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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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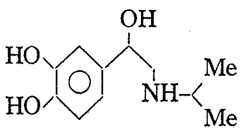
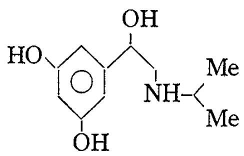
In a series of phenylethanolamine β-stimulants, transformation of hydroxyl groups of the catechol type into those of the resorcinol type has been reported to improve the bioavailability. Therefore, five possible positional isomers (**1**—**5**) of trimetoquinol (TMQ) with respect to its 6,7-dihydroxyl 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 (±)-TMQ and isoproterenol on intraduodenal administration.

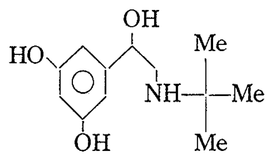
Keywords——1,2,3,4-tetrahydroisoquinolines; β-adrenoceptor activity; bronchodilator; trimetoquinol; catecholamine; positional isomer; structure-activity relationship; bioavailability; oral activity; intraduodenal administration

(−)-(1*S*)-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).


isoproterenol


orciprenaline


terbutaline

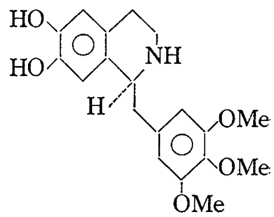
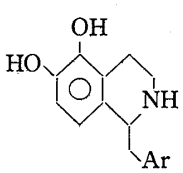

trimetoquinol (TMQ)

Chart 1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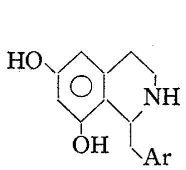
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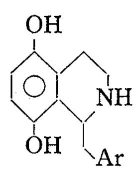
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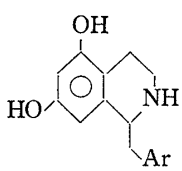
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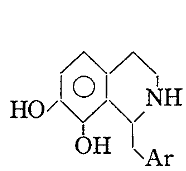

5

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; (±)-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 (**7**[6] and **8**[7]) in EtOH gave **1** and **2** in 75 and 47% yields, respectively (Chart 3).

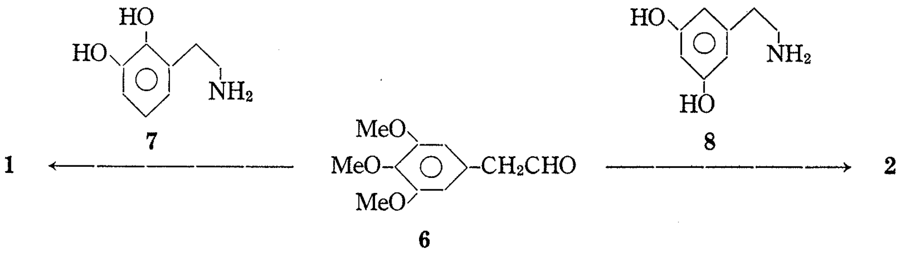


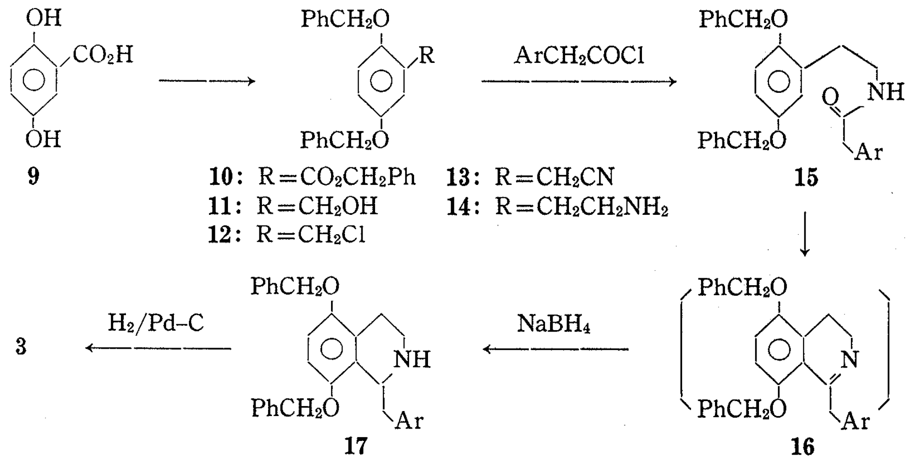
Chart 3

The 5,8-dihydroxyl derivative (**3**) was prepared by Bischler–Napieralski cyclization of the amide (**15**) (Chart 4).[8] 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 $NaBH_3(OCOCF_3)$[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.



