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Synthesis and Selective Activity of Cholinergic Agents with Rigid Skeletons. III[1]

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Dimethyl quaternary salts of *cis*- and *trans*-piperidine-3,4-diol acetonides (**9** and **15**) were prepared from readily available intermediates, 1-benzoyl and 1-ethoxycarbonyl derivatives of 1,2,5,6-tetrahydropyridine (**4a** and **4b**). The activity of **9** was examined and the presence of the rigid skeleton was shown to markedly decrease the cholinomimetic effect compared with the partially opened skeleton. The relationship between **9** and known potent muscarinic agents is discussed.

Keywords——cholinergic agents; muscarinic activity; design and synthesis; semi-rigid skeleton; quaternary salts of piperidine derivatives; dose-response curve; structure–activity relationship

In the preceding papers of this series,[1,2] the authors have presented the hypothesis that muscarinic activity requires the binding of agents to the muscarinic receptor in a particular conformation in which a common spatial configuration of four atoms, one carbon in a terminal methyl moiety, one ammonium nitrogen, and two oxygen atoms, is required. On this basis, compounds with rigid skeletons of the types B, C, D, E, and F (Fig. 1). were synthesized and

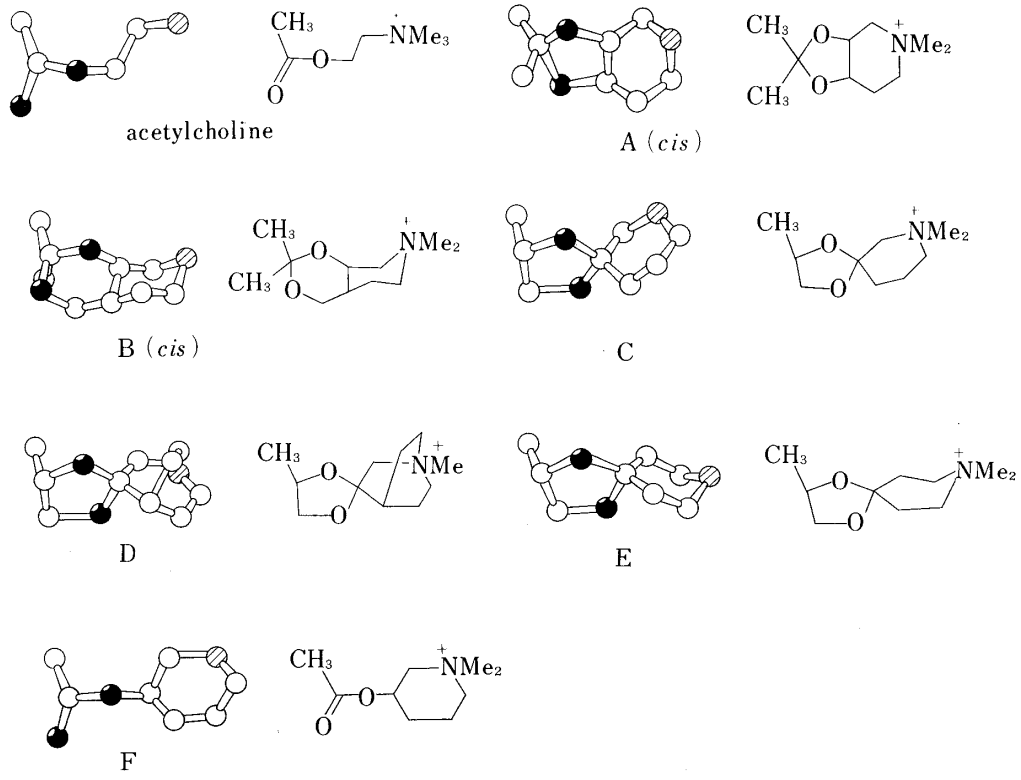

Fig. 1. Structures and Molecular Shapes of Acetylcholine, Designed Compound (A), and Related Synthetic Compounds (B—F)

○, carbon; ◍, nitrogen; ◕, oxygen.

their cholinomimetic activitirs were examined to investigate in detail the relationship between the spatial arrangement of the specified atoms and the activity.

