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Studies on 1,2,3,4-Tetrahydroisoquinoline Derivatives. I. Syntheses and β -Adrenoceptor Activities of Positional Isomers of Trimetoquinol with Respect to Its 6,7-Dihydroxyl Groups

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In a series of phenylethanolamine β -stimulants, transformation of hydroxyl groups of the catechol type into those of the resorcinol type has been reported to improve the bioavailability. Therefore, five possible positional isomers (1—5) of trimetoquinol (TMQ) with respect to its 6,7-dihydroxyl groups were synthesized and tested for bronchodilating activity. Among these positional isomers, the 5,7-dihydroxyl derivative (4) exhibited more potent bronchodilating activity and longer duration of activity than ($\pm$)-TMQ and isoproterenol on intraduodenal administration.

Keywords—1,2,3,4-tetrahydroisoquinolines; β -adrenoceptor activity; bronchodilator; trimetoquinol; catecholamine; positional isomer; structure-activity relationship; bioavailability; oral activity; intraduodenal administration

(-)-(1S)-6,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (trimetoquinol, TMQ), a potent β -adrenergic stimulant, is now being used clinically as an effective bronchodilator. The structure-activity relationships of some sixty derivatives of TMQ were investigated extensively by Iwasawa and Kiyomoto.¹⁾ As regards the position of the two hydroxyl groups, however, the 6,7-dihydroxyl structure (catechol type) remained common in those derivatives.

In recent years, transformation of hydroxyl groups of catechol type into those of resorcinol type in a series of phenylethanolamine β -stimulants (*e.g.* isoproterenol) has been reported to improve the bioavailability (*e.g.* orciprenaline and terbutaline)²⁾ (Chart 1).

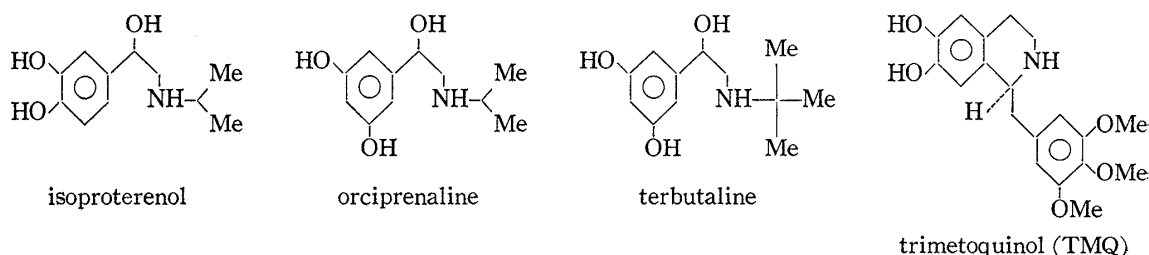
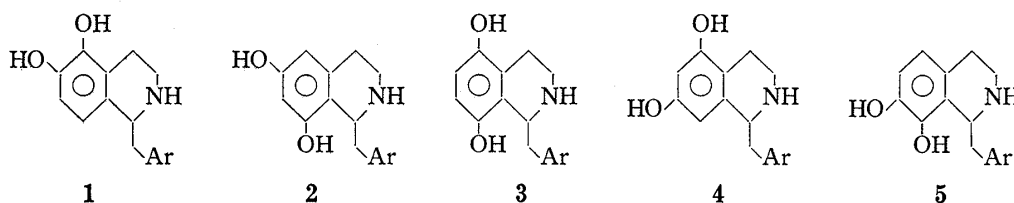


Chart 1



Ar: 3,4,5-trimethoxyphenyl

Chart 2

Therefore, it seemed of interest to synthesize positional isomers of TMQ with respect to its dihydroxyl moiety. This paper describes the syntheses and bronchodilating activities of the five possible positional isomers; ($\pm$)-5,6-, 6,8-, 5,8-, 5,7-, and 7,8-dihydroxyl congeners (1–5) of TMQ^{3,5)} (Chart 2).

Chemistry

Five dihydroxyl derivatives of 1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolines (TMI) (1–5) were synthesized by diverse routes, depending on the positions of their hydroxyl groups.

By using the Pictet–Spengler procedure for tetrahydroisoquinoline synthesis, 5,6- and 6,8-dihydroxy-TMI (1 and 2) were readily synthesized. Treatment of 3,4,5-trimethoxyphenylacetaldehyde (6) with the dihydroxyphenethylamines (7⁶⁾ and 8⁷⁾ in EtOH gave 1 and 2 in 75 and 47% yields, respectively (Chart 3).

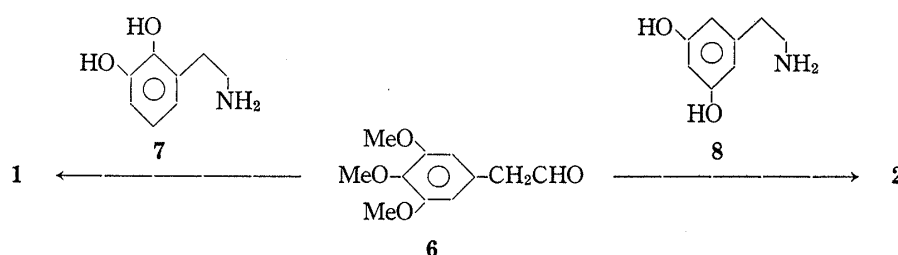


Chart 3

The 5,8-dihydroxyl derivative (3) was prepared by Bischler–Napieralski cyclization of the amide (15) (Chart 4).⁹⁾ Treatment of 2,5-dihydroxybenzoic acid (9) with benzyl chloride in the presence of K_2CO_3 in dimethylformamide (DMF) gave the tribenzyl compound (10), which in turn was reduced with LiAlH_4 to give the alcohol (11).

The benzyl chloride (12), prepared from the alcohol (11) in the usual manner, was converted to the benzyl cyanide (13) by treatment with NaCN in DMSO in 90.4% yield.

The cyanide (13) was reduced with $\text{NaBH}_3(\text{OCOCF}_3)$ ⁹⁾ to give the corresponding amine (14) in 53.6% yield. The phenethylamine (14) was condensed with 3,4,5-trimethoxyphenylacetyl chloride to afford the amide (15), which was transformed *via* the 3,4-dihydroisoquinoline (16) into the tetrahydroisoquinoline (17) by successive treatments with POCl_3 in refluxing benzene and NaBH_4 in MeOH (35.6% yield).

Finally, catalytic reduction of 17 on 10% Pd-C gave the desired phenol (3) in 83% yield.

