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The Synthesis of 7,8-Dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol

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The synthesis of 7,8-dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol (**6**) was undertaken in an attempt to confirm the hypothesis that an equatorial conformation of the amino group in 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol derivatives (**1**) might be essential for the β-adrenoceptor activity.

4-(2,3-Dimethoxyphenyl)cyclohexanone (**13**) which was prepared *via* several steps from 2,3-dimethoxyphenylacetonitrile (**7**), was led to a tetralone derivatives (**17**) by oxime formation, Beckmann rearrangement, hydrolysis and cyclization, by way of **14**, **15**, and **16**. Compound **6** was derived from **17** by a five-step sequence of reactions.

The β-adrenoceptor activity of **6**, in which the amino moiety is fixed in an axial conformation, proved to be about one-thousandth of that of *l*-isoproterenol.

Keywords——catecholamine derivative; hexahydromethanobenzazocinol; benzomorphan derivative; conformationally fixed compound; β-adrenoceptor; β-adrenergic activity

We recently reported that a series of *trans*-N-substituted 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**), which are conformationally restricted analogs of adrenergic catecholamines, exhibited potent β-adrenoceptor stimulating activities with predominant β_2-directing properties.[2)] The virtual absence of α-adrenergic activity even in the 2-amino (**1**, R=H) and 2-methylamino (**1**, R=CH_3) derivatives, which are analogs of norepinephrine and epinephrine, respectively, suggested that functional groups in the structure **1** are arranged so as to occupy nearly ideal positions for interaction with the β-adrenoceptor.

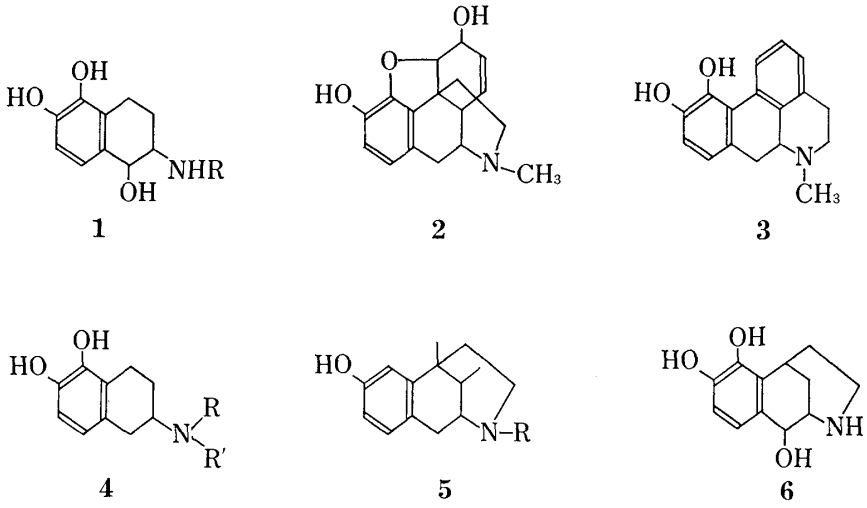

Fig. 1

1) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*

2) *a*) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975); *b*) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.*, **25**, 632 (1977); *c*) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.*, **25**, 2917 (1977).

It is noteworthy that the 2-amino-1,2,3,4-tetrahydronaphthalene skeleton also constitutes a part of other pharmacologically important substances, *e.g.* morphine (**2**) and apomorphine (**3**), a representative analgesic and a typical dopaminergic agonist, respectively. Recent investigations by Cannon *et al.* have revealed that 2-aminotetrahydronaphthalene derivatives (**4**) showed potent dopaminergic activity.[3] On the other hand, benzomorphan derivatives (**5**) which are derived from morphine are potent analgesics.[4] The similarity in the structures of **4**, **5** and **1** might suggest that the structures of the receptors of morphine, dopamine and adrenergic catecholamines are at least partly similar to each other, and the difference in biological activity might thus be brought about by the differences in conformation and pK_a, as well as other subtle changes around the binding site.