This paper deals with the synthesis of piperidinuim salts of type A, which is regarded as a ring modified form of type B, and possesses a dioxolane ring differing in position from those of spiro-ketal types, E and F. The skeletons of related compounds are illustrated in

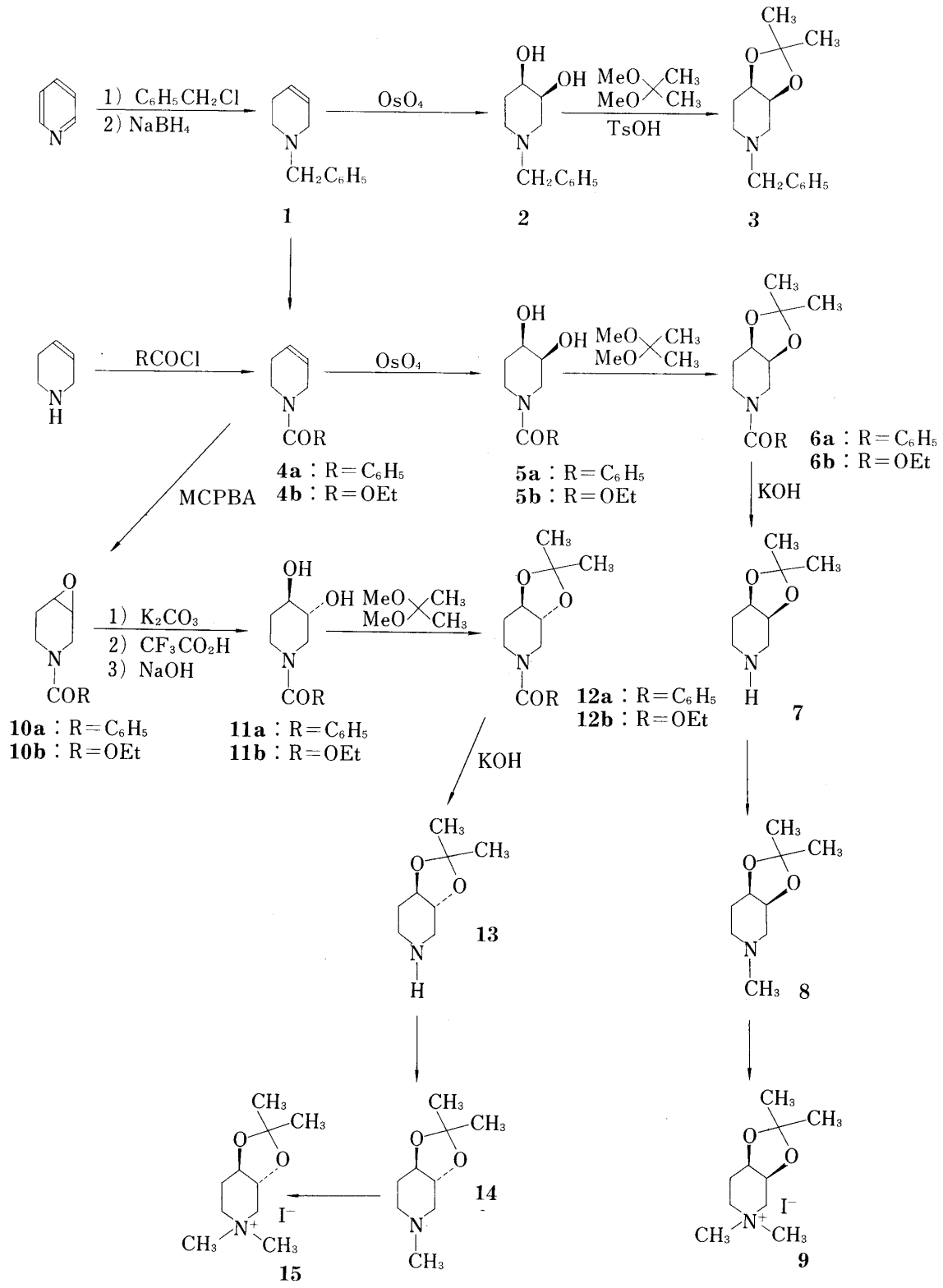

Chart 1

Fig. 1. The pharmacological properties of type A compounds are also described and the relationships among the various types are discussed.