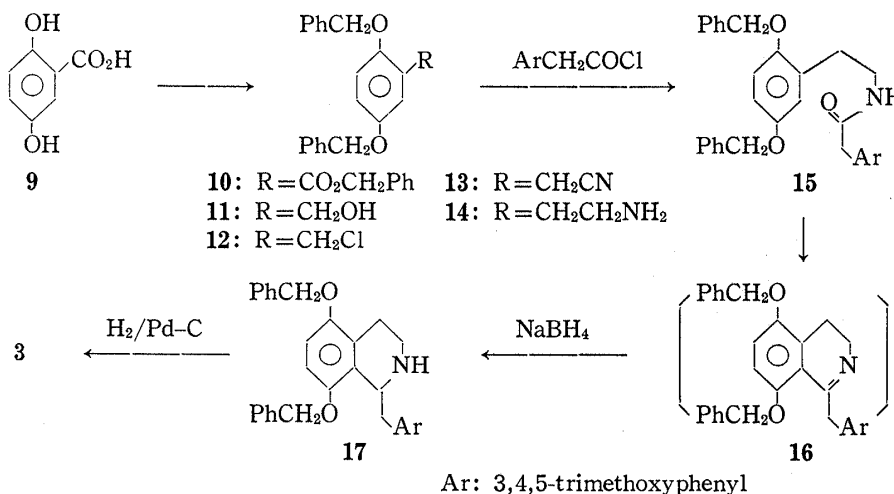
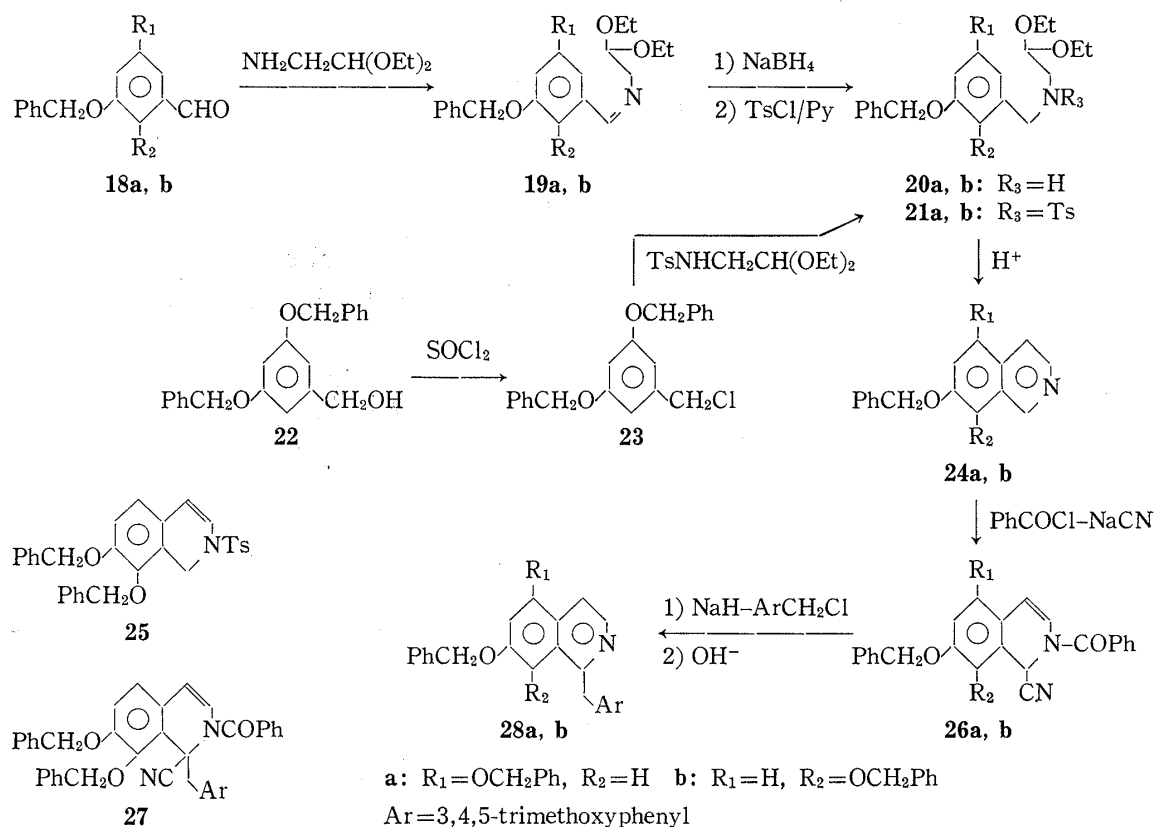


Chart 4

The preparation of 5,7- and 7,8-dihydroxy-TMI (**4** and **5**) was achieved by the rather long sequence of reactions outlined in Chart 5 and 6; the isoquinoline (**24a, b**) served as key intermediates. The intermediates (**24a, b**) were prepared from the benzaldehyde (**18a, b**)¹⁰⁾ **b**¹¹⁾ by several steps based on Jackson's method for isoquinoline synthesis.¹²⁾ The aldehydes (**18a, b**) were condensed with aminoacetaldehyde diethylacetal and the resulting imines (**19a, b**) were reduced with NaBH₄ to give the benzylamine derivatives (**20a, b**) in 93% and 42% yields, respectively. Treatment of **20a, b** with *p*-toluenesulfonyl chloride afforded the N-tosyl amides (**21a, b**). More conveniently, **21a** was obtained in excellent yield by condensation of the benzylchloride (**23**) [prepared by chlorination of **22**¹⁰⁾] with N-tosylaminoacetaldehyde diethylacetal. Jackson cyclization of **21a** readily gave the isoquinoline (**24a**) in 95% yield. On the other hand, similar treatment of the 2,3-dibenzyloxy derivative (**21b**) gave only the N-tosyl-1,2-dihydroisoquinoline (**25**) in 65% yield. When treated with *t*-BuOK in *t*-BuOH, **25** readily underwent aromatization, giving the isoquinoline (**24b**) in 97% yield.

Conversion of **24a, b** to the Reissert compounds (**26a, b**) proceeded smoothly. Alkylation of **26a, b** with 3,4,5-trimethoxybenzyl chloride in the presence of NaH in DMF followed by alkaline hydrolysis gave the 1-benzylisoquinolines (**28a, b**) in 83% and 48% yields, respectively.



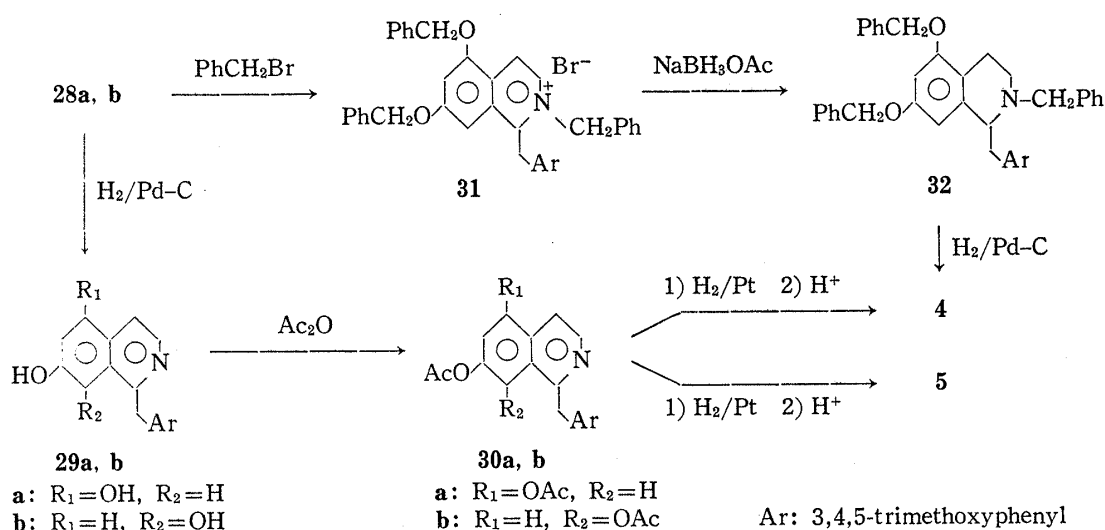


Chart 6

TABLE I

Compound No.	Appearance (Recryst. solvent)	mp (dec.)	Formula	Analysis (%)		
				Calcd	Found	
				C	H	N
1	Prisms (EtOH)	235—237°	$\text{C}_{19}\text{H}_{23}\text{NO}_5 \cdot \text{HBr}$	53.52 (53.46)	5.67 (5.81)	3.29 (3.49)
2	Needles (iso-PrOH)	237—240°	$\text{C}_{19}\text{H}_{23}\text{NO}_5 \cdot \text{HBr}$	53.52 (53.45)	5.67 (5.79)	3.29 (3.13)
3	Prisms (EtOH-Et ₂ O)	243—247°	$\text{C}_{19}\text{H}_{23}\text{NO}_5 \cdot \text{HCl}$ EtOH	58.92 (58.82)	7.06 (7.06)	3.27 (3.24)
4	Prisms (EtOH-H ₂ O)	206—209°	$\text{C}_{19}\text{H}_{23}\text{NO}_5 \cdot 1/2\text{H}_2\text{SO}_4$ EtOH	57.26 (57.14)	6.86 (6.82)	3.18 (3.13)
5	Scales (EtOH-AcOEt)	215—217°	$\text{C}_{19}\text{H}_{23}\text{NO}_5 \cdot \text{HCl}$	59.76 (59.33)	6.34 (6.46)	3.67 (3.77)

