Notes

[Chem. Pharm. Bull. 33(7)2996—3000(1985)]

Synthesis of Pyrrolidine Derivatives with Pharmacological Activity. XI.[1] The Lora-Tamayo Reaction of 3-Methyl-1,1-diphenyl-1,4-butanediol with Acetonitrile–Stannic Chloride Complex. Synthesis of 1,2,5-Trimethyl-3-diphenylmethylenepyrrolidines

SADAO OHKI,* TATSUO NAGASAKA, NAGANORI OZAWA, TOKUHIRO WATANABE, HIDEAKI MATSUDA, and FUMIKO HAMAGUCHI

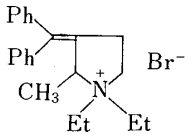
Tokyo College of Pharmacy, 1432–1 Horinouchi Hachioji, Tokyo 192–03, Japan

(Received October 1, 1984)

The synthesis and anticholinergic activities of 1,1,2,5-tetramethyl-3-diphenylmethylenepyrrolidinium iodides are described. An unusual reaction of 3-methyl-1,1-diphenyl-1,4-butanediol (**6**) with acetonitrile–stannic chloride complex (Lora-Tamayo reaction) in phosphoryl chloride resulted in the formation of 2,5-dimethyl-3-diphenylmethylene-1-pyrroline (**9**), involving the migration of the methyl group. The structure of **9** was confirmed by an alternative synthetic method.

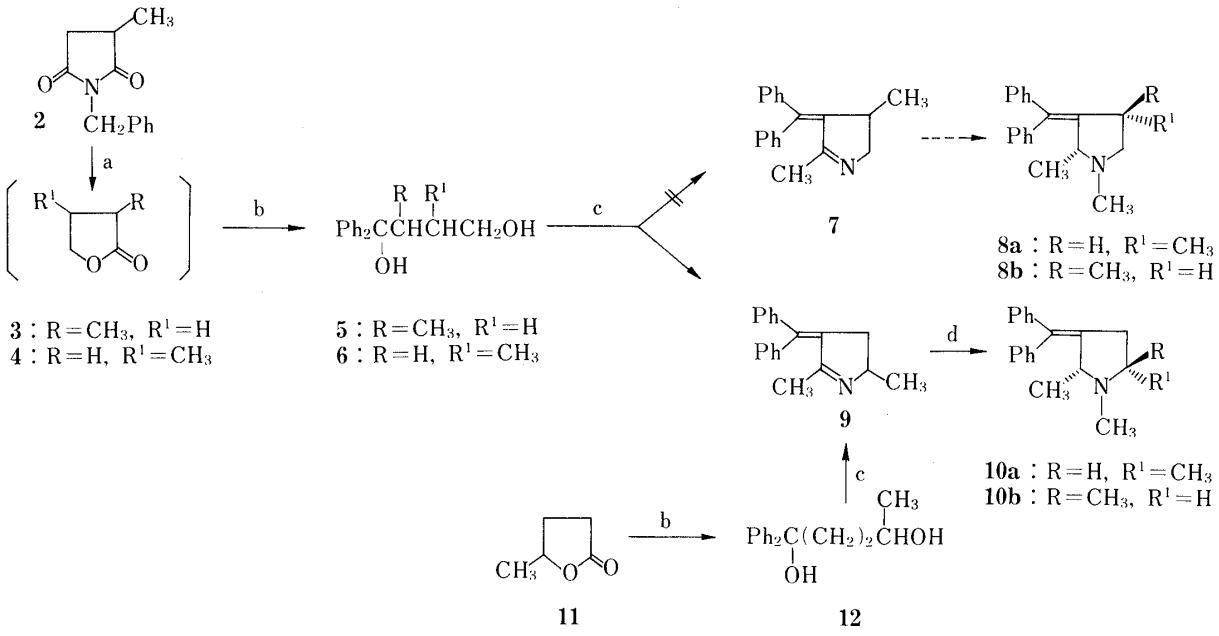
Keywords——Lora-Tamayo reaction; methyl migration; Grignard reaction; 1,2,5-trimethyl-3-diphenylmethylenepyrrolidine; anticholinergic activity

