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Syntheses and β-Adrenergic Blocking Activities of the Optical Isomers of 8-Acetonyloxyl-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril

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The optical isomers of 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril were prepared from the optically active epichlorhydrin, and their β-adrenergic blocking activities were examined. The (*S*)(−)-isomer was shown to be about 200 times more potent on atrial and 100 times more potent on tracheal preparations, and was also about 3 times more β_1-selective than the (*R*)(+)-isomer.

Keywords——optical isomer; 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril; 3,4-dihydrocarbostyril; epichlorhydrin; β-adrenergic; atrial; tracheal; *MTPA-Cl; NMR

Previously, the authors[1] synthesized a series of 5-(3-amino-2-hydroxypropoxy)-8-alkoxy-3,4-dihydrocarbostyrils as β_1-selective blocking agents, and showed that 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril hydrochloride hydrate (OPC-1427, Bometolol hydrochloride) (I) has potent anti-isoproterenol activity and high β_1-selectivity in anesthetized mongrel dog, and on isolated guinea pig atrial and tracheal preparations.[2] In the present paper, the optical isomers of I were synthesized and their anti-isoproterenol activities on isolated guinea pig atrial and tracheal preparations were examined. The (*S*)(−)-isomer (Ia) was more potent and more β_1-selective than the (*R*)(+)-isomer (Ib).

Chemistry

We synthesized that optical isomers of I from the optical isomers of epichlorhydrin.[3] A mixture of (*R*)(−)-epichlorhydrin, 5-hydroxy-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (II)[1] and piperidine was heated to give a diastereomeric mixture of (*R*) (−)-5-(3-chloro-2-hydroxypropoxy)-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IIIa). Compound IIIa was treated with KOH to give (*S*)(+)-5-(2,3-epoxypropoxy)-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IVa). Reaction of IVa with N-benzyl-3,4-dimethoxyphenethylamine and treatment with conc.HCl gave (*S*)(−)-5-[3-N-benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril hydrochloride (Va). Reaction of the free base of Va with $ClCH_2COCH_3$ in the presence of K_2CO_3 gave (*S*)(−)-8-acetonyloxy-5-[3-(N-benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (VIa). The crude VIa was hydrogenated over 10% palladium on charcoal to give (*S*)(−)-8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (Ia). In the same manner, (*R*)(+)-8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (Ib) was prepared (Chart 1).

We reported that 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (I) exists as two tautomers of extended type and linkage type on the basis of its nuclear magnetic resonance (NMR) spectrum.[1] The optical isomers of I also exist as two tautomers on the basis of the appearance of two signals for methyl protons of the acetonyloxy group at 1.73 ppm and 2.20 ppm (3: 2) in the NMR (90 MHz, DMSO-d_6) spectrum. To