Biological Results

The bronchodilating activities of the positional isomers (1—5) in anesthetized cats against serotonin-induced bronchoconstriction were compared to those of (±)-TMQ and isoproterenol (Iso).¹⁴⁾ The data are summarized in Tables II and III. On intravenous administration, the bronchodilating activities of (±)-TMQ, 1, and 4 were approx. 1/3, 1/1000, and 1/4 of that of Iso, respectively, while those of 2, 3, and 5 were less than 1/10000 of that of Iso (Table II). In order to assess oral activity, Iso, (±)-TMQ, and 4, which showed potent bronchodilating actions on intravenous administration, were given into the duodenum. As shown in Table III, the doses required to reduce the serotonin-induced bronchoconstriction by approx. 75% of the control were 100, 20, and 10 μg/kg for Iso, (±)-TMQ, and 4, respectively. Thus, 4 exhibited the most potent bronchodilating action, the potency of which was approx. 10 times that of Iso and approx. 2 times that of (±)-TMQ. It was also found that the duration of bronchodilating action of 4 was considerably longer than those of (±)-TMQ and Iso.

It has been reported that the bronchodilating activity of phenylethanolamine derivatives is reduced but the duration of action is prolonged when hydroxyl groups of the catechol type were replaced by those of the resorcinol type.²⁾ In the case of TMI derivatives, however, replacement of catechol type hydroxyl groups ((±)-TMQ) by resorcinol type hydroxyl groups

TABLE II. Bronchodilating Activities of Positional Isomers of ($\pm$)-Trimetoquinol (TMQ) after Intravenous Administration in Anesthetized Cats

Compound	ED ₅₀ ^{a)} (Geometric mean)	Potency ratio (Iso=1000)
Isoproterenol	0.033	1000
($\pm$)-TMQ	0.087	380
1	35	0.94
2	>300	<0.1
3	>300	<0.1
4	0.13	250
5	>300	<0.1

a) Calculated in micrograms per kilogram for 50% inhibition of serotonin (20 μ g/kg, *i.v.*)-induced bronchoconstriction.

TABLE III. Bronchodilating Activities of ($\pm$)-TMQ, 4 and Isoproterenol after Intraduodenal Administration in Anesthetized Cats

	No. of animals	Dose (μ g/kg)	Peak response ^{a)} % $\pm$ S.E.	Half-duration ^{b)} (min)
Isoproterenol	5	100	84.9 $\pm$ 6.0	75
($\pm$)-TMQ	5	20	77.6 $\pm$ 5.2	150
4	6	10	72.5 $\pm$ 6.1	>210

a) Peak inhibition of serotonin (20 μ g/kg, *i.v.*)-induced bronchoconstriction.

b) Defined as the period from the administration to the point of half-recovery from the peak response.

(4) did not cause a significant decrease in bronchodilating activity. On the other hand, the duration of action of the latter was longer than that of the former.

Further details of the bronchodilating and other biological activities of 4 have already been published.^{4,5)}

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi IR-215 spectrometer, NMR spectra with a JEOL MH-60, PMX-60 or FX-100 spectrometer [with TMS as an internal (in CDCl₃ or DMSO-*d*₆) or external (in D₂O) standard], and mass spectra with a Hitachi RMS-4 or RMU-6M spectrometer.

5,6-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (1)—A solution of 2,3-dihydroxyphenethylamine·HBr 7 (2.34 g, 10 mmol) and 3,4,5-trimethoxyphenylacetaldehyde 6 (3.60 g, 17.1 mmol) in EtOH (20 ml) was refluxed for 25 hr, then cooled. The resulting precipitates were collected by filtration and recrystallized from EtOH to give 1 (3.21 g, 75%) as colorless prisms, mp 235–237° (dec.). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3500, 3120. MS *m/e*: 181, 164 (base). NMR (D₂O) δ : 3.93 (3H, s, OCH₃), 3.95 (6H, s, OCH₃ $\times$ 2), 6.72 (2H, s, H(2') and H(6')), 6.76 and 6.99 (1H each, a pair of AB type d, *J* = 8 Hz, H(7) and H(8)).

6,8-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (2)—A solution of 3,5-dihydroxyphenethylamine·HBr (8) (5.0 g, 21 mmol) and 3,4,5-trimethoxyphenylacetaldehyde (6) (5.35 g, 25.5 mmol) in EtOH (80 ml) was refluxed for 3.5 hr. After removal of the solvent, the residue was crystallized from isopropyl alcohol to give 2 (4.30 g, 47%) as colorless needles, mp 237–240° (dec.). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3625 (weak), 3240, 3095. MS *m/e*: 181, 164 (base). NMR (D₂O) δ : 3.90 (3H, s, OCH₃), 3.93 (6H, s, OCH₃ $\times$ 2), 6.49 (2H, s, H(5) and H(7)), 6.67 (2H, s, H(2') and H(6')).

Benzyl 2,5-Dibenzoyloxybenzoate (10)—A stirred mixture of 2,5-dihydroxybenzoic acid (9) (3.08 g, 20 mmol), benzyl chloride (8.93 g, 70 mmol), and K₂CO₃ (16.6 g, 120 mmol) in DMF (30 ml) was heated at 100° for 20 hr under argon. After cooling, the reaction mixture was diluted with AcOEt and inorganic material was filtered off. The filtrate was washed successively with 10% aq. NaOH and H₂O, dried (Na₂SO₄), and concentrated. The residue was crystallized from EtOH–Et₂O to give 10 (7.88 g, 93%) as colorless needles, mp 88.5–89.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1725, 1700. MS *m/e*: 424 (M⁺). NMR (CDCl₃) δ : 4.97 (2H, s, –OCH₂C₆H₅), 5.03 (2H, s, –OCH₂C₆H₅), 5.30 (2H, s, –CO₂CH₂C₆H₅), 7.31 (15H, s, –C₆H₅ $\times$ 3), 6.9–7.5 (3H, m, aromatic protons). Anal. Calcd for C₂₈H₂₄O₄: C, 79.22; H, 5.70. Found: C, 79.07; H, 5.90.

2,5-Dibenzyloxybenzyl Alcohol (11)—The ester (10) (8.5 g, 20 mmol) was added to a stirred suspension of LiAlH_4 (1.52 g, 40 mmol) in THF (100 ml) and the mixture was stirred for 1.5 hr at room temperature. The reaction mixture was treated with H_2O to decompose excess LiAlH_4 , and extracted with Et_2O . The Et_2O extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from $\text{EtOH-H}_2\text{O}$ to give 11 (4.2 g, 65.6%) as colorless needles, mp 56.6–58.5°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3380. MS m/e : 320 (M^+). NMR (CDCl_3) δ : 2.29 (1H, s, OH, exchanges with D_2O), 4.64 (2H, s, $\text{ArCH}_2\text{-OH}$), 4.95 and 4.98 (2H each, s, $-\text{OCH}_2\text{C}_6\text{H}_5 \times 2$), 6.75–7.0 (3H, m, aromatic protons), 7.32 (10H, s, $-\text{C}_6\text{H}_5 \times 2$). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{O}_3$: C, 78.72; H, 6.29. Found: C, 78.90; H, 6.47.

