ethyl cyanoacetate[7] (26.9 g, 0.2 mol) was added and the mixture was stirred at room temperature for 30 min. After removal of EtOH *in vacuo*, the residue was diluted with H_2O (80 ml) and extracted with benzene. The usual work-up gave ethyl 2-cyano-3-methylsuccinate (**10**) as an oily liquid, bp 108° (0.35 mmHg) (reported[7] bp 156° (20 mmHg)). Yield, 29.6 g (70%). A mixture of **10** (7 g) in EtOH (70 ml) was hydrogenated over Raney nickel (0.7 g) at 150 atm and 106° for 8 hr. After filtration, the reaction mixture was evaporated *in vacuo* to give ethyl 3-methyl-2-oxo-4-pyrrolidinecarboxylate (**11**) as an oily liquid, bp 106—109° (0.4 mmHg). Yield, 4.1 g (73%). To a solution of **11** (0.856 g, 0.005 mol) in anhyd. benzene (5 ml) Na metal wire (0.115 g, 0.005 g. atom) was added and the reaction mixture was stirred at room temperature. In about 40 min, sodium wire dissolved completely, and a solution of MeI (0.71 g, 0.005 mol) in anhyd. benzene (5 ml) was added to the solution, which was stirred at room temperature for 1 hr and allowed to stand overnight. After filtration, the reaction mixture was evaporated under reduced pressure to give **12** as an oil, bp 108—109° (1.2 mmHg). Yield, 0.415 g (45%). *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.62; H, 8.25; N, 7.29. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2860 (N–CH_3), 1745 (ester), 1705 (five-membered lactam). Mass Spectrum *m/e*: 185 (M^+).

α,α-Diphenyl-1,3-dimethyl-2-oxo-4-pyrrolidinemethanol (13)——To an anhyd. ether solution of PhMgBr (0.008 mol) [prepared from Mg (0.194 g) and bromobenzene (1.264 g) in anhyd. ether (15 ml)] was added a solution of the lactam (**12**) (0.32 g, 0.0017 mol) in anhyd. ether (5 ml), and the reaction mixture was stirred at room temperature for 1 hr and allowed to stand overnight. After evaporation *in vacuo*, to the reaction mixture was added 10% NH_4Cl solution to decompose the adduct. The precipitate formed was collected by filtration and chromatographed over alumina (5.5 g) (Brockmann grade II—III (Merck)). Elution with $CHCl_3$ followed by evaporation gave **13** as colorless needles from EtOH, mp 210—211°. Yield, 0.275 g (53.0%). *Anal.* Calcd. for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.00; H, 7.47; N, 4.48. IR ν_{max}^{KBr} cm^{-1}: 2810 (N–$C\underline{H}_3$), 1705 (five-membered lactam carbonyl), 743, 703. NMR ($CDCl_3$) δ (ppm): 0.8 (3H, d, J=7.5 Hz, $C_{(3)}$–$C\underline{H}_3$), 2.7 (3H, s, N–$C\underline{H}_3$), 3.0—3.4 (3H, m, $C_{(4)}$–$\underline{H}$ and $C_{(5)}$–$\underline{H}_2$), 3.42 (1H, s, O$\underline{H}$),[14] 7.10—7.50 (10H, m, $(C_6\underline{H}_5)_2C$). Mass Spectrum *m/e*: 295 (M^+).

1,3-Dimethyl-2-oxo-4-diphenylmethylenepyrrolidine (14)——A mixture of **13** (40 mg) and oxalic acid (40 mg) was heated at 140° for 30 min. When cooled, the reaction mixture was washed with saturated $NaHCO_3$ and H_2O. The residual oil was dissolved in hot EtOH (6 ml), filtered and cooled to afford **14** as white needles, mp 141—142°. Yield, 15 mg (41%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3050, 3026, 1660 (five-membered lactam carbonyl). NMR ($CDCl_3$) δ (ppm): 0.75 (3H, d, J=7.5 Hz, $C_{(3)}$–$C\underline{H}_3$), 1.15 (1H, q, J=7.5 Hz, $C_{(3)}$–$\underline{H}$), 2.35 (3H, s, N–$C\underline{H}_3$), 3.28 (2H, s, $C_{(5)}$–$\underline{H}_2$). Mass Spectrum *m/e*: 277 (M^+). UV λ_{max}^{EtOH} nm: 246.

