Stirring was continued for 4 hr at room temperature and then excess amine was washed out with Et_2O. The residue was washed with H_2O and dissolved in MeOH. Insoluble material was removed by filtration. The filtrate was adjusted to pH 1—2 with concentrated hydrochloric acid and the resulting solution was evaporated to dryness. The residue was extracted with H_2O (active C), concentrated and recrystallized from H_2O to give 175 g (27% from 8-hydroxycarbostyril) of compound **4** as the hydrochloride, mp 241—243° (dec.). *Anal.* Calcd for $C_{20}H_{21}ClN_2O_3$: C, 64.43; H, 5.68; N, 7.51. Found: C, 64.51; H, 5.51; N, 7.39.

5-(2-Benzylamino-1-hydroxybutyl)-8-hydroxycarbostyril (5)——A solution of 110 g (0.295 mol) of **4** in 2.3 l of MeOH was adjusted to pH 9 with aqueous 10 N NaOH, with stirring and cooling in ice-water. Sodium borohydride (40 g) was added in small portions to this solution and stirring was continued for 5 hr at room temperature. The resulting solution was cooled in ice-water with stirring, adjusted to pH 2 with concentrated hydrochloric acid and concentrated. The residue was dissolved in MeOH, insoluble material was filtered off and the filtrate was evaporated to dryness. The residue was then dissolved in MeOH and the solution was concentrated to remove boron as methyl borate. The residue was recrystallized from MeOH to give 65 g (56%) of *erythro*-5-(2-benzylamino-1-hydroxybutyl)-8-hydroxycarbostyril (**5a**) as the hydrochloride monohydrate, mp 182—184°. *Anal.* Calcd for $C_{20}H_{25}ClN_2O_4$: C, 61.14; H, 6.41; N, 7.13. Found: C, 61.36; H, 6.37; N, 7.18. NMR (Me_2SO-d_6–D_2O) δ: 5.61 (1H, d, J=3.4 Hz, >C<u>H</u>–OH).

The mother liquor after recrystallization of compound **5** was concentrated and the residue was crystallized from acetone to give 15 g of crude *threo*-5-(2-benzylamino-1-hydroxybutyl)-8-hydroxycarbostyril (**5b**). NMR (Me_2SO-d_6-D_2O) δ: 5.34 (1H, d, J=7.5 Hz, >C<u>H</u>–OH).

***erythro*-5-(2-Amino-1-hydroxybutyl)-8-hydroxycarbostyril (2a)**——Palladium black (3 g) was added to a solution of 30 g (0.076 mol) of **5a** in 500 ml of MeOH and 100 ml of H_2O, and reduction was carried out in a Paar hydrogenator for 2 days at room temperature. The catalyst was removed and the solvent was evaporated off. The residual crystalline solid was recrystallized from H_2O to give 20 g (87%) of **2a** as the hydrochloride monohydrate, mp 170—171° (dec.). *Anal.* Calcd for $C_{13}H_{19}ClN_2O_4$: C, 51.57; H, 6.33; N, 9.25. Found: C, 51.41; H, 6.66; N, 9.41. NMR (D_2O) δ: 8.29 and 6.76 (1H, d, J=10.0 Hz, C_4–H and C_3–H), 7.48 and 7.18 (1H, d, J=8.2 Hz, aromatic CH), 5.72 (1H, d, J=4.2 Hz, >C<u>H</u>–OH), 3.76 (1H, m, >C<u>H</u>–N), 1.75 (2H, m, C<u>H_2</u>CH_3) and 1.13 (3H, t, CH_3). TLC: *Rf* 0.30.

***threo*-5-(2-Amino-1-hydroxybutyl)-8-hydroxycarbostyril (2b)**——Palladium black (1 g) was added to a solution of 10 g of crude **5b** in 170 ml of MeOH and 30 ml of H_2O, and reduction was carried out in a Paar hydrogenator for 40 hr at room temperature. The catalyst was removed, the solvent was evaporated off and the residual crystalline solid was recrystallized from H_2O to give 4.5 g (62%) of **2b** as the hydrochloride, mp 220—222° (dec.). *Anal.* Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.76; H, 5.95; N, 9.58. NMR (D_2O) δ: 8.33 and 6.72 (1H, d, J=10.0 Hz, C_4–H and C_3–H), 7.38 and 7.15 (1H, d, J=8.2 Hz, aromatic CH), 5.37 (1H, d, J=7.6 Hz, >C<u>H</u>–OH), 3.70 (1H, m, >C<u>H</u>–N), 1.68 (2H, m, C<u>H_2</u>CH_3) and 1.14 (3H, t, CH_3). TLC: *Rf* 0.26.

Acknowledgement We are grateful to Professor Y. Tamura of the Faculty of Pharmaceutical Sciences, Osaka University, for helpful advice.