The conformation of the aminoethanol moiety in **1** has been postulated to be *trans*-diequatorial,[2a,5] while the amino group in benzomorphan exists in an axial conformation with respect to the tetrahydronaphthalene ring. It appeared to be of interest, therefore, to synthesize 7,8-dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol (**6**), in which the structures of **1** and **5** are incorporated in one molecule with the amino group being fixed in an axial conformation, and to examine its β-adrenergic activity.

Our synthetic strategy involved the construction of a 6,7-benzomorphan skeleton having appropriate functionalities, removal of the protective groups on the catechol moiety, and catalytic reduction of the C_1-carbonyl group to alcohol (**6**) at the final step. Although several synthetic methods[6] for 6,7-benzomorphan derivatives are known, the most promising synthetic route to our dimethoxy compound appeared to be that of Mitsuhashi and his coworkers,[6c] since each step of their procedure was carried out under relatively mild conditions. Therefore we undertook the initial synthesis of 7,8-dimethoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-one (**19**) by procedures similar to those of Mitsuhashi.

4-(2,3-Dimethoxyphenyl)cyclohexanone (**13**), which was required as a key intermediate in the synthesis, was prepared by the following procedure (Chart 1), referring to the preparation

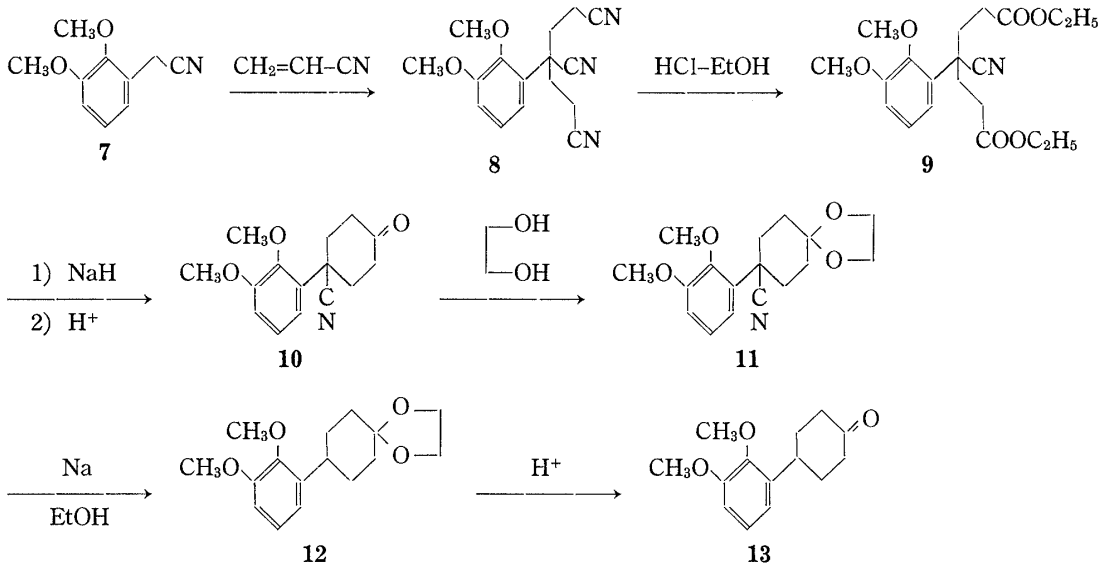

Chart 1

3) J.G. Cannon, J.C. Kim, M.A. Aeem, and J.P. Long, *J. Med. Chem.*, **15**, 348 (1972).
4) E.L. May and L.T. Sargent, "Analgesics," ed. by G. de Stevens, Academic Press, New York, 1965; N.B. Eddy and E.L. May, "Synthetic Analgesics," Part II(B), Pergamon Press, Oxford, 1966.
5) M. Motohashi, Y. Wada, K. Kamiya, M. Nishikawa, *Chem. Pharm. Bull.*, accepted.
6) *a*) K. Kanematsu, R.T. Parfitt, A.E. Jacobson, J.H. Ager, and E.L. May, *J. Am. Chem. Soc.*, **90**, 1064 (1968); *b*) K. Kanematsu, M. Takeda, A.E. Jacobson, and E.L. May, *J. Med. Chem.*, **12**, 405 (1969); *c*) K. Mitsuhashi, S. Shiotani, R. Oh-uchi, and K. Shirai, *Chem. Pharm. Bull.*, **17**, 434 (1969).

