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Sympathomimetic Amines having a 3,4-Dihydrocarbostyril Nucleus

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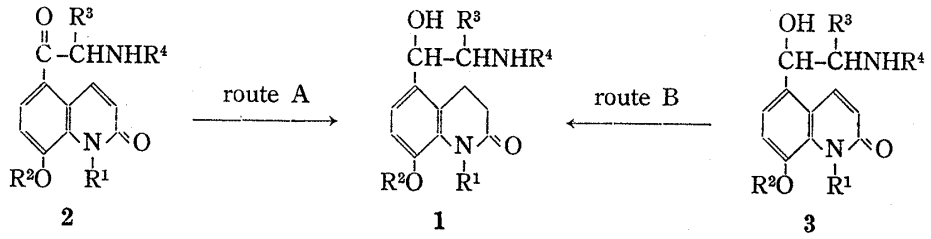
A series of new sympathomimetic amines having a 3,4-dihydrocarbostyril nucleus was synthesized. These compounds have two weakly acidic hydrogen atoms in locations similar to those of the hydroxyl groups of adrenergic agents containing catechol. One *threo*-isomer **1i**-*threo* was synthesized by inversion of the corresponding *erythro*-isomer by the S_Ni reaction.

Keywords——sympathomimetic amines; 3,4-dihydrocarbostyril derivatives; catalytic reduction; inversion; S_Ni reaction; β-adrenoceptor stimulant activities

Recently many β-selective sympathomimetic amines, such as clenbuterol,[2a] carbuterol,[2b] bitolterol[2c] and reproterol,[2d] have been investigated to develop useful bronchodilators. Previously we reported that procaterol, containing a carbostyril nucleus, was a potent and β-selective bronchodilator.[3] We also tested the activities of a series of new sympathomimetic amines having a 3,4-dihydrocarbostyril nucleus. This paper reports the syntheses of various 5-(2-substituted-amino-1-hydroxyalkyl)-3,4-dihydro-8-hydroxycarbostyrils (**1**).

The sympathomimetic amines with a 3,4-dihydrocarbostyril nucleus in the series shown in Table I were mainly synthesized by catalytic reduction of 5-(2-substituted-amino-1-oxoalkyl)-8-hydroxycarbostyrils (**2**) (route A) or 5-(2-substituted-amino-1-hydroxyalkyl)-8-hydroxycarbostyrils (**3**) (route B), as outlined in Chart 1. The starting materials **2** and **3** were previously reported by Yoshizaki, *et al.* and compounds **3** (where R^3 is an alkyl group) were in the *erythro*-forms.[3a]



2 **1** **3**

Chart 1

Compounds **1h**-*erythro* and **1i**-*erythro* were synthesized from precursor secondary-amino ketones by catalytic reduction over palladium black. The reaction afforded the *erythro*-isomers in agreement with previous findings on other sympathomimetic amines.[4] The

1) Location: *Kagasuno, Kawauchi-cho, Tokushima.*

2) *a*) J. Keck, G. Krüger, K. Noll, and H. Machleidt, *Arzneim.-Forsch.*, **22**, 861 (1972); *b*) C. Kaiser, D.F. Colella, M.S. Schwartz, E. Garvey, and J.R. Wardell, Jr., *J. Med. Chem.*, **17**, 49 (1974); *c*) B.F. Tullar, H. Minatoya, and R.R. Lorenz, *J. Med. Chem.*, **19**, 834 (1976); *d*) K.H. Klingler, *Arzneim.-Forsch.*, **27**, 4 (1977).

3) *a*) S. Yoshizaki, K. Tanimura, S. Tamada, Y. Yabuuchi, and K. Nakagawa, *J. Med. Chem.*, **19**, 1138 (1976); *b*) S. Yoshizaki, Y. Manabe, S. Tamada, K. Nakagawa, and S. Tei, *ibid.*, **20**, 1103 (1977).

