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Studies on the Syntheses of Heterocyclic Compounds. D.[1] Novel Cleavage of Tetrahydroprotoberberines with Trifluoroacetic Anhydride

Tetsuji Kametani, Shiroshi Shibuya, Shoji Hirata, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University[2]

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Treatment of 5,6,13,13a-tetrahydro-10-hydroxy-2,3,11-trimethoxy-8H-dibenzo[*a*,*g*]-quinolizine (**10**) with trifluoroacetic anhydride afforded 2-(2-trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-6-hydroxy-5-methoxyindene (**13**). 5,6,13,13a-Tetrahydro-12-hydroxy-2,3,11-trimethoxy-8H-dibenzo[*a*,*g*]quinolizie (**11**) under the same conditions as in the case of **10** yielded 2-(2-trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-4-hydroxy-5-methoxyindene (**18**).

Hofmann degradation and von Braun reaction have been known as the useful reactions for the structural elucidation of tetrahydroberberine bases. The former reaction on metho-salt of xylopinine (**1**)[3] gave the methine base (**2**). Similarly, the metho-salt derived from corydaline (**3**) and mesocorydaline (**5**) under Hofmann degradation conditions afforded (**4**) and (**6**), respectively.[4] In contrast with this behavior, von Braun degradation of canadine (**7**) gave two products (**8**) and (**9**).[5] Thus, tetrahydroprotoberberine bases under Hofmann or von Braun reaction conditions resulted in cleavage of the C_{13a}-nitrogen bond or C_6-nitrogen bond. Recently protoberberines were found to be an important key intermediate[6] for the synthesis of ochotensine derivatives and rhoeadine type compounds. We have been investigated an another type of degradation reaction involving a fission of C_8-nitrogen bond in order to obtain a synthetic intermediate which seems to be potentially useful for the syntheses of ochotensinan and rhoeadine skeleton.

Firstly, 5,6,13,13a-tetrahydro-10-hydroxy-2,3,11-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (**10**) was heated with trifluoroacetic anhydride in a sealed tube at 180°. Treatment of the crude product (**12**) with methanol, followed by purification with silica gel column chromatography, yielded 2-(2-trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-6-hydroxy-5-methoxyindene (**13**), the molecular formula, $C_{22}H_{22}O_5NF_3$, of which was established by mass spectrometry and microanalysis. Its infrared (IR) spectrum revealed the presence of hydroxy and secondary amide absorption due to phenolic and trifluoroacetamide group at 3450, 3350, and 1710 cm^{-1}, respectively. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) showed a singlet at 3.69 ppm due to methylene protons at the 1-position of an indene skeleton. Moreover, the presence of $C_6H_5CH_2CH_2NHCOCF_3$ group was strongly supported by the A_2B_2 type methylene signals at 2.83—3.62 ppm in its NMR spectrum. Basic hydrolysis of **13**, followed by reductive methylation of **14**, gave the compound (**15**), the NMR ($CDCl_3$) spectrum of which showed N,N-dimethyl signal at 2.38 ppm, ethanamine signals at 2.5—3.05 ppm, and a singlet attributable to the C_1-methylene group of **15** at 3.67 ppm. Therefore, the cleaved product obtained from **10** was assigned to the structure (**13**). The mass spectra of **13**, **14**, and **15**, which showed a peak at *m/e* 311 due to ion a, also strongly supported

1) Part CDCXIX, T. Kametani, T. Yamanaka, and K, Nyu, *J. Heterocyclic Chcm.*, in press.
2) Location: *Aobayama, Sendai.*
3) M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, **80**, 885 (1960).
3) P.W. Jeffs, "The Alkaloids," IX, edited by R.H.F. Manske, Academic Press, New York, 1967, p. 78.
5) I. Sallay and R.H. Ayers, *Tetrahedron*, **19**, 1397 (1963).
6) M. Shamma and J.F. Nugent, *Chem. Commun.*, **1971**, **1642** and references are cited therein.