2,5-Dibenzyloxybenzyl Chloride (12)—A solution of SOCl_2 (2.02 g, 16.9 mmol) in CH_2Cl_2 (6 ml) was added dropwise to a stirred mixture of 11 (4.16 g, 13 mmol), pyridine (1.04 g, 13 mmol), C_6H_6 (12 ml), and CH_2Cl_2 (4 ml) with cooling below 10°, and the mixture was stirred at 4° for 1 hr. The reaction mixture was poured into ice-water and extracted with C_6H_6 . The organic layer was washed successively with H_2O , dil. aq. NaOH, and brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOH to give 12 (3.91 g, 88.8%) as colorless needles, mp 78–81.5°. MS m/e : 340 and 338 (M^+). NMR (CDCl_3) δ : 4.63 (2H, s, $\text{ArCH}_2\text{-Cl}$), 4.98 and 5.04 (2H each, s, $-\text{OCH}_2\text{C}_6\text{H}_5 \times 2$), 6.8–7.1 (3H, m, aromatic protons), 7.32 (10H, s, $-\text{C}_6\text{H}_5 \times 2$). Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{ClO}_2$: C, 74.44; H, 5.65; Cl, 10.46. Found: C, 74.73; H, 5.79; Cl, 10.12.

2,5-Dibenzyloxybenzyl Cyanide (13)—A solution of 12 (3.88 g, 11.5 mmol) in DMSO (20 ml) was added to a stirred suspension of NaCN (1.12 g, 22.9 mmol) in DMSO (12 ml) and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice-water and extracted with AcOEt . The AcOEt extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOH to give 13 (3.41 g, 90.4%) as colorless needles, mp 94–96°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2250. MS m/e : 329 (M^+). NMR (CDCl_3) δ : 3.66 (2H, s, ArCH_2CN), 5.01 (4H, s, $-\text{OCH}_2\text{C}_6\text{H}_5 \times 2$), 7.34 (10H, s, $-\text{C}_6\text{H}_5 \times 2$), 6.8–7.1 (3H, m, aromatic protons). Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.06; H, 6.04; N, 3.91.

2,5-Dibenzyloxyphenethylamine (14)—A solution of $\text{CF}_3\text{CO}_2\text{H}$ (5.13 g, 45 mmol) in THF (27 ml) was added to a stirred suspension of NaBH_4 (1.71 g, 45 mmol) in THF (8 ml) at 10° and the mixture was stirred for 30 min at room temperature. A solution of 13 (2.96 g, 9 mmol) in THF (45 ml) was added to this solution of $\text{NaBH}_4(\text{OCOCF}_3)$. After being stirred at room temperature for 3 hr, the reaction mixture was treated with H_2O to decompose excess reagent. The mixture was concentrated, and extracted with CHCl_3 . The CHCl_3 extracts were washed with H_2O , dried (Na_2SO_4), and concentrated. The residue was treated with 5% ethanolic HCl solution, and evaporated to dryness *in vacuo* to leave a colorless solid which was recrystallized from $\text{EtOH-Et}_2\text{O}$ to give 14·HCl (1.79 g, 53.6%) as colorless needles, mp 150–151.5°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2400–2750. MS m/e : 333 (M^+). NMR (CDCl_3) δ : 3.09 (4H, br.s, $-\text{CH}_2\text{CH}_2\text{-NH}_2$), 4.91 (2H, s, $-\text{OCH}_2\text{C}_6\text{H}_5$), 4.97 (2H, s, $-\text{OCH}_2\text{C}_6\text{H}_5$), 6.72 (2H, s, H(3) and H(4)), 6.87 (1H, s, H(6)), 7.27 (10H, s, $-\text{C}_6\text{H}_5 \times 2$). Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_2 \cdot \text{HCl}$: C, 71.44; H, 6.54; N, 3.79; Cl, 9.58. Found: C, 71.49; H, 6.52; N, 3.80; Cl, 9.41.

N-(2,5-Dibenzyloxyphenethyl)-2-(3,4,5-trimethoxyphenyl)acetamide (15)—A solution of 3,4,5-trimethoxyphenylacetyl chloride [prepared from 3,4,5-trimethoxyphenylacetic acid (1.77 g, 6.5 mmol) and SOCl_2 (4.64 g, 39 mmol) in refluxing C_6H_6 for 1 hr] in C_6H_6 (5 ml) was added portionwise to a stirred mixture of 14·HCl (1.67 g, 5 mmol), K_2CO_3 (2.7 g, 20 mmol), CHCl_3 (30 ml), and H_2O (20 ml) with cooling below 5°. The whole was stirred at room temperature for 3 hr, then the organic layer was separated, washed successively with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOH-hexane to give 15 (2.56 g, 72.8%) as colorless needles, mp 99.5–100.5°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3255, 1640. MS m/e : 541 (M^+). NMR (CDCl_3) δ : 2.79 (2H, t, $J=6.3$ Hz, $\text{ArCH}_2\text{CH}_2\text{N}$), 3.34 (2H, s, $-\text{COCH}_2\text{Ar}$), 3.43 (2H, t, $J=6.3$ Hz, $\text{ArCH}_2\text{CH}_2\text{N}$), 3.69 (6H, s, $\text{OCH}_3 \times 2$), 3.79 (3H, s, OCH_3), 4.90 and 4.96 (2H each, s, $-\text{OCH}_2\text{C}_6\text{H}_5 \times 2$), 5.1–5.4 (1H, m, NHCO , exchanges with D_2O), 6.28 (2H, s, aromatic protons), 6.74 (3H, s, aromatic protons), 7.32 (10H, s, $-\text{C}_6\text{H}_5 \times 2$). Anal. Calcd for $\text{C}_{33}\text{H}_{35}\text{NO}_6$: C, 73.17; H, 6.51; N, 2.59. Found: C, 73.02; H, 6.67; N, 2.59.

5,8-Dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (17)—A mixture of 15 (5.41 g, 10 mmol), POCl_3 (3.06 g, 20 mmol) and C_6H_6 (150 ml) was refluxed for 4.5 hr. The reaction mixture was concentrated to dryness *in vacuo*, and the oily residue was dissolved in MeOH (70 ml). NaBH_4 (1.9 g, 50 mmol) was added portionwise to the resulting solution with ice-water cooling. The reaction mixture was stirred at room temperature for 42 hr, then concentrated, and the residue was extracted with CHCl_3 . The CHCl_3 extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was converted to the oxalate and crystallized from AcOEt to give 17·oxalate (2.19 g, 35.6%) as a colorless solid, mp 204–208° (dec.). Recrystallization from MeOH gave 17·oxalate as colorless prisms, mp 206–208° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1715, 1625. MS m/e : 525 (M^+ , faint), 344. NMR ($\text{DMSO}-d_6$) δ : 3.59 (3H, s, OCH_3), 3.61 (6H, s, $\text{OCH}_3 \times 2$), 5.09 (4H, s, $-\text{OCH}_2\text{C}_6\text{H}_5 \times 2$), 6.41 (2H, s, H(2') and H(6')), 7.02 (2H, s, H(6) and H(7)), 7.42 (10H, s, $-\text{C}_6\text{H}_5 \times 2$). Anal. Calcd for $\text{C}_{33}\text{H}_{35}\text{NO}_5 \cdot \text{C}_2\text{H}_2\text{O}_4$: C, 68.28; H, 6.06; N, 2.28. Found: C, 67.86; H, 6.17; N, 2.33.

