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Synthesis of 5-(2-Allylamino-1-hydroxyalkyl)-8-hydroxycarbostyrils, New β-Adrenoceptor Stimulants

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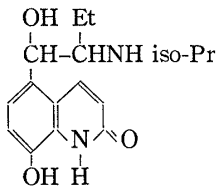
A series of 5-(2-allylamino-1-hydroxyalkyl)-8-hydroxycarbostyrils (**4**) was synthesized. The β-adrenoceptor stimulant activities of *erythro*-5-(2-allylamino-1-hydroxypropyl)-8-hydroxycarbostyril (**4b**) in anesthetized dogs were determined.

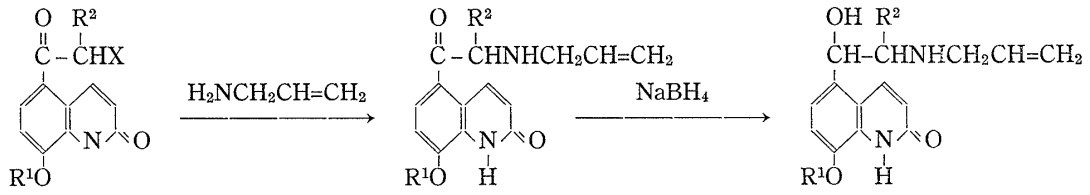
Keywords——β-adrenoceptor stimulants; allylamino group; amination; hydride reduction; β-adrenoceptor stimulant activities

In recent years many attemps have been made to obtain new β-adrenoceptor stimulants, leading to the development of clenbuterol,[2] carbuterol[3] and bitolterol.[4] Authors[5] also developed a new bronchodilator procaterol, *erythro*-5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxycarbostyril (**1**), which showed very potent bronchodilator activity and weak side effects in double blind tests at an oral dose of 0.05—0.1 mg/body twice a day. In attempts to improve the bronchodilator activity and β-selectivity of **1**, various 5-(2-allylamino-1-hydroxyalkyl))8-hydroxycarbostyrils (**4**) were synthesized and the pharmacological activities of *erythro*-5-(2-allylamino-1-hydroxypropyl)-8-hydroxycarbostyril (**4b**) as a representative compound were examined in anesthetized dogs.



1

Compounds **4** were synthesized as outlined in Chart **1**. Treatment of 5-(2-halogeno-1-oxoalkyl)-8-hydroxycarbostyrils (**2**), which were synthesized by the reported method,[5a] with excess allylamine gave 5-(2-allylamino-1-oxoalkyl)-8-hydroxycarbostyrils (**3**). Reduction of **3** with sodium borohydride in methanol afforded **4**. Yields and melting points of compounds **3** and **4** are listed in Tables I and II. The configurations of compounds **4** (where R^2=alkyl group) were assigned as *erythro* on the basis of chemical[6] and spectral evidence.[7] Sodium borohydride reduction of the α-aminoketones was reported to yield *erytho* isomers



2 **3** **4**

Chart 1

1) Location: *a) Kagasuno, Kawauchi-cho, Tokushima*; *b) 133-1 Yamadakami, Suita, Osaka.*
2) J. Keck, G. Krüger, K. Noll, and H. Machleidt, *Arzneim.-Forsch.*, **22**, 861 (1972).
3) C. Kaiser, D.F. Colella, M.S. Schwartz, E. Garvey, and J.R. Wardell, Jr., *J. Med. Chem.*, **17**, 49 (1974).
4) B.F. Tullar, H. Minatoya, and R.R. Lorenz, *J. Med. Chem.*, **19**, 834 (1976).
5) *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).
6) J. Van Dijk and H.D. Moed, *Rec. Trav. Chim. Pays-Bas*, **78**, 22 (1959).
7) P.S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).

Table I. 5-(2-Allylamino-1-oxoalkyl)-8-hydroxycarbostyrils (3)

Compd	R^1	R^2	Formula	mp[a] °C	Recrystn. solvent	Yield[b] %	Analysis (%) Calcd (Found) C	H	N
3a	H	H	$C_{14}H_{14}N_2O_3 \cdot HCl$	277—279	H_2O–acetone	32	57.05 (56.93)	5.13 5.05	9.50 9.41)
3b	H	Me	$C_{15}H_{16}N_2O_3 \cdot HCl \cdot 0.25H_2O$	253—254	MeOH–acetone	22	57.51 (57.59)	5.63 5.47	8.94 8.83)
3c	H	Et	$C_{16}H_{18}N_2O_3 \cdot HCl \cdot H_2O$	250—253	MeOH–Et_2O	28	56.39 (56.04)	6.21 5.93	8.22 8.18)
3d	Me	H	$C_{15}H_{16}N_2O_3 \cdot HCl \cdot H_2O$	218—220	MeOH–Et_2O	35	55.13 (55.14)	5.86 5.90	8.57 8.51)

a) Decomposition.
b) Total yield from 8-hydroxycarbostyril.