4) J.F. Hyde, E. Browning, and R. Adams, *J. Am. Chem. Soc.*, **50**, 2287 (1928); J. Van Dijk and H.D. Moed, *Rec. Trav. Chim. Pays-Bas*, **78**, 22 (1959); *idem, ibid.*, **80**, 573 (1961).

coupling constants for protons on adjacent asymmetric centers of **1h**-*erythro* and **1i**-*erythro* were, respectively, 3.4 Hz at 5.22 ppm and 4.0 Hz at 5.21 ppm[3,5]

To confirm the *erythro*-stereoconfiguration of compound **1i**-*erythro*, its *threo*-isomer was synthesized by the S_Ni reaction,[3b,6] as outlined in Chart 2. Compound **1i**-*erythro* was ben-

Table I. 5-(2-Substituted-amino-1-hydroxyalkyl)-3,4-dihydro-8-hydroxycarbostyrils (**1**)

Compd.	R^1	R^2	R^3	R^4	Formula[a]	Route	mp °C	Recrystn. solvent	Yield %	Analysis (%) Calcd. (Found) C	H	N
1a	H	H	H	H	$C_{11}H_{14}N_2O_3 \cdot HCl$	B	270—272	MeOH–AcOEt	48	51.07 (51.27)	5.84 (6.23)	10.82 (10.66)
1b	H	H	H	iso-Pr	$C_{14}H_{20}N_2O_3 \cdot HCl$	A	203—204[b]	MeOH–ether	59	55.91 (55.67)	7.04 (7.36)	9.31 (9.28)
1c	H	H	H	*sec*-Bu	$C_{15}H_{22}N_2O_3 \cdot HCl$	A	183—184	EtOH–acetone	51	57.23 (57.25)	7.36 (7.52)	8.90 (9.07)
1d	H	H	H	*tert*-Bu	$C_{15}H_{22}N_2O_3 \cdot HCl$	B	240—241	MeOH–ether	53	57.23 (57.14)	7.36 (7.71)	8.90 (8.77)
1e	H	H	H	CMe_2CH_2Ph	$C_{21}H_{26}N_2O_3 \cdot HCl \cdot 2H_2O$	B	120—121	Water	64	59.08 (58.95)	7.32 (7.56)	6.56 (6.60)
1f	H	H	H		$C_{17}H_{24}N_2O_3 \cdot HBr$	B	162—163[b]	iso-PrOH–acetone	78	52.99 (52.79)	6.54 (6.87)	7.27 (7.23)
1g-*erythro*	H	H	Me	iso-Pr	$C_{15}H_{22}N_2O_3 \cdot HCl \cdot 0.5H_2O$	B	211—213	EtOH	51	55.64 (55.39)	7.47 (7.68)	8.65 (8.72)
1h-*erythro*	H	H	Me	*tert*-Bu	$C_{16}H_{24}N_2O_3 \cdot HCl \cdot 0.5H_2O$	A	229—231[b]	Water	58	56.88 (56.61)	7.76 (8.06)	8.29 (8.10)
1i-*erythro*	H	H	Et	iso-Pr	$C_{16}H_{24}N_2O_3 \cdot HCl \cdot 0.5H_2O$	A	196—198[b]	MeOH–ether	71	56.88 (56.66)	7.76 (8.11)	8.29 (8.15)
1i-*threo*	H	H	Et	iso-Pr	$C_{16}H_{24}N_2O_3 \cdot HCl$		212—214[b]	MeOH–ether		58.44 (58.11)	7.66 (7.90)	8.52 (8.42)
1j-*erythro*	H	H	Et	*sec*-Bu	$C_{17}H_{26}N_2O_3 \cdot HCl \cdot 0.5H_2O$	B	205—207	EtOH–acetone	60	58.03 (57.84)	8.02 (8.28)	7.96 (7.82)
1k	Me	H	H	iso-Pr	$C_{15}H_{22}N_2O_3 \cdot HCl$	B	196—197	EtOH	57	57.23 (56.99)	7.36 (7.69)	8.90 (8.70)
1l	H	Me	H	iso-Pr	$C_{15}H_{22}N_2O_3 \cdot HCl$	A	206—208[b]	EtOH	65	57.23 (56.95)	7.36 (7.67)	8.90 (8.90)

a) Salts and degrees of hydration are shown with the formulas.
b) Decomposition.