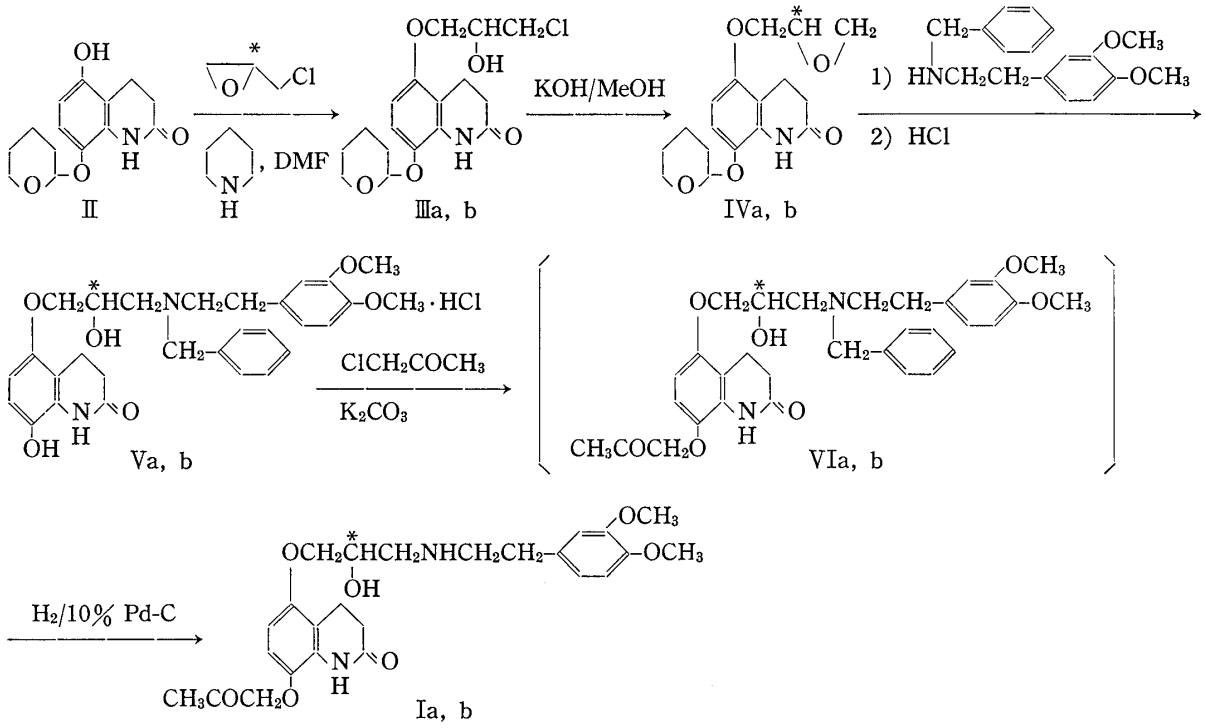

Chart 1

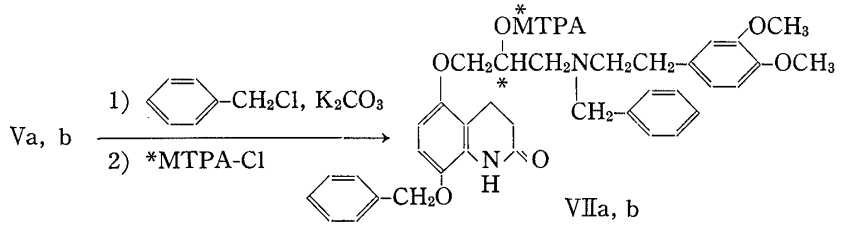

Chart 2

determine the optical purity, after benzylation of Va, 8-benzyl-Va was acetylated with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (*MTPA-Cl)[4] to give VIIa (Chart 2).

In the same manner, VIIb was obtained. 8-Benzylated V (racemic) was also acetylated with *MTPA-Cl. The NMR spectrum of *MTPA-VII (racemic) ($CDCl_3$, 200 MHz) showed clearly two singlet signals at near 5.03 ppm assignable to methylene of the benzyloxy group. However, VIIa showed only one singlet signal at 5.024 ppm and VIIb showed only one singlet signal at 5.042 ppm. On the basis of the above observations, we concluded that the optical purities of VIIa and VIIb were about 100%.

Table I. Antagonistic Activity against Isoproterenol of Optical Isomers as determined with Isolated Guinea-Pig Atrial and Tracheal Preparations

Compound	PA_2 (mean ± S.E.)		Selectivity[a]
	Atrium(n)[b]	Trachea(n)	
Ia	8.02 ± 0.05(5)	5.91 ± 0.14(4)	123.0
Ib	5.61 ± 0.11(4)	3.94 ± 0.06[c] (4)	44.7

S.E.: standard error.
a) Selectivity = anti-log(PA_2 Value in atrium − PA_2 Value in trachea).
b) Number of experiments.
c) Calculated by the method of Van Rossum.[5]

Anti-isoproterenol[1]: The antagonistic activity against isoproterenol of Ia and Ib on isolated guinea pig atrial and tracheal preparations is shown in Table I. The (*S*)(−)-isomer (Ia) was shown to be about 200 times more potent on atrial and 100 times more potent on tracheal preparations and was also about 3 times more β_1-selective than the (*R*)(+)-isomer (Ib).

Experimental

All melting points are uncorrected. NMR spectra were recorded on Varian EM-390 and Bruker WH-200 (200 MHz) spectrometers using 3-(trimethylsilyl)propanesulfonic acid sodium salt (DSS) or tetramethylsilane as an internal standard. Optical rotations were measured with a Union Giken PM-71 polarimeter.

