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A Facile Synthesis of Aminocarboxylic Acid Derivatives, New Anti-ulcer Agents

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3-[*p*-(*trans*-4-Aminomethylcyclohexylcarbonyl)phenyl]propionic acid hydrochloride (**1a**), a new anti-ulcer agent, was newly synthesized from *trans*- or mixed *trans*/*cis*-4-aminomethylcyclohexanecarboxylic acid and methyl 3-phenylpropionate (**4**) in three steps. Friedel-Crafts reaction of the acid chloride **3** and **4** was performed without any particular protection of the amino group of **3**. 3-[*p*-(4-Aminomethylbenzoyl)phenyl]propionic acid hydrochloride (**1b**) was also obtained from 4-aminomethylbenzoic acid in a similar process.

Keywords——3-[*p*-(*trans*-4-aminomethylcyclohexylcarbonyl)phenyl]propinoic acid; 3-[*p*-(4-aminomethylbenzoyl)phenyl]propionic acid; Friedel–Crafts reaction; anti-ulcer agent; *trans*-4-aminomethylcyclohexanecarboxylic acid; methyl 3-phenylpropionate

Various synthetic drugs have been used in the treatment and prevention of peptic ulcers.[1] Among them, inhibitors of gastric acid secretion including histamine H_2 receptor antagonists[2] and anti-cholinergic agents are well known as anti-ulcer agents. On the other hand, it was recently revealed[3] that gastric defensive factors such as gastric mucosal blood flow and glycoprotein production in the mucosal tissue must play important roles in gastric function. Compounds that promote these defensive factors may also be important as anti-ulcer agents.

We have synthesized novel aminocarboxylic acid derivatives in order to find new anti-ulcer agents which act mainly on these defensive mechanisms.[4] Anti-ulcerogenic effects of 3-[*p*-(*trans*-4-aminomethylcyclohexylcarbonyl)phenyl]propionic acid hydrochloride (**1a**) in experimentally induced ulcer models have been reported.[5]

A practical route to **1a** and an analogue of **1a**, 3-[*p*-(4-aminomethylbenzoyl)-phenyl]propionic acid hydrochloride (**1b**) is reported here. The synthetic sequences leading to compound **1a** are outlined in the Chart 1.