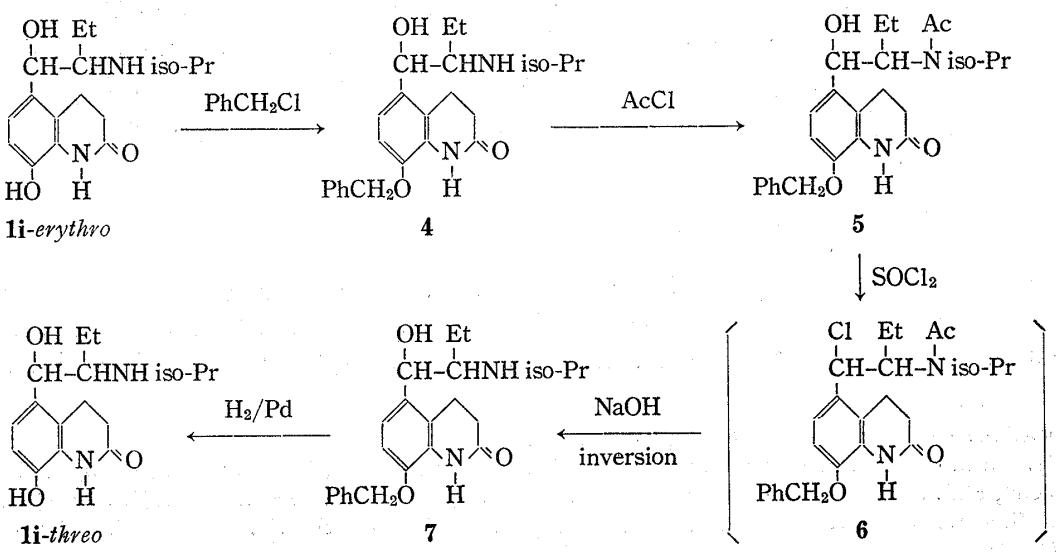


Chart 2

5) P.S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).
6) M.J. Mardle, H. Smith, B.A. Spicer, and R.H. Poyser, *J. Med. Chem.*, **17**, 513 (1974).

zylated with benzyl chloride in alkaline solution to give the 8-benzyloxy derivative (**4**). Compound **4** was acetylated with acetyl chloride in chloroform to the N-acetyl derivative (**5**). The hydroxyl group of **5** was replaced by a chlorine group with thionyl chloride to give the *erythro*--chloride (**6**), and **6** was hydrolyzed by NaOH with inversion. The resulting *threo*-8-benzyloxy derivative (**7**) was catalytically debenzylated over palladium black to give compound **1i**-*threo*. The nuclear magnetic resonance (NMR) spectrum of **1i**-*threo* showed a doublet (J= 8.2 Hz) at 5.00 ppm.[3b,5]

The series of new sympathomimetic amines with a 3,4-dihydrocarbostyril nucleus has two acidic hydrogen atoms in locations similar to those of the hydroxyl groups of adrenergic agents containing catechol, as shown in Chart 3. The weakly acidic hydrogen atom at the 1 position of the 3,4-dihydrocarbostyril nucleus (**1**) is probably substituted for the *meta*-hydroxyl group of catecholamines (**8**). The representative compound, **1b**, showed β-adrenoceptor stimulant activities in an *in vitro* test on guinea pigs[7] as shown in Table II. The broncho-relaxing activity of compound **1b** was 132 times more than that of *l*-isoproterenol on guinea pig tracheal smooth muscles, while the activity on heart was 0.087 times less than that of *l*-isoproterenol on guinea pig right atria. These results indicate the availability of compound **1b** as a potent and selective β-adrenoceptor stimulating agent.