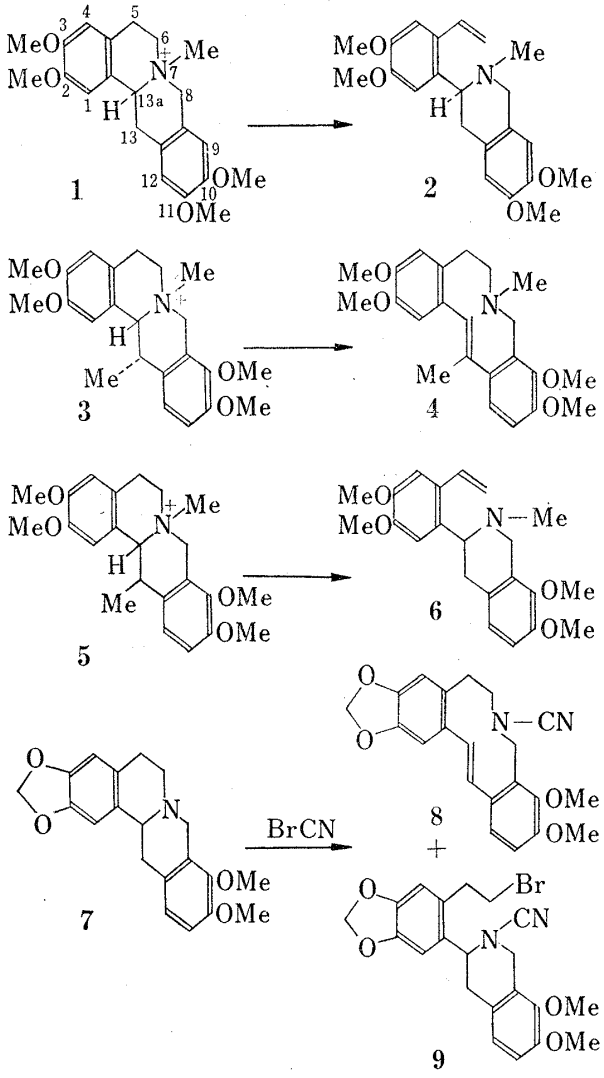
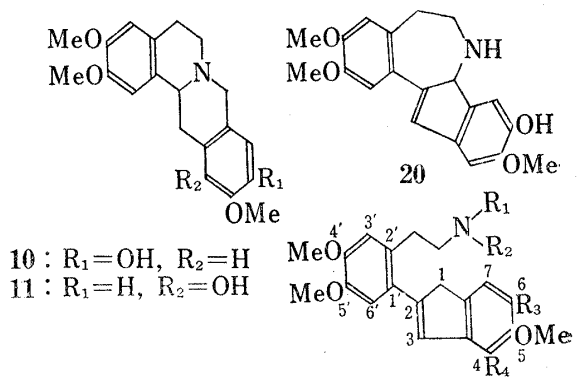


Chart 1



10 : R_1=OH, R_2=H
11 : R_1=H, R_2=OH

12: R_1=R_4=H, R_2=$COCF_3$, R_3=$OCOCF_3$
13: R_1=R_4=H, R_2=$COCF_3$, R_3=OH
14: R_1=R_2=R_4=H, R_3=OH
15: R_1=R_2=Me, R_3=OH, R_4=H
16: R_1=R_4=H, R_2=$COCF_3$, R_3=OMe
17: R_1=R_3=H, R_2=$COCF_3$, R_4=$OCOCF_3$
18: R_1=R_3=H, R_2=$COCF_3$, R_4=OH
19: R_1=R_2=R_3=H, R_4=OH

Chart 2

the above structures. Methylation of **13** with diazomethane afforded **16**, the mass spectrum of which showed a peak at *m/e* 325 (ion c) instead of *m/e* 311 (ion a).

