A HIGHLY EFFICIENT SYNTHESIS OF 1-METHYL-, 1-BENZYL-, AND 1-PHENYL-1,2,3,4-TETRAHYDROISOQUINOLINES BY A MODIFIED PUMMERER REACTION

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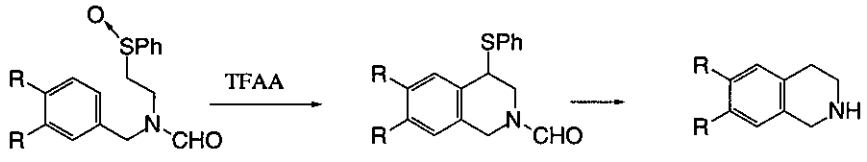
Abstract -- (±)-1-Methyl- (**13b**), (±)-1-benzyl- (**13c**), and (±)-1-phenyl- (**13d**)-1,2,3,4-tetrahydroisoquinolines, which are supposed to participate in the pathogenesis of Parkinson's disease, were prepared by using a modified Pummerer reaction as a key step in excellent overall yields from the commercially available ketones (**4b-c**).

Isoquinoline alkaloids formed endogenously in mammals have received attention since they are supposed to participate in the pathogenesis of Parkinson's disease.[1] Recently, Takano *et al.* developed a route of synthesizing 1,2,3,4-tetrahydroisoquinolines (TIQs) *via* sulfoxide-mediated electrophilic intramolecular cyclization by Pummerer reaction.[2] In the preceding paper,[3] we reported two revised methods of Takano's TIQ synthesis; one is the use of trifluoroacetic anhydride (TFAA) in benzene at room temperature (Method A) and the other involves a sequential treatment with TFAA and BF_3•Et_2O (Method B). Method A is only applicable to the synthesis of TIQs possessing OMe group in the benzene ring (ex. **1a**). On the other hand, Method B is highly efficient for preparing TIQs which do not possess OMe group in the benzene ring (ex. **1b**). We also found that the formyl group used for *N*-protection plays an important role in effecting the intramolecular cyclization.[3]

In this paper we describe a highly efficient synthesis of 1-methyl-, 1-benzyl- and 1-phenyl-1,2,3,4-tetrahydroisoquinolines (1-MeTIQ, 1-BnTIQ, and 1-PhTIQ) which expands the utility of the modified Pummerer reaction. The target compounds are known to be present in mammalian brain, and 1-MeTIQ

protects Parkinsonism,[4] while 1-BnTIQ induces the syndrome[5] and 1-PhTIQ is a candidate involved in the pathogenesis of Parkinson's disease.[6]



1 **2** **3**

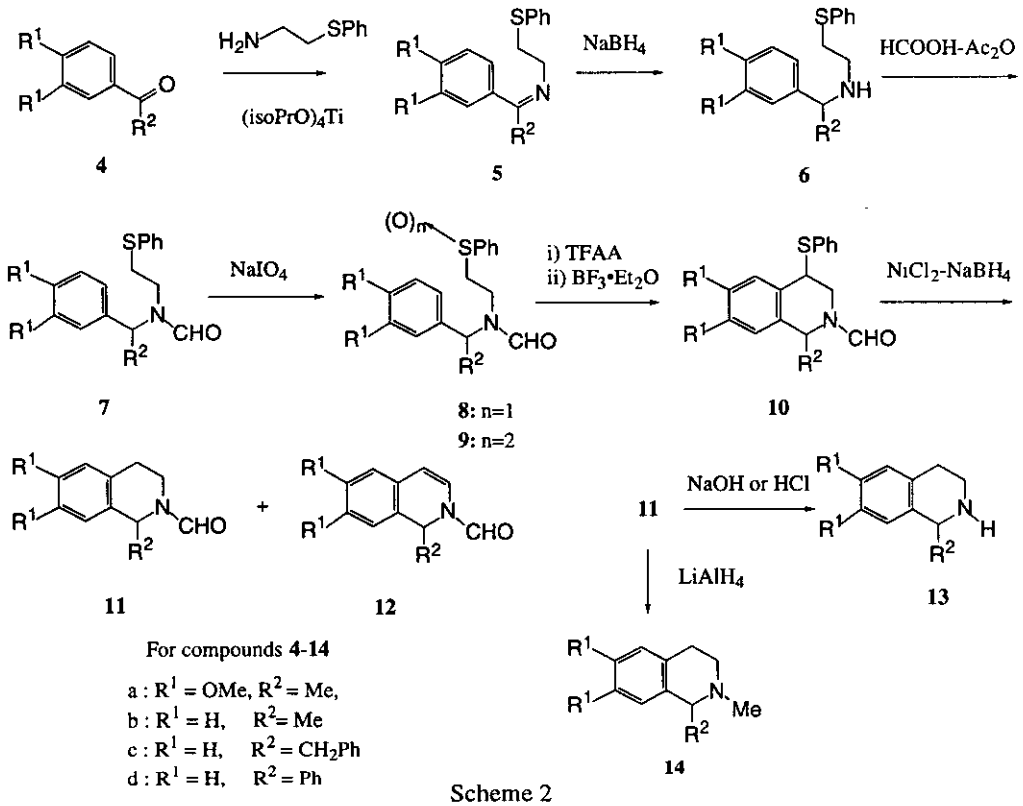
a: R =OCH_3
b: R =H

Scheme 1

N-Arylmethyl-*N*-[2-(phenylsulfinyl)ethyl]formamides (**8a-d**) were prepared in good overall yields as follows (Table 1). Condensation of ketones (**4a-d**) with 2-phenylthioethylamine[7] in the presence of titanium tetraisopropoxide[8] followed by $NaBH_4$ reduction of the resulting imines (**5a-d**) gave *N*-arylmethyl-2-(phenylthio)ethylamines (**6a-d**) in good yields. Treatment of **6a-d** with 98-100% formic acid-acetic anhydride gave *N*-formyl derivatives (**7a-d**) in excellent yields. The products were then oxidized with sodium metaperiodate to give sulfoxides (**8a-d**), though sulfones (**9a-d**) were yielded as each by-product in a few percent yields.