of the 3,4-dimethoxy isomer by Horning.[7] Thus, 2,3-dimethoxyphenylacetonitrile (**7**) was allowed to react with acrylonitrile in the presence of potassium hydroxide to give 3-(2,3-dimethoxyphenyl)-1,3,5-pentanetricarbonitrile (**8**). Treatment of **8** with ethanolic hydrogen chloride under reflux afforded diethyl 4-cyano-4-(2,3-dimethoxyphenyl)heptanedioate (**9**). An attempt to prepare **9** directly by Michael reaction of ethyl acrylate with **7** under similar conditions failed owing to the low reactivity of the ester. Dieckmann condensation of **9** with sodium hydride followed by acid hydrolysis gave 1-(2,3-dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (**10**). After leading **10** to the ethylene acetal (**11**), **11** was treated with sodium in ethanol to give 4-(2,3-dimethoxyphenyl)cyclohexanone ethylene acetal (**12**), from which **13** was obtained by acid hydrolysis.

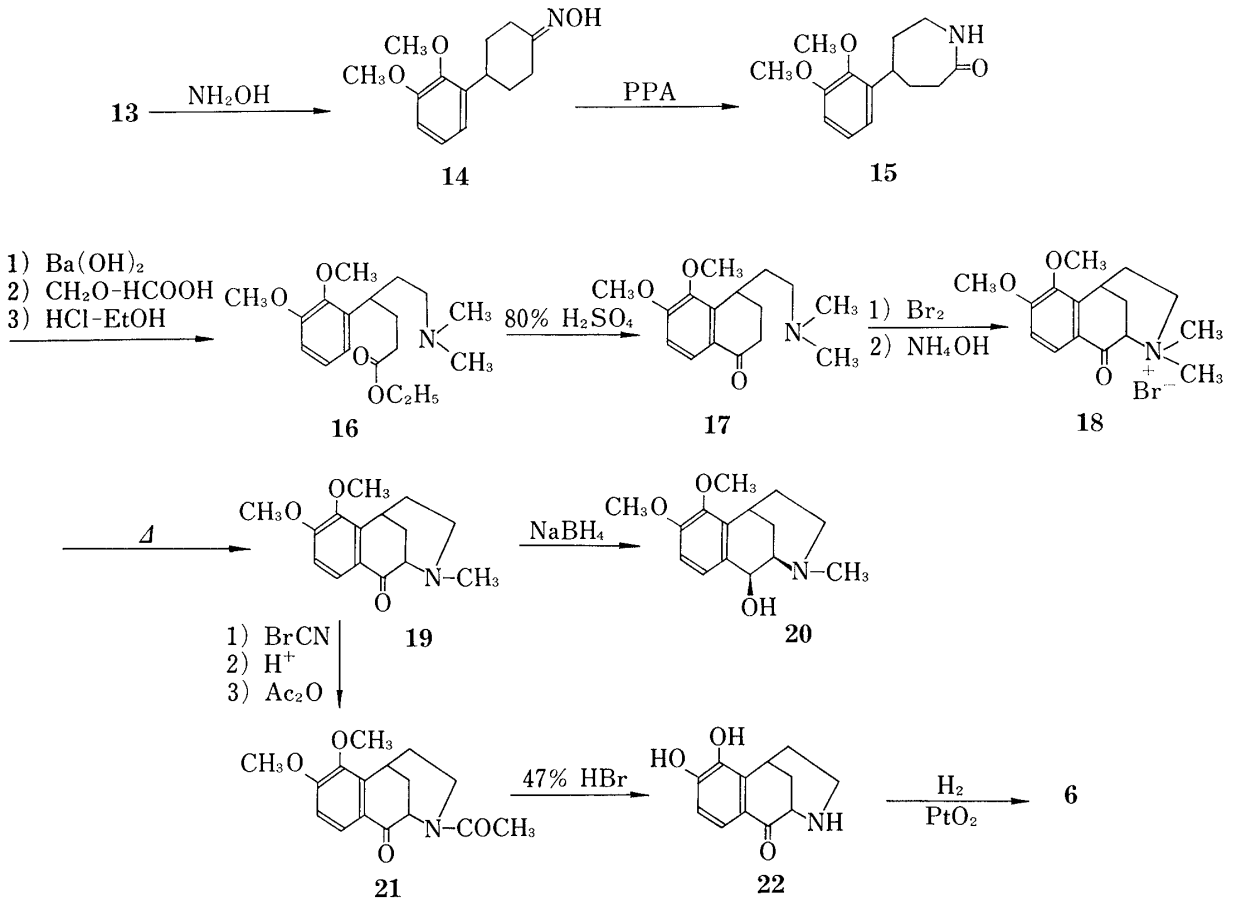

Chart 2

The synthetic route to **6** from **13** is illustrated in Chart 2. Thus, **13** was led to the oxime (**14**) by reaction with hydroxylamine, then **14** was subjected to Beckmann rearrangement by treatment with polyphosphoric acid to give 5-(2,3-dimethoxyphenyl)-ε-caprolactam (**15**) in 44% yield. Hydrolysis of **15** with barium hydroxide followed by methylation with formalin–formic acid gave 4-(2,3-dimethoxyphenyl)-6-dimethylaminohexanoic acid. An attempt was made to cyclize this amino acid to the tetralone derivative, but treatment with polyphosphoric acid led to immediate decomposition of the material, though the same reaction has been reported to be successful in the analog without methoxy groups.[6c] This result suggested that the cyclization should be carried out under milder conditions for our compound. Therefore the amino acid was converted to the ester (**16**) with ethanolic hydrogen chloride and the oxalate of **16** was heated in 85% sulfuric acid at 75—80° for 20 min to give the desired 5,6-dimethoxy-