(*R*)(−)-5-(3-Chloro-2-hydroxypropoxy)-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IIIa)——A mixture of 10.5 g of II, 16.7 g of (*R*)(−)-epichlorhydrin and 3 drops of piperidine in 6 ml of DMF was stirred at 60—65°C for 9.5 h. After removal of (*R*)(−)-epichlorhydrin and DMF by evaporation, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on a column of silica gel using $CHCl_3$–MeOH (200: 1) as an eluent. Ether was added to the fraction containing IIIa. The crystalline precipitate was collected by filtration to give IIa (4.74 g, 21.0%) as a colorless powder, mp 115.5—118.5°C, $[\alpha]_D^{25}$ −0.6° (c=1.001, MeOH). NMR ($CDCl_3$): 1.40—2.15 (6H, m, 3,4,5-position of pyranyl H), 2.40—3.08 (5H, m, $-C\underline{H}_2C\underline{H}_2-$, $-O\underline{H}$), 3.37—4.32 (7H, m, 6-position of pyranyl 2H, $-OC\underline{H}_2C\underline{H}(OH)C\underline{H}_2Cl$), 5.23 (1H, br. s, 2-position of pyranyl H), 6.46, 6.96 (each 1H, d, J=9 Hz, aromatic H), 7.86 (1H, br. s, $-N\underline{H}CO-$). *Anal.* Calcd for $C_{17}H_{22}ClNO_5$: C, 57.38; H, 6.23; N, 3.94. Found: C, 57.04; H, 6.18; N, 3.95.

(*S*)(−)-5-(3-Chloro-2-hydroxypropoxy)-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IIIb)——In the same manner as above, IIIb, mp 113.5—116.5°C, $[\alpha]_D^{25}$ −1.6° (c=1.044, MeOH) was obtained. *Anal.* Calcd for $C_{17}H_{22}ClNO_5$: C, 57.38; H, 6.23; N, 3.94. Found: C, 57.06; H, 6.09; N, 3.98.

(*S*)(+)-5-(2,3-Epoxypropoxy)-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IVa)——A solution of 4.2 g of IIIa in 50 ml of MeOH was added to a solution of 6.8 ml of 3.5 N KOH in MeOH and the whole was stirred at room temperature for 1 h. The reaction mixture was neutralized with 1 N HCl and evaporated to dryness under reduced pressure. Then, in the same manner as for IIIa, IVa was obtained (3.13 g, 83.0%) as a colorless powder, mp 111.5—113°C, $[\alpha]_D^{25}$ +19.2° (c=1.011, MeOH). NMR ($CDCl_3$) ppm: 1.45—2.15 (6H, m, 3,4,5-position of pyranyl H), 2.45—3.13 (6H, $-C\underline{H}_2C\underline{H}_2-$, $-OCH_2\underline{C}\overset{\diagup O \diagdown}{\underline{H}}-C\underline{H}_2$), 3.20—4.33 (5H, m, 6-position of pyranyl 2H, $-OC\underline{H}_2\underline{C}\overset{\diagup O \diagdown}{\underline{H}}-CH_2$), 5.23 (1H, br. s, 2-position of pyranyl H), 6.44, 6.95 (each 1H, d, J=9 Hz, aromatic H), 7.85 (1H, br. s, $-N\underline{H}CO-$). *Anal.* Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.82; H, 6.57; N, 4.37.

(*S*)(−)-5-[3-(N-benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride (Va)——A solution of 3.04 g of IVa and 5.17 g of N-benzyl-3,4-dimethoxyphenethylamine in 30 ml of MeOH was heated under reflux for 4.5 h. The reaction mixture was evaporated to dryness under reduced pressure. To the residue, 200 ml of acetone and 0.96 ml of conc. HCl were added with cooling in an ice bath, and the whole was stirred for 20 min. After removal of precipitated crystals, 0.79 ml of conc. HCl was added to the filtrate and the whole was stirred at room temperature overnight. The crystalline precipitate was collected by filtration to give crude Va (5.1 g, 92.5%), $[\alpha]_D^{25}$ −24.6° (c=1.154, MeOH). Recrystallization from MeOH gave crude Va (2.58 g), $[\alpha]_D^{25}$ −19.1° (c=1.022, MeOH). The mother solution was evaporated to dryness under reduced pressure. Acetone was added to the residue and the mixture was stirred at room temperature overnight. The crystalline precipitate was collected by filtration to give crude Va (2.28 g), $[\alpha]_D^{25}$ −29.4° (c=1.07, MeOH). This treatment was repeated until the optical rotation of Va was constant. Pure Va (0.75 g, 14.5%) was obtained as colorless crystals, mp 110—112°C, $[\alpha]_D^{25}$ −32.4° (c=1.042, MeOH) NMR·(DMSO-d_6) ppm: 2.20—2.83 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 2.90—4.00 [14H, m, $-C\underline{H}_2\underline{C}H(OH)C\underline{H}_2N<$, $>N-C\underline{H}_2C\underline{H}_2-$, 3.73, 3.76 (each 3H, s, 2×$-OC\underline{H}_3$)], 4.12—4.76 (3H, m, $>N-C\underline{H}_2-Ph$, $-CH_2\underline{C}\underline{H}(OH)CH_2N-$), 6.30—7.00, 7.39—7.89 (each 5H, m, aromatic H), 8.73 (1H, br. s, $-N\underline{H}CO-$). *Anal.* Calcd for $C_{29}H_{34}N_2O_6\cdot HCl$: C, 64.14; H, 6.50; N, 5.16. Found: C, 64.14; H, 6.49; N, 5.15.