As an intermediate for A, compound **1** was prepared by quaternization of pyridine with benzyl chloride followed by reduction with sodium borohydride by a modification of the procedure of Oediger and Joop.[3] The hydrochloride of this intermediate was oxidized with osmium tetroxide and potassium chlorate to give the *cis*-diol **2** as an oil. The ketalization of **2** with formaldehyde, acetaldehyde, and acetone in the presence of hydrochloric acid, *p*-toluenesulfonic acid (TsOH) or perchloric acid, failed, but the acetonide **3** was obtained by using dimethoxypropane and TsOH though in low yield (28%). The oxidation of **1** with *m*-chloroperbenzoic acid gave a mixture of N-oxides but not the desired epoxide, which was anticipated as an intermediate for *trans*-A. Since protection with the benzyl group seemed to be unsatisfactory, the route to A was altered to start from acyl-protected material. Thus 1-benzoyl- and 1-ethoxycarbonyl-1,2,5,6-tetrahydropyridine (**4a** and **4b**) were prepared as intermediates. The tetrahydropyridine was benzoylated by the Schotten–Baumann procedure to give **4a**, while compound **1** was converted to **4b** by refluxing it with ethyl chloroformate. Oxidation of **4a** with osmium tetroxide and potassium chlorate by a modification of the method of Petrow and Stephenson[4] gave *cis*-1-benzoylpiperidine-3,4-diol (**5a**) as crystals. Similar oxidation was applied to **4b**, giving *cis*-1-ethoxycarbonylpiperidine-3,4-diol (**5b**) as an oil. The ketalization of **5a** and **5b** with acetaldehyde was examined but pure products were not obtained. Therefore condensation with acetone was investigated by refluxing **5a**, TsOH, and molecular sieves 4Å in acetone for a long period. The acetonide (**6a**) was obtained in 66% yield. The reactions of **5a** and **5b** with a mixture of dimethoxypropane, acetone, TsOH, and molecular sieves shortened the reaction time and produced acetonides (**6a** and **6b**) in satisfactory yields. Each acyl-ketal (**6a** and **6b**) was hydrolyzed with aqueous potassium hydroxide to the free base. An attempt to convert **6a** to **8** with lithium aluminum hydride[5] failed and the starting material was recovered. Methylation of **7** with methyl iodide in ether resulted in a low yield of the monomethyl compound. The yield of **8** was increased by using *n*-butyllithium or triethylamine, but the product was contaminated with unchanged **7**. The methylation of **7** was achieved by a reductive procedure with formaldehyde and sodium cyanoborohydride in methanol without contamination. Quaternization of **8** with methyl iodide gave *cis*-A, compound **9**, as hygroscopic crystals.

The *trans*-isomer of A was synthesized starting from compound **1**. The intermediates, **1a** and **1b**, were oxidized with *m*-chloroperbenzoic acid to the epoxides, **10a** and **10b**, which were converted to the diols, **11a** and **11b**, respectively, by treatment with trifluoroacetic acid followed by sodium hydroxide. The *trans*-diol, **11a** was reacted with a mixture of dimethoxypropane and acetone in the presence of TsOH and molecular sieves 4Å under reflux for 15 h to obtain the *trans*-ketal **12a**. The yield was increased when bis(*p*-nitrophenyl)phosphate[9] was used instead of TsOH and acetone was removed from the solvent. The ethoxycarbonyl diol, **11b**, was also converted to the corresponding ketal, **12b**, by the latter method. The *trans*-ketals were hydrolyzed, methylated, and quaternized in a manner similar to that described for the *cis* series giving trans A, compound **15**, as crystals.

Pharmacology and Discussion

Figure 2 shows dose-response curves for the contraction of guinea-pig ileum. The contraction was recorded isotonically by the Magnus method in comparison with that of ACh in Locke solution (NaCl, 9.0 g; KCl, 0.42 g; $CaCl_2$, 0,24 g; $NaHCO_3$, 1.0 g; glucose, 1.0 g/l; pH 7.2—7.4) at 25±1°C. The average contraction values of 5 experiments are plotted.

The curve of *cis*-A, compound **9**, was compared with those of acetylcholine, the known potent muscarinic agents, *cis*- and *trans*-2-methyl-4-trimethylammoniomethyldioxolanes (**16** and **17**),[6,7] and compounds **18**, **19**, **20**, and **21**[2] which were previously reported by us.

trans A (**15**) could not be tested because insufficient sample was available.

Compound **9** showed a marked decrease in either contractile response or affinity compared with the corresponding dioxane compound **19**. The decrease in potency with the change of dioxane to dioxolane suggests that the relative position of O or C–CH_3 plays an important role in the receptor binding. The change of the piperidinium ring (**19**) to a pyrrolidinium ring (**21**) is shown to cause essentially no change in activity but the *trans*-junction of the piperidinum ring and dioxane (**20**) results in a considerable decrease in potency. Ring closure around the nitrogen atom seems to lower the activity, on the basis of a comparison of piperidinium and pyrrolidinium salts with potent compounds **16** and **17**.