Synthesis of 1,2,4-trimethyl-3-diphenylmethylenepyrrolidine (**8a** and **8b**) alkyl halides, analogues of Prifinium Bromide[2a] (**1**, 1,1,-diethyl-2-methyl-3-diphenylmethylenepyrrolidinium bromide[2b]) was planned in order to examine the anticholinergic activities of the products. We intended to prepare **8a** and **8b** through application of the Lora-Tamayo reaction,[3] which was considered the most suitable for the synthesis of 3-diphenylmethylenepyrrolidine derivatives.[4,5] However, 1,2,5-trimethyl-3-diphenylmethylenepyrrolidines (**10a** and **10b**), previously reported,[5] were obtained unexpectedly. The results are shown in Chart 1.



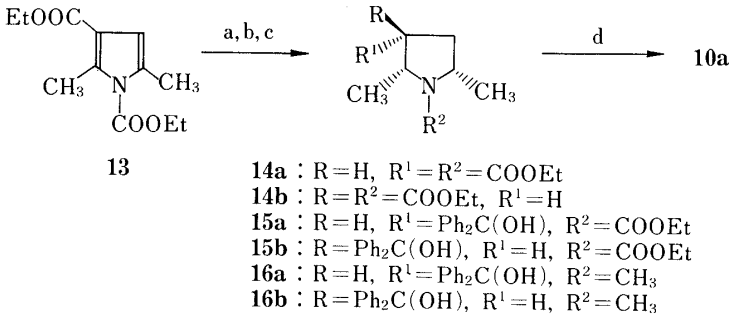
1

The reduction of *N*-benzyl-α-methylsuccinimide with sodium borohydride followed by alkaline hydrolysis afforded a mixture of α- and β-methyl-γ-butyrolactones (**3** and **4**) in a ratio of 1 : 1.4. The Grignard reaction of this mixture with phenylmagnesium bromide gave an inseparable mixture of butanediols (**5** and **6**), which was transformed to the cyclized basic compound on heating with acetonitrile–stannic chloride complex (Lora-Tamayo reaction) in phosphoryl chloride. Since **5** could not be cyclized to a pyrroline, the cyclized amine obtained was expected to be compound **7** derived from **6**. However, the product was identical with the pyrroline **9**[5a] having methyl groups at the 2- and 5-positions of pyrrolidine), which was derived previously from γ-methyl-γ-butyrolactone (**11**) (Chart 1). This was also confirmed by the finding that **10a** and **10b** derived from **9** were identical with the corresponding



a: i) $NaBH_4$, ii) NaOH, iii) H_3O^+. b: PhMgBr.
c: CH_3CN, $SnCl_4$. d: i) CH_3I, ii) $NaBH_4$.

Chart 1



a: H_2/PtO_2 (**13**→**14a**, **14b**).
b: PhMgBr (**14a**→**15a**, **14b**→**15b**).
c: $LiAlH_4$ (**15a**→**16a**, **15b**→**16b**).
d: AcOH–20% H_2SO_4 (2 : 3).

Chart 2

compounds[5b] previously reported.

For an unequivocal confirmation of its structure, **10a** was also synthesized by the method shown in Chart 2. Diethyl 2,5-dimethylpyrrole-1,3-dicarboxylate (**13**), easily prepared from ethyl 2,5-dimethylpyrrole-3-carboxylate,[6] was catalytically hydrogenated with platinum dioxide to give a stereoisomeric mixture of pyrrolidines in the ratio of 5 : 1. An equilibration reaction of this mixture with sodium ethoxide caused the ratio to become 7 : 5. This means that the predominant isomer obtained by the catalytic reduction is compound **14a**, all of whose substituents are *cis*, and the minor isomer is compound **14b** whose substituents at the 2- and 3-positions are *trans*. The Grignard reaction of **14a** and **14b**, separated by fractional distillation, with phenylmagnesium bromide afforded the diphenylcarbinols **15a** and **15b**, respectively. It was observed that *trans*-**15b** was formed more easily than *cis*-**15a**. Reduction of **15a** and **15b** with lithium aluminum hydride afforded the 1,2,5-trimethylpyrrolidines **16a** and