7) E.C. Horning, M.G. Horning, M.S. Fish, and M.W. Rutenberg, *J. Am. Chem. Soc.*, **74**, 775 (1952).

4-dimethylaminoethyl-3,4-dihydro-2*H*-naphthalen-1-one (**17**) in 58% yield; this compound was isolated as the crystalline hydrobromide. Bromination of **17** with bromine in acetic acid followed by treatment with aqueous ammonia gave the quaternary salt **18**. When **18** was heated at 190—200° in octanol, it was exclusively converted to **19**. Reduction of **19** with sodium borohydride stereoselectively afforded the *cis*-alcohol **20** (70%), whose nuclear magnetic resonance (NMR) spectrum showed C_1–H at δ 5.0 (J=6 Hz).[8] Compound **19** was converted to N-acetyl derivative (**21**) in 35% yield by treatment with cyanogen bromide, acid hydrolysis and acetylation of the resulting demethylated product with acetic anhydride; 30% of the starting material **19** was recovered. Hydrolysis of **21** by heating in 47% hydrobromic acid gave 7,8-dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-one (**22**·HBr) in 84% yield. Catalytic reduction of **22**·HBr over platinum oxide yielded the title compound **6**·hydrobromide as a colorless crystalline powder in 95% yield. In the NMR spectrum of **6**·HBr the C_1–H appeared as two bands at δ 4.9 (J=6 Hz) and δ 4.6 (J=0). From the coupling constants and results of integration of each signal, **6**·HBr was judged to be a *ca.* 3:1 mixture of 1,2-*cis* and *trans* derivatives.

The β_2-adrenoceptor activity of **6** was measured *in vitro* using isolated tracheal strips of a guinea pig according to the methods described in the preceding paper.[2a] It was found that **6** showed only a weak β-agonistic activity, one-thousandth of that of *l*-isoproterenol. This result is consistent with the hypothesis[2a] that a configuration of the amino group corresponding to the equatorial conformation of the amino group in **1** is essential for β-adrenergic agonist activity.

