Experimental

All melting points were measured on a micro hot-stage and uncorrected. Conditions of TLC and ^{13}C NMR spectra determination are referred to the previous paper.[4]

Extraction and Identification of Glucosides——The dried leaves (145 g) harvested in September (1977), were extracted with hot MeOH. After concentration of the solution, the MeOH-extract was digested with H_2O and the suspension was washed with ether and then extracted with *n*-BuOH (saturated with H_2O). The BuOH-extract (10.0 g) was chromatographed on silica gel by eluting with $CHCl_3$: MeOH: H_2O (200: 30: 1) affording three fractions (A, B, and C).

The less polar fraction-A was subjected to re-chromatography on silica gel by eluting with AcOEt: MeOH: H_2O (800: 35: 10), yielding three colorless crystalline glucosides, **1**, **2**, and **3** which were proved to be identical with paniculosides-I, -II, and -III, respectively by comparison of TLC, ^{13}C NMR spectra, melting points, and optical rotations; **1**: mp 135—139° (from MeOH–H_2O), $[\alpha]_D^{10}$ −63.0° (c=0.07, MeOH), yield 0.028%; **2**: mp 230—234° (from MeOH–H_2O), $[\alpha]_D^{20}$ −60.0° (c=0.1, MeOH), yield 1.1%; **3**: mp 153—157° (from MeOH–H_2O), $[\alpha]_D^{20}$ −118.0° (c=0.1, MeOH), yield 0.8%.

The more polar fraction-B was re-chromatographed on silica gel by eluting with $CHCl_3$: MeOH (5: 1), to give colorless prisms, mp 155—157° (from MeOH–H_2O), $[\alpha]_D^{10}$ −63.8° (c=0.08, MeOH), yield 0.12%, which were proved to be identical with paniculoside-IV by comparison of TLC, ^{13}C NMR spectra, and other physical constants. The optical rotation of paniculoside IV in our previous paper[4] (+65.6°) was mis-typewritten and should be corrected as above.

The most polar fraction-C was re-chromatographed on silica gel by eluting with AcOEt: MeOH: H_2O (420: 40: 35) to give colorless prisms, mp 173—175° (from MeOH–H_2O), $[\alpha]_D^{10}$ +59.0° (c=0.15, MeOH), yield 0.22%, which were identified with paniculoside-V by comparison of TLC, ^{13}C NMR spectra, and other physical constants.

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Oxidation of Procaterol to 5-Formyl-8-hydroxycarbostyril

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5-Formyl-8-hydroxycarbostyril (**5**), one of the major metabolites of procaterol (**1**), was synthesized by oxidation of **1** and 8-benzyloxy procaterol (**2**).

Keywords——procaterol; 5-formyl-8-hydroxycarbostyril; oxidation; sodium metaperiodate; *m*-chloroperoxybenzoic acid

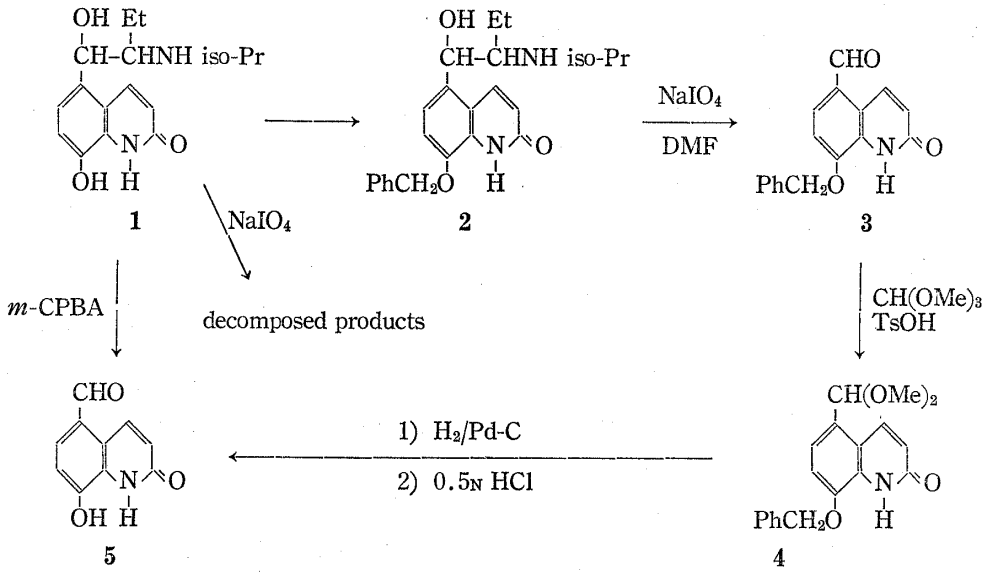
Recently we reported on procaterol, 5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxycarbostyril (**1**), which is a potent and selective β-adrenoceptor stimulating agent.[2] Shimizu, *et al.*[3] investigated the metabolic fate of **1** in the rat and found that one of the major metabolites of **1** was 5-formyl-8-hydroxycarbostyril (**5**). To obtain an authentic sample of **5**, we investigated the oxidation reaction of **1**.