1,4-Dimethyl-3-diphenylmethylenepyrrolidine (7d)——A mixture of **14** (55 mg, 0.0002 mol) and $LiAlH_4$ (30 mg, 0.0008 mol) in anhyd. ether (30 ml) was gently refluxed for 4 hr. The reaction mixture was neutralized with 5% HCl, ether layer was separated, and extracted with 5% HCl. The combined acidic phase was made alkaline with solid K_2CO_3 with ice-cooling, and extracted with ether. The extract was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give **7d** as an oily liquid, bp 86—88° (0.8 mmHg). Yield, 9.14 mg (17.5%). Mass Spectrum *m/e*: 263 (M^+). Methiodide (**2**), mp 231—232°, was identified with the sample obtained as above by mixed melting point test and by comparison of IR and UV spectra.

14) This signal disappeared when D_2O was added.

Ethyl 1,3-Dimethyl-2-thio-4-pyrrolidinecarboxylate (15)——A mixture of the lactam (**12**) (1.7 g) and P_2S_5 (3.0 g) in anhyd. benzene (20 ml) was refluxed with good stirring for 6 hr. To a residue obtained on evaporation of benzene was added H_2O (20 ml) and the mixture was heated at 90° for 30 min until the solid substance dissolved and an oily liquid separated. The reaction mixture was extracted with $CHCl_3$. Usual work-up gave **15** as an oily liquid, bp 132—135° (3.5 mmHg). Yield, 1.44 g (60.4%). Mass Spectrum *m/e*: 201 (M^+).

Ethyl 1,3-Dimethyl-4-pyrrolidinecarboxylate (16)——A mixture of **15** (3.0 g) and Raney nickel (12 g) in EtOH (100 ml) was refluxed for 7 hr. Usual work-up gave **16** as an oily liquid, bp 98° (23 mmHg). Yield, 1.34 g (52%). IR ν_{max}^{film} cm^{-1}: 2788 (N–C<u>H</u>$_3$), 1735 (carbonly). Mass Spectrum *m/e*: 171 (M^+).

α,α-Diphenyl-1,3-dimethyl-4-pyrrolidinemethanol (17)——To a solution of the Grignard reagent [prepared from Mg (0.76 g) and bromobenzene (4.95 g) in anhyd. ether (30 ml)], a solution of **16** (1.35 g) in ether (6 ml) was added dropwise, and the solution was refluxed for 4 hr. The usual work-up gave a crystalline mass, which was chromatographed over Al_2O_3 [10 g, Brockmann grade II—III (Merck)]. Elution with $CHCl_3$–MeOH (10: 1, v/v) and evaporation of the solvent gave 1.12 g of a white powder, which was recrystallized from *n*-hexane to give isomer A (**17**) as colorless needles, mp 112—113°. Yield, 0.909 g (40.9%). IR ν_{max}^{KBr} cm^{-1}: 2810 (N–C<u>H</u>$_3$), 751, 704. *Anal.* Calcd. for $C_{19}H_{23}ON$: C, 81.0; H, 8.24; N, 4.98. Found: C, 80.55; H, 8.28; N, 4.62. Mass Spectrum *m/e*: 281 (M^+). Successive elution with the same solvent gave isomer B as white needles, mp 209—210°. Yield, 85.2 mg (3.8%). IR ν_{max}^{KBr} cm^{-1}: 2810, 1603, 751, 704. *Anal.* Calcd. for $C_{19}H_{23}ON \cdot 1/2H_2O$: C, 76.20; H, 8.42; N, 4.68. Found: C, 76.34; H, 8.42; N, 4.39.

