Synthesis and Pharmacological Evaluation of 7-Substituted Procaterol Derivatives

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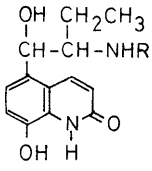
A series of procaterol derivatives having a substituent at the 7-position of the carbostyril moiety was synthesized. Halogenation of procaterol and its homologues gave the 7-halogeno derivatives (3). Nitration of the procaterol analogues afforded the 7-nitro derivatives (4), and the catalytic reduction of 4 gave the 7-amino derivatives (5). These compounds showed weak β-adrenoceptor stimulant activities in anesthetized dog.

Keywords procaterol derivative; halogenation; nitration; catalytic reduction; β-adrenoceptor stimulant activity

Procaterol (**1**, R=isopropyl) is an extremely potent and highly selective β-adrenoceptor agonist which has a carbostyril moiety,[2,3] and it has been widely used as a bronchodilator (Meptin) for the treatment of asthmatic patients at an oral dose of 0.05 mg twice a day. We have previously reported some derivatives of procaterol and their pharmacological activities as a part of our search for novel, potent and selective β-adrenoceptor stimulants.[4–6] Furthermore, we synthesized a series of procaterol derivatives with a substituent at the 7-position of compounds (**1**). A selective β-adrenoceptor agonist, clenbuterol (**2**), has been reported as a similar analogue of catecholamines.[7,8] The pharmacological evaluation of the new 7-substituted procaterol derivatives has been performed using anesthetized dogs.

A series of procaterol derivatives having a substituent on the carbostyril nucleus was synthesized as outlined in Chart 1; the compounds are listed in Table I. Bromination of procaterol derivatives (**1**) with a slight excess of bromine in glacial acetic acid gave the 7-bromo derivatives (**3a, b**). Chlorination of compounds **1** with chlorine in



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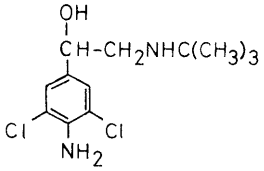

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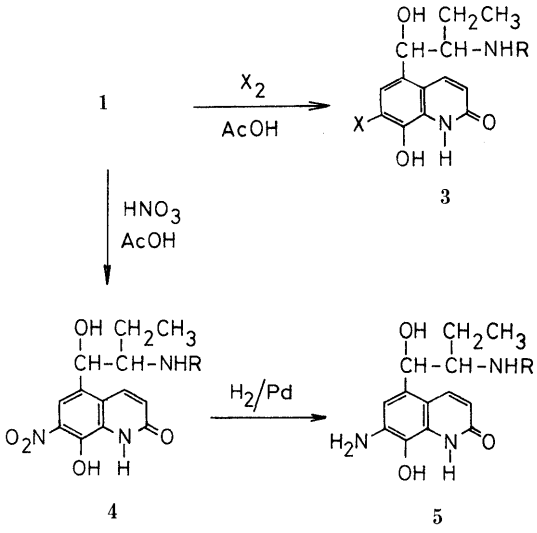