1) Location: *Kagasuno, Kawauchi-cho, Tokushima.*
2) *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).
3) T. Shimizu, H. Mori, E. Tabusa, S. Morita, Y. Yasuda, and K. Nakagawa, *Xenobiotica*, in press.

Stevens and Chang[4] synthesized benzaldehyde by periodate oxidation of α-(1-dimethylamino-1-methylethyl)benzyl alcohol. The periodate oxidation of 8-benzyloxy procaterol (**2**)[2b] is shown in Chart 1. Compound **2** was oxidized with sodium metaperiodate in N,N-dimethylformamide (DMF) to give 8-benzyloxy-5-formylcarbostyril (**3**) in 80% yield. To protect the formyl group, **3** was acetalized in absolute methanol with methyl orthoformate in the presence of *p*-toluenesulfonic acid as catalyst to afford 8-benzyloxy-5-dimethoxymethylcarbostyril (**4**) in 86% yield. Compound **4** was catalytically debenzylated over 5% palladium black in ethanol, and the resulting 8-hydroxyacetal was hydrolyzed without separation with 0.5 N hydrochloric acid to give 5-formyl-8-hydroxycarbostyril (**5**) as pale straw colored crystals, mp 315—317° (dec.), in 92% yield. The periodate oxidation of **1** gave only decomposition products, probably because **5** was unstable in alkaline medium.

To obtain **5** directly from **1**, the peroxyacid oxidation of **1** was investigated. Compound **1** was oxidized to **5** with *m*-chloroperoxybenzoic acid as shown in Chart 1. The reaction was performed in DMF at room temperature to give **5** in 36% yield. This reaction did not proceed completely and the yield was rather low.

As described above, compound **5** was obtained by oxidation of **1**. This synthesis depends on the stability of **5** against oxidation.



m-CPBA: *m*-chloroperoxybenzoic acid
TsOH: *p*-toluenesulfonic acid

Chart 1

Experimental[5]

8-Benzyloxy-5-formylcarbostyril (**3**)——To a solution of 600 g (1.58 mol) of **2** (mp 142—143°) in 6.3 l of DMF was added in one portion 22.5 l of 0.1 N sodium metaperiodate aqueous solution warmed to 60° with stirring. After 30 min, 30 kg of ice was added to the reaction mixture. The precipitate was collected, washed with water and recrystallized from AcOEt to give 352 g (80%) of **3**, mp 150—151°. *Anal.* Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.50; H, 4.72; N, 5.15. NMR (Me_2SO-d_6) δ: 10.06 (1H, s, CHO).

8-Benzyloxy-5-dimethoxymethylcarbostyril (**4**)——A solution of 279 g (1.0 mol) of **3**, 120 g (1.13 mol) of methyl orthoformate and 2 g of *p*-toluenesulfonic acid in 2 l of absolute MeOH was stirred for 3 hr at room temperature. To neutralize the catalyst, a little sodium carbonate powder was added to the reaction mix-

4) C.L. Stevens and C.H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).
5) 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.

ture with stirring, and the mixture was filtered. The filtrate was evaporated to dryness and the residue was extracted with 1.2 l of $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to one third of its initial volume. To the resulting solution was added 0.5 l of ether and the precipitate of 280 g (86%) of **4**, mp 135—136°, was collected. *Anal.* Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.24; H, 5.62; N, 4.42. NMR (Me_2SO-d_6) δ: 5.58 [1H, s, CH(OMe)$_2$].