1,4-Dimethyl-3-diphenylmethylenepyrrolidine (7d) and Its Methiodide (2)——A mixture of isomer A (**17**) (90 mg, mp 112—113°), 20% H_2SO_4 (4 ml) and AcOH (4 ml) was heated under reflux for 8 hr. The reaction mixture was neutralized with solid $NaHCO_3$ with ice-cooling, and extracted with ether. The extract was dried over Na_2SO_4 and filtered. The solvent was evaporated under a reduced pressure to give **7d** as an oil. UV λ_{max}^{EtOH} nm: 247.

Methiodide (**2**), colorless needles from acetone–ether (5: 1, v/v), mp 231—232°. Yield, 46.4 mg (35.7%). This methiodide was identified with a sample obtained *via* **6d** as shown in Chart 1 or *via* **13** as shown in Chart 2 by mixed mp and comparison of IR, UV and NMR spectra.

Diethyl 2-Methyl-3-oxo-1,4-pyrrolidinedicarboxylate (18)——Twelve grams of 50% oily NaH was washed with petr. ether (15 ml) and decanted under nitrogen atmosphere. This procedure was repeated three times to give 6 g (0.25 mol) of almost pure NaH, to which was added anhyd. benzene (40 ml). To this mixture, a solution of ethyl N-ethoxycarbonylalaninate (47.25 g, 0.25 mol) in anhyd. benzene (20 ml) was added dropwise with ice-cooling. After the reaction mixture was stirred for 1 hr at room temperature, it was gently refluxed for 1 hr until the solution became transparent. To this solution, a solution of ethyl acrylate (27.5 g, 0.275 mol) in anhyd. benzene (20 ml) was added dropwise, and the mixture was refluxed gently for 3 hr. After cooled, 10% HCl was added to the mixture with ice-cooling, and the whole was stirred. The benzene layer was separated and the acidic solution was extracted with $CHCl_3$. The combined extract was dried over Na_2SO_4. Usual work-up gave an oily syrup, bp 115—128° (0.6 mmHg), which proved to contain two components; **18** and diethyl 2-methyl-3-oxo-1,2-pyrrolidinedicarboxylate (**19**). Yield, 26.74 g (46.3%). Ten grams of the syrup was dissolved in ether (30 ml). At first, the ether solution was extracted with 2% NaOH solution. The alkaline extract was acidified with 2% HCl and extracted with ether, using salting-out with NaCl. The ether extract was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated *in vacuo* to give **18** as a pale yellow oil, bp 112—115° (0.2 mmHg). Yield, 6.98 g (68%). IR ν_{max}^{film} cm^{-1}: 1765 (five-membered ring ketone), 1735 (ester), 1723 (urethane). $FeCl_3$ test was positive. *Anal.* Calcd. for $C_{10}H_{17}O_5N$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.20; H, 7.33; N, 5.90. Secondly, the mother ether layer was dried over Na_2SO_4 and evaporated *in vacuo* to give **19**, as a colorless oil, bp 110—112° (2 mmHg). Yield, 3.02 g (30.2%). *Anal.* Calcd. for $C_{10}H_{17}O_5N$: C, 54.31; H, 7.04; N, 5.76. Found: C, 53.96; H, 7.19; N, 6.11. IR ν_{max}^{film} cm^{-1}: 1765 (five-membered ring ketone), 1730 (ester), 1724 (urethan). $FeCl_3$ test was negative.