Chart 1

TABLE I. 7-Substituted Procaterols

Compd.	R	Substituent at 7-position	Formula	mp (°C)	Recrystn. solvent	Yield (%)	Analysis (%) Calcd (Found)		
							C	H	N
3a	H	Br	$C_{13}H_{15}BrN_2O_3 \cdot HBr \cdot 0.5H_2O$	214—216 (dec.)	MeOH–Et_2O	47	37.44 (37.41)	4.11 4.22	6.72 6.74)
3b	$(CH_3)_2CH$	Br	$C_{16}H_{21}BrN_2O_3 \cdot HBr \cdot H_2O$	178—180 (dec.)	MeOH–acetone	56	41.05 (41.30	5.17 5.13	5.98 6.01)
3c	H	Cl	$C_{13}H_{15}ClN_2O_3 \cdot HCl \cdot 0.75H_2O$	196—198 (dec.)	MeOH–Et_2O	45	46.93 (46.97	5.30 5.55	8.42 8.34)
3d	CH_3CH_2	Cl	$C_{15}H_{19}ClN_2O_3 \cdot HCl \cdot 2H_2O$	179—181 (dec.)	MeOH–Et_2O	43	47.00 (46.97	6.31 5.98	7.31 7.40)
3e	$(CH_3)_2CH$	Cl	$C_{16}H_{21}ClN_2O_3 \cdot HCl \cdot H_2O$	173—175 (dec.)	MeOH–Et_2O	58	50.67 (50.54	6.38 6.59	7.39 7.32)
4a	CH_3CH_2	NO_2	$C_{15}H_{19}N_3O_5 \cdot HCl$	216—218 (dec.)	Water	63	50.35 (50.06	5.63 5.51	11.74 11.48)
5a	CH_3CH_2	NH_2	$C_{15}H_{21}N_3O_3 \cdot 2HCl \cdot C_3H_7OH$	266—268 (dec.)	iso-PrOH	55	50.95 (50.93	7.36 7.34	9.90 9.57)
5b[a]	$(CH_3)_2CH$	NH_2							

a) Compound **5b** was previously reported. See ref. 9.

TABLE II. Pharmacological Results in Dogs

Compd.	Inhibition of bronchoconstriction, dose at ED_{50} (μg/kg)	Increase in heart rate, dose at ED_{25} (μg/kg)
3e	60.0	*a)*
5b	67.5	*b)*
Procaterol	0.14	0.96
l-Isoproterenol	0.069	0.019

a) ED_6 at 300 μg/kg. *b)* ED_{20} at 100 μg/kg.

glacial acetic acid similarly afforded the 7-chloro analogues (**3c—e**). Nitration of compound **1** (R=ethyl) with nitric acid (*d* 1.42) in glacial acetic acid gave the 7-nitro derivative (**4a**) as described previously,[9] and then catalytic reduction of **4a** using palladium black gave the 7-amino analogue (**5a**).

The β-adrenoceptor stimulant activities of compounds **3e** and **5b** were examined by *in vivo* assay in anesthetized dogs. Their bronchodilator activities and effects on the heart were evaluated in terms of inhibition of histamine-induced bronchospasm and increase in the heart rate, respectively. The results are shown in Table II.

Compound **3e**, 7-chloroprocaterol, showed weak β-adrenoceptor agonist activities. Its bronchodilator activity was 429 times less potent than that of procaterol. The effect of **3e** on the heart was very weak and its ED_6 value was 300 μg/kg. Compound **5b**, 7-aminoprocaterol, also showed weak pharmacological activities. The bronchodilator activity of **5b** was 482 times less potent than that of procaterol, and its effect on the heart was also very weak. These results indicated that the substitution at the 7-position of procaterol significantly decreased the β-adrenoceptor stimulant activities, although the β-selectivity was retained. These significant decreases in the β-adrenoceptor agonist activities may be due to the steric effects of the 7-substituent on the binding to β-adrenoceptors.

Experimental

Chemistry Melting points were determined by the capillary method and are given as uncorrected values. Elemental analyses were done in a Yanagimoto MT-2 CHN recorder. ^{1}H-NMR spectra were recorded with a Bruker AC-250 spectrometer using tetramethylsilane as an internal standard.

General Procedure. *erythro*-7-Bromo-8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril (3b) A solution of 8.8 g (27.5 mmol) of bromine in 50 ml of AcOH was added dropwise to a solution of 7.7 g (25 mmol) of *erythro*-8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril monohydrate in 300 ml of AcOH under stirring at room temperature. After 1 h, the reaction mixture was evaporated and a small amount of iso-PrOH was added to the residue. The resulting crystalline solid was collected and recrystallized from MeOH–acetone to give 6.5 g (56%) of **3b** as the hydrobromide monohydrate, mp 178—180 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 8.31 and 6.74 (d, 1H, J=10.0 Hz, C_4H and C_3H), 7.51 (s, 1H, C_6H), 5.58 (br s, 1H, C<u>H</u>–OH), 3.52 and 3.21 (m, 1H, CHNCH), 1.54 (m, 2H, CH_2), 1.35 (q, 6H, $C(CH_3)_2$), 0.60 (t, 3H, CH_3).