Secondly, the similar reaction as above was examined with regards to 5,6,13,13a-tetrahydro-12-hydroxy-2,3,11-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (**11**), which was prepared as follows. Condensation of 2-benzyloxy-3-methoxyphenylacetic acid (**22**) with homoveratrylamine (**21**) gave the corresponding amide (**23**), the Bischler–Napieralski reaction of which with phosphoryl chloride gave the 3,4-dihydroisoquinoline (**24**). Reduction of **24** with sodium borohydride, followed

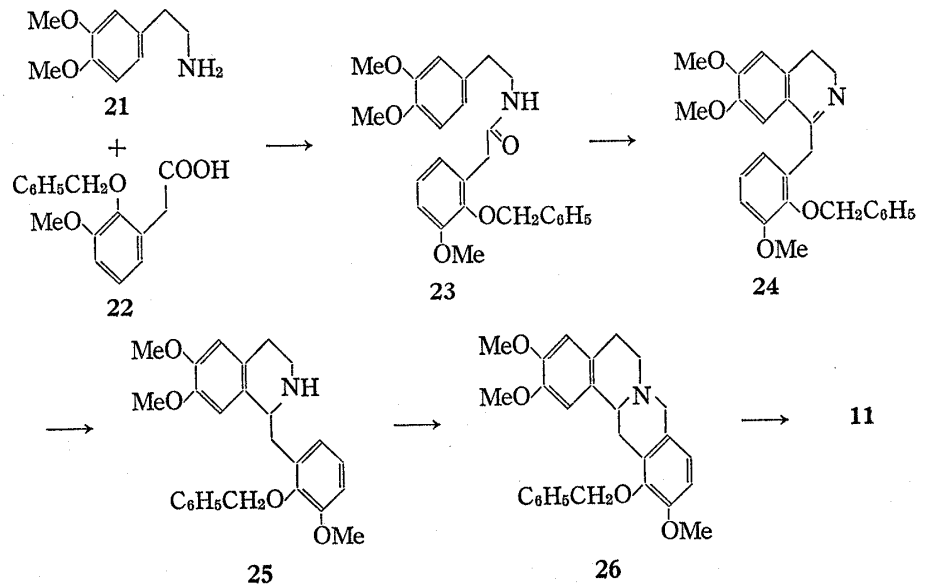


Chart 3

by the Mannich reaction of **25**, afforded the tetrahydroprotoberberine base (**26**). Debenzylation of **26** yielded the expected phenolic base (**11**), which was treated with trifluoroacetic anhydride under the same conditions as in case of **10**. Thus there was obtained 2-(2-trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-4-hydroxy-5-methoxyindene (**18**), the NMR ($CDCl_3$), IR ($CHCl_3$), and mass spectra of which were similar to those of **13** as shown in the experimental section. Basic hydrolysis of **18** afforded the phenolic base (**19**), the high resolution mass spectrum of which verified the molecular formula, $C_{20}H_{23}O_4N$ (M^+: Calcd.: 341.1626. Found: 341.1644).

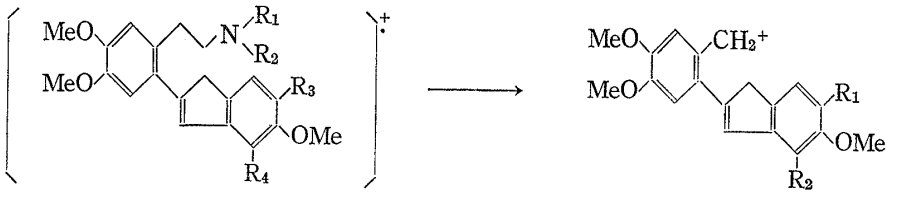


Chart 4

The possible fragmentation pattern of these products was shown in Chart 4.

These novel products **13** and **18** would be formed *via* the stilbene intermediate (**27**) as shown in Chart 5, but no attempts to obtain the benzazepine derivative (**20**), which would be a key intermediate for the synthesis of the rhoeadine type alkaloids, were successful.