Since it has been reported that the activities of the 2,2-dimethyl analogs of **16** and **17** are much lower than those of the monomethyl compounds,[6] the potencies of the C-dimethyl compounds (**9**, **19**, **20**, and **21**) might be considered in a similar light.

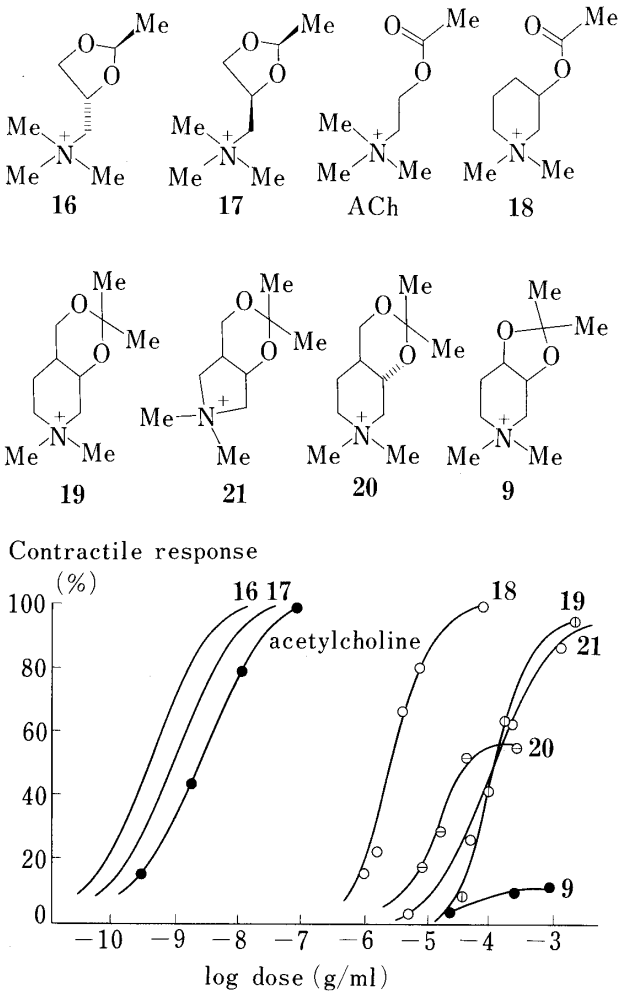

Fig. 2. Dose-response Curves (Guinea-pig Ileum Contraction) and Structural Relationship of Synthesized Compound (**9**) and Muscarinic Compounds Related to **9**

Experimental

1-Benzyl-1,2,5,6-tetrahydropyridine (1)——Benzyl chloride (16 g) was added dropwise to pyridine (10 g) and heated for 1 h at 140°C. After cooling, the solid was dissolved in EtOH (400 ml) and $NaBH_4$ (10 g) was added to the stirred solution. The mixture was stirred for an additional 6 h, and H_2O (200 ml) was added. The solution was decanted from the solid, which was washed with Et_2O (100 ml × 2). The combined solution was washed with saturated NaCl, dried over Na_2SO_4, and concentrated to remove the solvent. The residue was distilled under reduced pressure to give an oil, bp_{17} 127—128°C (10.1 g, 48%), which was converted to the hydrochloride by passing gaseous HCl through its Et_2O solution. The hydrochloride, mp 195—197°C, showed no depression of mixed melting point with authentic sample.

1-Benzylpiperidine-cis-3,4-diol (2)——The hydrochloride of **1** (2.09 g) was dissolved in H_2O (30 ml) (pH 4) and K_2CO_3 was added to make pH 7. $KClO_3$ (1.88 g) and then OsO_4 solution (20 mg in 3.3 ml of H_2O) were added in small portions to the stirred solution, and the mixture was warmed at 70—80°C for 10 h, then extracted with Et_2O. The H_2O layer was concentrated to dryness and the residue was extracted with tetrahydrofuran. The Et_2O and tetrahydrofuran extracts were combined and dried over Na_2SO_4, and the solvent was removed by distillation. The residue was distilled at $bp_{0.7}$ 150—155°C (bath temp.), mp 62°C (1 g, 50%).