Experimental[9]

2,3-Dimethoxyphenylacetonitrile (**7**)——$NaBH_4$ (40 g) was added portionwise to a stirred solution of 2,3-dimethoxybenzaldehyde (290 g) in MeOH (1 l) at room temperature. The reaction mixture was diluted with excess water and extracted with $CHCl_3$ (1 l). After drying the extract over Na_2SO_4, pyridine (45 ml) was added, followed by dropwise addition of $SOCl_2$ (220 ml) at room temperature with stirring. Excess $SOCl_2$ was decomposed by addition of water. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give 2,3-dimethoxybenzylchloride (315 g) as an oil. This was dissolved in EtOH (600 ml) and added to a heated solution of KCN (129 g) in water (200 ml) with stirring. The mixture was refluxed for 1 hr, cooled, poured into excess water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. Distillation of the residue gave 259 g (84%) of **7** as a colorless oil, bp_{30} 170—180° (lit. bp_{13} 154—161°).[10]

3-(2,3-Dimethoxyphenyl)-1,3,5-pentanetricarbonitrile (**8**)——Acrylonitrile (6 ml) and a solution of KOH (6.3 g) in MeOH (15 ml) were added to a stirred solution of **7** (200 g) in *tert*-BuOH (400 ml). The resulting solution was treated dropwise with acrylonitrile (120 g) at a rate such that the temperature was maintained at 30—40°. When the addition was complete, stirring was continued for a further 2 hr. The reaction mixture was poured into water (1 l) and extracted with Et_2O (1.5 l). The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **8** (300 g, 94%) as a colorless oil. IR ν_{max}^{Nujol} cm^{-1}: 2250 (C≡N). NMR ($CDCl_3$) δ: 1.9—2.8 (m, 8H), 3.8 (s, 3H), 3.9 (s, 3H), 6.9—7.1 (m, 3H).

Diethyl 4-Cyano-4-(2,3-dimethoxyphenyl)heptanedioate (**9**)——A solution of **8** (300 g) in 20% HCl–EtOH (600 ml) was heated under reflux for 7 hr. After removing the solvent by evaporation under reduced pressure, the residue was dissolved in 20% HCl–EtOH (500 ml). The solution was refluxed for a further 5 hr and concentrated *in vacuo*. The residue was triturated with water (2 l) and extracted with $CHCl_3$ (1 l). The extract was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated down *in vacuo* to give **9** (370 g, 93%) as a pale yellow oil. IR ν_{max}^{Neat} cm^{-1}: 2220 (C≡N), 1730 (C=O). NMR ($CDCl_3$) δ: 1.1 (t, J=7 Hz, 6H), 2.1—2.7 (m, 8H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (q, J=7 Hz, 4H), 6.8—7.1 (m, 3H).

8) The determination of the relative configuration of the amino and hydroxyl groups in hydroxybenzomorphan has been described in the literature; J.J. Fauly and J.B. LaPidus, *J. Med. Chem.*, **16**, 181 (1973).

9) All melting points were determined on a micro hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer. NMR spectra were recorded on a Varian T-60 or HA-100 machine using Me_4Si as a standard. The mass spectra (MS) were measured with a Hitachi RMU-60 mass spectrometer.

10) R. Delaby, G. Tsutsas, and M.C. Jendrot, *Bull. Soc. Chim. France*, **1956** 1830.

1-(2,3-Dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (10)——Compound **9** (370 g) was added dropwise to a refluxed suspension of NaH (50% in oil, 50 g) in toluene (500 ml) during 3 hr under a nitrogen atmosphere. When the addition was complete, the reaction mixture was cooled, poured into water (1 l) and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo* until toluene was removed completely. AcOH (300 ml), conc. HCl (200 ml) and water (100 ml) were added to the residue. The mixture was refluxed for a further 2.5 hr, cooled, and poured into water. After making the solution alkaline with dilute NaOH, the aqueous solutions was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Crystallization of the residue from EtOH gave **10** (40 g, 16%) as colorless prisms. The filtrate was concentrated and the residue was subjected to column chromatography on silica gel (benzene) to give additional **10** (31.5 g, 12%). mp 133—135°. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.46; H, 6.60; N, 5.21. IR ν_{max}^{Nujol} cm^{-1}: 2220 (C≡N), 1720 (C=O).