The intramolecular cyclization of *N*-formyl sulfoxide (**8a**) with OMe groups in the benzene ring, on treatment with TFAA in benzene at room temperature (Method A), readily occurred to give *N*-formyl-6,7-dimethoxy-1-methyl-4-phenylthio-TIQ (**10a**) in a quantitative yield. On the other hand, application of this condition to the sulfoxide (**8b**) without OMe group in the benzene ring, caused merely extensive decomposition to yield an intractable mixture. However, this situation dramatically changed when the Method B condition was applied to this reaction. After **8b** was treated with TFAA in benzene at room temperature for 1 h, BF_3•Et_2O was added to this solution. This mixture was allowed to react for further 1 h at room temperature. Thus, the reaction gave *N*-formyl-1-methyl-4-phenylthio-TIQ (**10b**) in 97% yield. Other *N*-formyl sulfoxides (**8c**) and (**8d**) on similar treatment with TFAA and BF_3•Et_2O gave *N*-formyl-1-benzyl- (**10c**) and *N*-formyl-1-phenyl-4-phenylthio-TIQ (**10d**) in 96% and 94% yields, respectively. The ^{1}H-NMR spectra of the TIQs showed very complex signals, suggesting that the compounds are a mixture of stereoisomers at C-1 and C-4 positions. In fact, the respective diastereomers of **10d** were obtained by column chromatographic separation in 87% and 7% yields. This diastereomeric relationship of these compounds, although the stereochemistry was not clarified, was confirmed by yielding the same TIQ (**11d**) on reductive desulfurization with $NiCl_2$-$NaBH_4$.

Thus, the intramolecular cyclization *via* the Pummerer reaction using Method B proceeded very smoothly, proving that the method is very effective for constructing TIQ skeleton even in the cases without activating group (OMe) in the nucleophilic benzene ring.



Scheme 2

Reductive elimination of the phenylthio group of **10a-d** with $NiCl_2$-$NaBH_4$ in MeOH-THF gave *N*-formyl-TIQs (**11a-d**) in excellent yields as shown in Table 1, although 1,2-elimination products (**12a-d**) of phenylthiol group were accompanied in a few percent yields. The ^{1}H-NMR spectra of **11a-d** measured either at room temperature or at 90℃ showed signals due to two rotational isomers of the formyl group as observed in *N*-acetyl TIQ derivatives.[9]

The formyl group of **11a-d** was readily deprotected by alkaline or acid hydrolysis to give 6,7-dimethoxy-1-MeTIQ (salsolidine) (**13a**), 1-MeTIQ (**13b**), 1-BnTIQ (**13c**), and 1-PhTIQ (**13d**). $LiAlH_4$ reduction of **11a-d** gave *N*-methyl-6,7-dimethoxy-1-MeTIQ (carnegine) (**14a**), *N*-methyl-1-MeTIQ (**14b**), *N*-methyl-1-BnTIQ (**14c**), and *N*-methyl-1-PhTIQ (**14d**) as shown in Table 1. Thus, (±)-1-MeTIQ, (±)-1-BnTIQ and (±)-1-PhTIQ, and their *N*-methyl derivatives were prepared in 7 steps from the respective ketone in

55-68% overall yields.

This method for preparing TIQ is excellent not only in high efficiency but also in ready availability of the starting material, and has an advantage of isotope-labeling into the TIQ skeleton since this route includes two reductive steps using sodium borohydride.

Table 1. Preparation of 1,2,3,4-Tetrahydroisoquinolines

		Sulfoxides		Pummerer Reaction	Desulfurization		Hydrolysis		Reduction	
Ketones		Overall Yield (%)			Yield (%)					
	1-R^2			Method*	4-PhSTIQ		*N*-Formyl-TIQ		TIQ		*N*-MeTIQ	
4a	Me	**8a**	87	A	**10a**	96	**11a**	88	**13a**	91	**14a**	86
4b	Me	**8b**	89	B	**10b**	97	**11b**	85	**13b**	93	**14b**	89
4c	CH_2Ph	**8c**	69	B	**10c**	96	**11c**	89	**13c**	93	**14c**	94
4d	Ph	**8d**	83	B	**10d**	94	**11d**	89	**13d**	92	**14d**	91

* A : TFAA, B: TFAA-BF_3•Et_2O.

EXPERIMENTAL

General Notes. Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were obtained as films for oils and gums, and KBr disks for solids with a JASCO FT/IR-5000 spectrophotometer, and are given in cm^{-1}. NMR spectra were measured on a JEOL JNM-EX 90 (^1H, 90 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, and br = broad. LRMS and HRMS were taken on a JEOL JMS-AX 505H spectrometer at 70 eV (EIMS) or at 270 eV (CIMS, reactant gas: *iso*-butane) using direct or GC/MS inlet systems, and figures in parentheses indicate the relative intensities. TLC was performed on Merck precoated Silica gel 60 F_{254} plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness. The known TIQs were also characterized by MS, IR, and ^1H-NMR examinations.

Preparation of *N*-Arylmethyl-2-(phenylthio)ethylamines (6a-d)

A mixture of **4a-d** (5 g), 2-phenylthioethylamine[7] (1.2 molar eq), and titanium tetraisopropoxide (1.5 molar eq) was heated at 80°C for 3 h. After cooling, the reaction mixture was diluted with MeOH (100 mL). To this solution, $NaBH_4$ (1 molar eq) was added in small portions under ice-cooling. The reaction mixture was stirred at rt for 1 h and concentrated *in vacuo*. Water (*ca* .40 mL) was added to the residue, and the mixture was diluted with MeOH (*ca.* 500 mL). After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in water and extracted with $CHCl_3$. The products (**6a-d**) were purified by column chromatography.