17 (Free base): colorless scales (from $\text{EtOH-Et}_2\text{O}$), mp 151.5–152.5°. Anal. Calcd for $\text{C}_{33}\text{H}_{33}\text{NO}_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.62; H, 6.77; N, 2.81.

5,8-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3)—A solution of 17 (1.00 g, 1.9 mmol) in a mixture of 1 N HCl (50 ml) and THF (50 ml) was hydrogenated on 10% Pd-C

(1.0 g) at 3.87 times atmospheric pressure and at room temperature for 20 hr. After removal of the catalyst by filtration, the filtrate was concentrated. The residue was recrystallized from EtOH-Et₂O to give 3·EtOH (675 mg, 83%) as colorless prisms, mp 243–247° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3360, 3250, 2470–2790. NMR (D₂O) δ : 1.30 (3H, t, $J=7$ Hz, CH₃CH₂OH), 3.77 (2H, q, $J=7$ Hz, CH₃CH₂OH), 3.86 (3H, s, OCH₃), 3.90 (6H, s, OCH₃×2), 6.64 (2H, s, H(2') and H(6')), 6.84 and 6.92 (1H each, a pair of AB type d, $J=8$ Hz, H(6) and H(7)).

3,5-Dibenzyloxybenzylideneaminoacetaldehyde Diethyl Acetal (19a)—A solution of 18a (19.1 g, 60 mmol) and aminoacetaldehyde diethyl acetal (9.30 g, 70 mmol) in dry C₆H₆ (50 ml) was refluxed for 3 hr using a Dean-Stark apparatus. After removal of the solvent, the residue was crystallized from hexane to give 19a (24.3 g, 93%) as colorless needles, mp 59–60°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1645. MS m/e : 433 (M⁺). NMR (CDCl₃) δ : 1.15 and 1.17 (3H each, t, $J=7$ Hz, -OCH₂CH₃×2), 3.54 and 3.56 (2H each, q, $J=7$ Hz, -OCH₂-CH₃×2), 3.72 (2H, d, $J=6$ Hz, NCH₂CH), 4.76 (1H, t, $J=6$ Hz, NCH₂CH), 5.02 (4H, s, -OCH₂C₆H₅×2), 6.65 (1H, d, $J=2.5$ Hz, H(4)), 6.97 (2H, d, $J=2.5$ Hz, H(2) and H(6)), 7.2–7.5 (10H, m, -C₆H₅×2), 8.13 (1H, s, ArCH=N). Anal. Calcd for C₂₇H₃₁NO₄: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.96; H, 7.26; N, 3.23.

N-3,5-Dibenzyloxybenzylaminoacetaldehyde Diethyl Acetal (20a)—A mixture of Schiff base 19a (12.3 g, 28.3 mmol) and NaBH₄ (1.1 g, 29 mmol) in EtOH (150 ml) was refluxed for 2 hr. After removal of the solvent, H₂O was added to the residue and extraction was carried out with AcOEt. The AcOEt extracts were washed with H₂O, dried (Na₂SO₄), and concentrated to give 20a (12.7 g, 100%) as a colorless oil. IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 3350. MS m/e : 435 (M⁺). The product was characterized as the oxalate, which was recrystallized from MeOH-acetone to give colorless needles, mp 151–152° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1710 (br), 1610 (sh), 1595. NMR (CDCl₃) δ : 1.13 (6H, t, $J=7$ Hz, -OCH₂CH₃×2), 4.08 (2H, s, ArCH₂N), 4.95 (4H, s, -OCH₂-C₆H₅×2), 6.50 (1H, d, $J=2$ Hz, H(4)), 6.73 (2H, d, $J=2$ Hz, H(2) and H(6)), 7.34 (10H, s, -C₆H₅×2), 10.09 (3H, brs, exchanges with D₂O). Anal. Calcd for C₂₇H₂₃NO₄·C₂H₂O₄: C, 66.27; H, 6.71; N, 2.66. Found: C, 65.97; H, 6.72; N, 2.62.

3,5-Dibenzyloxybenzyl Chloride (23)—A solution of SOCl₂ (9.3 ml) in C₆H₆ (20 ml) was added dropwise to a stirred mixture of 22 (32.0 g, 0.1 mol), pyridine (8.0 g, 0.1 mol), CH₂Cl₂ (20 ml), and C₆H₆ (100 ml) with ice-cooling below 25°. The reaction mixture was stirred at room temperature for 2 hr, then diluted with C₆H₆ (100 ml). The C₆H₆ solution was washed successively with H₂O, 5% aq. NaOH and brine, dried (Na₂SO₄), and concentrated to leave a pale yellow oil, which was crystallized from benzene-hexane (1:10, v/v) to give 23 (30.9 g, 91%) as colorless needles, mp 77–79°. NMR (CDCl₃) δ : 4.54 (2H, s, ArCH₂Cl), 5.07 (4H, s, -OCH₂C₆H₅×2), 6.7 (3H, brs, aromatic protons), 7.47 (10H, s, -C₆H₅×2).

N-3,5-Dibenzyloxybenzyl-N-tosylaminoacetaldehyde Diethyl Acetal (21a)—a) *p*-Toluenesulfonyl chloride (2.4 g, 12 mmol) was added to a stirred solution of 20a (5.0 g, 11.5 mmol) in dry pyridine (20 ml) with ice-cooling. The reaction mixture was stirred at room temperature for 4 hr, then poured into cold 10% aq. HCl and extracted with AcOEt. The extract was washed with H₂O, dried (Na₂SO₄), and concentrated to leave 21a (7.1 g, 93%) as a slightly brown oil. IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 1335, 1150. MS m/e : 589 (M⁺). NMR (CDCl₃) δ : 1.13 (6H, t, $J=7$ Hz, -OCH₂CH₃×2), 2.34 (3H, s, -C₆H₄CH₃), 3.22 (2H, d, $J=5.5$ Hz, NCH₂CH-), 4.47 (2H, s, ArCH₂N), 4.55 (1H, t, $J=5.5$ Hz, NCH₂CH), 4.87 (4H, s, -OCH₂C₆H₅×2), 6.3–6.5 (3H, m, aromatic protons), 7.27 (2H, d, $J=8$ Hz, H(3') and H(5')), 7.33 (10H, s, -C₆H₅×2), 7.70 (2H, d, $J=8$ Hz, H(2') and H(6')).

b) A mixture of 3,5-dibenzyloxybenzyl chloride 23 (30.1 g, 89 mmol), N-tosylaminoacetaldehyde diethyl acetal (24.3 g, 84.5 mmol) and anhydrous K₂CO₃ (23.4 g, 170 mmol) in DMSO (100 ml) was stirred at room temperature for 4 hr. The reaction mixture was diluted with C₆H₆ (250 ml), and inorganic material was filtered off. The filtrate was washed successively with H₂O and brine, dried (Na₂SO₄), and concentrated to leave the tosylate 21a (51.2 g, 100%).

5,7-Dibenzyloxyisoquinoline (24a)—A mixture of 21a (51.2 g, 86.9 mmol), 10% aq. HCl (35 ml), and dioxane (110 ml) was refluxed with stirring for 11 hr. After cooling, isopropanol (6 ml) and Et₂O (150 ml) were added to the reaction mixture. The resulting precipitates were collected by filtration, washed with Et₂O, and dried to give 24a·HCl (23.7 g) as pale yellow needles, mp 219–220° (dec.). The filtrate and washings were concentrated and the residue was made basic with 5% aq. NaOH, then extracted with C₆H₆. The C₆H₆ layer was washed successively with 5% aq. NaOH and H₂O, dried (Na₂SO₄), and concentrated. The residue was treated with methanolic HCl and crystallized from MeOH-Et₂O to give 24a·HCl (6.74 g, 95% overall yield), mp 217–218° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3250, 2060.