1-(2,3-Dimethoxyphenyl)-4,4-ethylenedioxycyclohexanecarbonitrile (11)——A mixture of **10** (71.5 g), ethyleneglycol (21 ml), toluene (300 ml) and *p*-TsOH (0.3 g) was refluxed in a flask equipped with a water separator for 4 hr. After cooling, the reaction mixture was washed with water, dried over Na_2SO_4 and concentrated. The oily residue (**11**, 83 g, 99%) was recrystallized from EtOH to give colorless prisms. mp 87—88°. *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.36; H, 6.97; N, 4.63. IR ν_{max}^{Nujol} cm^{-1}: 2200 (C≡N).

4-(2,3-Dimethoxyphenyl)cyclohexanone Ethyleneacetal (12)——Sodium sand (38 g) was prepared in 250 ml of dry toluene, then a solution of **11** (83 g) in a mixture of toluene (100 ml) and EtOH (40 g) was added at a rate such that refluxing continued without external heating. When the addition of the acetal was complete, EtOH (40 g) and 95% EtOH (100 ml) were successively added dropwise to decompose the remaining sodium. The mixture was stirred for 1 hr at room temperature, then poured into water (1 l). The separated organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give **12** (70 g, 92%) as a yellow viscous oil, which was crystallized from petroleum ether to give colorless needles, mp 88—89°. *Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.92; H, 7.86.

4-(2,3-Dimethoxyphenyl)cyclohexanone (13)——A mixture of **12** (70 g), EtOH (300 ml), water (200 ml) and conc. HCl (50 ml) was refluxed for 2.5 hr. After cooling, the reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **13** (55 g, 93%) as a viscous oil, which was crystallized from EtOH–cyclohexane to give colorless prisms. mp 108—110°. *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.17; H, 7.79. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O).

4-(2,3-Dimethoxyphenyl)cyclohexanone Oxime (14)——A mixture of **13** (55 g), hydroxylamine·HCl (60 g) and pyridine (250 ml) was heated at 110° for 1 hr. After cooling, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with diluted HCl, dried over Na_2SO_4 and concentrated *in vacuo* to give **14** (47 g, 81%) as an oily residue, which was recrystallized from EtOH to give colorless crystals. mp 116—117°. *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.14; H, 7.65; N, 5.33. IR ν_{max}^{Nujol} cm^{-1}: 3240 (OH).

5-(2,3-Dimethoxyphenyl)-ε-caprolactam (15)——A mixture of **14** (47 g) and polyphosphoric acid (500 g) was heated at 100—110° for 10 min. After cooling, the reaction mixture was diluted with ice-water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to give a brown viscous oil, which was dissolved in MeOH. After decolorization with activated charcoal, the solution was concentrated to a small volume to precipitate **15** (14.6 g, 31%) as colorless prisms. The filtrate was evaporated to dryness and the residue was subjected to column chromatography on silica gel, eluted with $CHCl_3$–MeOH (25: 1), to afford additional **15** (6.1 g, 13%). mp 181—183°. *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 66.98; H, 7.72; N, 5.46. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3050 (NH), 1660 (C=O).

Ethyl 4-(2,3-Dimethoxyphenyl)-6-dimethylaminohexanoate (16)——A mixture of **15** (13 g), $Ba(OH)_2 \cdot 8H_2O$ (91 g) and water (750 ml) was refluxed for 20 hr. The reaction mixture was neutralized with dilute H_2SO_4 and filtered with celite. The filtrate was evaporated to dryness. The residue was mixed with formic acid (80 ml) and formalin (37%, 30 ml). The resulting mixture was heated at 100° for 1.5 hr. The excess formalin and formic acid were removed *in vacuo*, HCl–EtOH (20%, 100 ml) was added to the residue, and the solution was heated at 100° for 1 hr. After the removal of EtOH followed by addition of water (100 ml) the aqueous solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo* to give **16** as an oil, which was converted to the hydrogen oxalate (13.2 g, 60%) by treatment with oxalic acid (4 g) in EtOH (20 ml), followed by dilution with ether. mp 132—134°. *Anal.* Calcd for $C_{18}H_{29}NO_4 \cdot C_2H_2O_4$: C, 58.10; H, 7.56; N, 3.39. Found: C, 57.66; H, 7.52; N, 3.45. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). NMR (DMSO-d_6) δ: 1.1 (t, J=7 Hz, 3H), 1.6—2.3 (m, 6H), 2.7 (s, 6H), 2.7—3.2 (m, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 4.0 (q, J=7 Hz, 2H), 6.7—7.1 (m, 3H).