Ar: 3,4,5-trimethoxyphenyl

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**,[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 $NaBH_4$ 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.

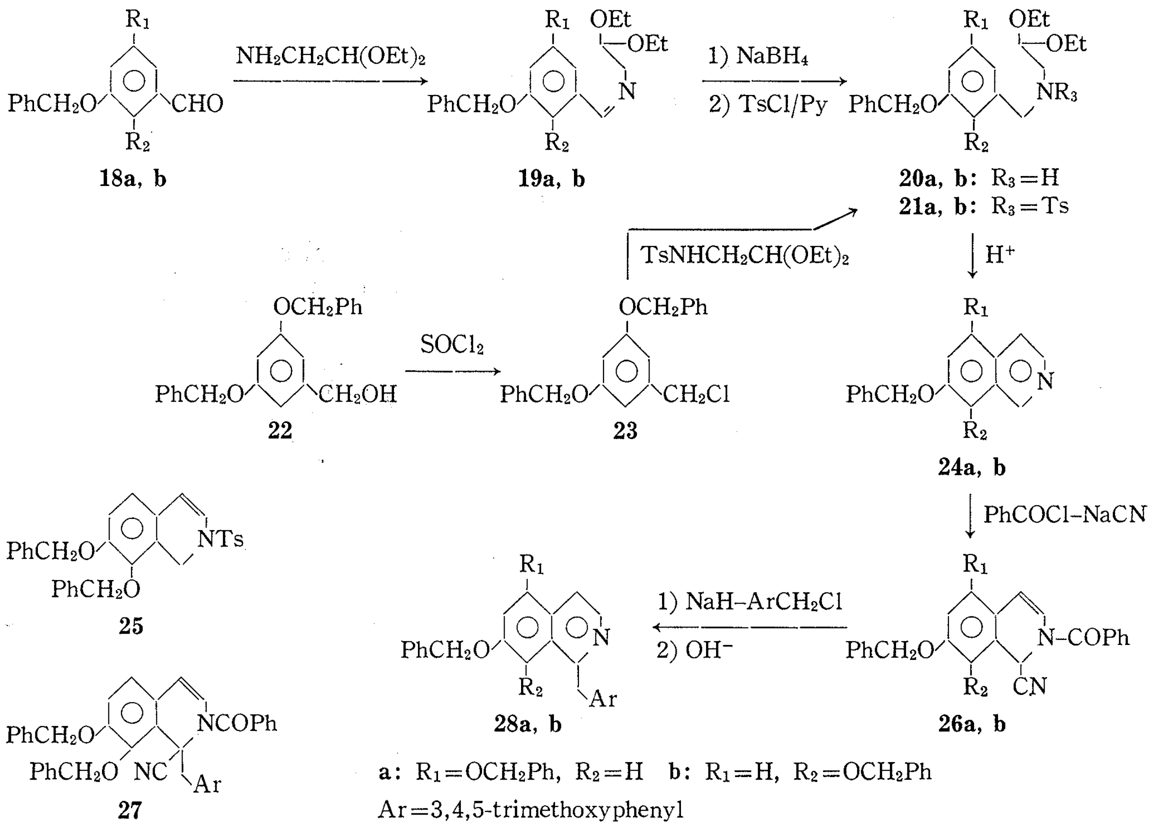


Chart 5

Hydrogenolysis of **28a, b** on 10% Pd-C afforded the phenols (**29a, b**). Catalytic hydrogenation of the O-acetates[13] of **29a, b** on PtO_2 and subsequent acidic hydrolysis gave 5,7- and 7,8-dihydroxy-TMI (**4** and **5**) in 94 and 39% yields, respectively (Chart 6). However, the conversion of **28a** to **4** *via* the N-benzyl quaternary salt (**31**) was much more convenient. Reduction of **31** with $NaBH_3(OAc)$[9] gave an 89.6% yield of the tetrahydro derivative (**32**). Hydrogenolysis of **32** on 10% Pd-C effected removal of the three benzyl groups and gave **4** in 85% yield.

