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Studies on 3,5-Dioxopiperidines and Related Compounds[1]: Synthesis of 5-(3-*tert*-Butylamino-2-hydroxy)propoxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine

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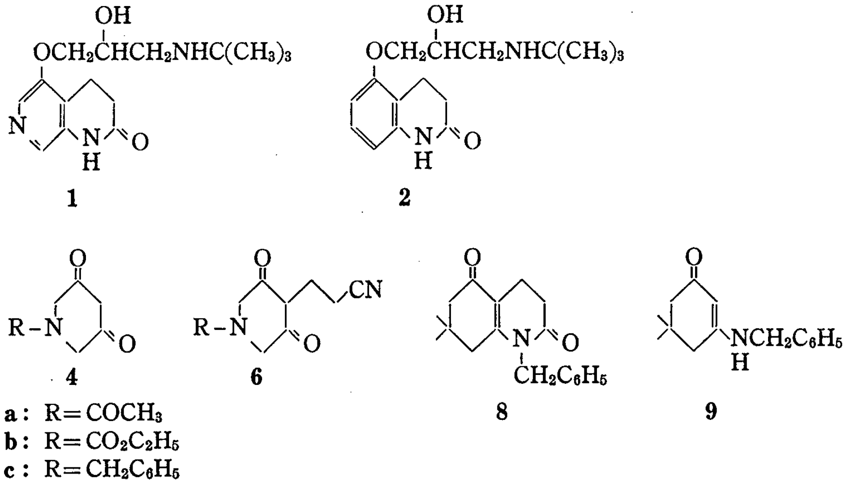
The 7-aza analog (**1**·HCl) of 5-(3-*tert*-butylamino-2-hydroxy)propoxy-3,4-dihydrocarbostyril·hydrochloride (**2**·HCl, carteolol·HCl) was prepared as part of a search for new adrenergic receptor antagonists. Thermal treatment of 1-acetyl-3-benzylamino-5-oxo-3,4-dehydropiperidine (**3**), derived from N-acetylpiperidine-3,5-dione (**4a**) by treatment with acryloyl chloride, gave 7-acetyl-1-benzyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydro-1,7-naphthyridine (**7**). Dehydrogenation of **7** on 5% palladium carbon, and subsequent reductive debenzylation with liquid ammonia and sodium gave 5-hydroxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (**5**). Alkylation of **5** with epichlorohydrin, treatment with alkali and amination with *tert*-butylamine gave 5-(3-*tert*-butylamino-2-hydroxy)-propoxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine·hydrochloride (**1**·HCl) in 45% overall yield from **5**.

Keywords——3,5-dioxopiperidines; 7-aza analog of 5-(3-*tert*-butylamino-2-hydroxy)-propoxy-3,4-dihydrocarbostyril·hydrochloride; acryloylation of β-aminovinyl ketone; reductive debenzylation with liquid ammonia and sodium; adrenergic receptor antagonist

It has been reported that a benzene ring in some antihistamines can be replaced by a pyridine ring with full retention of biological activity or with more effective activity.[2] This result prompted us to prepare a 7-aza analog (**1**) of 5-(3-*tert*-butylamino-2-hydroxy)propoxy-3,4-dihydrocarbostyril (**2**, carteolol),[3] whose hydrochloride has significant adrenergic β-receptor blocking activity and has been used clinically very recently.[4] We report here a novel synthesis of **1** by the thermal reaction of acryloyl chloride and the β-benzylaminovinylketone (**3**) derived from N-acetylpiperidine-3,5-dione (**4a**), followed by aromatization, deacetylation, debenzylation, and alkylation reactions.

Initially, we attempted the synthesis of 7-aza-5-hydroxy-3,4-dihydrocarbostyril (**5**) *via* cyanoethylation of 3,5-dioxopiperidines (**4a**—**c**),[1] followed by cyclization and subsequent



a: R=$COCH_3$
b: R=$CO_2C_2H_5$
c: R=$CH_2C_6H_5$

Fig. 1

aromatization based on the previously reported method for the synthesis of the ordinary 5-hydroxy-3,4-dihydrocarbostyril from cyclohexane-1,3-dione.[5] Unfortunately, reaction of **4** with acrylonitrile, under various conditions, failed to give the desired cyanated materials (**6**). This failure of the cyanoethylation of **4** necessitated a search for an alternative route for the preparation of **5**.