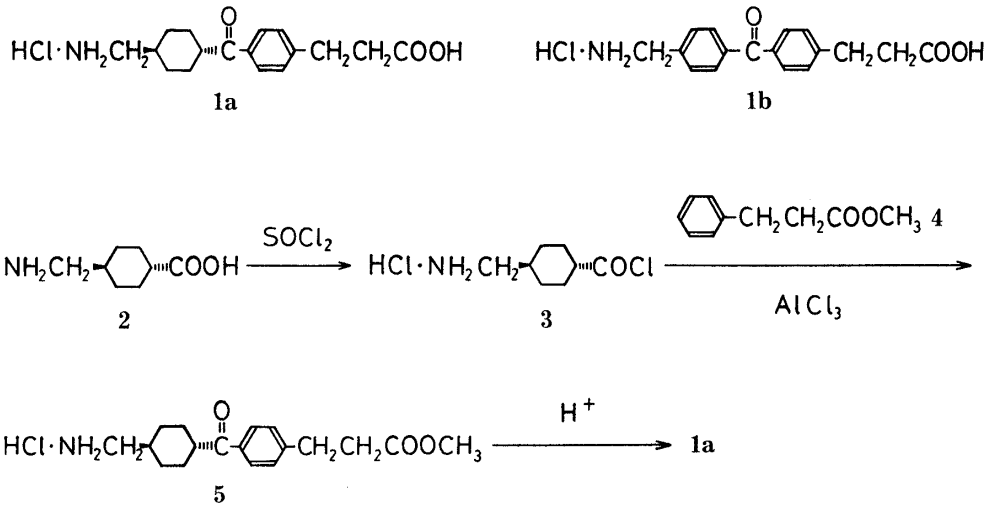

Chart 1

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Friedel–Crafts reaction of the acid chloride **3**, obtained by chlorinating *trans*-4-aminomethylcyclohexanecarboxylic acid (**2**) with thionyl chloride,[6] and methyl 3-phenylpropionate (**4**) in the presence of anhydrous aluminum chloride provided the methyl aminocarboxylate derivative **5** in the yield of 69%. In this reaction, we found that no particular protection of the amino group[7] (*e.g.* with an acetyl, benzyloxycarbonyl, or phthalimido group) was necessary for prevention of undesirable reactions. In the earlier synthesis of 3-(*p*-glycylphenyl)propionic acid hydrochloride,[8] an intermediate chlorambucil analogue, phthalimido derivative of glycine was used in the Friedel–Crafts reaction with methyl 3-phenylpropionate (**4**) to obtain methyl 3-(*p*-phthalimidoacetylphenyl)propionate. Finally, compound **5** was hydrolyzed with aqueous hydrochloric acid to yield quantitatively the crystalline compound **1a**.

In the same manner, 3-[*p*-(4-aminomethylbenzoyl)phenyl]propionic acid hydrochloride (**1b**) was synthesized from 4-aminomethylbenzoic acid hemisulfate in 57% yield, except that the acid chloride derivative was obtained by chlorination with phosphorus pentachloride.

Compound **1a** can have two geometrical isomers (*trans* and *cis* form) at the cyclohexane ring. In this synthesis of **1a**, the *trans* form of the final product was retained,[9] but when **1a** was treated with acidic solution at high temperature it was confirmed by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC) to be partially converted to the *cis* form. In 1.5 N hydrochloric solution at 100 °C, **1a** reached a state of equilibrium containing 14.4% of the *cis* isomer from the initially pure *trans* isomer, and the content of *cis* isomer decreased to 3.2% when the mixture was cooled to 70 °C gradually. Similarly, 14.6% and 1.8% of the *cis* isomer was formed as an equilibrium mixture in 0.75 N hydrochloric solution at 100 and 70 °C, respectively, but none was formed in the absence of hydrochloric acid at any temperature within 1 h.

This result suggested that pure *trans*-4-aminomethylcyclohexanecarboxylic acid (**2**) is not necessary in this scheme. In fact we found that **1a** was obtained in a good yield due to isomerization in the final step from 4-aminomethylcyclohexanecarboxylic acid containing 60% of the *cis* form as the starting material.

Further investigation on the pharmacological effects of these compounds is in progress.

Experimental

Melting points were determined by using a Mettler FP-61 melting point apparatus. Infrared (IR) spectra were measured with a JASCO A-10 spectrometer. Proton-nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a Varian EM 360 spectrometer using $(CH_3)_4Si$ as an internal standard.

Methyl 3-[*p*-(*trans*-4-Aminomethylcyclohexylcarbonyl)phenyl]propionate Hydrochloride (5)——Thionyl chloride (11.4 g) was added portionwise to a suspension of 5.0 g of *trans*-4-aminomethylcyclohexanecarboxylic acid (**2**) in 40 ml of benzene, and this mixture was heated at 40 °C for 2 h. The solvent was evaporated off under reduced pressure, and the residue was suspended in 50 ml of carbon disulfide. Anhydrous aluminum chloride (12.7 g) and 5.2 g of methyl 3-phenylpropionate (**4**) were added to the suspension at 0 °C and the whole was heated at 50 °C for 2 h. After the reaction, the solvent was distilled off under reduced pressure, and the residue was treated with 20 g of ice-water to decompose the aluminum chloride. The crystalline product was filtered off and recrystallized from acetone–water to give 7.5 g of **5** (69% yield) as colorless crystals, mp 235 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3450, 1730, 1670. NMR ($CDCl_3$) δ: 0.9—2.2 (10H, m, cyclohexane H), 2.4—3.0 (6H, m, $-CH_2-$), 3.65 (3H, s, $-OCH_3-$), 7.25 (2H, d, J=8 Hz, ArH), 7.85 (2H, d, J=8 Hz, ArH).

