Synthesis of Procaterol Derivative Having a Piperidylmethanol Group and Its β-Adrenoceptor Stimulant Activities

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A procaterol derivative (6) having a piperidylmethanol group was synthesized by the nucleophilic reaction of a 5-formylcarbostyril derivative with pyridyllithium, followed by selective catalytic reductions to afford the *erythro*-isomer. Compound 6 showed non-selective β-adrenoceptor agonist activities like those of *l*-isoproterenol in an *in vivo* assay using anesthetized dogs.

Keywords *erythro*-piperidylmethanol; nucleophilic reaction; selective catalytic reduction; procaterol derivative; β-adrenoceptor agonist activity

We have developed a β-selective adrenoceptor agonist, procaterol (**1**), which has an 8-hydroxycarbostyril group as a bioisostere for the catechol nucleus of catecholamines.[1,2] Sympathomimetic amines having a carbostyril nucleus usually have potent and β-selective adrenoceptor agonist activities. In the course of investigations on procaterol derivatives, however, we found that the piperidylmethanol derivative of procaterol showed non-selective β-adrenoceptor agonist activities like those of *l*-isoproterenol, although the prototype piperidylmethanol derivative rimiterol (**2**) was reported as a β-selective adrenoceptor stimulant.[3,4] In this paper we report the synthesis of a procaterol derivative which has a piperidylmethanol group as a cyclic side chain and its pharmacological evaluation on anesthetized dogs.

The procaterol derivative (**6**) having a piperidylmethanol group was synthesized according to the scheme shown in Chart 1. A tetrahydrofuran (THF) solution of 8-benzyloxy-5-formylcarbostyril (**3**)[5] was treated with α-pyridyllithium to give α-pyridylmethanol (**4**) in 43% yield. Compound **4** was debenzylated by selective catalytic reduction using 5% palladium black to give the 8-hydroxycarbostyril derivative (**5**) in 73% yield. The pyridyl group of compound **5** was selectively reduced with platinum oxide to afford *erythro*-piperidylmethanol (**6**) in 41% yield. In agreement of this assignment, the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (dimethyl sulfoxide-d_6 (DMSO-d_6)–D_2O) of compound **6** showed a methine proton signal as a doublet (J=2.8 Hz) at 5.35 ppm.[2]

Compound **6** showed β-adrenoceptor stimulant activities in an *in vivo* assay using anesthetized dogs. The bronchodilator activity and effects on the heart of compound **6** were evaluated in terms of the inhibition of histamine-induced bronchospasm and increase in the heart rate, respectively. As shown in Table I, compound **6** showed 8.9 and 4.3 times less potent bronchodilator activity than those of *l*-isoproterenol and procaterol, respectively. The effect on the heart rate of compound **6** was 12 times less than that of *l*-isoproterenol, and 4.3 times more than that of procaterol. These results indicate that compound **6** is, unexpectedly, a non-selective β-adrenoceptor agonist like *l*-isoproterenol. The exceptional lack of β-selectivity in compound **6** as a derivative of procaterol is considered to be due to the increase in the size of the molecule, since compound **6** has a carbon–carbon double bond at the 3,4-position of the carbostyril nucleus and the piperidyl group as a bulky cyclic side chain moiety.

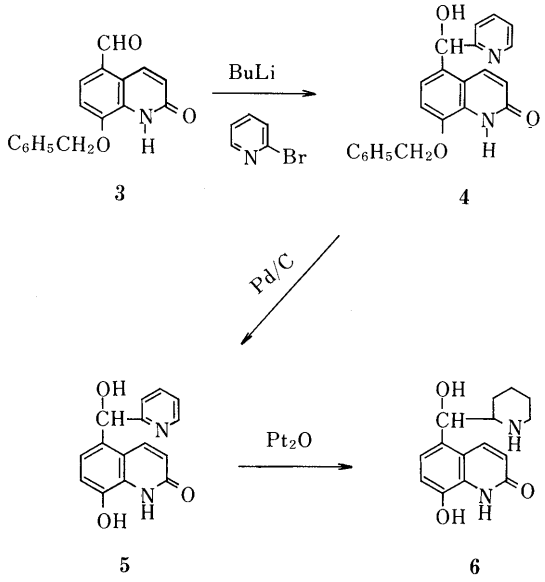
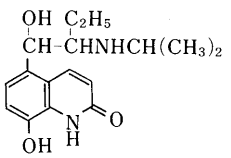


Chart 1

TABLE I. β-Adrenoceptor Agonist Activities of Compound **6**

Compd.	No. of dogs	Inhibition of bronchoconstriction, dose at ED_{50}[a)]	Increase in heart rate, dose at ED_{25}[a)]
6	2	0.47	0.28
Procaterol	5	0.11	1.2
l-Isoproterenol	2	0.053	0.023

a) μg/kg.