Ethyl (*cis*-3-Hydroxy-4-ethoxycarbonyl)-2-methyl-1-pyrrolidinecarboxylate (20)——A solution of **18** (5.0 g) in glacial AcOH (20 ml) was catalytically hydrogenated over the Adams catalyst (0.5 g) at room temperature under atmospheric pressure for 2 hr. Hydrogen uptake was 588 ml (theoretical amount: 543 ml (18°)). Usual treatment gave a colorless liquid (**20**) (4.59 g, 91%), bp 138° (0.5 mmHg). *Anal.* Calcd. for $C_{11}H_{19}O_5N$: C, 53.86, H, 7.81; N, 5.71. Found: C, 53.61; H, 7.71; N, 6.01.

Ethyl (*trans*-3-Hydroxy-4-ethoxycarbonyl)-2-methyl-1-pyrrolidinecarboxylate (22)——To a solution of **18** (0.243 g) in MeOH (5 ml) $NaBH_4$ (0.35 g) was added with ice-cooling and this mixture was stirred at room temperature for 0.5 hr, followed by refluxing for 2 hr. The cooled solution was neutralized with 10% AcOH (1 ml) and extracted with ether. The extract was dried over Na_2SO_4 and the solvent was evaporated to give **22**, as a thick oil, bp 106° (0.26 mmHg). Yield, 0.149 g (61.0%). *Anal.* Calcd. for $C_{11}H_{19}O_5N$: N, 5.71. Found: N, 5.96.

Ethyl 4-Ethoxycarbonyl-2-methyl-1-(Δ³-pyrroline)carboxylate (21)——To a solution of *cis* derivative (**20**) (0.9 g) in pyridine (20 ml) $POCl_3$ (7 ml) was added dropwise with ice-cooling at a constant rate during 30 min. The solution was stirred at room temperature for 18 hr, and the resulting brownish solution was poured into ice-water (10 g), which was extracted with two 20-ml portions of ether. The extract was washed successively with two 5-ml portions of 10% HCl, two 5-ml portions of saturated $NaHCO_3$ and H_2O (5 ml).

The extract was dried over Na_2SO_4 and evaporated *in vacuo* to give **21** as an oil, bp 87—88° (3 mmHg). Yield, 0.75 g (81%). IR ν_{max}^{film} cm^{-1}: 1730 (ester), 1723 (urethan), 1650 780, 706. UV λ_{max}^{EtOH} nm: 237. *Anal.* Calcd. for $C_{11}H_{17}O_4N$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.00; H, 7.43; N, 5.96.

Diethyl 2-Methyl-1,4-pyrrolidinedicarboxylate (23)——A solution of **21** (1.00 g) and glacial AcOH (5 ml) in EtOH (5 ml) was catalytically hydrogenated over 5% Rh-C (1 g) at room temperature under atmospheric pressure for 2 hr. Hydrogen uptake was 114.8 ml (theoretical: 104.7 ml at 17°). Usual treatment gave a colorless liquid (**23**), bp 114—115° (8 mmHg). Yield, 0.814 g (83.4%). *Anal.* Calcd. for $C_{11}H_{19}O_4N$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.48; H, 8.32; N, 5.67.

α,α-Diphenyl-1-ethoxycarbonyl-2-methyl-4-pyrrolidinemethanol (24)——To a solution of **23** (0.535 g, 2.33 mol) in anhyd. tetrahydrofuran (THF) (10 ml) a solution of PhMgBr (5.14 mmol) in THF (10 ml) (prepared from 0.125 g of Mg and bromobenzene (0.807 g) in anhyd. THF) was added at room temperature and stirring was continued for 4 hr under reflux. The reaction mixture was hydrolyzed with NH_4Cl solution. The resulting solution was extracted with ether. Evaporation of the solvent gave **24** as a thick syrup, bp 184—189° (0.85 mmHg). Yield, 0.586 g (74.1%). IR ν_{max}^{film} cm^{-1}: 3472 (OH), 1691 (urethan), 755, 700. UV λ_{max}^{EtOH} nm: 248.