Physical constants of the five dihydroxyl derivatives of TMI thus obtained are listed in Table I.

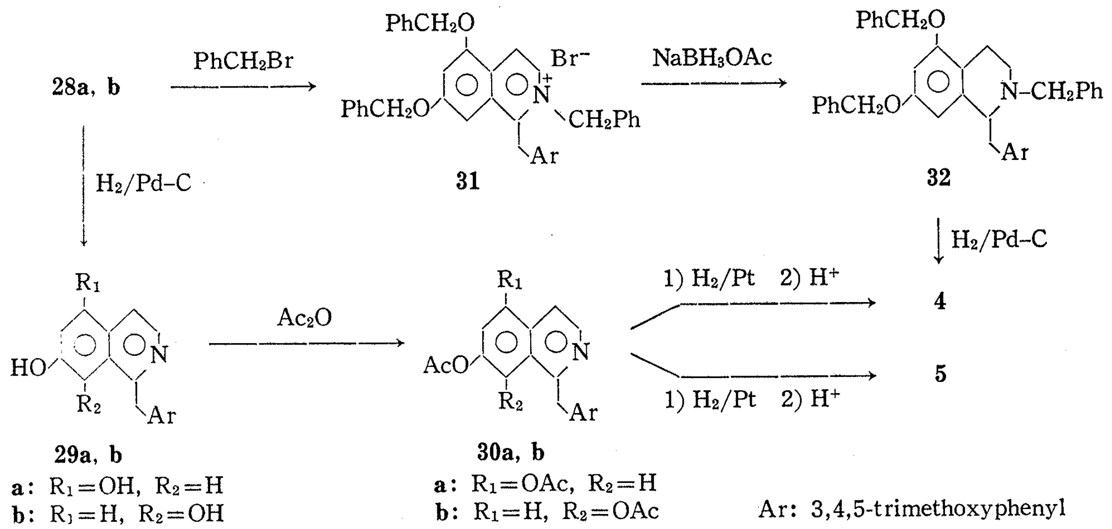


Chart 6

Table I

Compound No.	Appearance (Recryst. solvent)	mp (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N
1	Prisms (EtOH)	235—237°	$C_{19}H_{23}NO_5 \cdot HBr$	53.52 (53.46)	5.67 (5.81)	3.29 (3.49)
2	Needles (iso-PrOH)	237—240°	$C_{19}H_{23}NO_5 \cdot HBr$	53.52 (53.45)	5.67 (5.79)	3.29 (3.13)
3	Prisms ($EtOH-Et_2O$)	243—247°	$C_{19}H_{23}NO_5 \cdot HCl$ EtOH	58.92 (58.82)	7.06 (7.06)	3.27 (3.24)
4	Prisms ($EtOH-H_2O$)	206—209°	$C_{19}H_{23}NO_5 \cdot 1/2H_2SO_4$ EtOH	57.26 (57.14)	6.86 (6.82)	3.18 (3.13)
5	Scales (EtOH-AcOEt)	215—217°	$C_{19}H_{23}NO_5 \cdot HCl$	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 (±)-Trimetoquinol (TMQ) after Intravenous Administration in Anesthetized Cats

Compound	ED_{50}[a] (Geometric mean)	Potency ratio (Iso=1000)
Isoproterenol	0.033	1000
(±)-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 μg/kg, *i.v.*)-induced bronchoconstriction.

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

	No. of animals	Dose (μg/kg)	Peak response[a] % ± S.E.	Half-duration[b] (min)
Isoproterenol	5	100	84.9±6.0	75
(±)-TMQ	5	20	77.6±5.2	150
4	6	10	72.5±6.1	>210

a) Peak inhibition of serotonin (20 μg/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 $CDCl_3$ or DMSO-d_6) or external (in D_2O) 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 ν_{max}^{Nujol} cm^{-1}: 3500, 3120. MS *m/e*: 181, 164 (base). NMR (D_2O) δ: 3.93 (3H, s, OCH_3), 3.95 (6H, s, $OCH_3 \times 2$), 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 ν_{max}^{Nujol} cm^{-1}: 3625 (weak), 3240, 3095. MS *m/e*: 181, 164 (base). NMR (D_2O) δ: 3.90 (3H, s, OCH_3), 3.93 (6H, s, $OCH_3 \times 2$), 6.49 (2H, s, H(5) and H(7)), 6.67 (2H, s, H(2′) and H(6′)).