16b, respectively, and both were converted to **10a** in quantitative yields by dehydration. Compound **10a** and its methiodide were identical with the corresponding authentic samples prepared by the methods shown in Chart 1.

The Wagner–Meerwein type migration of the methyl group occurred on heating 3-methyl-1,1-diphenyl-1,4-butanediol (**6**) with acetonitrile–stannic chloride complex in phosphoryl chloride, and **9** was formed, probably *via* 1,1-diphenyl-1,3-pentadiene, which was also expected to be formed from 4-methyl-1,1-diphenyl-1,4-butanediol (**12**).

Synthesis of 1,2,4-trimethyl-3-diphenylmethylenepyrrolidines (**8a** and **8b**) is described in the next report.[7]

In a pharmacological examination of anticholinergic activities by the Magnus method, the relative potencies of the methiodides of **10a** and **10b** were almost the same, 0.31 and 0.30, respectively, with respect to atropine defined as 1.00.

Experimental

All melting points were determined with a micro-melting point apparatus (Yanagimoto) and are uncorrected. Infrared (IR), ultraviolet (UV in EtOH), and mass spectra were measured on a Hitachi EPI-G3 spectrophotometer, a Hitachi 200-10 spectrophotometer, and a Hitachi RMU-7L mass spectrometer, respectively. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-PS-100 (100 MHz) spectrometer. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane, TMS). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. 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). Thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (Kieselgel 60 F_{254}, Merck) and the spots were detected by UV irradiation.