24a (Free base): colorless needles (from EtOH), mp 113–115°. MS m/e : 341 (M⁺). NMR (CDCl₃) δ : 5.16 (4H, s, -OCH₂C₆H₅×2), 6.82 and 6.88 (1H each, d, $J=2.5$ Hz, H(6) and H(8)), 7.2–7.6 (10H, m, -C₆H₅×2), 7.95 and 8.40 (1H each, a pair of AB type d, $J=6$ Hz, H(4) and H(3), respectively), 9.07 (1H, s, H(1)). Anal. Calcd for C₂₃H₁₉NO₂: C, 80.94; H, 5.57; N, 4.11. Found: C, 81.02; H, 5.80; N, 3.99.

2-Benzoyl-5,7-dibenzyloxy-1,2-dihydroisoquinoline-1-carbonitrile (26a)—A solution of benzoyl chloride (6.4 g, 46 mmol) in CH₂Cl₂ (20 ml) was added dropwise to a stirred mixture of 24a (3.30 g, 9.7 mmol), KCN (3.0 g, 46 mmol), CH₂Cl₂ (30 ml), and H₂O (15 ml) with ice-cooling over a period of 2 hr. The whole was stirred at room temperature for 3 hr, then the CH₂Cl₂ layer was separated, washed successively with 1% aq. NaOH and H₂O, dried (Na₂SO₄), and concentrated. The residual oil was chromatographed on silica gel

[Et₂O-hexane (1:1, v/v)] to give a solid, which was recrystallized from EtOH to afford **26a** (4.0 g, 64%) as colorless needles, mp 123–125°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1680. MS *m/e*: 472 (M⁺). NMR (CDCl₃) δ : 5.00 (4H, s, -OCH₂C₆H₅ × 2), 6.2–6.6 (5H, m), 7.1–7.5 (15H, m, -C₆H₅ × 3). Anal. Calcd for C₃₁H₂₄N₂O₃: C, 78.81; H, 5.08; N, 5.93. Found: C, 78.98; H, 4.97; N, 6.01.

5,7-Dibenzyloxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (28a)—A solution of **26a** (1.18 g, 2.5 mmol) in DMF (10 ml) was added to a suspension of NaH (180 mg of 65% mineral oil dispersion, washed with hexane) in DMF (15 ml) with cooling at -10° under argon. The mixture was stirred at -10° for 30 min, then a solution of 3,4,5-trimethoxybenzyl chloride (700 mg, 3.23 mmol) in DMF (10 ml) was added and stirring was continued at -5 to -10° for 1.5 hr. A solution of KOH (420 mg) in H₂O (10 ml) was added to the reaction mixture and the whole was stirred at 30–40° for 1 hr. After cooling, the resulting mixture was poured into ice-water and extracted with C₆H₆. The C₆H₆ extracts were washed with H₂O, dried (Na₂SO₄), and concentrated. The residual solid was recrystallized from C₆H₆-hexane to give **28a** (1.07 g, 83%) as colorless needles, mp 158–160°. MS *m/e*: 521 (M⁺). NMR (CDCl₃) δ : 3.80 (6H, s, OCH₃ × 2), 3.86 (3H, s, OCH₃), 4.60 (2H, s, C(1)-CH₂Ar), 5.13 and 5.26 (2H each, s, -OCH₂C₆H₅ × 2), 6.63 (2H, s, H(2') and H(6')), 6.91 and 7.22 (1H each, d, *J* = 2 Hz, H(6) and H(8)), 8.13 and 8.62 (1H each, d, *J* = 6 Hz, H(4) and H(3), respectively). Anal. Calcd for C₃₃H₃₁NO₅: C, 75.98; H, 5.99; N, 2.69. Found: C, 75.94; H, 6.11; N, 2.81.

5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (29a)—A solution of **27a** (200 mg, 0.4 mmol) in EtOH (250 ml) was hydrogenated on 10% Pd-C (50 mg) at atmospheric pressure and room temperature for 3 hr. After removal of the catalyst by filtration, the filtrate was evaporated to dryness to leave a solid, which was recrystallized from EtOH to give **29a** (95 mg, 72%) as colorless needles, mp 270–275° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400. MS *m/e*: 341 (M⁺). NMR (DMSO-*d*₆) δ : 3.67 (3H, s, OCH₃), 3.77 (6H, s, OCH₃ × 2), 4.43 (2H, s, C(1)-CH₂Ar), 6.70 (2H, s, H(2') and H(6')), 6.81 and 7.08 (1H each, d, *J* = 2 Hz, H(6) and H(8)), 7.88 (1H, d, *J* = 6 Hz, H(4)), 8.36 (1H, d, *J* = 6 Hz, H(3)). Anal. Calcd for C₁₉H₁₉NO₅: C, 66.86; H, 5.57; N, 4.11. Found: C, 67.01; H, 5.48; N, 4.21.

5,7-Diacetoxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (30a)—Ac₂O (955 mg, 9.4 mmol) was added to a stirred solution of **29a** (800 mg, 2.3 mmol) in dry pyridine (30 ml) with cooling. The reaction mixture was stirred at room temperature for 4 hr, then treated with H₂O and extracted with AcOEt. The AcOEt extracts were washed with H₂O, dried (Na₂SO₄), and concentrated. Recrystallization of the residue from AcOEt-hexane gave **30a** (900 mg, 90%) as colorless prisms, mp 118–120°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1770, 1760. MS *m/e*: 425 (M⁺). NMR (CDCl₃) δ : 2.33 and 2.44 (3H each, s, OAc × 2), 3.79 (9H, s, OCH₃ × 3), 4.54 (2H, s, C(1)-CH₂Ar), 6.52 (2H, s, H(2') and H(6')), 7.34 and 7.92 (1H each, d, *J* = 2 Hz, H(6) and H(8)), 7.58 and 8.52 (1H each, d, *J* = 6 Hz, H(4) and H(3), respectively). Anal. Calcd for C₂₃H₂₃NO₇: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.95; H, 5.60; N, 3.31.

30a·HCl: colorless needles (from MeOH-Et₂O), mp 186–190° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1760, 1645, 1630. NMR (CDCl₃) δ : 2.41 and 2.50 (3H each, s, OAc × 2), 3.75 (3H, s, OCH₃), 3.84 (6H, s, OCH₃ × 2), 4.98 (2H, s, C(1)-CH₂Ar), 6.93 (2H, s, H(2') and H(6')), 7.73 and 8.48 (1H each, d, *J* = 2 Hz, H(6) and H(8)), 8.14 and 8.48 (1H each, d, *J* = 6.6 Hz, H(4) and H(3), respectively). Anal. Calcd for C₂₃H₂₃NO₇·HCl: C, 59.81; H, 5.24; N, 3.03. Found: C, 59.41; H, 5.28; N, 2.94.

5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hemisulfate (4)—A solution of **30a·HCl** (780 mg, 1.7 mmol) in EtOH (200 ml) was hydrogenated on PtO₂ (0.3 g) at atmospheric pressure and room temperature for 2 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in 9% ethanolic HCl (50 ml) and heated under reflux for 5 min. After removal of the solvent, the residue was solidified with MeOH-Et₂O to give **4·HCl** (600 mg, 94%) as a colorless solid. The product was characterized as the sulfate, which was recrystallized from EtOH-H₂O to afford **4·EtOH** as colorless prisms, mp 206–209° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3150. MS *m/e*: 181, 164 (base). NMR (D₂O) δ : 1.25 (3H, t, *J* = 7 Hz, CH₃CH₂OH), 3.71 (2H, q, *J* = 7 Hz, CH₃CH₂OH), 3.82 (3H, s, OCH₃), 3.84 (6H, s, OCH₃ × 2), 6.20 and 6.46 (1H each, d, *J* = 2 Hz, H(6) and H(8)), 6.57 (2H, s, H(2') and H(6')).