Table II. 5-(2-Allylamino-1-hydroxyalkyl)-8-hydroxycarbostyrils (4)

Compd	R^1	R^2	Formula	mp[a] °C	Recrystn. solvent	Yield %	Analysis (%) Calcd (Found) C	H	N
4a	H	H	$C_{14}H_{16}N_2O_3 \cdot HCl$	232—233	H_2O	70	56.66 (56.51)	5.77 5.79	9.44 9.47)
4b	H	Me	$C_{15}H_{18}N_2O_3 \cdot HCl \cdot H_2O$	179—181	H_2O	47	54.80 (54.87)	6.44 6.35	8.52 8.58)
4c	H	Et	$C_{16}H_{20}N_2O_3 \cdot HCl \cdot 0.5H_2O$	147—150	H_2O	35	57.57 (57.70)	6.64 6.39	8.39 8.35)
4d	Me	H	$C_{15}H_{18}N_2O_3 \cdot HCl \cdot 0.5H_2O$	241—242	H_2O–EtOH	55	56.34 (56.44)	6.30 6.00	8.76 8.78)

a) Decomposition.

as major products.[6] In the NMR spectra, compounds **4** show spin-spin coupling constants (3.0—4.0 Hz) due to the hydrogen-hydrogen interactions on the two adjacent asymmetric centers of the *erythro* isomers.[7]

Compounds **4** should possess potent bronchodilator activities and high β-selectivities because the allyl group has a large space filling effect around the nitrogen atom of the side chain.[8] As we expected, compound **4b** was found to show β-adernoceptor stimulant activities in an *in vivo* assay using anesthetized dogs. Its bronchodilator activity and effects on the heart were evaluated in terms of the inhibition of histamine-induced bronchospasm and increase in the heart rate, respectively.[9] As shown in Table III, compound **4b** had one-third

Table III. β-Adrenoceptor Stimulant Activities of Compound **4b**

Compd	No. of dogs	Inhibition of bronchoconstriction dose at ED_{50}[a]	Increase in heart rate dose at ED_{25}[a]
4b	4	0.136	b)
l-Isoproterenol	4	0.043	0.027

a) μg/kg.
b) ED_{11} at 10 μg/kg.

8) A.M. Lands, A. Arnold, J.P. McAuliff, F.P. Luduena, and T.G. Brown, Jr., *Nature* (London), **214**, 597 (1967).
9) The assay is described in ref. 5*b*.

of the bronchodilator activity of *l*-isoproterenol and had very weak effect on the heart rate. These results indicate that **4b** is a potent and highly selective β-adrenoceptor stimulant, and may be practically useful as a bronchodilator.

Experimental[10]

5-(2-Allylamino-1-oxopropyl)-8-hydroxycarbostyril (3b)——Allylamine (50 ml) was added to 50.0 g of crude 5-(2-bromo-1-oxopropyl)-8-hydroxycarbostyril with shaking. After 3 hr, the resulting solution was evaporated to dryness and the residue was dissolved in iso-PrOH. The solution was adjusted to pH 1—2 with concentrated hydrochloric acid and evaporated to dryness. The residual solid was collected, washed with iso-PrOH and dissolved in MeOH. The solution was made alkaline with KOH–MeOH solution, adjusted to pH 1 with concentrated hydrochloric acid under cooling in ice-water and evaporated to dryness. The residue was recrystallized from MeOH–acetone to give 7.60 g (22% from 8-hydroxycarbostyril) of **3b**.

5-(2-Allylamino-1-hydroxypropyl)-8-hydroxycarbostyril (4b)——A suspension of 1.20 g (0.0038 mol) of **3b** in 50 ml of MeOH was adjusted to pH 9, then 1 g of sodium borohydride was added in small portions with stirring and cooling in ice-water. After completion of reduction, the reaction mixture was adjusted to pH 1 and the precipitate was filtered off. The filtrate was evaporated to dryness. The residue was dissolved in MeOH and evaporated to dryness to remove boron as methyl borate. The residue was recrystallized from H_2O to give 0.60 g (47%) of **4b**. NMR (Me_2SO-d_6–D_2O) δ: 5.63 (1H, d, J=4.0 Hz, =C<u>H</u>–OH). Compound **4c**: NMR (D_2O) δ: 5.75 (1H, d, J=3.0 Hz, =C<u>H</u>–OH).

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10) 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 Hitachi R-20B spectrometer.

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Application of High-performance Liquid Chromatography to the Isolation of Ginsenoside-Rf, -Rg_2, and -Rh_1 from a Crude Saponin Mixture of Ginseng[1]

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The minor components of ginseng saponins, ginsenoside-Rf, -Rg_2, and -Rh_1, were isolated from the crude saponin fraction by a high-performance liquid chromatography (HPLC) procedure involving preparative HPLC on silica gel followed by semi-preparative HPLC on a column packing of Carbohydrate Analysis. This method was rapid and convenient.

Keywords——*Panax ginseng* C.A. Meyer; ginsenoside-Rf; ginsenoside-Rg_2; ginsenoside-Rh_1; high-performance liquid chromatography; isolation

In our previous paper, an improved method for the isolation of ginsenoside-Rb_1, -Rb_2, -Rc, -Rd, -Re, and -Rg_1 by high-performance liquid chromatography (HPLC) was reported.[1] Now, in order to improve the separation and efficiency of isolation of ginsenoside-Rf, -Rg_2,

1) T. Nagasawa, T. Yokozawa, Y. Nishino, and H. Oura, *Chem. Pharm. Bull.*, **28**, 2059 (1980). This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1980.
2) Location: *a) 2630 Sugitani, Toyama, 930-01, Japan*; *b) 112 Ini-Dong, Chongro-Ku, Seoul, Korea.*