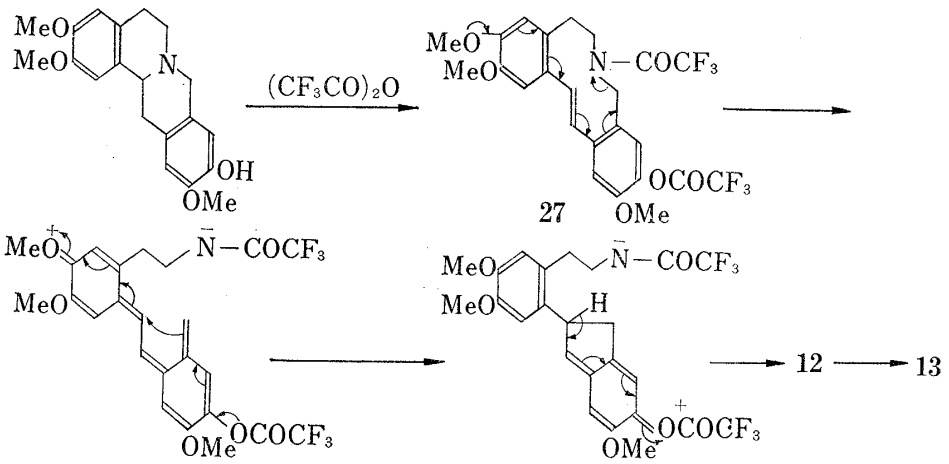


Chart 5

Experimental[7]

2-(2-Trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-6-hydroxy-5-methoxyindene (13)——A mixture of 2.5 g of the phenolic tetrahydroprotoberberine (10)[8] and 20 ml of trifluoroacetic anhydride was heated in a sealed tube at 180° for 6 hr. After cooling, the mixture was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. A solution of the residual oil (12) in 50 ml of MeOH was refluxed for 20 min, and the solvent was evaporated to leave 1.8 g of a brownish syrup, which was chromatographed on 40 g of silica gel. Removal of the elution with $CHCl_3$ afforded 0.8 g of **13** as colorless needles, mp 205—206° (from MeOH–ether). *Anal.* Calcd. for $C_{22}H_{22}O_5NF_3$: C, 60.41; H, 5.07;

7) All melting points are uncorrected. IR and NMR spectra were measured on a type EPI-3 Hitachi recording spectrometer and Hitachi R-20 spectrometer with tetramethylsilane as an internal reference, respectively. The mass spectra were taken with a Hitachi RMU-7 spectrometer.

8) D.H. Tedeschi, U.S. Patent, 3,272,707 [*C. A.*, **65**, 20110 (1866)].

N, 3.20. Found: C, 60.77; H, 4.69; N, 3.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 3350 (NH), 1710 (NHCOCF$_3$). NMR (in $CDCl_3$) δ: 2.83—3.62 (4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2NH$), 3.69 (2H, s, C_1-H_2), 3.8, 3.82, 3.85 (9H, each s, $3\times OCH_3$), 6.55, 6.72 (2H, each s, Ar-H), 6.96 (3H, s, Ar-H and C_3-H). Mass Spectrum *m/e*: 437 (M^+), 311 (ion a).

2-(2-Aminoethyl-4,5-dimethoxyphenyl)-6-hydroxy-5-methoxyindene (14)——A mixture of 0.2 g of **13**, 10 ml of MeOH and 1 ml of 10% K_2CO_3 aq. solution was refluxed for 10 min. After evaporation of the solvent, the remaining residue was diluted with 10% NH_4Cl aq. solution and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 150 mg of a pale brownish solid, which was recrystallized from MeOH–ether to give **14** as colorless needles, mp 105—106°. *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.97; H, 6.77; N, 4.06. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH). Mass Spectrum *m/e*: 341 (M^+), 312, 311 (ion a).