***N*-[1-(3,4-Dimethoxyphenyl)ethyl]-2-(phenylthio)ethylamine (6a)**: Eluent for column chro-

matography: AcOEt. Yield: 99%. Colorless oil. IR: 1593, 1510, 1464, 1263. ^{1}H-NMR: 1.33 (3H, d, *J*=7.0 Hz, =CHC<u>H</u>$_3$), 2.60-2.80 (2H, m, -SCH$_2$-), 2.95-3.15 (2H, m, -CH$_2$-), 3.53 (1H, q, *J*=7.0 Hz, =C<u>H</u>CH$_3$), 3.86, 3.87 (each 3H, s, 2 x -OCH$_3$), 6.80 (2H, s, Ar-H), 6.87 (1H, s, Ar-H), 7.10-7.40 (5H, m, Ar-H). EIMS *m/z*: 317 (M$^+$, 2), 303 (2), 194 (9), 193 (8), 165 (base peak), 150 (7), 109 (6), 91 (4). CIMS *m/z*: 318 (MH$^+$, 18), 165 (base peak).

***N*-(1-Phenylethyl)-2-(phenylthio)ethylamine (6b)**: Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 98%. Colorless oil. IR: 1584, 1481, 1452, 1439. ^{1}H-NMR: 1.34 (3H, d, *J*=6.5 Hz, =CHC<u>H</u>$_3$), 2.61-2.76 (2H, m, -SCH$_2$-), 2.95-3.10 (2H, m, -CH$_2$N=), 3.75 (1H, q, *J*=6.5 Hz, =C<u>H</u>CH$_3$), 7.10-7.30 (10H, m, Ar-H). EIMS *m/z*: 275 (M$^+$,4), 134 (51), 124 (21), 105 (base peak), 91 (10), 77 (13). CIMS *m/z*: 258 (MH$^+$, base peak), 148 (17), 134 (18), 105 (62). HRMS: Calcd for $C_{16}H_{19}NS$: 257.1238. Found: 257.1194.

***N*-(1,2-Diphenylethyl)-2-(phenylthio)ethylamine (6c)**: Eluent for column chromatography: *n*-hexane-AcOEt (3:1). Yield: 73%. Colorless plates, mp 51-53°C (from Et$_2$O). IR: 1584, 1456, 1286. ^{1}H-NMR: 2.40-3.00 (6H, m, -SCH$_2$CH$_2$N=, ArCH$_2$-), 3.80 (1H, dd, *J*=4.5, 6.0 Hz), 7.00-7.40 Hz (15H, m, Ar-H). EIMS *m/z*: 242 (M-91, base peak), 210 (7), 181 (48), 166 (11), 137 (88), 109 (23), 104 (9), 91 (9). CIMS *m/z*: 337 (MH$^+$, base peak), 242 (24), 224 (23), 181 (5). *Anal.* Calcd for $C_{22}H_{23}NS$: C, 79.24; H, 6.95; N, 4.20. Found: C, 79.25; H, 7.05; N, 4.18.

***N*-(1,1-Diphenylmethyl)-2-(phenylthio)ethylamine (6d)**: Eluent for column chromatography: *n*-hexane-AcOEt (2:1). Yield: 88%. Colorless oil. IR: 1584, 1493, 1483, 1454, 1439. ^{1}H-NMR: 2.70-2.92 (2H, m, -SCH$_2$-), 2.78-3.18 (-CH$_2$N=), 4.80 (1H, s, -CH=), 7.10- 7.50 (15H, m, Ar-H). EIMS *m/z*: 319 (M$^+$, 2), 196 (16), 182 (19), 167 (base peak), 152 (10), 105 (13), 77 (7). CIMS *m/z*: 320 (MH$^+$, base peak), 167 (37).

Formylation of 6

A mixture of **6a-d** (each 5 g), 98-100% formic acid (30 molar eq) and acetic anhydride (10 molar eq) was heated at 70°C for 1 h, then concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The products (**7a-d**) were purified by column chromatography.

***N*-[1-(3,4-Dimethoxyphenyl)ethyl]-*N*-[2-(phenylthio)ethyl]formamide (7a)**: Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 94%. Pale yellow oil. IR: 1663 (=N-CHO), 1591, 1581, 1417, 1257, 1147. ^{1}H-NMR: 1.50, 1.58 (total 3H, each d, *J*=7.0 Hz, =CHC<u>H</u>$_3$), 2.50-3.50 (total 4H, m, -SCH$_2$CH$_2$N=), 3.84, 3.88 (each 3H, s, 2 x -OCH$_3$), 4.71, 5.71 (total 1H, each q, *J*=7.0 Hz, =C<u>H</u>CH$_3$), 6.70-6.90 (total 3H, m, Ar-H), 7.10-7.30 (5H, m, Ar-H), 8.13, 8.37 (total 1H, each s, =N-CHO). EIMS *m/z*: 345 (M$^+$, 14), 316 (3), 209 (77), 194 (20), 180 (3), 165 (base peak), 150 (10), 109 (8). HRMS: Calcd for $C_{19}H_{23}NO_3S$: 345.1395. Found: 345.1360.