Benzyl 2,5-Dibenzyloxybenzoate (**10**)——A stirred mixture of 2,5-dihydroxybenzoic acid (**9**) (3.08 g, 20 mmol), benzyl chloride (8.93 g, 70 mmol), and K_2CO_3 (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 H_2O, dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOH–Et_2O to give **10** (7.88 g, 93%) as colorless needles, mp 88.5—89.5°. IR ν_{max}^{Nujol} cm^{-1}: 1725, 1700. MS *m/e*: 424 (M^+). NMR ($CDCl_3$) δ: 4.97 (2H, s $-O\underline{CH_2}C_6H_5$), 5.03 (2H, s, $-O\underline{CH_2}C_6H_5$), 5.30 (2H, s, $-CO_2\underline{CH_2}C_6H_5$), 7.31 (15H, s, $-C_6\underline{H_5} \times 3$), 6.9—7.5 (3H, m, aromatic protons). *Anal.* Calcd for $C_{28}H_{24}O_4$: 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 EtOH–H_2O to give **11** (4.2 g, 65.6%) as colorless needles, mp 56.6—58.5°. IR ν_{max}^{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, $ArC\underline{H}_2$-OH), 4.95 and 4.98 (2H each, s, $-OC\underline{H}_2C_6H_5\times 2$), 6.75—7.0 (3H, m, aromatic protons), 7.32 (10H, s, $-C_6\underline{H}_5\times 2$). *Anal.* Calcd for $C_{21}H_{20}O_3$: 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, $ArC\underline{H}_2$-Cl), 4.98 and 5.04 (2H each, s, $-OC\underline{H}_2C_6H_5\times 2$), 6.8—7.1 (3H, m, aromatic protons), 7.32 (10H, s, $-C_6\underline{H}_5\times 2$). *Anal.* Calcd for $C_{21}H_{19}ClO_2$: 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 ν_{max}^{Nujol} cm^{-1}: 2250. MS *m/e*: 329 (M^+). NMR ($CDCl_3$) δ: 3.66 (2H, s, $ArC\underline{H}_2CN$), 5.01 (4H, s, $-OC\underline{H}_2C_6H_5\times 2$), 7.34 (10H, s, $-C_6\underline{H}_5\times 2$), 6.8—7.1 (3H, m, aromatic protons). *Anal.* Calcd for $C_{22}H_{19}NO_2$: 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 CF_3CO_2H (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 $NaBH_3(OCOCF_3)$. 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 EtOH–Et_2O to give **14**·HCl (1.79 g, 53.6%) as colorless needles, mp 150—151.5°. IR ν_{max}^{Nujol} cm^{-1}: 2400—2750. MS *m/e*: 333 (M^+). NMR ($CDCl_3$) δ: 3.09 (4H, br.s, $-C\underline{H}_2C\underline{H}_2-NH_2$), 4.91 (2H, s, $-OC\underline{H}_2C_6H_5$), 4.97 (2H, s, $-OC\underline{H}_2C_6H_5$), 6.72 (2H, s, H(3) and H(4)), 6.87 (1H, s, H(6)), 7.27 (10H, s, $-C_6\underline{H}_5\times 2$). *Anal.* Calcd for $C_{22}H_{23}NO_2\cdot HCl$; 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 ν_{max}^{Nujol} cm^{-1}: 3255, 1640. MS *m/e*: 541 (M^+). NMR ($CDCl_3$) δ: 2.79 (2H, t, J=6.3 Hz, $ArC\underline{H}_2CH_2N$), 3.34 (2H, s, $-COC\underline{H}_2Ar$), 3.43 (2H, t, J=6.3 Hz, $ArCH_2C\underline{H}_2N$), 3.69 (6H, s, $OCH_3\times 2$), 3.79 (3H, s, OCH_3), 4.90 and 4.96 (2H each, s, $-OC\underline{H}_2C_6H_5\times 2$), 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, $-C_6\underline{H}_5\times 2$). *Anal.