The synthesis of the title compound (**1**) outlined in Chart 1 was achieved from the known 1-acetyl-3-benzylamino-5-oxo-3,4-dehydropiperidine (**3**).[6]

Treatment of **3** with acryloyl chloride in refluxing chlorobenzene for 10 h gave the bicyclic dione (**7**) as a major product, whose structure was determined by analysis of the elemental, mass (MS), infrared (IR), and nuclear magnetic resonance (NMR) spectral data in relation to those of the corresponding C-7 carbon analog of **7**, 1-benzyl-3,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-carbostyril (**8**), prepared by the reaction of 3-benzylamino-5,5-dimethylcyclohex-2-enone (**9**) with acryloyl chloride.[7] The formation of **7** can be explained by the same mechanism as reported for the formation of **8**. It involves an initial O- or N-acylation of **3** with acryloyl chloride followed by a [3,3]-sigmatropic rearrangement and cyclization onto the nitrogen atom. In contrast to the case of the reaction of **9** with acryloyl chloride, a small amount of the isomeric bicyclic dione **10**, which has a very similar *Rf* value on thin layer chromatography (TLC), was isolated in this reaction. All spectroscopic data are fully consistent with the

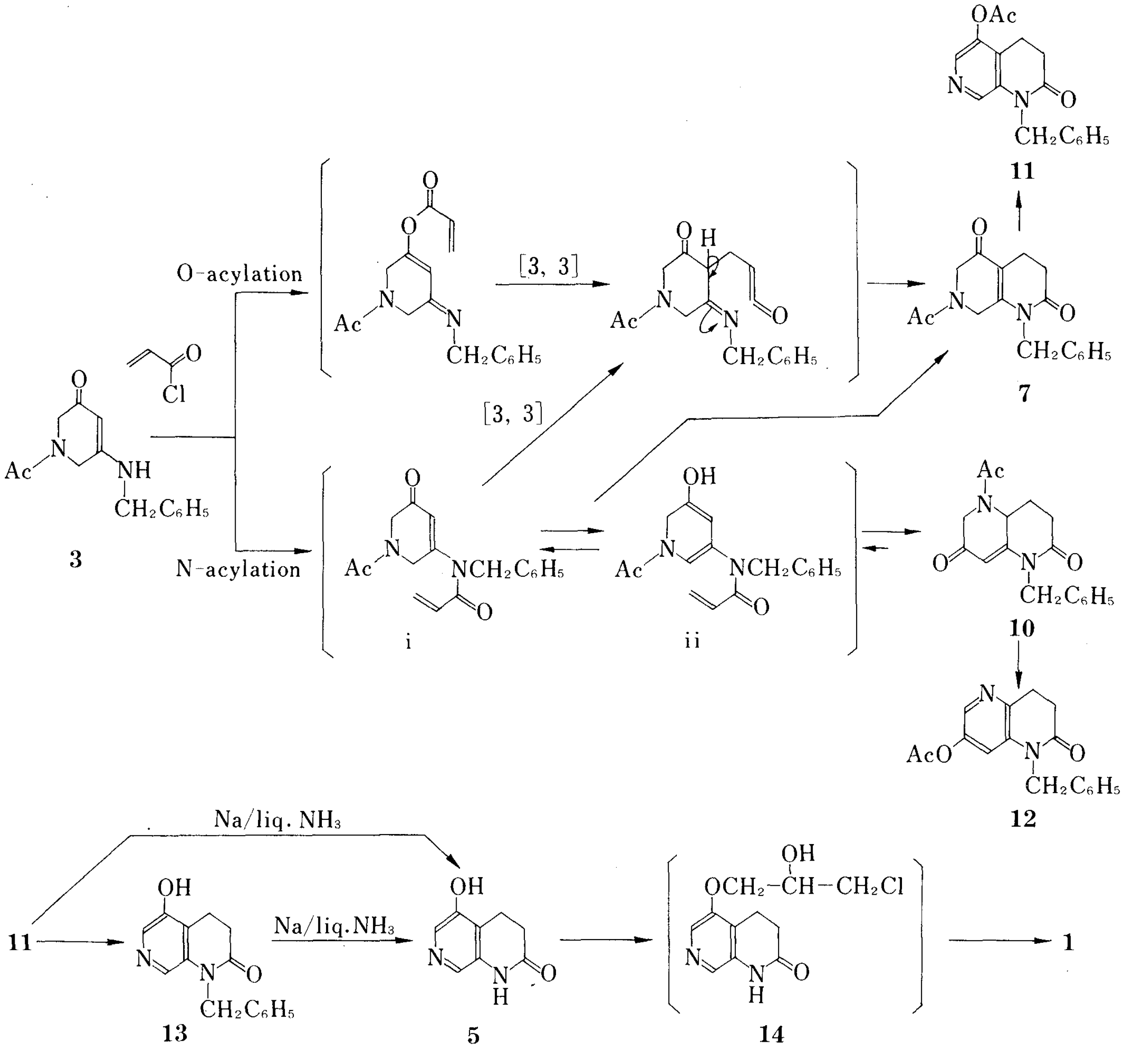


Chart 1

proposed structure **10**. The formation of **10** seems to occur *via* an intramolecular Michael-type cyclization onto the C-2 carbon of the intermediate (ii) derived from an initially formed N-acylated intermediate (i). The interconversion of i to ii may occur readily under the conditions used, because the dienol moiety in ii is stabilized by conjugation with the acetyl amino moiety.

Dehydrogenation of the bicyclic dione **7** on 5% palladium carbon in refluxing xylene for 30 h gave a 45% yield of 5-acetoxy-7-aza-1-benzyl-3,4-dihydrocarbostyril (**11**) and subsequent deacetylation was carried out with 10% aqueous hydrochloric acid–acetone to give 7-aza-5-hydroxy-1-benzyl-3,4-dihydrocarbostyril (**13**) in quantitative yield. Reductive debenzylation of **13** with liquid ammonia and sodium[8] gave the desired **5** in 45% yield. Both deacetylation and debenzylation could be performed at the same time by treatment with sodium in liquid ammonia, giving a 72% overall yield of **5** from **11**. The structures of these compounds **11**, **12**, **13**, and **5** were consistent with all spectroscopic and elemental data.

On the other hand, dehydrogenation of the bicyclic dione **10** under the same conditions gave the expected 7-acetoxy-5-aza-1-benzyl-3,4-dihydrocarbostyril (**12**) and the isomeric 7-aza-carbostyril (**11**) in 14 and 4% yields, respectively. The formation of **11** from **10** is explained by a retro-Michael addition of **10** to ii, subsequent enol-keto conversion to the intermediate i, and normal dehydrogenation of the cyclized product **7**. For preparative purposes, dehydrogenation of a mixture of the diones **7** and **10** without separation was found to give better results in terms of yield of **11** and convenience.

Alkylation of **5** with epichlorohydrin was carried out in methanol in the presence of a small amount of piperidine[9] to give 5-(3-chloro-2-hydroxy)propoxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (**14**), which was then aminated with *tert*-butylamine to give 5-(3-*tert*-butylamino-2-hydroxy)propoxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (**1**)·hydrochloride. Treatment of the hydrochloride with IRA-410 in methanol gave **1** in 37% overall yield from **5**, whose structure was supported by spectral and analytical data.

The antagonistic activity of **1**·hydrochloride against *l*-isoproterenol as tested in the right atrium of guinea-pigs was compared with that of carteolol·hydrochloride and expressed as pA_2 value calculated according to Yabuuchi.[10] The pA_2 value of **1**·hydrochloride [$pA_2=4.40\pm0.06$ ($n=4$)] was smaller than that of carteolol·hydrochloride [$pA_2=8.85\pm0.09$].