The Lora-Tamayo Reaction of 3-Methyl-1,1-diphenyl-1,4-butanediol (6); Synthesis of 1,2,5-Trimethyl-3-diphenylmethylenepyrrolidines (10a and 10b)——Excess $NaBH_4$ (24 g, 634 mmol) was added to a solution of *N*-benzyl-α-methylsuccinimide (**2**, 30.4 g, 150 mmol) in 90% MeOH (60 ml) over a period of 30 min. After being stirred at room temperature for 12 h, the reaction mixture was neutralized with 10% HCl and concentrated to a viscous mass, which was extracted with Et_2O. Evaporation of the Et_2O extract provided a crude mixture of 2-methyl- and 3-methyl-4-hydroxy-*N*-benzylbutyramides as a yellow oil in quantitative yield. The NMR spectrum ($CDCl_3$) of this oil showed methyl signals at δ 1.17 (3H, d, J=7 Hz) and 0.93 (3H, d, J=7 Hz) due to 2-methyl- and 3-methylbutyramides, respectively, in the ratio of 1 : 1.4. A mixture of the crude butyramides and 15% NaOH solution (100 ml) was refluxed for 6 h. After cooling, the reaction mixture was washed with Et_2O to remove benzylamine, concentrated to one-fourth of the original volume under reduced pressure, and acidified with concentrated HCl. The lactones were salted out with NaCl and extracted with Et_2O. The extract was washed with NaCl solution, dried over Na_2SO_4, and evaporated. The residual oil was distilled to give 6.4 g (43% from imide) of a mixture of α- and β-methylbutyrolactones (**3**[8a] and **4**[8b]) as a colorless oil (ratio 1 : 1.4),[8] bp 192—198 °C. IR (neat): 1770 cm^{-1}. A solution of the lactones (**3** and **4**, 6.4 g, 64 mmol) in dry Et_2O (20 ml) was added dropwise to a solution of PhMgBr in dry Et_2O (150 ml) [prepared from 3.5 g (144 mmol) of Mg and 22.1 g (140 mmol) of PhBr]. The reaction mixture was stirred for 12 h at room temperature and then treated with 2 N HCl. The organic layer was washed with 5% NaOH and H_2O, dried over Na_2SO_4, and evaporated to provide 17.5 g of 1,1-diphenylbutane-1,4-diols (**5** and **6**) as a pale yellow oil. IR (neat): 3400 (OH), 752, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (d, J=6 Hz, CH_3) and 0.93 (d, J=6 Hz, CH_3) (ratio 3 : 5). Phosphoryl chloride (30 ml) was added gradually to a mixture of the crude butanediols (**5** and **6**, 17.5 g), CH_3CN (11.2 g), and $SnCl_4$ (11.2 g). The whole was heated at 130—135 °C (bath temp.) for 3 h and allowed to stand overnight at room temp. Following the removal of $POCl_3$ under reduced pressure, the residual viscous oil was made alkaline with 20% NaOH and the separated oil was extracted with Et_2O. The Et_2O layer was extracted with 10% HCl several times and the HCl extract was made alkaline with 40% NaOH to give an amine, which was extracted with Et_2O. The Et_2O extract was dried over K_2CO_3 and evaporated to give 5.3 g (13.6% from imide) of a pyrroline (**9**)[5a] as a viscous oil. bp 165 °C (6 mmHg). IR (neat): 1690 cm^{-1}. UV: 286 nm. Methyl iodide (3 ml) was added to a solution of **9** (5.3 g) in dry benzene (20 ml) and the mixture was stirred at room temp. until the disappearance of **9** (confirmed by TLC). The separated crystals were filtered off and dissolved in 95% MeOH (100 ml). Sodium borohydride (4 g) was added portionwise to the MeOH solution for 30 min and the reaction mixture was neutralized with 10% HCl and evaporated under reduced pressure to give a residual mass, which was then extracted with Et_2O. This extract was dried over K_2CO_3 and evaporated to an oil which, on chromatographic separation by elution with benzene–acetone (9 : 1), gave 2.4 g (42.7%) of **10a**[5b] in the first fraction and 0.9 g (16%) of **10b**[5b] in the second. The methiodide (2.1 g, 57.9%) of **10a** was prepared by refluxing **10a** with MeI in benzene. mp 234—235 °C (lit.[5b] mp 222 °C), colorless plates from acetone. IR

(KBr): 1595, 780, 765, 720, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=7 Hz, C_2-CH_3), 1.48 (3H, d, J=7 Hz, C_5-CH_3), 2.80 (3H, s, N-CH_3), 3.39 (3H, s, N-CH_3), 4.42 (1H, m, C_5-H), 5.34 (1H, q, C_2-H), 7.2 (10H, m, C_6H_5). UV: 205, 217, 250 nm. *Anal.* Calcd for $C_{21}H_{26}IN$: C, 60.15; H, 6.24; N, 3.34. Found: C, 60.09; H, 6.07; N, 3.20. Methiodide (571 mg, 42%) of **10b** mp 235 °C (not described in the lit.[5b]), colorless plates from acetone. IR (KBr): 1590, 771, 760, 706, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, d, J=8 Hz, C_2-CH_3), 1.52 (3H, d, J=8 Hz, C_5-CH_3), 3.24 (3H, s, N-CH_3), 3.33 (3H, s, N-CH_3), 4.54 (1H, m, C_5-H), 4.76 (1H, q, C_2-H). UV: 205, 217, 250 nm. *Anal.* Calcd for $C_{21}H_{26}IN$: C, 60.15; H, 6.24; N, 3.34. Found: C, 60.12; H, 6.28; N, 3.31. The identity of the tertiary amines (**10a** and **10b**) and their methiodides with the compounds described in the literature[5b] was confirmed by IR and NMR spectral comparisons.