2-(4,5-Dimethoxy-2-dimethylaminoethylphenyl)-6-hydoxy-5-methoxyindene (15)——A mixture of 100 mg of **14**, 1.5 ml of 37% formalin, and 20 ml of MeOH was refluxed for 20 min. After cooling, to the above mixture was added 0.4 g of $NaBH_4$ under stirring. After the stirring had been continued for 0.5 hr, the solvent was removed. The residue was diluted with water and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was recrystallized from MeOH–ether to give **15** as colorless needles, mp 165—166°. *Anal.* Calcd. for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.60; H, 7.10; N, 3.84. NMR (in $CDCl_3$) δ: 2.38 (6H, s, $-N(CH_3)_2$), 2.5—3.05 (4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2N$), 3.67 (2H, s, C_1-H_2), 3.81 (9H, s, $3\times OCH_3$), 6.6, 6.75 (2H, each s, Ar-H), 6.93 (3H, broad s, Ar-H and C_3-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH). Mass Spectrum *m/e*: 369 (M^+), 311 (ion a).

2-(2-Trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-5,6-dimethoxyindene (16)——To a solution of 0.2 g of **13** in 20 ml of MeOH was added an excess of ethereal solution of diazomethane, and the mixture was allowed to stand for 12 hr. Evaporation of the solvent afforded 0.2 g of **16** as colorless needles, mp 160—162° (from MeOH–ether). *Anal.* Calcd. for $C_{23}H_{24}O_5NF_3$: C, 61.18; H, 5.36; N, 3.10. Found: C, 61.22; H, 5.34; N, 3.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (NH), 1710 (NHCOCF$_3$). Mass Spectrum *m/e*: 451 (M^+), 325 (ion c).

N-(3,4-Dimethoxyphenethyl)-2-benzyloxy-3-methoxyphenylacetamide (23)——A mixture of 5.4 g of homoveratrylamine (**21**) and 8 g of 2-benzyloxy-3-methoxyphenylacetic acid (**22**) was heated at 170—180° for 1.5 hr. After cooling, the mixture was recrystallized from benzene–*n*-hexane to give 11 g of **23** as colorless needles, mp 115—116°. *Anal.* Calcd. for $C_{26}H_{29}O_5N$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.80; H, 6.71; N, 3.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1660 (C=O).

1-(2-Benzyloxy-3-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (24)——A mixture of 8 g of the amide (**23**), 6 g of $POCl_3$, and 70 ml of dry benzene was refluxed for 2 hr. The solvent was evaporated and the remaining residue was washed with *n*-hexane. Recrystallization of the resulting solid from EtOH–ether afforded 8 g of the isoquinoline derivative (**24**) hydrochloride, mp 217—218°. *Anal.* Calcd. for $C_{26}H_{27}O_4N \cdot HCl$: C, 68.79; H, 6.22; N, 3.09. Found: C, 68.69; H, 6.18; N, 3.08.

1-(2-Benzyloxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (25)——To a stirred solution of 7 g of the isoquinoline (**24**) hydrochloride in 100 ml of MeOH was added in small portions 3 g of $NaBH_4$ within 0.5 hr. After the stirring had been continued for further 0.5 hr, the mixture was refluxed for 0.5 hr. The solvent was evaporated and the remaining residue was diluted with water, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. The resulting residue was recrystallized from ether–*n*-hexane to give 6 g of **25** as colorless needles, mp 100—102°. *Anal.* Calcd. for $C_{26}H_{29}O_4N$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.69; H, 6.70; N, 3.32.

12-Benzyloxy-5,6,13,13a-tetrahydro-2,3,11-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (26)——A mixture of 8 g of the isoquinoline (**25**), 40 ml of 98% formic acid, and 40 ml of 37% formalin was heated on a water-bath for 3 hr. The mixture was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 7 g of **26** as colorless needles, mp 169—170° (from MeOH–ether). *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.24; H, 6.58; N, 3.24. NMR (in $CDCl_3$) δ: 2.3—3.8 (9H, m, methylene CH_2 and C_{13a}-H), 3.8 (3H, s, OCH_3), 3.82 (6H, s, $2\times OCH_3$), 4.96 (2H, s, $C_6H_5CH_2O$), 6.54, 6.60 (2H, each s, C_1-H and C_4-H), 6.75 (2H, s, C_9-H and C_{10}-H), 7.2—7.45 (5H, m, Ar-H).