***N*-(1-Phenylethyl)-*N*-[2-(phenylthio)ethyl]formamide (7b)**: Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 98%. Pale yellow oil. IR: 1669 (=N-CHO), 1584, 1439, 1419. ^{1}H-NMR: 1.52, 1.60 (total 3H, each d, *J*=6.5 Hz, =CHC<u>H</u>$_3$), 2.50-3.50 (4H, m, -SCH$_2$CH$_2$N=), 4.75, 5.75 (total 1H, each q, *J*= 6.5 Hz, =C<u>H</u>CH$_3$), 7.10-7.45 (10H, m, Ar-H), 8.14, 8.38 (total 1H, each s, =N-CHO). EIMS *m/z*: 285 (M$^+$, 24), 176 (8), 136 (96), 123 (10), 105 (base peak), 91 (8), 77 (17). HRMS: Calcd for $C_{17}H_{19}NOS$: 285.1187. Found 285.1161.

***N*-(1,2-Diphenylethyl)-*N*-[2-(phenylthio)ethyl]formamide (7c)**: Eluent for column chromatography: *n*-hexane-AcOEt (3:1). Yield: 99%. Pale yellow gum. IR: 1667 (=N-CHO), 1584, 1497, 1483, 1439, 1408. ^{1}H-NMR: 2.10-3.75 (6H, m, -SOCH$_2$CH$_2$N=, ArCH$_2$-), 4.74, 5.71 (total 1H, dd and t, *J*=6.0, 9.0 Hz and *J*=7.0 Hz, -CH=), 7.00-7.60 (15H, m, Ar-H), 7.93, 8.02 (total 1H, each s, =N-CHO). EIMS *m/z*: 361 (M$^+$, 7), 270 (69), 242 (60), 181 (54), 166 (19), 137 (base peak), 136 (98), 109 (32). HRMS: Calcd for $C_{23}H_{23}NOS$: 361.1500. Found 361.1458.

***N*-(1,1-Diphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (7d)**: Eluent for column chromatography: *n*-hexane-AcOEt (2:1). Yield: 98%. Colorless gum. IR: 1667 (=N-CHO), 1584, 1439, 1398, 1274. ^{1}H-NMR: 2.20-2.40, 2.72-2.92, 3.40-3.70 (total 4H, each m, -SCH$_2$CH$_2$N=), 5.90, 6.84 (total 1H, each s, -CH=), 7.00-7.50 (15H, m, Ar-H), 8.19, 8.35 (total 1H, each s, =N-CHO). EIMS *m/z*: 347 (M$^+$, 27), 318 (10), 182 (6), 167 (70), 152 (15), 136 (base peak). HRMS: Calcd for $C_{22}H_{21}NOS$: 347.1344. Found 347.1364.

Oxidation of 7 with $NaIO_4$

A solution of sodium metaperiodate (1.5 molar eq) in H_2O (10 mL) was added to a solution of **7a-d** (each 4 g) in MeOH (80 mL), and the mixture was stirred at rt for 15-20 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The products (**8a-d**) and the by-products (**9a-d**) were separated by column chromatography.

***N*-[1-(3,4-Dimethoxyphenyl)ethyl]-*N*-[2-(phenylsulfinyl)ethyl]formamide (8a)**: Eluent for column chromatography: AcOEt-MeOH (95:5). Yield: 94%. Pale yellow gum. IR: 1665 (=N-CHO), 1520, 1421, 1257, 1149. ^{1}H-NMR: 1.50, 1.52, 1.64, 1.66 (total 3H, each d, *J*=7.0 Hz, =CHC$\underline{H}_3$), 2.20-3.70 (4H, m, -SCH$_2$CH$_2$N=), 3.87, 3.88 (total 6H, each s, 2 x -OCH$_3$), 4.76, 5.75 (total 1H, each q, *J*= 7.0 Hz, =C$\underline{H}$CH$_3$), 6.73, 6.82 (total 3H, each br s, Ar-H), 7.40-7.70 (5H, m, Ar-H), 8.10, 8.30, 8.34, 8.39 (total 1H, each s, =N-CHO). EIMS *m/z*: 362 (MH$^+$, 63), 346 (14), 316 (4), 236 (22), 198 (9), 165 (base peak), 127 (8).

***N*-[1-(3,4-Dimethoxyphenyl)ethyl]-*N*-[2-(phenylsulfonyl)ethyl]formamide (9a)**: Eluent for column chromatography: AcOEt-MeOH (95:5). Yield: 5.5%. Pale yellow gum. IR: 1669 (=N-CHO), 1518, 1419, 1259, 1149. ^{1}H-NMR: 1.45, 1.61 (total 3H, each d, *J*=7.0 Hz, =CHC$\underline{H}_3$), 2.50-4.10 (4H, m, -SO$_2$CH$_2$CH$_2$N=), 3.87, 3.89 (each 3H, s, 2 x -OCH$_3$), 4.75, 5.72 (total 1H, each q, *J*=7.0 Hz, =C$\underline{H}$CH$_3$), 6.71 (1H, s, Ar-H), 6.75-6.90 (total 2H, m, Ar-H), 7.40-7.95 (5H, m, Ar-H), 8.13, 8.30 (total 1H, each s, =N-CHO). EIMS *m/z*: 377 (M$^+$, 32), 348 (base peak), 334 (14), 208 (32), 180 (15), 165 (30), 139 (9), 77 (8). HRMS: Calcd for $C_{19}H_{23}NO_5S$: 377.1297. Found 377.1335.

***N*-(1-Phenylethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (8b)**: Eluent for column chromatography: AcOEt. Yield: 93%. Colorless gum. IR: 1669 (=N-CHO), 1446, 1046. ^{1}H-NMR: 1.51, 1.54, 1.66, 1.68 (total 3H, each d, *J*= 6.5 Hz, =CHC$\underline{H}_3$), 2.20-3.80 (4H, m, -SCH$_2$CH$_2$N=), 4.81, 5.75, 5.85 (total 1H, each q, *J*=6.5 Hz, =C$\underline{H}$CH$_3$), 7.20-7.60 (10H, m, Ar-H), 8.14, 8.27, 8.36, 8.40 (total 1H, each s, =N-CHO). CIMS *m/z*: 302 (MH$^+$, base peak), 286 (38), 176 (43), 141 (8), 105 (7).