* Calcd for $C_{33}H_{35}NO_6$: 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 ν_{max}^{Nujol} cm^{-1}: 1715, 1625. MS *m/e*: 525 (M^+, faint), 344. NMR (DMSO-d_6) δ: 3.59 (3H, s, OCH_3), 3.61 (6H, s, $OCH_3\times 2$), 5.09 (4H, s, $-OC\underline{H}_2C_6H_5\times 2$), 6.41 (2H, s, H(2′) and H(6′)), 7.02 (2H, s, H(6) and H(7)), 7.42 (10H, s, $-C_6\underline{H}_5\times 2$). *Anal.* Calcd for $C_{33}H_{35}NO_5\cdot C_2H_2O_4$: 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 EtOH–Et_2O), mp 151.5—152.5°. *Anal.* Calcd for $C_{33}H_{33}NO_5$: 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–Et_2O to give **3**·EtOH (675 mg, 83%) as colorless prisms, mp 243—247° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3360, 3250, 2470—2790. NMR (D_2O) δ: 1.30 (3H, t, J=7 Hz, $C\underline{H}_3CH_2OH$), 3.77 (2H, q, J=7 Hz, $CH_3C\underline{H}_2OH$), 3.86 (3H, s, OCH_3), 3.90 (6H, s, $OCH_3\times2$), 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 C_6H_6 (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 ν_{max}^{Nujol} cm^{-1}: 1645. MS m/e: 433 (M^+). NMR ($CDCl_3$) δ: 1.15 and 1.17 (3H each, t, J=7 Hz, $-OCH_2C\underline{H}_3\times2$), 3.54 and 3.56 (2H each, q, J=7 Hz, $-OC\underline{H}_2CH_3\times2$), 3.72 (2H, d, J=6 Hz, $NC\underline{H}_2CH$), 4.76 (1H, t, J=6 Hz, $NCH_2C\underline{H}$), 5.02 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 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, $-C_6\underline{H}_5\times2$), 8.13 (1H, s, $ArC\underline{H}$=N). *Anal.* Calcd for $C_{27}H_{31}NO_4$: 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 $NaBH_4$ (1.1 g, 29 mmol) in EtOH (150 ml) was refluxed for 2 hr. After removal of the solvent, H_2O was added to the residue and extraction was carried out with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to give **20a** (12.7 g, 100%) as a colorless oil. IR $\nu_{max}^{liq.}$ 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 ν_{max}^{Nujol} cm^{-1}: 1710 (br), 1610 (sh), 1595. NMR ($CDCl_3$) δ: 1.13 (6H, t, J=7 Hz, $-OCH_2C\underline{H}_3\times2$), 4.08 (2H, s, $ArC\underline{H}_2N$), 4.95 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 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, $-C_6\underline{H}_5\times2$), 10.09 (3H, brs, exchanges with D_2O). *Anal.* Calcd for $C_{27}H_{23}NO_4\cdot C_2H_2O_4$: 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 $SOCl_2$ (9.3 ml) in C_6H_6 (20 ml) was added dropwise to a stirred mixture of **22** (32.0 g, 0.1 mol), pyridine (8.0 g, 0.1 mol), CH_2Cl_2 (20 ml), and C_6H_6 (100 ml) with ice-cooling below 25°. The reaction mixture was stirred at room temperature for 2 hr, then diluted with C_6H_6 (100 ml). The C_6H_6 solution was washed successively with H_2O, 5% aq. NaOH and brine, dried (Na_2SO_4), 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 ($CDCl_3$) δ: 4.54 (2H, s, $ArC\underline{H}_2Cl$), 5.07 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 6.7 (3H, brs, aromatic protons), 7.47 (10H, s, $-C_6\underline{H}_5\times2$).