Experimental[11]

Conversion of 1-Acetyl-3-benzylamino-5-oxo-3,4-dehydropiperidine (3) into 7-Acetyl-1-benzyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydro-1,7-naphthyridine (7) and 5-Acetyl-1-benzyl-2,7-dioxo-1,2,3,4,4a,5,6,7-octahydro-1,5-naphthyridine (10) by Treatment with Acryloyl Chloride——A solution of acryloyl chloride (20 mmol) in chlorobenzene (50 ml) was added dropwise to a csolution of the β-benzylaminovinylketone (3) (20 mmol) in chloroform (100 ml), over 1 h. After the solution had been refluxed for 10 h, acryloyl chloride (10 mmol) was added. The mixture was heated for an additional 5 h to complete the reaction, then concentrated *in vacuo* to give a syrup, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent. Recrystallization of the solid material obtained from the first fraction from ethyl acetate gave the bicyclic dione **7** (32%) as colorless crystals, mp 149.5—150.5°C. *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.27; H, 6.03; N, 9.41. IR ν_{max}^{tablet} cm^{-1}: 1695, 1650, and 1625; NMR ($CDCl_3$) δ: 2.09 (3H, s, Ac), 2.67 (4H, s, $=CCH_2CH_2CO$), 4.01 (2H, s, NCH_2CO), 4.47 (2H, s, NCH_2 C=), 5.00 (2H, s, CH_2Ph), and 7.00—7.40 (5H, m, ArH); UV λ_{max}^{EtOH} 298 nm; MS *m/e* 298 (M^+). The material eluted next was dried under reduced pressure to give the bicyclic dione **10** (8%) as a yellow foam. Exact mass calcd. for $C_{17}H_{18}N_2O_3$: 298.1318. Found: 298.1324. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695, 1655, 1640, and 1600; NMR ($CDCl_3$) δ: 2.13 (3H, s, Ac), 2.13—3.12 (5H, m, NCH_2CH_2CO), 3.29—4.23 (2H, q, NCH_2CO), 4.96 (2H, s, CH_2Ph), 5.68 (1H, s, CH=), and 7.00—7.40 (5H, m, ArH); UV λ_{max}^{EtOH} 281 nm. Spectroscopic data were fully consistent with the proposed structure, while satisfactory analytical data could not be obtained because of the instability of the product.

Dehydrogenation of the Dione (7) to 5-Acetoxy-1-benzyl-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (11) on Palladium-carbon——A stirred suspension of **7** (3.35 mmol) and 5% palladium-carbon (2 g) in xylene (20 ml) was heated at 130—140°C for 30 h. Insoluble materials were filtered off, and the filtrate was concentrated *in vacuo* to give a syrup, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give a residue. Recrystallization from ethyl acetate–*n*-hexane gave pure **11** (45%) as colorless crystals, mp 97—98°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found:

C, 68.85; H, 5.15; N, 9.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1670, and 1595; NMR ($CDCl_3$) δ: 2.33 (3H, s, Ac), 2.80 (4H, s, =CH_2CH_2CO), 5.16 (2H, s, CH_2Ph), 7.21 (5H, s, ArH), 8.01 [1H, s, ArH], and 8.06 (1H, s, ArH); MS *m/e* 296 (M^+).

Dehydrogenation of the Dione (10) to 11 and 7-Acetoxy-1-benzyl-1,2,3,4-tetrahydro-2-oxo-1,5-naphthyridine (12) on Palladium-carbon——A stirred suspension of **10** (0.24 mmol) and 5% palladium-carbon (144 mg) in xylene (2 ml) was heated at 130°C for 30 h. Work-up as described for the dehydrogenation of **7** gave **11** and **12** (**11**: **12**=2: 7, 28%). Preparative TLC on silica gel with ethyl acetate as a developing solvent gave **12** as crystals. Recrystallization from ether gave pure **12** (25%), mp 117—119°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.64; H, 5.32; N, 9.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765. 1675, and 1595; NMR ($CDCl_3$) δ: 2.24 (3H, s, Ac), 2.76—3.07 (2H, m, CH_2CO), 3.07—3.31 (2H, m, =CCH_2), 5.16 (2H, s, CH_2Ph), 6.93 (1H, d, J=2 Hz, ArH), 7.17—7.43 (5H, m, ArH), and 7.97 (1H, d, J=2 Hz, ArH); MS *m/e* 296 (M^+).