***N*-(1-Phenylethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (9b)**: Eluent for column chromatography: AcOEt. Yield: 6.5%. Pale yellow gum. IR: 1669 (=N-CHO), 1448, 1307, 1151. ^{1}H-NMR: 1.46, 1.62 (total 3H, each d, *J*=6.5 Hz, =CHC$\underline{H}_3$), 2.50-3.70 (4H, m, -SCH$_2$CH$_2$N=), 4.79, 5.72 (total

1H, each q, *J*=6.5 Hz, =C<u>H</u>CH$_3$), 7.10-7.90 (10H, m, Ar-H), 8.13, 8.31 (total 1H, each s, =N-CHO). EIMS *m/z*: 317 (M$^+$, 9), 288 (base peak), 274 (11), 148 (22), 120 (14), 105 (45), 77 (16). HRMS: Calcd for $C_{17}H_{19}NO_3S$: 317.1085. Found 317.1059.

***N*-(1,2-Diphenylethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (8c)**: Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 95%. Colorless gum. IR: 1667 (=N-CHO), 1497, 1446, 1417, 1044. ^{1}H-NMR: 2.00-4.00 (6H, m, -SOCH$_2$CH$_2$N=), 4.65-4.95, 5.50-5.90 (total 1H, each m, -CH=), 7.05-7.60 (15H, m, Ar-H), 8.00, 8.03, 8.10, 8.14 (total 1H, each s, =N-CHO). CIMS *m/z*: 378 (M$^+$, base peak), 362 (16), 252 (34), 198 (4), 181 (7), 141 (5).

***N*-(1,2-Diphenylethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (9c)**: Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 1.7%. Colorless gum. IR: 1669 (=N-CHO), 1450, 1307, 1151. ^{1}H-NMR: 2.30-2.75, 3.00-3.85 (-SO$_2$CH$_2$CH$_2$N=, ArCH$_2$-), 4.78, 5.65 (total 1H, each dd, *J*=7.0, 8.5 Hz, -CH=), 7.00-7.80 (15H, m, Ar-H), 7.90, 7.98 (total 1H, each s, =N-CHO). EIMS *m/z*: 302 (M-91, 18), 274 (base peak), 180 (13), 165 (5), 132 (21), 104 (15), 91 (6), 77 (11). CIMS *m/z*: 394 (MH$^+$, 65), 274 (54), 252 (60), 214 (base peak), 181 (76), 169 (35).

***N*-(1,1-Diphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (8d)**: Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 97%. Colorless gum. IR: 1669 (=N-CHO), 1495, 1446, 1116, 1085, 1046. ^{1}H-NMR: 2.02-2.25, 2.50-3.15, 3.30-4.20 (total 4H, each m, -SCH$_2$CH$_2$N=), 5.97, 6.88 (total 1H, each s, -CH=), 7.00-7.80 (15H, m, Ar-H), 8.17, 8.43 (total 1H, each s, =N-CHO). CIMS *m/z*: 364 (M$^+$, base peak), 348 (14), 282 (7), 256 (4), 238 (13), 107 (59), 152 (8).

***N*-(1,1-Diphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]foramide (9d)**: Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 3.2%.Colorless cake. IR: 1669 (=N-CHO), 1495, 1448, 1307, 1151. ^{1}H-NMR: 2.95-3.15, 3.60-3.85 (each 2H, m, -SO$_2$CH$_2$CH$_2$N=), 5.98, 6.82 (total 1H, -CH=), 7.10-7.90 (15H, m, Ar-H), 8.14, 8.37 (total 1H, each s, =N-CHO). EIMS *m/z*: 379 (M$^+$, 10), 350 (base peak), 326 (5), 210 (12), 182 (13), 167 (21), 165 (17), 152 (7). HRMS: Calcd for $C_{22}H_{21}NO_3S$: 379.1242. Found 379.1250.

General Procedure for the Pummerer Cyclization of Sulfoxides (8)

Method A: TFAA (5 molar eq) was added to a solution of a sulfoxide (**8a**) (3 g, 8.31 mM) in dry benzene (50 mL) at rt, and the mixture was stirred for 20 h. The reaction mixture was concentrated *in vacuo*, and the product (**10a**) were purified by column chromatography.

Method B: TFAA (5 molar eq) was added to a solution of a sulfoxide **8b-d** (each 3 g) in dry benzene (50 mL) at rt, and the mixture was stirred for 1 h. BF_3•Et_2O (3 molar eq) was added and stirring was continued at the same temperature for 1 h. The reaction mixture was washed with 5% NaOH-H_2O. The products (**10b-d**) were purified by column chromatography. The Pummerer reaction of **8d** gave separable two diastereomers (**10d-A**, yield: 87%, **10d-B**, yield 6.6%, total yield: 93.6%) by column chromatography. Each diastereomers (**10d-A** and **10d-B**) gave the same products (**11d**) and (**12d**) by reductive desulfulization.

2-Formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-4-phenylthioisoquinoline (10a): Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 96%. Colorless gum. IR: 1669 (=N-CHO), 1518, 1439, 1257. ^{1}H-NMR: 1.45, 1.53 (total 3H, each d *J*=6.5 Hz, =CHC<u>H</u>$_3$), 3.20-4.90 (3.5H,

-SCHCH$_2$N=, =CHCH$_3$), 3.86, 3.88, 3.90 (total 6H, each s, 2 x -OCH$_3$), 5.44 (0.5H, q, *J*=6.5 Hz, =CHCH$_3$), 6.56, 6.59, 6.74, 6.77 (total 2H, each s, Ar-H), 7.20-7.70 (5H, m, Ar-H), 8.03, 8.26, 8.46 (total 1H, each s, =N-CHO). EIMS *m/z*: 343 (M^+, 2), 234 (base peak), 218 (64), 206 (17), 190 (56), 174 (26), 146 (13), 110 (16). HRMS: Calcd for $C_{19}H_{21}NO_3S$: 343.1243. Found: 343.1205.