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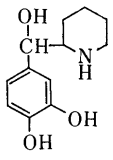

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Experimental[6]

Chemistry **α-(2-Pyridyl)-(8-benzyloxy-5-carbostyril)methanol (4)** A solution of α-bromopyridine (5.6 g, 27 mmol) in 50 ml of THF was cooled to −60 °C, and 16 ml of 15% *n*-butyllithium solution in hexanes was added. The mixture was stirred for 1 h at −60 °C, then a solution of 2.8 g (10 mmol) of 5-formyl-8-benzyloxycarbostyril **3** in 100 ml of THF, cooled

to −60 °C, was added. The reaction mixture was stirred for 2 h at −60 °C, then brought to room temperature, and 10 ml of water was added. The mixture was evaporated and the residue was extracted with 50 ml of $CHCl_3$. The extract was washed with water, dried with Na_2SO_4 and evaporated. The resulting solid was dissolved in 20 ml of EtOH and acidified with concentrated HCl to pH 1—2. The precipitate was collected and recrystallized from MeOH–EtOH to give 1.7 g (43%) of **4** as the hydrochloride, mp 196—197 °C (dec.). *Anal.* Calcd for $C_{22}H_{19}ClN_2O_3$: C, 66.92; H, 4.85; N, 7.09. Found: C, 66.63; H, 4.99; N, 6.99.

α-(2-Pyridyl)-(8-hydroxy-5-carbostyril)methanol (5) A solution of 0.70 g (1.8 mmol) of compound **4** hydrochloride in 40 ml of MeOH was reduced with 0.1 g of 5% palladium carbon at room temperature for 16 h. The catalyst was removed, the solvent was evaporated off, and the residue was recrystallized from MeOH to give 0.40 g (73%) of **5** as the hydrochloride 0.25-hydrate, mp 207—210 °C (dec.). *Anal.* Calcd for $C_{15}H_{13.5}ClN_2O_{3.25}$: C, 58.26; H, 4.40; N, 9.06. Found: C, 57.98; H, 4.67; N, 8.79.

***erythro*-α-(2-Piperidyl)-(8-hydroxy-5-carbostyril)methanol (6)** A mixture of 0.20 g (0.65 mmol) of compound **5**, 0.03 g of platinum oxide, 10 ml of AcOH and 30 ml of MeOH was reduced at room temperature under a hydrogen atmosphere of 3.5 kg/cm^2 for 7 h. The catalyst was removed and the solvent was evaporated off. The residue was converted to the free base with saturated $NaHCO_3$ aqueous solution, and the precipitate was collected and washed with water. The solid was converted to its hydrochloride in EtOH and recrystallized from MeOH to give 0.084 g (41%) of **6** as the hydrochloride dihydrate, mp 184—185 °C (dec.). *Anal.* Calcd for $C_{15}H_{23}ClN_2O_5$: C, 51.95; H, 6.68; N, 8.08. Found: C, 52.05; H, 6.92; N, 8.12. ^{1}H-NMR (DMSO-d_6–D_2O) δ: 8.19 (1H, d, J=9.8 Hz), 7.17 (1H, d, J=8.2 Hz), 7.02 (1H, d, J=8.2 Hz), 6.60 (1H, d, J=9.8 Hz), 5.35 (1H, d, J=2.8 Hz, C<u>H</u>–OH), 3.40—2.75 (3H, m), 1.8—1.1 (6H, m).

Pharmacology Adult male mongrel dogs, weighing 10—15 kg, were anesthetized by intravenous injection of 30 mg/kg body weight of sodium pentobarbital. The anesthetized dogs were placed on their backs and a cannula was inserted into the trachea. Histamine at a dose of 10 μg/kg body weight was given as a bronchoconstrictor 1 min after injecting aqueous solutions of various concentrations of the test compounds through the femoral vein. Artificial respiration was carried out by the Konzett–Rössler method.[7] The volume of air inhaled was measured with a differential transducer (San-ei Sokki, type 1236) to determine the bronchial resistance and the values obtained were recorded on a polygraph. The ED_{50} values of the test compounds were determined from dose–response curves and compared with that of *l*-isoproterenol. The heart rate was measured simultaneously with a heart rate meter triggered from the blood pressure through a pressure transducer (San-ei Sokki, type 1236) attached to the cannulated femoral artery. The ED_{25} values of the test compounds (producing an increase in the heart rate of 25 beats/min) were determined from dose-response curves and compared with that of *l*-isoproterenol. To inhibit spontaneous respiration and to keep anesthetic conditions constant during the test period, sodium pentobarbital was infused continuously during the experiment at a dose of 4 mg/kg body weight per hour, using an automatic injector.

References and Notes

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6) Melting points (uncorrected) were determined by the capillary method. Elemental analyses were done in a Yanagimoto MT-2 CHN recorder. ^{1}H-NMR spectra were recorded with a Brucker AC-250 spectrometer; the data obtained were consistent with the assigned structures of the compounds described in this section.
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