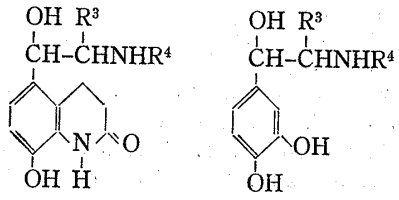


Chart 3

Table II. β-Adrenoceptor Stimulant Activities[7] of Compound **1b**

Compound	Bronchial muscle[a] (Intrinsic activity)	Cardiac muscle[b] (Intrinsic activity)	Separation ratio[c]
1b	132 (1.33)	0.087 (1.17)	1520
l-Isoproterenol	1 (1)	1 (1)	1

a) Relative potency (*l*-isoproterenol=1) from isolated guinea pig trachea preparation.
b) Relative potency (*l*-isoproterenol=1) from isolated guinea pig right atria preparation.
c) Relative potency on bronchial muscle divided by relative potency on cardiac muscle.

Experimental[8]

General Procedure for Catalytic Reduction——To a suspension of 0.01 mol of either **2** or **3** in 50—100 ml of water was added 10—20 weight percent of palladium black or 10% palladium carbon, and reduction was carried out at 60—70° in a Paar hydrogenator. After completion of the reaction, the catalyst was removed and the solvent was evaporated. The residue was crystallized from acetone and recrystallized from the solvent listed in Table I to give the alkanolamine with a 3,4-dihydrocarbostyril nucleus. The acid salts of alkanolamines were usually hygroscopic and some of them were hydrated. Compound **1i**-*erythro*: NMR (D_2O) δ: 7.10 and 6.80 [2H, d, J=8.4 Hz, CH (Ar)], 5.21 (1H, d, J=4.0 Hz, >C<u>H</u>–OH), 3.9—3.1 [2H, m (br), C<u>H</u>–NH–C<u>H</u>], 3.1—2.8 and 2.7—2.4 [4H, m (br), C_3–H and C_4–H], 2.0—1.4 [2H, m (br), >CH–C<u>H</u>$_2$–CH$_3$], 1.41 [6H, d, J=6.4 Hz, CH(C<u>H</u>$_3$)$_2$], and 0.70 (3H, t, CH_3); TLC: *Rf* 0.43. Compound **1h**-*erythro*: NMR (D_2O) δ: 5.22 (1H, d, J=3.4 Hz, >C<u>H</u>–OH).

***erythro*-8-Benzyloxy-3,4-dihydro-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril (4)**——A mixture of 36.0 g (0.1 mol) of compound **1i**-*erythro* in 105 ml of 2 N NaOH, 200 ml of MeOH and 15.2 g (0.12 mol) of benzyl chloride was refluxed for 3 hr. The solvent was evaporated and the residue was extracted with

7) The assay is described in ref. 3*a*.
8) Melting points (uncorrected) were determined by the capillary method. Elemental microanalyses were done in a Yanagimoto MT-2 CHN recorder. NMR spectra were recorded with a Varian EM-360 spectrometer. TLC was carried out on E. Merck Kieselgel F_{254} with $CHCl_3$–MeOH–HCOOH (40:10:1) as solvent.

$CHCl_3$. The $CHCl_3$ layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated. The residue was recrystallized from MeOH to give 32.6 g (85%) of **4**, mp 81—83°. *Anal.* Calcd. for $C_{23}H_{28}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.25; H, 7.91; N, 7.43. NMR ($CDCl_3$) δ: 7.8 [1H, s (br), NH–CO], 7.33 [5H, s (br), C_6H_5], 7.18 and 6.82 [2H, d, J=8.8 Hz, CH (Ar)], 5.01 (2H, s, O–C<u>H</u>$_2$C$_6$H$_5$), 4.83 (1H, d, J=4.0 Hz, >C<u>H</u>–OH), 3.1—2.3 (6H, overlapping C<u>H</u>–NH–C<u>H</u>, C_3–H and C_4–H), 1.11 [6H, d, J=6.4 Hz, CH(C<u>H</u>$_3$)$_2$], 1.1 [2H, CH–C<u>H</u>$_2$–CH_3, overlapped with CH(C<u>H</u>$_3$)$_2$], and 0.8 (3H, t, CH_3).