2-Formyl-1,2,3,4-tetrahydro-1-methyl-4-phenylthioisoquinoline (10b): Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 97%. Pale yellow gum. IR: 1671 (=N-CHO), 1582, 1433, 1400. ^{1}H-NMR: 1.46, 1.51 (total 3H, each d, *J*=6.5 Hz, =CHCH$_3$), 3.10-3.90, 4.60-4.80 (total 3H, each m, -SCHCH$_2$N=), 4.83, 5.51 (total 1H, each q, *J*=6.5 Hz, =CHCH$_3$), 7.00-7.90 (9H, m, Ar-H), 8.00, 8.23, 8.43 (total 1H, each s, =N-CHO). EIMS *m/z*: 183 (M^+, 3), 174 (71), 173 (base peak), 158 (43), 146 (30), 144 (22), 130 (46), 129 (55). CIMS *m/z*: 284 (MH^+, base peak), 216 (3), 176 (35), 175 (11), 174 (50), 173 (13). HRMS: Calcd for $C_{17}H_{17}NOS$: 283.1030. Found: 283.1018.

2-Formyl-1,2,3,4-tetrahydro-1-phenylmethyl-4-phenylthioisoquinoline (10c): Eluent for column chromatography: *n*-hexane-AcOEt (2:1). Yield: 96%. Colorless cake. IR: 1669 (=N-CHO), 1582, 1495, 1431, 1402. ^{1}H-NMR: 2.80-3.55, 4.30-4.90 (5.5H, -SCHCH$_2$N=, ArCH$_2$-, -CH=), 5.74 (0.5H, t, *J*=6.0 Hz, -CH=), 6.95-7.75 (14H, m, Ar-H), 7.65, 7.95 (total 1H, each s =N-CHO). EIMS *m/z* 268 (M-91, base peak), 240 (8), 158 (50), 130 (84), 123 (11), 103 (10), 91 (7). CIMS *m/z*: 360 (MH^+, base peak), 252 (45), 250 (35).

2-Formyl-1,2,3,4-tetrahydro-1-phenyl-4-phenylthioisoquinoline (10d-A) (diastereomer A): Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 87%. Colorless plates. mp 148-150°C (from AcOEt-*n*-hexane). IR: 1669 (=N-CHO), 1493, 1481, 1458, 1429, 1400, 1361. ^{1}H-NMR: 3.05-3.80, 4.40-4.65 (total 3H, each m, -SCHCH$_2$N=), 5.80, 6.70 (total 1H, each s, -CH=), 6.90-7.70 (14H, m, Ar-H), 8.05 8.66 (total 1H, each s, =N-CHO). EIMS *m/z*: 345 (M^+, 1), 235 (base peak), 208 (14), 206 (18.7), 178 (13), 158 (55), 130 (57), 103 (11). CIMS *m/z*: 346 (MH^+, base peak). 236 (9). *Anal.* Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05. Found: C, 76.40; H, 5.69; N, 4.04.

2-Formyl-1,2,3,4-tetrahydro-1-phenyl-4-phenylthioisoquinoline (10d-B) (diastereomer B): Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 6.6%. Pale yellow gum. IR: 1671 (=N-CHO), 1454, 1431, 1398, 1185. ^{1}H-NMR: 3.05-3.90, 4.25-4.60 (total 3H, each m, -SCHCH$_2$N=), 5.68, 6.62 (total 1H, each s, -CH=), 6.70-8.04 (14H, m, Ar-H), 8.06, 8.41 (total 1H, each s, =N-CHO). EIMS *m/z*: 345 (M^+, 22), 235 (base peak), 208 (19), 206 (19), 178 (20), 158 (71), 130 (74), 103 (13). HRMS: Calcd for $C_{22}H_{19}NOS$: 345.1187. Found: 345.1161.

Reductive Desulfurization of 2-Formyl-4-phenylthio-TIQs (10)

$NaBH_4$ (10.5 molar eq) was added in small portions to a stirred solution of one of **10a-d** (each 2 g) with $NiCl_2 \cdot 6H_2O$ (3.5 molar eq) in MeOH-THF (3:1) (120 mL) under ice-cooling. After the addition, stirring was continued at rt for 30 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in water, acidified with 5% HCl-H_2O, and extracted with $CHCl_3$. The products (**11a-d**) and the by-products (**12a-d**) were separated by column chromatography.

2-Formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (11a): Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 88%. Colorless gum. (lit.,[10] mp 79-80°C). IR: 1665 (=N-CHO), 1520, 1435, 1257. ^{1}H-NMR: 1.46, 1.53 (total 3H, each d, *J*=7.0 Hz, =CHCH$_3$), 2.60-4.50 (total

4H, m, $ArCH_2CH_2N$=), 3.86 (6H, s, 2 x -OCH_3), 4.70, 5.38 (total 1H, each q, J=7.0 Hz, =C<u>H</u>CH_3), 6.58, 6.60 (each 1H, s, Ar-H), 8.13, 8.29 (total 1H, each s, =N-CHO). EIMS *m/z*: 235 (M^+, 28), 220 (base peak), 192 (34), 176 (13), 148 (7). HRMS: Calcd for $C_{13}H_{17}NO_3$: 235.1209. Found 235.1246.