2-Benzyl-5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)isoquinolinium Bromide (31)—A mixture of **28a** (31.3 g, 60 mmol) and benzyl bromide (43.1 g, 252 mmol) in THF (125 ml) was refluxed for 18 hr. After removal of the solvent, the residue was crystallized from MeOH (15 ml)-H₂O (2 ml)-Et₂O (240 ml) to give **31** (42.6 g, 100%) as yellow needles, mp 160–162°. MS *m/e*: 612 (M⁺). NMR (CDCl₃) δ : 3.61 (6H, s, OCH₃ × 2), 3.75 (3H, s, OCH₃), 5.15 (2H, s, C(1)-CH₂Ar), 5.23 and 5.25 (2H each, s, -OCH₂C₆H₅ × 2), 6.17 (2H, s, H(2') and H(6')), 6.30 (2H, s, N⁺-CH₂C₆H₅), 7.18–7.40 (17H, m, H(6), H(8) and C₆H₅ × 3), 8.44 (1H, d, *J* = 6.9 Hz, H(4)), 8.99 (1H, d, *J* = 6.9 Hz, H(3)). Anal. Calcd for C₄₀H₃₈BrNO₅·H₂O: C, 67.58; H, 5.17; Br, 11.25; N, 1.97. Found: C, 67.17; H, 5.57; Br, 11.36; N, 2.01.

2-Benzyl-5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (32)—NaBH₃OAc (9.6 g, 100 mmol) was added to a suspension of **31** (14.5 g, 20.4 mmol) in THF (70 ml), and the mixture was refluxed with stirring for 2 hr. After cooling, the reaction mixture was poured into ice-water and extracted with CHCl₃. The CHCl₃ extracts were washed with H₂O, dried (Na₂SO₄), and concentrated. The residue was treated with 10% ethanolic HCl solution, and concentrated *in vacuo* to leave a colorless solid, which was recrystallized from MeOH-Et₂O to afford **32·HCl** (12.1 g, 89.6%) as colorless prisms, mp 132–136° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3655, 3400 (br). Anal. Calcd for C₄₀H₄₁NO₅·HCl·1/2H₂O: C, 72.66; H, 6.55; N, 2.12. Found: C, 72.39; H, 6.80; N, 2.11.

32·Oxalate: colorless prisms (from EtOH), mp 148—149° (dec.). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1730 (br), 1640 (br). *Anal.* Calcd for C₄₀H₄₁NO₅·C₂H₂O₄: C, 71.47; H, 6.14; N, 1.98. Found: C, 71.24; H, 6.27; N, 1.96.

32 (Free base): colorless needles (from EtOH), mp 104—106°. MS m/e : 615 (M⁺). NMR (CDCl₃) δ : 3.74 (6H, s, OCH₃ × 2), 3.83 (3H, s, OCH₃), 4.86 and 5.04 (2H each, s, -OCH₂C₆H₅ × 2), 5.99 and 6.47 (1H each, d, J = 2 Hz, H(6) and H(8)), 6.27 (2H, s, H(2') and H(6')), 7.19, 7.34 and 7.37 (15H, s, -C₆H₅ × 3). *Anal.* Calcd for C₄₀H₄₁NO₅: C, 78.02; H, 6.71; N, 2.27. Found: C, 77.86; H, 6.78; N, 2.31.

5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hemisulfate (4)—A solution of 32 (2.46 g, 4 mmol) in a mixture of MeOH (30 ml) and H₂O (5 ml) containing conc. H₂SO₄ (200 mg, 2 mmol) was hydrogenated on 10% Pd-C (1.0 g) at 3.2 times atmospheric pressure and at room temperature for 20 hr. After removal of the catalyst by filtration, the filtrate was concentrated. The residue was recrystallized from EtOH-H₂O to give 4·EtOH (1.50 g, 85%) as colorless prisms, mp 203—209° (dec.).

2,3-Dibenzyloxybenzylideneaminoacetaldehyde Diethyl Acetal (19b)—A mixture of aminoacetaldehyde diethyl acetal (1.33 g, 10 mmol) and 2,3-dibenzyloxybenzaldehyde (18b) (3.18 g, 10 mmol) was heated at 85—90° for 10 min. The reaction mixture was diluted with C₆H₆, and dried (Na₂SO₄). After removal of the solvent, the residue was crystallized from hexane to give 19b (2.70 g, 62%) as colorless needles, mp 52°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1640. MS m/e : 433 (M⁺). NMR (CDCl₃) δ : 1.18 (6H, t, J = 7 Hz, -OCH₂CH₃ × 2), 4.73 (1H, t, J = 6 Hz, -CH(OEt)₂), 5.03 (4H, s, -OCH₂C₆H₅ × 2), 6.8—7.6 (13H, m), 8.49 (1H, s, ArCH=N). *Anal.* Calcd for C₂₇H₃₁NO₄: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.78; H, 7.20; N, 3.20.

N-2,3-Dibenzyloxybenzylaminoacetaldehyde Diethyl Acetal (20b)—A mixture of Schiff base 19b (22 g, 51 mmol) and NaBH₄ (5.0 g, 130 mmol) in EtOH (150 ml) was refluxed for 2 hr. After removal of the solvent, the residue was treated with H₂O and extracted with C₆H₆. The C₆H₆ extracts were dried (Na₂SO₄) and concentrated to leave a colorless oil, which was chromatographed on silica gel [AcOEt-hexane (2:1, v/v)] to give 20b (14.8 g, 67%) as a colorless oil. IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3330. MS m/e : 435 (M⁺).

N-2,3-Dibenzyloxybenzyl-N-tosylaminoacetaldehyde Diethyl Acetal (21b)—*p*-Toluenesulfonyl chloride (7.0 g, 37 mmol) was added to a stirred solution of 20b (14.8 g, 34 mmol) in pyridine (40 ml) with cooling and the mixture was stirred at room temperature for 12 hr. The reaction mixture was then poured into H₂O and extracted with C₆H₆. The C₆H₆ extracts were washed successively with 10% aq. HCl and H₂O, dried (Na₂SO₄), and concentrated to leave 21b (20.0 g, 100%) as a colorless oil. IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 1340, 1160. MS m/e : 589 (M⁺). NMR (CDCl₃) δ : 1.05 (6H, t, J = 7 Hz, -OCH₂CH₃ × 2), 2.37 (3H, s, -C₆H₄CH₃), 3.1—3.7 (6H, m), 4.47 (2H, s, ArCH₂N), 4.50 (1H, t, J = 6 Hz, -CH(OEt)₂), 4.99 and 5.08 (2H each, s, -OCH₂C₆H₅ × 2), 6.91 (3H, s, aromatic protons), 7.1—7.4 (12H, m, aromatic protons), 7.60 (2H, d, J = 8 Hz, H(2') and H(6')).