1-Benzylpiperidine-*cis*-diol Acetonide (3)——Compound **2** (150 mg) was dissolved in 2,2-dimethoxypropane (1.5 ml) and *p*-toluenesulfonic acid (0.17 g) was added. The mixture was refluxed for 6 h. After addition of Me_2CO (5 ml), reflux was continued for an additional 6 h in a Dean–Stark apparatus. The reaction mixture was stirred with aqueous K_2CO_3 (20%, 5 ml) for 1 h and the solid was filtered off and washed with $CHCl_3$. The H_2O layer was concentrated under reduced pressure and the residue was extracted with $CHCl_3$. The washing and the extract were combined, dried (Na_2SO_4), and the solvent was evaporated off. The residue was distilled to collect a fraction of $bp_{1.0}$ 165—170°C (bath temp.) (50 mg). NMR ($CDCl_3$) δ: 2.25—2.51 (4H, m, $NC\underline{H}_2CH_2$ and NCH_2CH), 3.8—4.4 (2H, m, CH), 1.7—2.2 (2H, q, J=7 Hz, $NCH_2C\underline{H}_2$), 1.35 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.45 (2H, s, $C_6H_5C\underline{H}_2$), 7.26 (5H, s, C_6H_5).

1-Benzoyl-1,2,5,6-tetrahydropyridine (4a)——Benzoyl chloride (37 g, 0.26 mol) was added dropwise to an ice-chilled mixture of 1,2,5,6-tetrahydropyridine (18.2 g, 0.22 mol) and 10% NaOH (280 ml) under stirring. After the mixture had been stirred for an additional 2 h, the solution was extracted with $CHCl_3$ and the organic layer was dried (Na_2SO_4). The solvent was removed and the residual oil was distilled to give an oil, bp_3 133—138°C (36.3 g, 88.5%). The spectral data of this product were identical with those in the literature.

1-Ethoxycarbonyl-1,2,5,6-tetrahydropyridine (4b)[8]——Ethyl chloroformate (6.5 g, 60 mmol) was added to a refluxing solution of compound **1** (6.7 g, 39 mmol) in C_6H_6 (50 ml) with stirring. After reflux for 1 h, the mixture was washed with 10% HCl then H_2O, and dried over Na_2SO_4. The solvent was evaporated off and the residue was distilled, bp_{10} 80—94°C (4.5 g, 75%). NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz, $OCH_2\underline{CH_3}$), 1.9—2.3 (2H, m, 5-CH_2), 3.4—3.7 (2H, m, 6-CH_2), 3.8—4.1 (2H, m, 2-CH_2), 4.14 (2H, q, $J=7$ Hz, $OC\underline{H_2}CH_3$), 5.6—5.9 (2H, m, 3-CH and 4-CH).

1-Benzoylpiperidine-*cis*-3,4-diol (5a)——$KClO_3$ (1.8 g, 14 mmol) was added to a stirred mixture of compound **4a** (2.0 g, 10 mmol) in H_2O (30 ml), and then OsO_4 in H_2O (12 mg/ml, 0.83 ml, 3.9×10^{-5} mol) was added. The mixture was warmed at 50°C with stirring for 5 h. After cooling, the solution was extracted with C_6H_6. The H_2O layer was concentrated and the residue was extracted with hot $CHCl_3$. The $CHCl_3$ solution was distilled to remove the solvent and the residual solid was recrystallized from AcOEt containing a small amount of MeOH, mp 147—148°C (1.7 g, 72%). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.78; N, 6.45. NMR ($CDCl_3$) δ: 1.4—1.9 (2H, m, 3-CH_2), 2.8—3.5 (4H, m, 2-CH_2 and 6-CH_2), 3.5—4.2 (2H, m, 3-CH and 4-CH), 4.5—4.8 (2H, b, 2OH), 7.40 (5H, s, C_6H_5).

1-Ethoxycarbonylpiperidine-*cis*-3,4-diol (5b)——A solution of OsO_4 (6 mg in 1 ml of H_2O) was added to a stirred mixture of compound **4b** (1.0 g, 6.5 mmol) and $KClO_3$ (1.26 g) in H_2O (60 ml) and the whole was stirred for 20 min. The solution was warmed at 50°C for 4.5 h with stirring and extracted with C_6H_6. The H_2O layer was concentrated and the residue was extracted with hot $CHCl_3$. The solvent was evaporated from the extract and the residual oil was distilled, $bp_{0.75}$ 115—125°C (bath temp.) (0.69 g, 57%). *Anal.* Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.90; H, 8.11; N, 7.34. NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz, $OCH_2C\underline{H_3}$), 1.6—2.0 (2H, m, 5-CH_2), 2.8—3.1 (2H, br.s, 2OH), 3.4—3.7 (4H, m, 2-CH_2 and 6-CH_2), 3.7—4.0 (2H, m, 3-CH and 4-CH), 4.14 (2H, q, $J=7$ Hz, $OC\underline{H_2}CH_3$).