2-Formyl-1,2-Dihydro-6,7-dimethoxy-1-methylisoquinoline (12a): Eluent for column chromatography: AcOEt-*n*-hexane (2:1). Yield: 4.0%. Pale yellow gum. IR (KBr): 1686 (=N-CHO), 1636, 1518, 1342, 1270. ^{1}H-NMR: 1.31, 1.39 (total 3H, each d, J= 6.5 Hz, =CHC<u>H</u>$_3$), 3.87 (6H, s, 2 x -OCH_3), 4.95, 5.55 (total 1H, each q, J=6.5 Hz, =C<u>H</u>CH_3), 5.83, 5.96 (total 1H, d and dd, J=7.5 Hz and J=1.5, 7.5 Hz, olefinic-H), 6.44, 7.07 (total 1H, d and dd, J=7.5 Hz and J=1.5, 7.5 Hz, olefinic-H), 6.59, 6.62 (each 1H, s, Ar-H), 8.19, 8.28 (total 1H, each s, =N-CHO). EIMS *m/z*: 233 (M^+, 32), 218 (base peak), 203 (7), 190 (69), 175 (21), 174 (22), 146 (20), 117 (6). HRMS: Calcd for $C_{13}H_{15}NO_3$: 233.1052. Found 233.1072.

2-Formyl-1,2,3,4-tetrahydro-1-methylisoquinoline (11b): Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 85%. Colorless oil.[10] IR: 1671 (=N-CHO), 1433, 1400. ^{1}H-NMR: 1.48, 1.53 (total 3H, each d, J=6.5 Hz, =CHC<u>H</u>$_3$), 2.60-3.80, 4.25-4.55 (total 4H, each m, $ArCH_2CH_2N$=), 4.78, 5.46 (total 1H, each q, J=6.5 Hz, =C<u>H</u>CH_3), 7.00-7.30 (4H, m, Ar-H), 8.14, 8.29 (total 1H, each s, =N-CHO). EIMS *m/z*: 175 (M^+, 56), 160 (base peak), 132 (71), 117 (27), 115 (18), 105 (18), 91 (10), 77 (12). HRMS: Calcd for $C_{11}H_{13}NO$: 175.0997. Found 175.1034.

2-Formyl-1,2-dihydro-1-methylisoquinoline (12b): Eluent for column chromatography: AcOEt-*n*-hexane (1:1). Yield: 5.2%. Pale yellow oil. IR: 1686 (=N-CHO), 1634, 1574, 1458, 1423. ^{1}H-NMR: 1.33, 1.40 (total 3H, each d, J=6.5 Hz, =CHC<u>H</u>$_3$), 4.93, 5.61 (total 1H, each q, J=6.5 Hz, =C<u>H</u>CH_3), 5.89, 6.03 (total 1H, d and dd, J=7.5 Hz and J=1.5, 5.5 Hz, olefinic-H), 6.51 (0.8H, d, J=7.5 Hz, olefinic-H), 6.95-7.35 (4.2H, m, Ar-H, olefinic-H), 8.21, 8.29 (total 1H, each s, =N-CHO). EIMS *m/z*: 173 (M^+, 29), 158 (79), 130 (base peak), 115 (8), 103 (21), 77 (15). HRMS: Calcd for $C_{11}H_{11}NO$: 173.0840. Found 173.0851.

2-Formyl-1,2,3,4-tetrahydro-1-phenylmethylisoquinoline (11c): Eluent for column chromatography: *n*-hexane-AcOEt (2:1). Yield: 89%. Colorless gum. IR: 1669 (=N-CHO), 1495, 1435, 1402. ^{1}H-NMR: 2.50-3.70, 4.60-4.70 (6H, m, $ArCH_2CH_2N$=, $ArCH_2$-), 4.66, 5.64 (total 1H, dd and t, J=6.0, 8.5 Hz and J= 6.5 Hz, -CH=), 7.00-7.50 (9H, m, Ar-H), 7.57, 8.10 (total 1H, each s, =N-CHO). EIMS *m/z*: 160 (M-91, base peak), 132 (37), 117 (9), 105 (9). CIMS *m/z*: 252 (MH^+, base peak), 160 (13).

2-Formyl-1,2-dihydro-1-phenylmethylisoquinoline (12c): Eluent for column chromato-graphy: *n*-hexane-AcOEt (2:1). Yield: 4.8%. Colorless gum. IR: 1668 (=N-CHO), 1632, 1572, 1495, 1458, 1425. ^{1}H-NMR: 3.60-3.20 (2H, m, $ArCH_2$-), 4.79, 5.69 (total 1H, dd and t, J=5.0, 9.5 Hz and J=7.0 Hz, -CH=), 5.85, 6.13 (total 1H, d and dd, J=7.5 and J=1.2, 7.5 Hz, olefinic-H), 6.49, 6.57 (total 1H, d and dd, J=7.5 Hz and J=1.2, 7.5 Hz, olefinic-H), 6.90-7.40 (9H, m, Ar-H), 7.41, 8.28 (total 1H, each s, =N-CHO). EIMS *m/z*: 249 (M^+, 5), 218 (29), 189 (6), 159 (86), 131 (60), 103 (base peak), 91 (38), 77 (71). CIMS *m/z*: 250 (MH^+, base peak), 158 (37), 130 (13). HRMS: Calcd for $C_{17}H_{15}NO$: 249.1153. Found: 249.1134.

2-Formyl-1,2,3,4-tetrahydro-1-phenylisoquinoline (11d): Eluent for column chromatography: *n*-hexane-AcOEt (2:1). Yield: 89%. Colorless gum (lit.,[10] mp 78-80°C). IR: 1669 (=N-CHO), 1493, 1454,

1435, 1398. ^{1}H-NMR: 2.70-3.80, 4.05-4.40 (total 4H, each m, $ArCH_2CH_2N$=), 5.77, 6.68 (total 1H, each s, -CH=), 7.00-7.40 (9H, m, Ar-H), 8.16, 8.50 (total 1H, each s, =N-CHO). EIMS *m/z*: 237 (M^+, 95), 236 (base peak), 208 (15), 193 (16), 178 (25), 160 (47), 132 (40), 105 (14). HRMS: Calcd for $C_{16}H_{15}NO$: 237.1154. Found: 237.1174.