7,8-Dibenzyloxy-N-tosyl-1,2-dihydroisoquinoline (25)—A solution of 21b (10.9 g, 18.5 mmol) in dioxane (50 ml) containing conc. HCl (2.4 ml) was refluxed for 2 hr. After cooling, the reaction mixture was poured into H₂O and extracted with AcOEt. The AcOEt extracts were washed successively with saturated aq. NaHCO₃ and H₂O, dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography (silica gel, C₆H₆) to give 25 (6.0 g, 65%) to give a colorless solid, which was recrystallized from EtOH to afford 25 as colorless needles mp 104—106°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1635, 1345, 1165. MS m/e : 497 (M⁺). NMR (CDCl₃) δ : 2.35 (3H, s, -C₆H₄CH₃), 4.50 (2H, s, H(1) × 2), 4.95 and 5.05 (2H each, s, -OCH₂C₆H₅ × 2), 5.70 (1H, d, J = 7.9 Hz, H(4)), 6.57 and 6.74 (1H each, a pair of AB type d, J = 8.5 Hz, H(5) and H(6)), 6.62 (1H, d, J = 7.9 Hz, H(3)), 7.15 (2H, a pair of AB type d, J = 8.3 Hz, H(3') and H(5')), 7.30 and 7.33 (10H, s, -C₆H₅ × 2), 7.60 (2H, a pair of AB type d, J = 8.3 Hz, H(2') and H(6')). *Anal.* Calcd for C₃₀H₂₇NO₄S: C, 72.41; H, 5.41; N, 2.81. Found: C, 72.21; H, 5.60; N, 2.84.

7,8-Dibenzyloxyisoquinoline (24b)—A mixture of 25 (6.0 g, 12.1 mmol), *t*-BuOK (4.3 g, 35.2 mmol), and *t*-BuOH (50 ml) was heated at 90° for 2 hr. After cooling, the reaction mixture was poured into H₂O and extracted with AcOEt. The AcOEt extracts were washed with H₂O, dried (Na₂SO₄), and concentrated. The residual oil was chromatographed on silica gel (AcOEt) to give 24b (4.0 g, 97%) as a colorless solid, which was recrystallized from isopropyl ether to give an analytical specimen as colorless needles, mp 70—71°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1625. MS m/e : 341 (M⁺). NMR (CDCl₃) δ : 5.23 (4H, s, -OCH₂C₆H₅ × 2), 7.1—7.6 (13H, m), 8.31 (1H, d, J = 6 Hz, H(3)), 9.41 (1H, s, H(1)). *Anal.* Calcd for C₂₃H₁₉NO₂: C, 80.91; H, 5.61; N, 4.10. Found: C, 80.64; H, 5.80; N, 4.07.

2-Benzoyl-7,8-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2-dihydroisoquinoline-1-carbonitrile (27)—A solution of benzoyl chloride (4.20 g, 30 mmol) in CH₂Cl₂ (20 ml) was added dropwise to a stirred mixture of 24b (3.3 g, 9.7 mmol), KCN (1.95 g, 30 mmol), CH₂Cl₂ (30 ml), and H₂O (25 ml) with ice-cooling over a period of 1.5 hr. The whole was stirred at room temperature for 18 hr, then the CH₂Cl₂ layer was separated, dried (Na₂SO₄), and concentrated to leave an oil, which was chromatographed on silica gel (C₆H₆) to give the Reissert compound 26b (3.20 g, 70%) as a colorless oil. A solution of 26b (3.0 g, 6.4 mmol) in DMF (20 ml) was added to a stirred suspension of NaH (400 mg of 65% mineral oil dispersion, washed with hexane) in DMF (20 ml) at -10° over a period of 30 min. A solution of 3,4,5-trimethoxybenzyl chloride (1.70 g, 13.4 mmol) in DMF (15 ml) was added at -8° to this mixture and the whole was left to warm slowly to room temperature (0.5 hr). The reaction mixture was poured into H₂O and extracted with AcOEt. The AcOEt extracts were washed successively with H₂O and brine, dried (Na₂SO₄), and concentrated. Recrystallization of the residue from EtOH-isopropyl ether gave 27 (2.35 g, 57%) as colorless scales, mp 156—157°. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 2330 (weak), 1680, 1645. MS m/e : 625 (M⁺-27), 471 (M⁺-181). *Anal.* Calcd for C₄₁H₃₆N₂O₆: C,

75.44; H, 5.56; N, 4.29. Found: C, 75.15; H, 5.77; N, 4.30.

7,8-Dibenzyloxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (28b)—A mixture of **27** (2.2 g, 3.37 mmol), NaOH (5 g), EtOH (50 ml), and H₂O (10 ml) was refluxed for 2 hr. After removal of the solvent, H₂O was added to the residue and extraction was carried out with AcOEt. The AcOEt layer was washed successively with H₂O and brine, dried (Na₂SO₄), and concentrated. Recrystallization of the residue from EtOH–isopropylether gave **28b** (1.50 g, 85%) as colorless needles, mp 117–118°. MS *m/e*: 521 (M⁺). NMR (CDCl₃) δ : 3.55 (6H, s, OCH₃ $\times$ 2), 3.74 (3H, s, OCH₃), 4.81 (2H, s, C(1)–CH₂Ar), 5.03 and 5.20 (2H each, s, –OCH₂C₆H₅ $\times$ 2), 6.28 (2H, s, H(2') and H(6')), 8.34 (1H, d, *J* = 6 Hz, H(3)). Anal. Calcd for C₃₃H₃₁NO₅: C, 75.98; H, 5.99; N, 2.69. Found: C, 75.58; H, 6.08; N, 2.74.

7,8-Diacetoxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (30b)—A solution of **28b**·HCl (700 mg, 1.26 mmol) in EtOH (80 ml) was hydrogenated on 10% Pd–C (0.5 g) at atmospheric pressure and room temperature for 2 hr. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to leave **29b** as an oil, which was dissolved in pyridine (20 ml) and treated with Ac₂O (5 ml) at room temperature for 0.5 hr. The reaction mixture was poured into H₂O and extracted with C₆H₆. The C₆H₆ extracts were washed with H₂O, dried (Na₂SO₄), and concentrated. Recrystallization of the residue from isopropylether gave **30b** (440 mg, 82%) as colorless pillars, mp 125–126°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 1775. MS *m/e*: 425 (M⁺). NMR (CDCl₃) δ : 2.07 and 2.32 (3H each, s, OAc $\times$ 2), 3.70 (6H, s, OCH₃ $\times$ 2), 3.79 (3H, s, OCH₃), 4.74 (2H, s, C(1)–CH₂Ar), 6.26 (2H, s, H(2') and H(6')), 7.55 and 7.78 (1H each, a pair of AB type d, *J* = 10 Hz, H(5) and H(6)), 7.57 and 8.50 (1H each, d, *J* = 6 Hz, H(4) and H(3), respectively). Anal. Calcd for C₂₃H₂₃NO₇: C, 64.93; H, 5.45; N, 3.29. Found: C, 65.13; H, 5.71; N, 3.34.

7,8-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (5)—A solution of **30b**·HCl (400 mg, 0.87 mmol) in EtOH (80 ml) was hydrogenated on PtO₂ (0.5 g) at atmospheric pressure and room temperature for 4 hr. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the 7,8-diacetoxy derivative of **5** as an oil, which was dissolved in 10% ethanolic HCl (20 ml) and refluxed for 0.5 hr. After removal of the solvent *in vacuo*, the residue was recrystallized from EtOH–AcOEt to give **5** (130 mg, 39%) as pale yellow scales, mp 215–217° (dec.). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 3400 (br), 2930 (br). MS *m/e*: 181, 164 (base). NMR (D₂O) δ : 3.90 (3H, s, OCH₃), 3.94 (6H, s, OCH₃ $\times$ 2), 6.72 (2H, s, H(2') and H(6')), 6.86 and 7.07 (1H each, a pair of AB type d, *J* = 8 Hz, H(5) and H(6)).

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