***erythro*-5-(N-Acetyl-1-hydroxy-2-isopropylaminobutyl)-8-benzyloxy-3,4-dihydrocarbostyril (5)**——To a solution of 9.6 g (0.025 mol) of **4** and 5.1 g (0.05 mol) of triethylamine in 100 ml of $CHCl_3$ was added dropwise 3.9 g (0.05 mol) of acetyl chloride with stirring and cooling in ice-water. After 1 hr the $CHCl_3$ layer was washed with 10% Na_2CO_3 solution and water, and dried over Na_2SO_4. The solvent was evaporated and the residue was crystallized from ether to give 6.6 g (62%) of **5**, mp 180—182°. *Anal.* Calcd. for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.39; H, 7.71; N, 6.38. NMR ($CDCl_3$) δ: 7.82 [1H, s (br), NH–CO], 7.34 (5H, s, C_6H_5), 7.23 and 6.83 [2H, d, J=9.0 Hz, CH (Ar)], 6.2 [1H, s (br), >CH–O<u>H</u>], 5.03 (2H, s, O–C<u>H</u>$_2$–C_6H_5), 5.1—5.0 (1H, >C<u>H</u>–OH, overlapped with O–C<u>H</u>$_2$–C_6H_5), 4.00 [1H, m, NH–C<u>H</u>–(CH_3)$_2$], 4.44 [1H, q, NH–C<u>H</u>–CH_2CH_3], 3.2—2.8 and 2.7—2.3 (4H, m, C_3–H and C_4–H), 2.20 (3H, s, CH_3CO), 2.2—1.6 (2H, m, CH–C<u>H</u>$_2$–CH_3), 1.25 [6H, q, CH(C<u>H</u>$_3$)$_2$], and 0.74 (3H, t, CH_3).

***threo*-8-Benzyloxy-3,4-dihydro-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril (7)**——To 6.4 g (0.015 mol) of **5** was added 20 ml of $SOCl_2$ and after 2 hr the excess $SOCl_2$ was evaporated. The residue was dissolved in 240 ml of MeOH and 120 ml of 2 N NaOH and the resulting solution was stirred for 5 hr at room temperature and acidified with concentrated HCl with cooling in ice-water. The solvent was evaporated, the residue was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with water. The solvent was evaporated, the residue was dissolved in water, and the resulting solution was filtered (active C). The filtrate was evaporated, the residue was crystallized from acetone, and the crystalline solid was recrystallized from MeOH–ether to give 4.1 g (57%) of **7** as the hydrochloride, mp 252—254° (dec.). *Anal.* Calcd. for $C_{23}H_{31}ClN_2O_3$: C, 65.94; H, 7.46; N, 6.69. Found: C, 65.50; H, 7.55; N, 6.69. NMR (Me_2SO-d_6) δ: 4.86 (1H, d, J=8.6 Hz, >C<u>H</u>–OH).

***threo*-3,4-Dihydro-5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxycarbostyril (li-*threo*)**——To 2.0 g (0.0042 mol) of **7** in 80 ml of water was added 0.4 g of palladium black and the resulting suspension was hydrogenated in a Paar hydrogenator to give 1.2 g (88%) of **li**-*threo*. NMR (D_2O) δ: 7.12 and 6.90 [2H, d, J=8.4 Hz, CH (Ar)], 5.00 (1H, d, J=8.2 Hz, >C<u>H</u>–OH), 3.8—3.2 (2H, m, C<u>H</u>–NH–C<u>H</u>), 3.2—2.9 and 2.8—2.5 (4H, m, C_3–H and C_4–H), 1.9—1.3 (2H, m, CH–C<u>H</u>$_2$–CH_3), 1.40 [6H, q, CH(C<u>H</u>$_3$)$_2$], and 0.91 (3H, t, CH_3). TLC: *Rf* 0.37.

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