Diethyl 2,5-Dimethylpyrrole-1,3-dicarboxylate (13)——A mixture of ethyl 2,5-dimethylpyrrole-3-carboxylate[6] (6.93 g, 41 mmol), K (1.63 g, 42 mmol), and dry toluene (50 ml) was gently refluxed for 12 h, then cooled. A solution of ClCOOEt (4.5 g, 41 mmol) in dry toluene (10 ml) was added dropwise to the reaction mixture at 5—10 °C and stirring at 50 °C was continued for 10 min. After the removal of KCl by filtration, followed by evaporation of the filtrate, the residual oil was distilled to give a cleaner oil. bp 125—135 °C (3.5 mmHg). GLC (column temp. 150 °C, N_2 50 ml/min), t_R=3.0 (starting material) and 10.1 min (ratio 1 : 10). Chromatographic separation by elution with $CHCl_3$ gave 7.5 g (76%) of **13** (along with 0.78 g of the starting material). IR (neat): 1755, 1715 cm^{-1} (COOEt). TLC ($CHCl_3$), one spot. GLC, one peak.

Diethyl 2,5-Dimethylpyrrolidine-1,3-dicarboxylate (14a and 14b)——Catalytic hydrogenation of **13** (7.5 g) with PtO_2 (0.6 g) in EtOH (70 ml) containing concentrated HCl (10 drops) was continued till the theoretical volume of hydrogen had been absorbed. The catalyst was filtered off and the filtrate evaporated to an oil, which was dissolved in Et_2O. The extract was washed with $NaHCO_3$ solution and H_2O, dried over Na_2SO_4 and evaporated. The residual oil was then distilled to give 5.39 g (71%) of **14a** and **14b** as a colorless oil. bp 116—117 °C (3 mmHg). IR (neat): 1740, 1700 cm^{-1} (COOEt). TLC ($CHCl_3$), one spot. GLC (column temp. 150 °C, N_2 50 ml/min), t_R=4.25 and 5.30 min (ratio 1 : 5). A mixture of this oil (3.0 g), EtONa (prepared from 0.6 g of Na), and dry EtOH (10 ml) was warmed at 60 °C for 30 min. After evaporation of the EtOH, the residual yellow oil whose GLC showed two peaks at t_R=4.25 and 5.30 min (ratio 5 : 7) gave 0.5 g of bp 109 °C (3 mmHg) fraction and 0.72 g of bp 140 °C (3 mmHg) fraction on fractional distillation. By GLC, the former was found to consist of more than 90% of the stable 2,3-*trans*-form (**14b**) (t_R=4.25 min), and the latter, of more than 90% of the unstable 2,3-*cis*-form (**14a**) (t_R=5.30 min).

Ethyl *cis*-2,5-Dimethyl-3-(α-hydroxy-α,α-diphenyl)methylpyrrolidine-1-carboxylate (15a and 15b)——The Grignard reaction (room temp. 1.5 h, and reflux 2 h) of **14b** (crude, 500 mg, 2 mmol) with PhMgBr [prepared from 200 mg (8 mmol) of Mg and 1.35 g (8.6 mmol) of PhBr] in dry Et_2O (10 ml) followed by the ordinary work-up and chromatographic separation by elution with $CHCl_3$ gave 640 mg (88%) of **15b** as a solid. mp 133—135 °C. IR (KBr): 3350 (OH), 1665 (COOEt), 760, 750, 710 cm^{-1}. GLC (column temp. 250 °C, N_2 50 ml/min), t_R=3.85 min. *Anal.* Calcd for $C_{21}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.06; H, 7.74; N, 3.41.

A 0.75 g (52%) of 2,3-*cis*-form (**15a**) was also obtained from 1.0 g of crude **14a** by the same method. **15a**: mp 192—194 °C, colorless needles from isopropyl ether–EtOH. IR (KBr): 3500 (OH), 1680 (COOEt), 757, 750, 705, 700 cm^{-1}. GLC (column temp. 250 °C, N_2 50 ml/min), t_R=4.35. TLC ($CHCl_3$: MeOH = 1 : 1), one spot. *Anal.* Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.84; H, 7.71; N, 3.62.