1-Benzyl-5-hydroxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (13)——A solution of **11** (10 mg) and 10% aqueous hydrochloric acid (1 ml) in acetone (2 ml) was heated at 50°C for 1 h. After removal of acetone under reduced pressure, the aqueous solution was neutralized with sat. aqueous $NaHCO_3$. The resulting crystals were collected by filtration and recrystallized from methanol to give pure **13** (99%), mp 239—241°C. *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.42; H, 5.49; N, 11.09. IR ν_{max}^{tablet} cm^{-1}: 1680 and 1580; NMR (DMSO-d_6) δ: 2.61—2.94 (4H, m, CH_2CH_2CO), 5.13 (2H, s, CH_2Ph), 7.22 (5H, s, ArH), 7.64 (1H, s, ArH), and 7.86 (1H, s, ArH); MS *m/e* 254 (M^+).

5-Hydroxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (5)——i) Prepared from **11**: The N-benzyl-lactam (**11**) (0.34 mmol) was dissolved in condensed liquid ammonia (20 ml) with cooling in an isopropanol-dry ice bath. Freshly cut sodium (40 mg) was added in small pieces (10 mg each) over 30 min. The yellow slurry became blue and a permanent blue color appeared toward the end of the addition. After the mixture had been stirred at −50°C for an additional 30 min, ammonium chloride was added until the blue color disappeared and the ammonia was allowed to evaporate. Absolute methanol was added to the residue and the resulting sodium chloride was filtered off. The filtrate was concentrated *in vacuo* to give a residue, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give **5** (72%). A pure sample was obtained by recrystallization from methanol, mp over 300°C. Exact mass calcd for $C_8H_8N_2O_2$: 164.0581. Found: 164.0582. IR ν_{max}^{tablet} cm^{-1}: 1670 and 1590; NMR (DMSO-d_6): 2.25—2.68 (2H, m, CH_2CO), 2.68—3.081 (2H, m, =CCH_2), 7.71 (1H, s, ArH), and 7.84 (1H, s, ArH). Satisfactory analytical data were obtained from the O-acetate. *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.02; H, 4.70; N, 13.61.

ii) Prepared from **13**: The N-benzyl-lactam (**13**) (0.39 mmol) was treated with sodium (18 mg, 6 mg each) in liquid ammonia (8 ml) under the same conditions and work-up as described above gave **5** in 43% yield. The compound was identical with an authentic specimen obtained from **11**.

5-(3-Chloro-2-hydroxy)propoxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (14)——A mixture of 7-aza-5-hydroxy-3,4-dihydrocarbostyril (**5**) (0.37 mmol), epichlorohydrin (2.3 mmol), and one drop of piperidine was stirred at room temperature overnight. After removal of the resulting crystals, the filtrate was concentrated *in vacuo*. The residue was triturated with acetone to give crystals, which were recrystallized from methanol to give **14** (53%) as colorless crystals, mp 230—232°C, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1655 and 1570; MS *m/e* 257 (M^+). Spectroscopic data were consistent with the proposed structure, while satisfactory analytical data could not be obtained because of the instability of the product.

5-(3-*tert*-Butylamino-2-hydroxy)propoxy-1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridine (1)——A stirred mixture of **14** (0.097 mmol) and *tert*-butylamine (0.5 mmol) in methanol (0.4 ml) was warmed at 55—60°C for 6 h. The reaction mixture was evaporated to dryness *in vacuo* to give the crude **1**·hydrochloride (45% overall yield from **5**. Recrystallization of the hydrochloride from methanol gave pure **1**·HCl, mp over 300°C, IR ν_{max}^{tablet} cm^{-1}: 2330, 1650, 1595, and 1560. The hydrochloride was treated with IRA-410 in methanol (10 ml) to give **1** as crystals. Recrystallization from ethanol gave pure **1** (70%), mp 230°C (dec.). Exact mass calcd for $C_{15}H_{23}N_3O_3$: 293.1740. Found: 293.1743. *Anal.* Calcd for $C_{15}H_{23}N_3O_3 \cdot 2/3H_2O$: C, 58.99; H, 7.81; N, 13.76. Found: C, 58.94; H, 7.77; N, 13.56. IR ν_{max}^{tablet} cm^{-1}: 1660 and 1560. NMR (DMSO-d_6) δ: 1.04 (s, 9H, *tert*-C_4H_9), 6.92 (s, 1H, ArH), 7.10 (s, 1H, ArH), and other signals assignable to the expected structure.

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References and Notes

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