3-[*p*-(*trans*-4-Aminomethylcyclohexylcarbonyl)phenyl]propionic Acid Hydrochloride (1a)——A suspension of 7.5 g of **5** in 20 ml of 2 N hydrochloric acid was heated at 70 °C for 2.5 h, and then the aqueous hydrochloric acid was removed by distillation. The residue was recrystallized from water to give 6.3 g of **1a** (88% yield) as colorless crystals, mp 245 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3450, 1690, 1670. NMR (DMSO-d_6) δ: 0.9—2.2 (10H, m, cyclohexane H), 2.4—3.1 (6H, m, $-CH_2-$), 7.30 (2H, d, J=8 Hz, ArH), 7.85 (2H, d, J=8 Hz, ArH). *Anal.* Calcd for $C_{17}H_{23}NO_3 \cdot HCl$: C, 62.67; H, 7.42; N, 4.30. Found: C, 62.38; H, 7.31; N, 4.21.

3-[*p*-(4-Aminomethylbenzoyl)phenyl]propionic Acid Hydrochloride (1b)——Phosphorus pentachloride (18.5 g) was slowly added to a suspension of 5.0 g of *p*-aminomethylbenzoic acid hemisulfate in 75 ml of methylene chloride.

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The mixture was heated at 40 °C for 2.5 h and then cooled with ice. Carbon tetrachloride (75 ml) was added, followed by filtration to give 4.6 g of *p*-aminomethylbenzoyl chloride hemisulfate as white crystals. The resulting product was suspended in 80 ml of 1,2-dichloroethane and 8 g of anhydrous aluminum chloride and 3.5 g of methyl phenylpropionate (**4**) in 20 ml of 1,2-dichloroethane were added to the suspension at 0 °C. The mixture was stirred at 60 °C for 2 h, then the solvent was distilled off under reduced pressure. A small amount of ice-water was carefully added to the residue to decompose the excess aluminum chloride. The mixture was dissolved in 50 ml of 8 N NaOH solution and extracted with 70 ml of ethyl acetate three times. The organic layer was washed with water and dried over anhydrous sodium sulfate. Ethyl acetate was distilled off under reduced pressure and the residue was purified by silica gel column chromatography to give 4.68 g of methyl 3-[*p*-(4-aminomethylbenzoyl)phenyl]propionate (63% yield) as a colorless syrup. IR $\nu_{max}^{KBR}cm^{-1}$: 3450, 1730, 1650. NMR ($CDCl_3$) δ: 2.4—3.3 (4H, m, $-CH_2-$), 3.65 (3H, s, OCH_3), 3.95 (2H, s, $NH_2-\underline{CH_2}-$), 7.2—7.9 (8H, m, ArH). *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.34; H, 6.22; N, 4.35.

A suspension of 4.5 g of this product in 20 ml of 2 N hydrochloric acid was heated at 80 °C for 3 h and then the aqueous hydrochloric acid was removed by distillation. The residue was recrystallized from acetone–water to give 3.9 g of **1b** (91% yield) as colorless crystals, mp 218—220 °C. IR $\nu_{max}^{KBr}cm^{-1}$: 3000, 1740, 1700, 1650. NMR (CD_3OD) δ: 2.5—3.2 (4H, m, $-CH_2-$), 4.25 (s, 2H, $H_2N-\underline{CH_2}-$), 7.3—8.0 (8H, m, ArH). *Anal.* Calcd for $C_{17}H_{18}ClNO_3$: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.62; H, 5.57; N, 4.43.

3-[*p*-(*trans*-4-Aminomethylcyclohexylcarbonyl)phenyl]propionic Acid Hydrochloride (1a) from 4-Aminomethylcyclohexanecarboxylic Acid Containing 60% *cis* Form——Chlorination and Friedel–Crafts reaction were carried out to obtain methyl 3-[*p*-(4-aminomethylcyclohexylcarbonyl)phenyl]propionate as described above, from 4-aminomethylcyclohexanecarboxylic acid (5.0 g) containing 60% *cis* form as the starting material. The product was hydrolyzed with 20 ml of 2 N hydrochloric acid at 95 °C for 2 h at first and then at 70 °C for 1 h. After recrystallization from water, 5.9 g of **1a**, pure *trans* form, was obtained (57% yield).

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