5,6-Dimethoxy-4-dimethylaminoethyl-3,4-dihydro-2*H*-naphthalen-1-one (17)——A mixture of **16**·hydrogen oxalate (5 g) and 80% H_2SO_4 (50 g) was heated with stirring at 75—80° for 20 min and then poured into water (300 ml). The aqueous mixture was made alkaline with 10% NaOH, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in MeOH and treated with decolorizing charcoal. After the removal of MeOH, the residue was dissolved in a mixture of EtOH (10 ml) and HBr–AcOH (30%, 2 ml). Ether was added dropwise to precipitate **17**·HBr (2.5 g, 58%)

as colorless prisms. mp 215—216°. *Anal.* Calcd for $C_{16}H_{23}NO_3 \cdot HBr$: C, 53.64; H, 6.75; N, 3.91. Found: C, 53.23; H, 6.50; N, 3.66. IR ν_{max}^{Nujol} cm^{-1}: 1660 (NH). NMR (DMSO-d_6) δ: 1.8—3.6 (m, 9H), 2.8 (s, 6H), 3.8 (s, 3H), 3.9 (s, 3H), 7.1 (d, $J=9$ Hz, 1H), 7.7 (d, $J=9$ Hz, 1H).

7,8-Dimethoxy-3,3-dimethyl-1-oxo-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-3-ium Bromide (18)——Br_2 (1.53 g) was added dropwise to a stirred solution of **17**·HBr (3.2 g) in AcOH (30 ml) at room temperature. When the addition was complete, stirring was continued for 30 min. Ether (300 ml) and petroleum ether (300 ml) were added to the reaction mixture to deposit crystals, which were collected by filtration and dissolved in water (100 ml). Next, 28% NH_4OH (10 ml) was added to the aqueous solution, and the mixture was concentrated under reduced pressure. The residue was triturated with acetone, and the resulting precipitate was collected by filtration then dissolved in MeOH. The solution was decolorized with activated carbon and concentrated under reduced pressure. Acetone was added to the residue to deposit colorless crystals of **18** (2.7 g), contaminated with a small amount of NH_4Br. This product was used for the subsequent step without further purification. mp 213—215° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O). NMR (d_6-DMSO+D_2O) δ: 3.1 (s, 3H), 3.4 (s, 3H), 3.9 (s, 3H), 4.0 (s, 3H), 1.6—4.1 (m, 8H), 7.3 (d, $J=9$ Hz, 1H), 7.9 (d, $J=9$ Hz, 1H).

7,8-Dimethoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-one (19)——A mixture of the above crude **18** (1.5 g) and octanol (30 ml) was heated at 190—200° for 30 min with stirring under a nitrogen stream. After cooling, ether (200 ml) was added and the mixture was extracted three times with 10% HCl (total 100 ml). The aqueous layer was washed with ether, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and concentrated *in vacuo* to give **19** (0.7 g, 93%) as a viscous oil, which was converted to the hydrochloride, mp 100—103°. *Anal.* Calcd for $C_{15}H_{19}NO_3 \cdot HCl$: C, 53.97; H, 7.25; N, 4.20. Found: C, 54.05; H, 6.86; N, 4.29. IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O). MS *m/e*: 261 (M^+). NMR (d_6-DMSO+D_2O) δ: 2.3 (s, 3H), 3.8 (s, 3H), 3.9 (s, 3H), 1.6—4.0 (m, 8H), 7.2 (d, $J=9$ Hz, 1H), 7.8 (d, $J=9$ Hz, 1H). Hydrogen fumarate, colorless prisms, mp 153—157°. *Anal.* Calcd for $C_{15}H_{19}NO_3 \cdot C_4H_4O_4 \cdot 1/2H_2O$: C, 59.05; H, 6.26; N, 3.63. Found: C, 59.47; H, 5.96; N, 3.46.