2,5-*cis*-1,2,5-Trimethyl-3-(α-hydroxy-α,α-diphenyl)methylpyrrolidines (16a and 16b)——Lithium aluminum hydride (366 mg, 18 mmol) was added portionwise to a solution of **15b** (crude, 678 mg, 2 mmol) in dry THF (5 ml). The reaction mixture was refluxed for 2 h and after cooling, Et_2O saturated with H_2O was added. The Et_2O extract was washed with NaCl solution and dried over Na_2SO_4. Evaporation of the solvent gave a solid mass, which was recrystallized from isopropyl ether. **16b**: Yield, 169 mg (30%). IR (KBr): 3300 (br, OH), 750, 700 cm^{-1} (the C=O band of the ester disappears). GLC (column temp. 230 °C, N_2 50 ml/min), t_R=2.7 min.

A 280 mg (67%) yield of the 2,3-*cis*-form (**16a**) was also obtained from 500 mg of **15a** by the same method. **16a**: mp 131—133 °C, colorless plates from isopropyl ether. IR (KBr): 3400 (br), 707 cm^{-1} (the C=O band of the ester disappears). GLC (column temp. 250 °C, N_2 50 ml/min), t_R=1.8 min. TLC ($CHCl_3$: MeOH = 10 : 1), one spot. *Anal.* Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.39; H, 8.50; N, 4.37.

2,5-*cis*-1,2,5-Trimethyl-3-diphenylmethylenepyrrolidine (10a) from 16a and 16b——Compound **10a** was obtained from both **16a** and **16b** in quantitative yield by gentle refluxing for 60 h in a mixture of AcOH–20% aq. H_2SO_4 (2 : 3 volume). Compound **10a** and its methiodide (mp 234—235 °C) were shown to be identical with authentic samples prepared by the methods illustrated in Chart 1 on the basis of IR, NMR, and UV spectral comparisons and mixed melting point determination.

Acknowledgment We should like to express our appreciation to the staff members of the central analytical center of Tokyo College of Pharmacy for the elemental analyses, NMR and mass spectral measurements. We are also grateful to Fumio Honda and Takaharu Ono of the Central Laboratory, Fujisawa Pharmaceutical Industries, Ltd. for carrying out pharmacological tests.

References and Notes

1) Part X: N. Ozawa, F. Hamaguchi, T. Nagasaka, H. Matsuda, Y. Kosugi, and S. Ohki, *Yakugaku Zasshi*, **100**,

749 (1980).
2) *a*) This is the generic name [Padrin®, Riabal®]. *Cf.* The Merck Index, 10th ed., p. 1114; *b*) S. Ohki, M. Yoshino, and F. Hamaguchi, *Chem. Pharm. Bull.*, **16**, 320 (1968).
3) M. Lora-Tamayo, R. Madronero, and G. Garcia Munoz, *Chem. Ber.*, **93**, 289 (1960).
4) See Parts I—X of this series and references cited therein.
5) *a*) S. Ohki, F. Hamaguchi, T. Yanagi, and M. Yoshino, *Chem. Pharm. Bull.*, **14**, 187 (1966); *b*) S. Ohki and M. Yoshino, *ibid.*, **16**, 269 (1968).
6) A. Hantzsch, *Ber.*, **23**, 1474 (1890).
7) S. Ohki, T. Nagasaka, H. Matsuda, N. Ozawa, and F. Hamaguchi, *Chem. Pharm. Bull.*, submitted.
8) The ratio was determined by comparison of the NMR spectrum and GLC behavior of this mixture with those of authentic samples. *a*) W. H. Bentley, E. Haworth, and W. H. Perkin, Jr., *J. Chem. Soc.*, **1896**, 173; *b*) S. S. G. Sircar, *ibid.*, **1928**, 901.