1-Benzoylpiperidine-*cis*-3,4-diol Acetonide (6a)——A mixture of 2,2-dimethoxypropane (30 ml), TsOH (0.17 g), molecular sieve 4 Å (0.5 g), and compound **5a** (10.0 g, 45 mmol) was refluxed in Me_2CO (60 ml) for 5 h. The reaction mixture was filtered to remove solid material and 10% K_2CO_3 was added to make the solution alkaline. The mixture was extracted with $CHCl_3$ and the organic layer was dried (Na_2SO_4). The solvent was evaporated off, and the residue was distilled, bp_2 150—155°C (11.5 g, 97.4%). NMR ($CDCl_3$) δ: 1.34 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.7—2.2 (2H, m, 5-CH_2), 3.2—4.0 (4H, m, 2-CH_2 and 6-CH_2), 4.0—4.7 (2H, m, 3-CH and 4-CH), 7.40 (5H, s, C_6H_5). The product was used directly for the next step.

1-Ethoxycarbonylpiperidine-*cis*-3,4-diol Acetonide (6b)——Compound **5b** (3.0 g, 16 mmol), 2,2-dimethoxypropane (6 ml), TsOH (0.10 g), and molecular sieve 4 Å (0.5 g) were added to Me_2CO (25 ml), and the mixture was refluxed for 12 h. The solution was made alkaline by addition of 10% K_2CO_3, then filtered to remove solid material, and the solid was washed with $CHCl_3$. The solution was dried (Na_2SO_4), the solvent was evaporated off and the residue was distilled, bp_{13} 105—110°C (bath temp.) (3.0 g, 82.5%). NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz, $OCH_2C\underline{H_3}$), 1.34 (3H, s, CCH_3), 1.47 (3H, s, CCH_3), 1.7—2.0 (2H, m, 5-CH_2), 3.2—3.7 (4H, m, 2-CH_2 and 6-CH_2), 3.9—4.5 (2H, m, 3-CH and 4-CH), 4.14 (2H, q, $J=7$ Hz, $OC\underline{H_2}CH_3$). The distillate was used for the preparation of **7** without further purification.

Piperidine-*cis*-3,4-diol Acetonide (7)——i) Compound **6a** (5.4 g, 20 mmol) was refluxed in 10% KOH (50 ml) for 10 h. The reaction mixture was saturated with NaCl and extracted with $CHCl_3$. The extract was dried (Na_2SO_4), and the solvent was evaporated off to leave an oil, which was distilled under reduced pressure, bp_{20} 92—94°C (2.7 g, 82%).

ii) A mixture of compound **6b** (0.5 g, 2.2 mmol) and 10% KOH (20 ml) was refluxed for 4 h. The hydrolyzate was saturated with NaCl and extracted with $CHCl_3$. The dried (Na_2SO_4) extract was concentrated to give an oil, which was distilled, bp_{15} 170—180°C (bath temp.) (0.27 g, 79%). NMR ($CDCl_3$) δ: 1.35 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.6—2.0 (2H, q, $J=7$ Hz, 5-CH_2), 1.82 (1H, s, NH), 2.6—3.1 (2H, q, $J=7$ Hz, 6-CH_2; 2H, 2-CH_2), 3.9—4.4 (2H, m, 3-CH and 4-CH). This oil was converted to the 1-methyl derivatives (**8**) without purification.

1-Methylpiperidine-*cis*-3,4-diol Acetonide (8)——A mixture of compound **7** (0.33 g, 2.1 mmol) and HCHO (0.85 g, 10 mmol) in MeOH (5 ml) was stirred for 30 min at room temperature, then $NaBH_3CN$ (60 mg) was added and the whole was stirred for an additional 30 min. The solution was diluted with H_2O (3 ml) and MeOH was removed by distillation under reduced preseure. The residue was extracted with $CHCl_3$ and the extract was dried (Na_2SO_4). The organic layer was evaporated off to leave an oil, which was distilled, bp_{14} 80—90°C (bath temp.) (0.2 g, 55%).

1-Methylpiperidine-*cis*-3,4-diol Acetonide Methiodide (9)——MeI (1.35 g, 9.4 mmol) was added to a cooled solution of compound **8** (0.54 g, 3.2 mmol) in abs. Et_2O. The resulting crystals were filtered off and recrystallized from EtOH. mp 196—197°C (0.87 g, 90%). *Anal.* Calcd for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; N, 4.47. Found: C, 38.52; H, 6.72; N, 4.50.