2-Formyl-1,2-dihydro-1-phenylisoquinoline (12d): Eluent for column chromatography: *n*-hexane-AcOEt (2:1). Yield: 7.9%. Colorless gum. IR: 1684 (=N-CHO), 1632, 1572, 1493, 1456, 1421, 1336. ^{1}H-NMR: 5.91, 6.65 (total 1H, each s -CH=), 5.98, 6.06 (total 1H, d and dd, *J*=7.5 Hz and *J*=1.2, 7.5 Hz, olefinic-H), 6.58 (0.8H, d, *J*=7.5 Hz, olefinic-H), 6.80-7.40 (9.2H, m, Ar-H, olefinic-H), 7.53, 8.35 (total 1H, each s, =N-CHO). EIMS *m/z*: 235 (M^+, 71), 206 (12), 204 (10), 178 (8), 158 (base peak), 130 (84), 103 (14), 77 (9). HRMS: Calcd for $C_{16}H_{13}NO$: 235.0997. Found: 235.1023.

Hydrolysis of 2-Formyl-TIQs (11).

Alkaline hydrolysis---A solution of the 2-formyl-TIQs **11a**, **b**, and **d** (each 450 mg) in EtOH (10 mL)-10%NaOH was refluxed for 5-25 h (5 h for **11a-b**, 20 h for **11d**). The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water and extracted with $CHCl_3$. The products (**13a**,**b**, and **d**) were purified by column chromatography.

Acid hydrolysis---- A solution of **11c** (450 mg) in EtOH (10 mL)-10% HCl (4 mL) was refluxed for 30 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with dil. NaOH and extracted with $CHCl_3$.The product (**13c**) was purified by column chromatography.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-methylisoquinoline (13a) (Salsolidine): Eluent for column chromatography: $CHCl_3$-MeOH (8:2). Yield: 91%. Colorless oil. HCl salt: mp 194-195°C. Colorless needles (from EtOH-Et_2O) (lit.,[11] mp 188-189°C, HCl salt).

1,2,3,4-Tetrahydro-1-methylisoquinoline (13b): Eluent for column chromatography: $CHCl_3$-MeOH (8:2). Yield: 93%. Colorless oil. HCl salt: mp 182-184°C. Colorless needles (from EtOH-Et_2O) (lit.,[12] mp 183-184°C, HCl salt).

1,2,3,4-Tetrahydro-1-phenylmethylisoquinoline (13c): Eluent for column chromatography: $CHCl_3$-MeOH (9:1). Yield: 93%. Colorless gum. HCl salt: mp 172-174°C. Colorless plates (from EtOH-Et_2O) (lit.,[13] mp 170-172°C, HCl salt).

1,2,3,4-Tetrahydro-1-phenylisoquinoline (13d): Eluent for column chromatography: AcOEt. Yield: 92%. Colorless needles. mp 102-104°C (from AcOEt-*n*-hexane) (lit.,[14] mp 73-75°C, lit.,[15] mp 97-98°C).

$LiAlH_4$ Reduction of 2-Formyl-TIQs (11).

$LiAlH_4$ (2 molar eq) was added to a solution of **11a-d** (each 500 mg) in dry THF (20 mL) under ice-cooling, and the mixture was refluxed for 1-2 h. Et_2O saturated with water was added to the reaction mixture and insoluble material was filtered off. The product was purified by column chromatography to give **14a-d**. Yields are shown in Table 2.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,2-dimethylisoquinoline (14a) (Carnegine): Eluent for column chromatography: $CHCl_3$-MeOH (95:5). Yield: 86%. Colorless oil. HCl salt: mp 215-218°C. Colorless plate (from EtOH-Et_2O) (lit.,[16] mp 209-211°C, HCl salt).

1,2,3,4-Tetrahydro-1,2-dimethylisoquinoline (14b): Eluent for column chromatography:

$CHCl_3$- MeOH (9:1). Yield: 89%. Pale yellow oil. HCl salt: mp 199-203°C. Colorless plate (from EtOH-Et_2O). IR: 1493, 1450, 1373, 1292. ^{1}H-NMR: 1.39 (3H, d, *J*=6.5 Hz, =CHC<u>H</u>$_3$), 2.48 (3H, s, =NCH_3), 2.55-3.25 (4H, ArCH_2CH_2N=), 3.60 (1H, q, *J*=6.5 Hz, =C<u>H</u>CH_3), 7.11 (4H, s, Ar-H). EIMS *m/z*: 161 (M^+, 3), 160 (5), 146 (base peak), 131 (10), 117 (12), 115 (9), 103 (4). CIMS *m/z*: 162 (MH^+, base peak), 146 (7).

1,2,3,4-Tetrahydro-2-methyl-1-phenylmethylisoquinoline (14c): Eluent for column chromatog-raphy: $CHCl_3$-MeOH (9:1). Yield: 94%. Colorless gum. HCl salt: Colorless gum. IR: 1495, 1454, 1377. ^{1}H-NMR: 2.49 (3H, s, =NCH_3), 2.55-3.40 (6H, m, ArCH_2CH_2N=, ArCH_2-), 3.81 (1H, t, *J*= 6.2 Hz, -CH=), 6.70-7.30 (9H, m, Ar-H). EIMS *m/z*: 146 (M-91, base peak), 131 (8), 115 (3), 103 (3), 91 (3). CIMS *m/z*: 238 (MH^+, base peak), 146 (14).

1,2,3,4-Tetrahydro-2-methyl-1-phenylisoquinoline (14d): Eluent for column chromatography: *n*-hexane-AcOEt (3:1). Yield: 90%. Colorless cake. mp 41-43°C. (lit.,[14]: oil, lit.,[17] mp 72°C).

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