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 H_2O, dried (Na_2SO_4), and concentrated to leave **21a** (7.1 g, 93%) as a slightly brown oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1335, 1150. MS m/e: 589 (M^+). NMR ($CDCl_3$) δ: 1.13 (6H, t, J=7 Hz, $-OCH_2C\underline{H}_3\times2$), 2.34 (3H, s, $-C_6H_4C\underline{H}_3$), 3.22 (2H, d, J=5.5 Hz, $NC\underline{H}_2CH-$), 4.47 (2H, s, $ArC\underline{H}_2N$), 4.55 (1H, t, J=5.5 Hz, $NCH_2C\underline{H}$), 4.87 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 6.3—6.5 (3H, m, aromatic protons), 7.27 (2H, d, J=8 Hz, H(3′) and H(5′)), 7.33 (10H, s, $-C_6\underline{H}_5\times2$), 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 K_2CO_3 (23.4 g, 170 mmol) in DMSO (100 ml) was stirred at room temperature for 4 hr. The reaction mixture was diluted with C_6H_6 (250 ml), and inorganic material was filtered off. The filtrate was washed successively with H_2O and brine, dried (Na_2SO_4), 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 Et_2O (150 ml) were added to the reaction mixture. The resulting precipitates were collected by filtration, washed with Et_2O, 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 C_6H_6. The C_6H_6 layer was washed successively with 5% aq. NaOH and H_2O, dried (Na_2SO_4), and concentrated. The residue was treated with methanolic HCl and crystallized from MeOH–Et_2O to give **24a**·HCl (6.74 g, 95% overall yield), mp 217—218° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3250, 2060.