1-Benzoyl-3,4-epoxypiperidine (10a)——A solution of compound **4a** (0.5 g, 2.7 mmol) and *m*-chloroperbenzoic acid (MCPBA) (0.64 g, 3.7 mmol) in CH_2Cl_2 (20 ml) was stirred overnight at room temperature. Aqueous 10% Na_2SO_3 was then added to the solution until no peracid was detected (KI-starch). *m*-Chlorobenzoic acid was removed by extraction with 10% $NaHCO_3$ and the organic layer was washed with saturated NaCl, dried over $MgSO_4$ and concentrated to a syrup, which was distilled to give an oil, bp_3 150—155°C (bath temp.) (0.5 g, 92%). NMR ($CDCl_3$) δ: 1.8—2.2 (2H, m, 5-CH_2), 3.0—3.6 (2H, m, 3-CH and 4-CH), 3.6—4.0 (4H, m, 2-CH_2 and 4-CH_2), 7.38 (5H, s, C_6H_5). This product was subjected to hydrolysis without further purification.

1-Ethoxycarbonyl-3,4-epoxypiperidine (10b)——Compound **4b** (0.67 g) was dissolved in CH_2Cl_2 (5 ml). MCPBA (0.8 g) in CH_2Cl_2 (10 ml) was added to the stirred solution at 20°C. Aqueous 10% Na_2SO_3 was added to the stirred solution until no peracid was detected (KI-starch). The CH_2Cl_2 layer was washed successively with 5% $NaHCO_3$, H_2O, and saturated NaCl, and dried over $MgSO_4$. The solvent was evaporated off and the residue was distilled, bp_{14} 95—100°C (bath temp.) (0.53 g, 52%). NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.8—2.2 (2H, m, 5-CH_2), 3.1—3.6 (2H, m, 3-CH and 4-CH), 3.6—3.9 (4H, 2-CH_2 and 6-CH_2), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$).

1-Benzoylpiperidine-*trans*-3,4-diol (11a)——A mixture of compound **10a** (0.1 g, 0.5 mmol) and 5% K_2CO_3 in EtOH–H_2O (1 : 1) (5 ml) was refluxed for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was extracted with hot EtOH. The solvent was evaporated from the extract and the residue was extracted with $CHCl_3$. After the removal of $CHCl_3$ by evaporation, the residual oil was triturated with petroleum ether to crystallize. The product was recrystallized from AcOEt containing a small amount of MeOH, mp 138—140°C (0.05 g, 46%). IR ν_{max}^{neat} cm^{-1}: 1610 (ν_{CON}), 3330 (ν_{OH}). NMR ($CDCl_3$) δ: 1.3—1.7 (2H, m, 5-CH_2), 2.8—3.5 (4H, m, 2-CH_2 and 6-CH_2), 3.5—4.2 (2H, m, 3-CH and 4-CH), 4.6—5.1 (2H, br.s, 2OH), 7.39 (5H, s, C_6H_5). The product was used directly in the next step.

1-Ethoxycarbonylpiperidine-*trans*-3,4-diol (11b)——A solution of **10b** (1.2 g, 7 mmol) in CH_2Cl_2 (2 ml) was added dropwise with stirring to ice-cooled CF_3COOH (8.1 g, 70 mmol). The mixture was allowed to stand overnight, then the solvent was evaporated off and the residue was neutralized with 10% K_2CO_3. The mixture was extracted with CH_2Cl_2 and dried ($MgSO_4$). The extract was concentrated to leave an oil, which was distilled *in vacuo*, $bp_{0.3}$ 120—130°C (bath temp.) (0.5 g, 37%). NMR ($CDCl_3$) δ: 1.43 (6H, s, 2CH_3), 1.6—2.3 (2H, m, 5-CH_2), 2.8—3.2 (4H, m, 2-CH_2 and 6-CH_2), 3.2—3.7 (2H, m, 3-CH and 4-CH), 7.38 (5H, s, C_6H_5). This oil was hydrolyzed without further purification to yield **13**.