[Chem. Pharm. Bull. 28(11)3441—3443(1980)]

Synthesis of 8-Hydroxycarbostyril

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(Received June 28, 1980)

8-Hydroxycarbostyril (**4b**), which is a starting material for the synthesis of procaterol, was synthesized by two new routes.

Keywords——8-hydroxycarbostyril; 8-methoxycarbostyril; 3-ethoxyacrylanilides; 3,3-di-*n*-butoxypropionanilide; condensation

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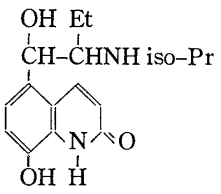
A new bronchodilator, procaterol [*erythro*-5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxycarbostyril (**1**)], which was recently developed by the authors can be synthesized by three steps starting from 8-hydroxycarbostyril.[2] As regards the synthesis of 8-hydroxycarbostyril, two routes *via* the rearrangement of 8-hydroxyquinoline *N*-oxide[3] and alkaline fusion of 8-hydroxyquinoline[4] have been reported. However, these methods are not suitable for use on an industrial scale. Thus, we investigated the following two routes to 8-hydroxycarbostyril (**4b**) using *o*-anisidine and *o*-aminophenol as starting materials.

Effenberger and Hartmann[5] reported the synthesis of carbostyril derivatives by cyclization of 3-ethoxyacrylanilides. First, we investigated this method as shown in Chart 1.



1

Acylation of *o*-anisidine (**2a**) with 3-ethoxyacryloyl chloride gave *N*-(3-ethoxyacryloyl)-*o*-anisidine (**3a**) in 90% yield. Cyclization of **3a** with concentrated hydrochloric acid followed by demethylation with 47% hydrobromic acid afforded **4b** in 39% yield. Similarly, acylation of *o*-aminophenol (**2b**) with 3-ethoxyacryloyl chloride gave *o*-(3-ethoxyacryloylamino)phenol (**3b**) in 68% yield and cyclization of **3b** with hydrochloric acid afforded **4b** in 33% yield.

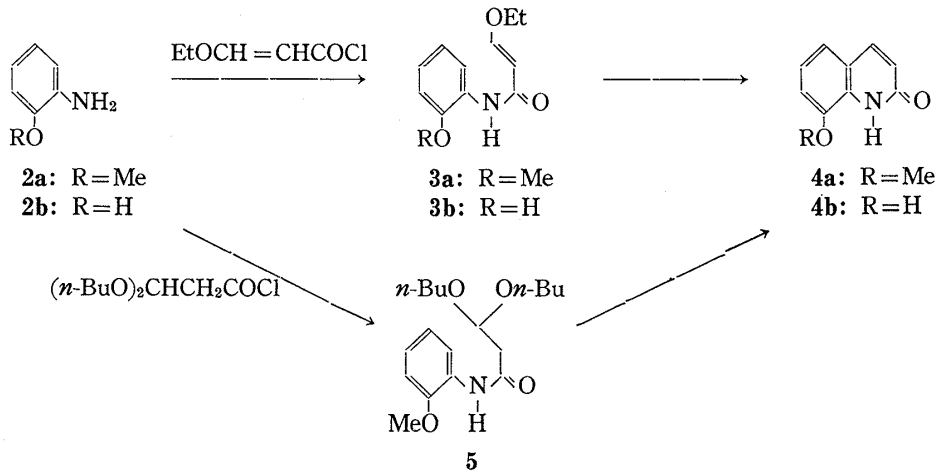


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Chart 1

Next, we tried a new route using 3,3-di-*n*-butoxypropionanilide as shown in Chart 1. Acylation of **2a** with 3,3-di-*n*-butoxypropionyl chloride afforded *N*-(3,3-di-*n*-butoxypropionyl)-*o*-anisidine (**5**). Cyclization of **5** with concentrated hydrochloric acid at 50—55° gave 8-methoxycarbostyril (**4a**) in 19% yield.

The method involving cyclization of **3a** followed by demethylation was found to be more favorable for the preparation of 8-hydroxycarbostyril.

Experimental[6]

***N*-(3-Ethoxyacryloyl)-*o*-anisidine (3a)**——A solution of 13.45 g (0.1 mol) of 3-ethoxyacryloyl chloride in 30 ml of Et_2O was added dropwise to a solution of 24.6 g (0.2 mol) of *o*-anisidine (**2a**) in 300 ml of Et_2O with stirring and cooling in ice-water. After 1 hr, the reaction mixture was washed with H_2O and evaporated to dryness. The residual crystalline solid was filtered and washed sufficiently with Et_2O–petroleum ether

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3) G.R. Pettit, W.C. Fleming, and K.D. Paull, *J. Org. Chem.*, **33**, 1089 (1968).
4) J. Diamant, *Monatsh. Chem.*, **16**, 760 (1895).
5) F. Effenberger and W. Hartmann, *Chem. Ber.*, **102**, 3260 (1969).
6) All melting points are uncorrected. Elemental microanalyses were carried out in a Yanagimoto MT-2 CHN recorder. NMR spectra were recorded with a Hitachi R-20A spectrometer.