5,6,13,13a-Tetrahydro-12-hydroxy-2,3,11-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (11)——A mixture of 3 g of **26**, 15 ml of conc. HCl, and 30 ml of EtOH was refluxed for 2 hr. The solvent was evaporated and the resulting solid was recrystallized from MeOH to give 2 g of protoberberine (**11**) hydrochloride, mp 217—220°. *Anal.* Calcd. for $C_{21}H_{23}O_4N \cdot HCl$: C, 64.69; H, 6.20; N, 3.59. Found: C, 64.44; H, 6.43; N, 3.63. The hydrochloride was basified with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave a pale brownish oil. NMR (in $CDCl_3$) δ: 2.5—3.8 (9H, m, methylene CH_2 and C_{13a}-H), 3.85 (6H, s, $2\times OCH_3$), 3.88 (3H, s, OCH_3), 6.57 (2H, s, C_9-H and C_{10}-H), 6.61, 6.78 (2H, each s, C_1-H and C_4-H).

2-(2-Trifluoroacetaminoethyl-4,5-dimethoxyphenyl)-4-hydroxy-5-methoxyindene (18)——A mixture of 2 g of **11** and 10 ml of trifluoroacetic anhydride was heated in a sealed tube at 180° for 6 hr. The mixture was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. A methanolic solution of the remaining residue (**17**) was refluxed for 0.5 hr. The solvent was evaporated to leave 1.5 g of a brownish oil, which was chromatographed on 30 g of silica gel using $CHCl_3$

as an eluant. Removal of the solvent afforded a pale brownish solid, which was recrystallized from MeOH–ether to give colorless needles, mp 150—152°. *Anal.* Calcd. for $C_{22}H_{22}O_5NF_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.28; H, 4.63; N, 3.33. NMR (in $CDCl_3$) δ: 2.92 (2H, m, $C_6H_5C\underline{H}_2CH_2N$), 3.46 (2H, m, $C_6H_5CH_2C\underline{H}_2N$), 3.69 (2H, s, C_1-H_2), 3.79 3.81, 3.83 (9H, each s, $3\times OCH_3$), 6.5 (1H, s, $C_{3'}$-H), 6.78 (2H, s, C_6-H and C_7-H), 7.06 7.15 (2H, each s, $C_{6'}$-H and C_3-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 3350 (NH), 1710 ($NHCOCF_3$). Mass Spectrum *m/e*: 437 (M^+), 311 (ion b).

2-(2-Aminoethyl-4,5-dimethoxyphenyl)-4-hydroxy-5-methoxyindene (19)——A mixture of 200 mg of **18**, 10 ml of MeOH and 1 ml of 10% K_2CO_3 aq. solution was refluxed for 20 min. After evaporation of the solvent, the resulting residue was diluted with 10% NH_4Cl aq. solution, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave 120 mg of **19** as pale brownish needles, the recrystallization of which from MeOH–ether afforded colorless needles, mp 178—180°. *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.01; H, 6.74; N, 4.04. NMR (in $CDCl_3$) δ: 2.88—3.2 (6H, m, $C_6H_5C\underline{H}_2C\underline{H}_2N\underline{H}_2$), 3.7 (2H, s, C_1-H_2), 3.78, 3.81, 3.83 (9H, each s, $3\times OCH_3$), 6.59 (1H, s, $C_{3'}$-H), 6.78 (2H, s, C_6-H and C_7-H), 7.18 (s, 2H, $C_{6'}$-H and C_3-H). Mass Spectrum *m/e*: 341.1644 (M^+: Calcd.: 341.1626), 312.1358 (Calcd. for $C_{19}H_{20}O_4$: 312.1360), 311.1242 (Calcd. for ion c: 311.1281).

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