1-Benzoylpiperidine-*trans*-3,4-diol Acetonide (12a)——A mixture of **11a** (0.47 g, 2.1 mmol), 2,2-dimethoxypropane (15 ml), molecular sieve 4 Å (0.5 g), and bis(*p*-nitrophenyl)phosphate (20 mg) was refluxed for 3 h. The solution was neutralized with K_2CO_3 (10%) and the molecular sieve was filtered off. The solvent was evaporated from the filtrate. The residue was extracted with $CHCl_3$ and the extract was dried (Na_2SO_4). The solvent was removed by distillation and the residual oil was distilled under reduced pressure, bp_4 160—168°C (bath temp.) (0.43 g, 78%). NMR ($CDCl_3$) δ: 1.43 (6H, s, 2CH_3), 1.6—2.3 (2H, m, 5-CH_2), 2.8—3.2 (4H, m, 2-CH_2 and 6-CH_2), 3.2—3.7 (2H, m, 3-CH and 4-CH), 7.38 (5H, s, C_6H_5). This oil was hydrolyzed to obtain **13**.

1-Ethoxycarbonylpiperidine-*trans*-3,4-diol Acetonide (12b)——A mixture of **11b** (0.5 g, 2.6 mmol), 2,2-dimethoxypropane (12 ml), molecular sieve 4 Å (0.5 g), and bis(*p*-nitrophenyl) phosphate (20 mg) was refluxed for 6 h. The mixture was neutralized with 10% K_2CO_3 and filtered to remove the molecular sieve. The sieve was washed with Et_2O. The filtrate was extracted with $CHCl_3$ and the extract was combined with the Et_2O washing. The solution was dried ($MgSO_4$) and the solvent was evaporated off to give an oil, which was distilled *in vacuo*, bp_8 100—110°C (bath temp.) (0.44 g, 74%). NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.45 (6H, s, 2CCH_3), 1.6—2.1 (2H, m, 5-CH_2), 2.8—3.0 (4H, m, 2-CH_2 and 6-CH_2), 3.2—3.7 (2H, m, 3-CH and 4-CH), 4.15 (2H, q, $OC\underline{H}_2CH_3$). This oil was directly subjected to hydrolysis.

Piperidine-*trans*-3,4-diol Acetonide (13)——i) Compound **12a** (0.42 g, 1.6 mmol) was mixed with 10% KOH (10 ml) and refluxed for 1 h. The mixture was washed with saturated NaCl and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to leave an oil, which was distilled, bp_8 85—92°C (bath temp.) (0.15 g, 57%).

ii) Compound **13b** (0.6 g, 2.6 mmol) was hydrolyzed with a mixture of 10% KOH (10 ml) and EtOH (2 ml) under reflux for 5 h. The mixture was washed with saturated NaCl then extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated to give an oil, which was distilled *in vacuo*, bp_8 82—90°C (bath temp.) (0.34 g, 82%). The products obtained from **12a** and **12b** showed identical NMR data and *Rf* values. NMR ($CDCl_3$) δ: 1.44 (6H, s, 2CH_3), 1.5 (1H, s, NH), 1.6—2.1 (2H, m, 5-CH_2), 2.4—2.9 (4H, m, 2-CH_2 and 6-CH_2), 3.0—3.5 (2H, m, 3-CH and 4-CH). The products were directly subjected to methylation.

1-Methylpiperidine-*trans*-3,4-diol Acetonide (14)——A solution of **13** (113 mg, 0.72 mmol) in MeOH (5 ml) was treated with 30% HCHO (0.3 g) at room temperature. The mixture was stirred for 30 min, then $NaBH_3CN$ (50 mg, 0.8 mmol) was added and stirring was continued for an additional 30 min. The mixture was then diluted with H_2O (3 ml) and MeOH was distilled off *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure, bp_8 70—75°C (bath temp.) (38 mg, 31%). NMR ($CDCl_3$) δ: 1.45 (6H, s, 2CCH_3), 1.7—2.2 (2H, m, 5-CH_2), 2.39 (3H, s, NCH_3), 2.5—2.9 (4H, m, 2-CH_2 and 6-CH_2), 3.0—3.6 (2H, m, 3-CH and 4-CH). This

oil was directly subjected to quaternization.

1-Methylpiperidine-*trans*-3,4-diol Acetonide Methiodide (15)——Compound **14** (69 mg, 0.4 mmol) was dissolved in Me_2CO (2 ml) and MeI (0.08 ml, 1.2 mmol) was added. After standing overnight, the mixture was filtered to collect crystals, mp 244—245°C (79 mg, 62%). *Anal.* Calcd for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; N, 4.47. Found: C, 38.28; H, 6.73; N, 4.65.

References and Notes

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