General Procedure. *erythro*-7-Chloro-8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril (3e) A solution of 2.8 g (40 mmol) of chlorine in 40 ml of AcOH was added in small portions to a solution of 6.2 g (20 mmol) of *erythro*-8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril monohydrate in 300 ml of AcOH under stirring and cooling with ice–water. After 2 h, the precipitated crystalline solid was collected, washed with Et_2O, and recrystallized from MeOH–Et_2O to give 4.4 g (58%) of **3e** as the hydrochloride monohydrate, mp 173—175 °C (dec.). ^{1}H-NMR (DMSO-d_6–D_2O) δ: 8.17 and 6.73 (d, 1H, J=10.0 Hz, C_4H and C_3H), 7.46 (s, 1H, C_6H), 5.64 (br s, 1H, C<u>H</u>–OH), 3.6—3.1 (m, 2H, CHNCH), 1.5 (m, 2H, CH_2), 1.40 (q, 6H, $C(CH_3)_2$), 0.59 (t, 3H, CH_3).

***erythro*-5-(2-Ethylamino-1-hydroxybutyl)-8-hydroxy-7-nitrocarbostyril (4a)** A solution of 2.0 ml of concentrated nitric acid (*d* 1.42) in 5 ml of AcOH was added dropwise to a solution of 4.0 g (14.3 mmol) of *erythro*-5-(2-ethylamino-1-hydroxybutyl)-8-hydroxycarbostyril monohydrate in 40 ml of AcOH under stirring and cooling with ice-water. After 30 min, 500 ml of Et_2O was added and the precipitated nitrate was collected. The nitrate was dissolved in aqueous NaOH solution, and the resulting solution was acidified with concentrated hydrochloric acid. The precipitate was recrystallized from water to give 3.1 g (63%) of **4a** as the hydrochloride, mp 216—218 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 8.34 and 6.80 (d, 1H, J=10.0 Hz, C_4H and C_3H), 7.88 (s, 1H, C_6H), 5.75 (br s, 1H, C<u>H</u>–OH), 3.2 (m, 3H, C<u>H</u>N$C\underline{H}_2$C), 1.6 (m, 2H, CCH_2C), 1.33 (t, 3H, $NCH_2C\underline{H}_3$), 0.61 (t, 3H, $CCH_2C\underline{H}_3$).

***erythro*-7-Amino-8-hydroxy-5-(2-ethylamino-1-hydroxybutyl)carbostyril (5a)** A suspension of 1.0 g (2.9 mmol) of compound **4a** and 0.1 g of palladium black in 30 ml of water was reduced at room temperature under a hydrogen atmosphere of 2.0 kg/cm for 2 h. After the catalyst was removed, the water layer was acidified with concentrated hydrochloric acid and evaporated off. The residue was crystallized from EtOH–Et_2O and recrystallized from iso-PrOH to give 0.65 g (55%) of **5a** as the dihydrochloride isopropanolate, mp 266—268 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 8.20 and 6.40 (d, 1H, J=9.9 Hz, C_4H and C_3H), 7.22 (s, 1H, C_6H), 5.72 (br s, 1H, C<u>H</u>–OH), 3.2 (m, 3H, C<u>H</u>N$C\underline{H}_2$C), 1.6 (m, 2H, CCH_2C), 1.33 (t, 3H, $NCH_2C\underline{H}_3$), 0.58 (t, 3H, $CCH_2C\underline{H}_3$).

Pharmacology. β-Adrenoceptor Agonist Assay Using Anesthetized Dogs 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.[10] 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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