(1 : 1) to give 19.8 g (90%) of **3a**, mp 93—94°. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.08; H, 6.77; N, 6.30. NMR ($CDCl_3$) δ: 7.57 (1H, d, J=12.2 Hz, =CH–OEt) and 5.33 (1H, d, J=12.2 Hz, =CH–CO).

***o*-(3-Ethoxyacryloylamino)phenol (3b)**——A solution of 6.73 g (0.05 mol) of 3-ethoxyacryloyl chloride in 20 ml of AcOEt was added dropwise to a suspension of 10.9 g (0.1 mol) of *o*-aminophenol (**2b**) in 200 ml of AcOEt with stirring and cooling in ice-water. After 2 hr, the reaction mixture was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from AcOEt–petroleum ether to give 7.0 g (68%) of **3b**, mp 128—130°. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.56; H, 6.37; N, 6.83. NMR ($CDCl_3$) δ: 7.57 (1H, d, J=12.0 Hz, =CH–OEt) and 5.37 (1H, d, J=12.0 Hz, =CH–CO).

***N*-(3,3-Di-*n*-butoxypropionyl)-*o*-anisidine (5)**——A suspension of 5.28 g (0.022 mol) of sodium 3,3-di-*n*-butoxypropionate[7] in 20 ml of $CHCl_3$ was treated dropwise with 3.39 g (0.022 mol) of phosphorus oxychloride with stirring and cooling in ice-water. After 30 min, a solution of 2.46 g (0.02 mol) of *o*-anisidine and 3.0 g of triethylamine in 20 ml of $CHCl_3$ was added in small portions to the reaction mixture. After 1 hr, the reaction mixture was washed successively with dil. HCl, dil. KOH and H_2O, dried over Na_2SO_4 and concentrated to give 6.6 g (quantitative yield) of **5** as an oil, which was used for the next procedure without further purification (the distillation of a sample of **5** was accompanied by decomposition).

8-Hydroxycarbostyril (4b)——A mixture of 5.0 g (0.0226 mol) of **3a** and 50 ml of concentrated hydrochloric acid was stirred for 24 hr at room temperature. The resulting solution was then poured into 500 ml of ice-water. The precipitate was collected, dried and recrystallized from MeOH–Et_2O to give 1.54 g (39%) of 8-methoxycarbostyril (**4a**), mp 111—113°. A suspension of 5.0 g (0.0286 mol) of **4a** in 50 ml of 47% hydrobromic acid was refluxed for 8 hr. The precipitate was collected after cooling, and washed with H_2O to give 4.6 g (quantitative yield) of **4b**, mp 301—304°. Compound **4b** was also obtained as follows. A mixture of 4.0 g (0.0193 mol) of **3b** and 40 ml of concentrated hydrochloric acid was shaken until it became a clear solution, then allowed to stand. After 24 hr, the precipitate was collected, washed with water, dried and purified with hot MeOH to give 1.03 g (33%) of **4b**.

8-Methoxycarbostyril (4a)——A solution of 5.6 g of **5** in 10 ml of MeOH was added to 50 ml of concentrated hydrochloric acid at 50—55° during 1 hr. The reaction mixture was then cooled and poured into 500 ml of ice-water. The precipitate was collected, dried and recrystallized from AcOEt–Et_2O to give 0.55 g (19%) of **4a**.

7) Sodium 3,3-di-*n*-butoxypropionate was prepared from *n*-butyl 3,3-di-*n*-butoxypropionate and sodium hydroxide in MeOH at room temperature.

[Chem. Pharm. Bull. 28(11)3443—3446(1980)]

Purines. XXI.[1] Synthesis of Adenine 1-Oxides Carrying an Allylic Side Chain at the 9-Position[2]

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(Received July 2, 1980)

9-Allyladenine 1-oxide (**3**) has been prepared from 1-ethoxyadenine (**6**) in 58% overall yield through an unequivocal synthetic route. The route consists of an initial allylation of **6** with allyl bromide and Et-O bond cleavage of the resulting 9-allyl-1-ethoxyadenine hydrobromide (**7**) by treatment with boiling pyridine. Replacement of allyl bromide by 3-methyl-2-butenyl bromide in the above reaction sequence afforded 9-(3-methyl-2-butenyl)adenine 1-oxide (**9**) in 59% overall yield through the 1-ethoxy derivative **8**.

1) Paper XX in this series, T. Fujii, T. Itaya, T. Saito, and M. Kawanishi, *Chem. Pharm. Bull.*, **26**, 1929 (1978).
2) A part of this work was reported in a preliminary form by T. Fujii, I. Inoue, T. Itaya, and T. Saito, *Heterocycles*, **12**, 1543 (1979).
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*