24a (Free base): colorless needles (from EtOH), mp 113—115°. MS m/e: 341 (M^+). NMR ($CDCl_3$) δ: 5.16 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 6.82 and 6.88 (1H each, d, J=2.5 Hz, H(6) and H(8)), 7.2—7.6 (10H, m, $-C_6\underline{H}_5\times2$), 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 $C_{23}H_{19}NO_2$: 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 CH_2Cl_2 (20 ml) was added dropwise to a stirred mixture of **24a** (3.30 g, 9.7 mmol), KCN (3.0 g, 46 mmol), CH_2Cl_2 (30 ml), and H_2O (15 ml) with ice-cooling over a period of 2 hr. The whole was stirred at room temperature for 3 hr, then the CH_2Cl_2 layer was separated, washed successively with 1% aq. NaOH and H_2O, dried (Na_2SO_4), and concentrated. The residual oil was chromatographed on silica gel

[Et_2O–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 ν_{max}^{Nujol} cm^{-1}: 1680. MS *m/e*: 472 (M^+). NMR ($CDCl_3$) δ: 5.00 (4H, s, $-OC\underline{H}_2C_6H_5\times 2$), 6.2—6.6 (5H, m), 7.1—7.5 (15H, m, $-C_6\underline{H}_5\times 3$). *Anal.* Calcd for $C_{31}H_{24}N_2O_3$: 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 H_2O (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 C_6H_6. The C_6H_6 extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residual solid was recrystallized from C_6H_6–hexane to give **28a** (1.07 g, 83%) as colorless needles, mp 158—160°. MS *m/e*: 521 (M^+). NMR ($CDCl_3$) δ: 3.80 (6H, s, $OCH_3\times 2$), 3.86 (3H, s, OCH_3), 4.60 (2H, s, C(1)–$C\underline{H}_2$Ar), 5.13 and 5.26 (2H each, s, $-OC\underline{H}_2C_6H_5\times 2$), 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 $C_{33}H_{31}NO_5$: 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 ν_{max}^{Nujol} cm^{-1}: 3400. MS *m/e*: 341 (M^+). NMR (DMSO-d_6) δ: 3.67 (3H, s, OCH_3), 3.77 (6H, s, $OC\underline{H}_3\times 2$), 4.43 (2H, s, C(1)–$C\underline{H}_2$Ar), 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 $C_{19}H_{19}NO_5$: 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)——Ac_2O (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 H_2O and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. Recrystallization of the residue from AcOEt–hexane gave **30a** (900 mg, 90%) as colorless prisms, mp 118—120°. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1760. MS *m/e*: 425 (M^+). NMR ($CDCl_3$) δ: 2.33 and 2.44 (3H each, s, OAc×2), 3.79 (9H, s, $OCH_3\times 3$), 4.54 (2H, s, C(1)–$C\underline{H}_2$Ar), 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 $C_{23}H_{23}NO_7$: 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–Et_2O), mp 186—190° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1760, 1645, 1630. NMR ($CDCl_3$) δ: 2.41 and 2.50 (3H each, s, OAc×2), 3.75 (3H, s, OCH_3), 3.84 (6H, s, $OCH_3\times 2$), 4.98 (2H, s, C(1)–$C\underline{H}_2$Ar), 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 $C_{23}H_{23}NO_7$·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 PtO_2 (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–Et_2O to give **4**·HCl (600 mg, 94%) as a colorless solid. The product was characterized as the sulfate, which was recrystallized from EtOH–H_2O to afford **4**·EtOH as colorless prisms, mp 206—209° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3150. MS *m/e*: 181, 164 (base). NMR (D_2O) δ: 1.25 (3H, t, J=7 Hz, $C\underline{H}_3CH_2OH$), 3.71 (2H, q, J=7 Hz, $CH_3C\underline{H}_2OH$), 3.82 (3H, s, OCH_3), 3.84 (6H, s, $OCH_3\times 2$), 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)–H_2O (2 ml)–Et_2O (240 ml) to give **31** (42.6 g, 100%) as yellow needles, mp 160—162°. MS *m/e*: 612 (M^+). NMR ($CDCl_3$) δ: 3.61 (6H, s, $OCH_3\times 2$), 3.75 (3H, s, OCH_3), 5.15 (2H, s, C(1)–$C\underline{H}_2$Ar), 5.23 and 5.25 (2H each, s, $-OC\underline{H}_2C_6H_5\times 2$), 6.17 (2H, s, H(2′) and H(6′)), 6.30 (2H, s, $N^+-C\underline{H}_2C_6H_5$), 7.18—7.40 (17H, m, H(6), H(8) and $C_6\underline{H}_5\times 3$), 8.44 (1H, d, J=6.9 Hz, H(4)), 8.99 (1H, d, J=6.9 Hz, H(3)). *Anal.* Calcd for $C_{40}H_{38}BrNO_5$·H_2O: 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)——$NaBH_3OAc$ (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 $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), 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–Et_2O to afford **32**·HCl (12.1 g, 89.6%) as colorless prisms, mp 132—136° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3655, 3400 (br). *Anal.* Calcd for $C_{40}H_{41}NO_5$·HCl·1/2H_2O: 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 ν_{max}^{Nujol} cm^{-1}: 1730 (br), 1640 (br). *Anal.* Calcd for $C_{40}H_{41}NO_5 \cdot C_2H_2O_4$: 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 ($CDCl_3$) δ: 3.74 (6H, s, $OCH_3 \times 2$), 3.83 (3H, s, OCH_3), 4.86 and 5.04 (2H each, s, $-OC\underline{H}_2C_6H_5 \times 2$), 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, $-C_6\underline{H}_5 \times 3$). *Anal.