1,1,5-Trimethyl-3-diphenylmethylenepyrrolidinium Iodide (3)——(i) Dehydration of **24**: (a) To a solution of **24** (0.5 g) in anhyd. EtOH (10 ml) HCl gas was saturated and the reaction mixture was allowed to stand overnight. The solvent was evaporated under reduced pressure, the residue was dissolved in ether (10 ml), and the organic layer was washed successively with saturated $NaHCO_3$ and H_2O, and dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was purified by distillation to give ethyl 2-methyl-4-diphenylmethylenepyrrolidine-1-carboxylate (**25**) as an oil, bp 108—113° (0.1 mmHg). Yield, 0.4048 g (85.5%). IR ν_{max}^{film} cm^{-1}: 3061, 1706, 1603, 770, 700. UV λ_{max}^{EtOH} nm: 248. NMR ($CDCl_3$) δ (ppm): 1.18 (3H, d, J=7.5 Hz, $C_{(2)}$–C$\underline{H}_3$), 1.21 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.17 (2H, q, J=7.5 Hz, $C\underline{H}_2$–CH_3), 7.10—7.60 (10H, m, $(C_6\underline{H}_5)_2C$). (b) A mixture of **24** (0.075 g) and I_2 (5 mg) in anhyd. benzene (15 ml) was refluxed for 16 hr in a flask fitted with the Dean-Stark water separator. The reaction mixture was washed with 20% $Na_2S_2O_3$ solution and dried over Na_2SO_4. After evaporation of benzene *in vacuo*, the residue was applied to a silica gel column. Elution with benzene gave **25**. Yield, 0.048 g (68%).

(ii) Reduction of **25**: A solution of **25** (0.175 g) and $LiAlH_4$ (0.104 g) in anhyd. ether (10 ml) was refluxed for 2 hr. To the cooled reaction mixture was added 10% HCl with ice-cooling to decompose excess reagent. The mixture was made alkaline with solid K_2CO_3 and the ether layer was separated. The aqueous layer was extracted with ether. The combined ether extract was dried over Na_2SO_4 and evaporated *in vacuo* to give an oil, which was applied to a silica gel column. Elution of the column with benzene and evaporation of the solvent under reduced pressure gave 1,5-dimethyl-3-diphenylmethylenepyrrolidine (**26**) as an oil. Yield, 0.060 g (40%). IR ν_{max}^{film} cm^{-1}: 3061, 2965, 2805 (N–CH_3), 1603, 1500, 760, 700. NMR ($CDCl_3$) δ (ppm): 1.12 (3H, s, $C_{(5)}$–C$\underline{H}_3$), 2.20 (3H, s, N–C$\underline{H}_3$), 7.10—7.70 (10H, m, $(C_6\underline{H}_5)_2C$). UV λ_{max}^{EtOH} nm: 246. Mass Spectrum *m/e*: 263 (M^+).

(iii) Methiodide (**3**): To the solution of **26** (40 mg) in anhyd. benzene (5 ml) was added CH_3I (0.15 ml) and the mixture was stirred at room temperature for 1 hr. After refluxing for 10 min on a steam bath, the reaction mixture was allowed to stand overnight. The precipitate formed was collected and recrystallized from EtOH to give 40 mg of **3** as colorless plates, mp 224—225°. *Anal.* Calcd. for $C_{20}H_{24}NI$: C, 59.26; H, 5.97; N, 3.46. Found: C, 59.33; H, 5.91; N, 3.22. IR ν_{max}^{KBr} cm^{-1}: 2960, 1600, 760, 700. UV λ_{max}^{EtOH} nm: 247. NMR ($CDCl_3$) δ (ppm): 1.46 (3H, d, J=7.5 Hz, $C_{(5)}$–C$\underline{H}_3$), 2.5—3.0 (3H, m, $C_{(5)}$–$\underline{H}$ and $C_{(4)}$–$\underline{H}_2$), 3.00, 3.50 (3H each, s, $\overset{+}{N}(C\underline{H}_3)_2$), 4.22, 5.17 (1H each, d, J=14 Hz, $C_{(2)}$–$\underline{H}_2$).

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