(*S*)(−)-8-Acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (Ia)——A suspension of 5.66 g of Va, 3 g of $NaHCO_3$, 100 ml of H_2O and 100 ml of $CHCl_3$ was stirred at room temperature for 30 min. The $CHCl_3$ layer was separated and washed with water, then dried over Na_2SO_4. After removal of the solvent, the residual oil was dissolved in 300 ml of acetone. A solution of 2.9 g of K_2CO_3 in 5 ml of H_2O was added to the acetone solution, then 1.93 g of $ClCH_2COCH_3$ was added slowly under reflux and the whole was refluxed for 2 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in 30 ml of iso-PrOH and 5 ml of H_2O. The solution was acidified with 10% H_2SO_4 and hydrogenated over 10% Pd-C at room temperature under atmospheric pressure until no more hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. A solution of 3 g of $NaHCO_3$ in 100 ml of H_2O and 100 ml of $CHCl_3$

were added to the residue, and the whole was stirred at 40°C for 1 h. The $CHCl_3$ layer was separated, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residual oil was purified by column chromatography [$CHCl_3$–MeOH (8: 1)] to give an oil. The oil was crystallized from AcOEt and the precipitated crystals were collected by filtration. Recrystallization from AcOEt gave Ia (2.0 g, 40.6%) as a colorless powder, mp 88.0—88.5°C, $[\alpha]_D^{25}$ −5.8° (c=0.907, MeOH). NMR ($CDCl_3$) ppm: 1.73, 2.20 (total 3H (3: 2), s, $-CH_2COCH_3$), 2.43—3.15 (10H, m, $-CH_2CH_2-$, $-CH_2CHCH_2NH-$, $-NHCH_2CH_2-$), 3.70—4.18, 4.56 [11H, m, $-OCH_2CHCH_2-$, $-OCH_2COCH_3$, 3.83 (6H, s, 2×$-OCH_3$)], 6.43—6.89 (5H, m, aromatic H). *Anal.* Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.33; H, 6.84; N, 5.58.

(*S*)(−)-8-Benzyloxy-5-[3-(N-benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (+)-α-Methoxy-α-trifluoromethylphenylacetate (VIIa)——A solution of 250 mg of Va, 117 mg of benzyl chloride and 250 mg of K_2CO_3 in 10 ml of acetone and 5 ml of H_2O was heated under reflux for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residual oil was dissolved with 3 ml of pyridine and 3 ml of CCl_4. Next, 180 mg of *MTPA·Cl was added and the whole was stirred at room temperature for 24 h. N,N-Diethylenediamine (160 mg) was then added and the mixture was stirred at room temperature for 20 min. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by column chromatography [$CHCl_3$–MeOH (8: 1)] to give VIIa as a colorless oil. NMR ($CDCl_3$) ppm: 2.36—2.90 (10H, m, $-CH_2CH_2-$, $-CH_2CHCH_2N<$, $>NCH_2CH_2-$), 3.41—3.96 [13H, m, $-OCH_2CHCH_2-$, $>N-CH_2$-Ph, 3.51 (3H, s, $CH_3O-C(CF_3)-$), 3.79, 3.82 (each 3H, s, 2×$-OCH_3$], 5.024 (2H, s, $-OCH_2$-ph), 5.41 (1H, m, $-OCH_2CHCH_2-$), 6.19 (1H, d, J=9 Hz, aromatic H), 6.62—6.78 (4H, m, aromatic H), 7.13—7.57 (15H, m, aromatic H), 7.77 (1H, br. s, $-NHCO-$).

References and Notes

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