* Calcd for $C_{40}H_{41}NO_5$: 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 H_2O (5 ml) containing conc. H_2SO_4 (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–H_2O 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 C_6H_6, and dried (Na_2SO_4). After removal of the solvent, the residue was crystallized from hexane to give **19b** (2.70 g, 62%) as colorless needles, mp 52°. IR ν_{max}^{Nujol} cm^{-1}: 1640. MS *m/e*: 433 (M$^+$). NMR ($CDCl_3$) δ: 1.18 (6H, t, $J=7$ Hz, $-OCH_2C\underline{H}_3 \times 2$), 4.73 (1H, t, $J=6$ Hz, $-C\underline{H}(OEt)_2$), 5.03 (4H, s, $-OC\underline{H}_2C_6H_5 \times 2$), 6.8—7.6 (13H, m), 8.49 (1H, s, ArC$\underline{H}$=N). *Anal.* Calcd for $C_{27}H_{31}NO_4$: 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 $NaBH_4$ (5.0 g, 130 mmol) in EtOH (150 ml) was refluxed for 2 hr. After removal of the solvent, the residue was treated with H_2O and extracted with C_6H_6. The C_6H_6 extracts were dried (Na_2SO_4) 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 $\nu_{max}^{liq.}$ 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 H_2O and extracted with C_6H_6. The C_6H_6 extracts were washed successively with 10% aq. HCl and H_2O, dried (Na_2SO_4), and concentrated to leave **21b** (20.0 g, 100%) as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1340, 1160. MS *m/e*: 589 (M$^+$). NMR ($CDCl_3$) δ: 1.05 (6H, t, $J=7$ Hz, $-OCH_2C\underline{H}_3 \times 2$), 2.37 (3H, s, $-C_6H_4C\underline{H}_3$), 3.1—3.7 (6H, m), 4.47 (2H, s, ArC$\underline{H}_2$N), 4.50 (1H, t, $J=6$ Hz, $-C\underline{H}(OEt)_2$), 4.99 and 5.08 (2H each, s, $-OC\underline{H}_2C_6H_5 \times 2$), 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 H_2O and extracted with AcOEt. The AcOEt extracts were washed successively with saturated aq. $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (silica gel, C_6H_6) 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 ν_{max}^{Nujol} cm^{-1}: 1635, 1345, 1165. MS *m/e*: 497 (M$^+$). NMR ($CDCl_3$) δ: 2.35 (3H, s, $-C_6H_4C\underline{H}_3$), 4.50 (2H, s, H(1)$\times$2), 4.95 and 5.05 (2H each, s, $-OC\underline{H}_2C_6H_5 \times 2$), 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, $-C_6\underline{H}_5 \times 2$), 7.60 (2H, a pair of AB type d, $J=8.3$ Hz, H(2′) and H(6′)). *Anal.* Calcd for $C_{30}H_{27}NO_4S$: 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 H_2O and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), 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 ν_{max}^{Nujol} cm^{-1}: 1625. MS *m/e*: 341 (M$^+$). NMR ($CDCl_3$) δ: 5.23 (4H, s, $-OC\underline{H}_2C_6H_5 \times 2$), 7.1—7.6 (13H, m), 8.31 (1H, d, $J=6$ Hz, H(3)), 9.41 (1H, s, H(1)). *Anal.* Calcd for $C_{23}H_{19}NO_2$: 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 CH_2Cl_2 (20 ml) was added dropwise to a stirred mixture of **24b** (3.3 g, 9.7 mmol), KCN (1.95 g, 30 mmol), CH_2Cl_2 (30 ml), and H_2O (25 ml) with ice-cooling over a period of 1.5 hr. The whole was stirred at room temperature for 18 hr, then the CH_2Cl_2 layer was separated, dried (Na_2SO_4), and concentrated to leave an oil, which was chromatographed on silica gel (C_6H_6) 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 H_2O and extracted with AcOEt. The AcOEt extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and concentrated. Recrystallization of the residue from EtOH–isopropyl ether gave **27** (2.35 g, 57%) as colorless scales, mp 156—157°. IR ν_{max}^{KBr} cm^{-1}: 2330 (weak), 1680, 1645. MS *m/e*: 625 (M$^+-27$), 471 (M$^+-181$). *Anal.* Calcd for $C_{41}H_{36}N_2O_6$: 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 H_2O (10 ml) was refluxed for 2 hr. After removal of the solvent, H_2O was added to the residue and extraction was carried out with AcOEt. The AcOEt layer was washed successively with H_2O and brine, dried (Na_2SO_4), 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 ($CDCl_3$) δ: 3.55 (6H, s, $OCH_3 \times 2$), 3.74 (3H, s, OCH_3), 4.81 (2H, s, C(1)–$\underline{H}$... $C\underline{H}_2Ar$), 5.03 and 5.20 (2H each, s, –$O\underline{CH_2}C_6H_5 \times 2$), 6.28 (2H, s, H(2′) and H(6′)), 8.34 (1H, d, J=6 Hz, H(3)). *Anal.* Calcd for $C_{33}H_{31}NO_5$: 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 Ac_2O (5 ml) at room temperature for 0.5 hr. The reaction mixture was poured into H_2O and extracted with C_6H_6. The C_6H_6 extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. Recrystallization of the residue from isopropylether gave **30b** (440 mg, 82%) as colorless pillars, mp 125—126°. IR ν_{max}^{KBr} cm^{-1}: 1775. MS *m/e*: 425 (M^+). NMR ($CDCl_3$) δ: 2.07 and 2.32 (3H each, s, OAc×2), 3.70 (6H, s, $OCH_3 \times 2$), 3.79 (3H, s, OCH_3), 4.74 (2H, s, C(1)–$C\underline{H}_2Ar$), 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 $C_{23}H_{23}NO_7$: 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 PtO_2 (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 ν_{max}^{KBr} cm^{-1}: 3400 (br), 2930 (br). MS *m/e*: 181, 164 (base). NMR (D_2O) δ: 3.90 (3H, s, OCH_3), 3.94 (6H, s, $OCH_3 \times 2$), 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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