5-Formyl-8-hydroxycarbostyril (5)——To a solution of 280 g (0.86 mol) of **4** in 10 l of EtOH was added 10 g of 5% palladium carbon, and reduction was carried out in a 50 l hydrogenator under 5 atomospheres of hydrogen gas at 50°. After 1 hr the catalyst was removed and the filtrate was evaporated to dryness. To the residue was added 9 l of MeOH and 2 l of 0.5 N hydrochloric acid, and the resulting solution was stirred for 1 hr at room temperature and cooled. The precipitate was collected and washed with water and MeOH to give 150 g (92%) of **5** as pale straw colored crystals, mp 315—317° (dec.). *Anal.* Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.50; H, 3.42; N, 7.77. NMR (Me_2SO-d_6) δ: 10.05 (1H, s, CHO), 9.04 and 6.74 [1H, d, J=9.6 Hz, C_4–H and C_3–H], and 7.69 and 7.16 [1H, d, J=8.4 Hz, CH (Ar)].

Oxidation of Procaterol (1) with *m*-Chloroperoxybenzoic Acid——To a solution of 25 g (0.081 mol) of 5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxycarbostyril monohydrate [(**1**), mp 149—151° (dec.)] in 150 ml of DMF was added 25 g (0.145 mol) of *m*-chloroperoxybenzoic acid (Aldrich Chemical Company, Inc.) in small portions with stirring at room temperature. After 1 hr the reaction mixture was poured into 1 l of ice-water. The resulting precipitate was collected, washed with EtOH and recrystallized with DMF to give 5.5 g (36%) of **5**.

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The β-*p*-Nitrobenzyl Ester to Minimize Side Reaction during Treatment of Aspartyl Peptides with Methanesulfonic Acid[1,2]

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When Boc-Asp(OBzl)-Ser(Bzl)-OBzl was deblocked with methanesulfonic acid–anisole to obtain free dipeptide, a few degree of α to β shift was observed. Boc-Asp-(OBzl)-Thr(Bzl)-OBzl had similar property. When β-carboxyl group was protected with *p*-nitrobenzyl group stable to methanesulfonic acid–anisole, no detectable α to β shift was observed. Boc-Asp(ONb)-Ser(Bzl)-Asp(OBzl)-Pro-Arg(MBS)-ONb was treated with methanesulfonic acid-anisole, followed by catalytic hydrogenation or treatment with zinc powder in acetic acid for the cleavage of *p*-nitrobenzyl group to give Asp-Ser-Asp-Pro-Arg.

Keywords——Boc-Asp(ONb)-Ser(Bzl)-OBzl; Boc-Asp(ONb)-Thr(Bzl)-OBzl; Z-Asp-(OBzl)-His-OBzl; Boc-Asp(OBzl)-Gly-OBzl; Z-Asp(OBzl)-Val-OBzl

The methanesulfonic acid (MsOH)–anisole reagent has been found to cleave efficiently a number of protecting groups currently employed in peptide chemistry without significant side reactions.[4]

We have found that α to β shift of aspartyl peptides occurs during the treatment of β-benzyl aspartyl peptides with this reagent and this side reaction can be minimized when *p*-nitrobenzyl ester (ONb) is used as a protecting group of β-carboxyl group of the aspartic residue.

1) A part of this work was presented at the 15th Symposium on Peptide Chemistry, Osaka, 1977.
2) Abbreviations used are those recommended by IUPAC–IUB Commission of Biochemical Nomenclature: *Biochemistry*, **11**, 1726 (1972). Other abbreviations: DMF=dimethylformamide, AP-M=amino-peptidase M.
3) Location: *Komatsushima, Sendai 983, Japan.*
4) H. Yajima, Y. Kiso, N. Fujii and H. Irie, *Chem. Pharm. Bull.* (Tokyo), **23**, 1164 (1975).