7,8-Dimethoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol (20)——A stirred solution of **19**·HCl (2 g) in MeOH (30 ml) was treated portionwise with $NaBH_4$ (1.5 g) at room temperature. After stirring for 30 minutes, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in a mixture of fumaric acid (0.5 g) and MeOH (50 ml) and treated with decolorizing charcoal. After concentration to 10 ml under reduced pressure, the solution was diluted with ether (200 ml) to precipitate **20**·fumarate (1.5 g, 70%) as colorless prisms, mp 154—157°. *Anal.* Calcd for $C_{15}H_{21}NO_3 \cdot 1/2C_4H_4O_4 \cdot 2H_2O$: C, 57.13; H, 7.62; N, 3.92. Found: C, 56.78; H, 7.17; N, 3.95. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH). NMR (d_6-DMSO+D_2O) δ: 2.9 (s, 3H), 3.75 (s, 3H), 3.8 (s, 3H), 1.3—3.8 (m, 9H), 5.0 (d, $J=6$ Hz, 1H), 6.95 (d, $J=8$ Hz, 1H), 7.2 (d, $J=8$ Hz, 1H).

3-Acetyl-7,8-dimethoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol (21)——A solution of BrCN (3.3 g) in $CHCl_3$ (20 ml) was added to a solution of **19** (3.3 g) in $CHCl_3$ (20 ml), and the resulting mixture was refluxed for 5 hr. After adding 10% HCl (200 ml) to the mixture, $CHCl_3$ was distilled off, and the solution was refluxed for a further 8 hr. The reaction mixture was neutralized with NH_4OH and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and concentrated *in vacuo* to give an oily residue, which was heated with Ac_2O (10 ml) at 80° for 5 minutes. After removing excess Ac_2O under reduced pressure, the residue was chromatographed on silica gel (acetone: benzene=1: 4). The first fraction provided **21** (1.3 g, 35%) as colorless prisms, mp 150—151°, on crystallization from ether–petroleum ether. *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.47; H, 6.65; N, 4.82. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1640 (C=O). The second fraction afforded **20** (1 g, 30%).

7,8-Dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-one (22)——A mixture of **21** (1.2 g) and 47% HBr (30 ml) was refluxed for 8 hr. The mixture was then evaporated to dryness and the residue was dissolved in MeOH (50 ml). The resulting solution was decolorized with activated charcoal and concentrated *in vacuo*. The residue was triturated with acetone (50 ml) to give **22**·HBr (1.05 g, 84%) as colorless prisms, which showed no definite mp, decomposing gradually above 270°. *Anal.* Calcd for $C_{12}H_{13}NO_3 \cdot HBr$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.02; H, 4.70; N, 4.36. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). MS *m/e*: 219 (M^+). NMR (d_6-DMSO+D_2O) δ: 1.6—4.0 (m, 8H), 6.9 (d, $J=8$ Hz, 1H), 7.4 (d, $J=8$ Hz, 1H).

7,8-Dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol (6)——A solution of **22**·HBr (1.0 g) in 95% EtOH (20 ml) was subjected to catalytic reduction over PtO_2 (0.3 g) at ambient temperature and pressure. After 1 eq. hydrogen had been absorbed, the catalyst was filtered off and the filtrate was concentrated under reduced pressure below 40°. The residue was triturated with acetone (5 ml) and ether (100 ml) to deposit **6**·HBr (1 g, 95%) as pale yellow crystals, which showed no definite mp. *Anal.* Calcd for $C_{12}H_{15}NO_3 \cdot HBr \cdot 1/2H_2O$: C, 46.31; H, 5.51; N, 4.50. Found: C, 46.80; H, 5.30; N, 4.41. MS *m/e*: 221 (M^+). NMR (d_6-DMSO+D_2O) δ: 1.4—3.7 (m, 8H), 4.6 (s, 0.25H), 4.9 (d, $J=6$ Hz, 0.75H), 6.6—6.9 (m, 2H).

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