APPLICATION OF THE LEWIS ACID CATALYZED [4+2]CYCLOADDITION REACTION TO SYNTHESIS OF NATURAL QUINOLINE ALKALOIDS

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Abstract ——— Lewis acid catalyzed [4+2]cycloaddition reaction of the Schiff base with the olefin was applied to the syntheses of some natural quinoline alkaloids. The extension of [4+2]cycloaddition using the acetal and the orthoester as dienophiles or using s-triazine derivative as a Schiff base is also described. The electrocyclic reaction of the Schiff base was also examined to synthesize the quinoline compound.

We have already reported[1] the synthesis of tetrahydroquinoline derivatives by Lewis acid catalyzed [4+2]cycloaddition *reaction of the Schiff bases as dienes* with some dienophiles possessing an electron donating substituent (Fig.). In our continuous study we found that the similar reaction of the Schiff bases[1c] **1** and **2** with ethyl vinyl ether afforded the unexpected aromatized quinoline derivatives **3** and **4**[2] in 11% and 16.5% yields, respectively, though tetrahydroquinolines **5** and **6** were obtained[1c] when 3,4-dihydro-2H-pyran was used as a dienophile. The aromatized compounds were already supplied[1b] in only the case of vinyl acetate as a dienophile. These facts suggested that only acyclic dienophiles brought about aromatization resulting from elimination of the oxygen substituent, followed by dehydrogenation. So we tried to apply this type reaction for the synthesis of natural quinoline alkaloids. The treatment of the Schiff base **7**,[3] easily prepared from aniline and piperonal, with ethyl vinyl ether in the presence of boron trifluoride etherate afforded the desired compound dubamine[4] (**8**) but in very poor yield. Similarly attempt to synthesize **10**, which had already been converted[5a] into cuspareine (**11**), was achieved in moderate yield employing the Schiff base **9**

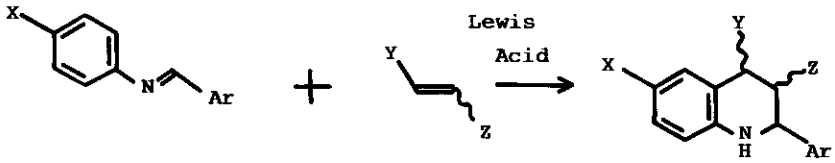
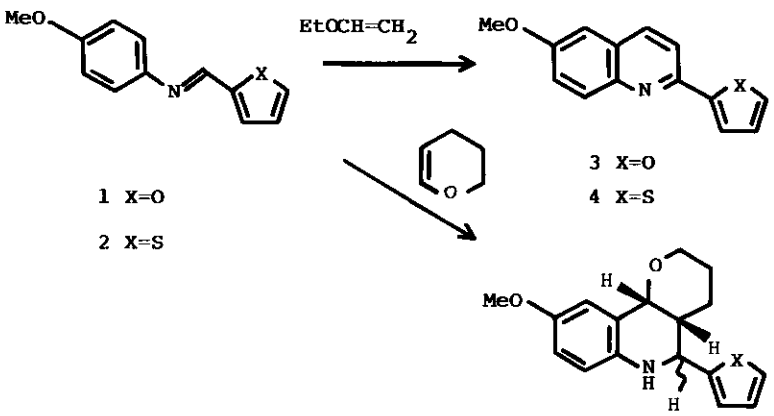


Fig.



1 X=O

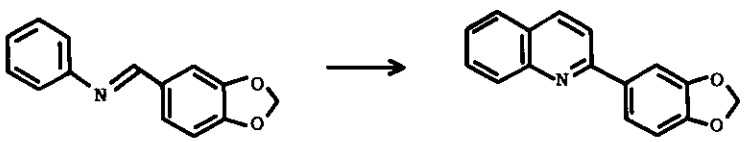
2 X=S

3 X=O

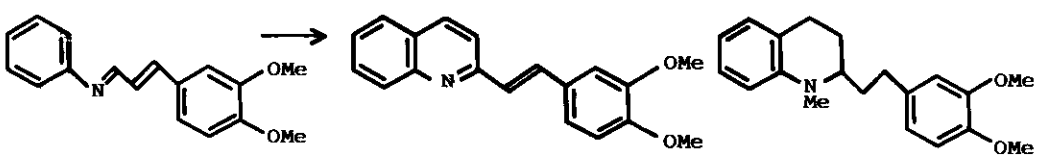
4 X=S

5 X=O

6 X=S



7 8

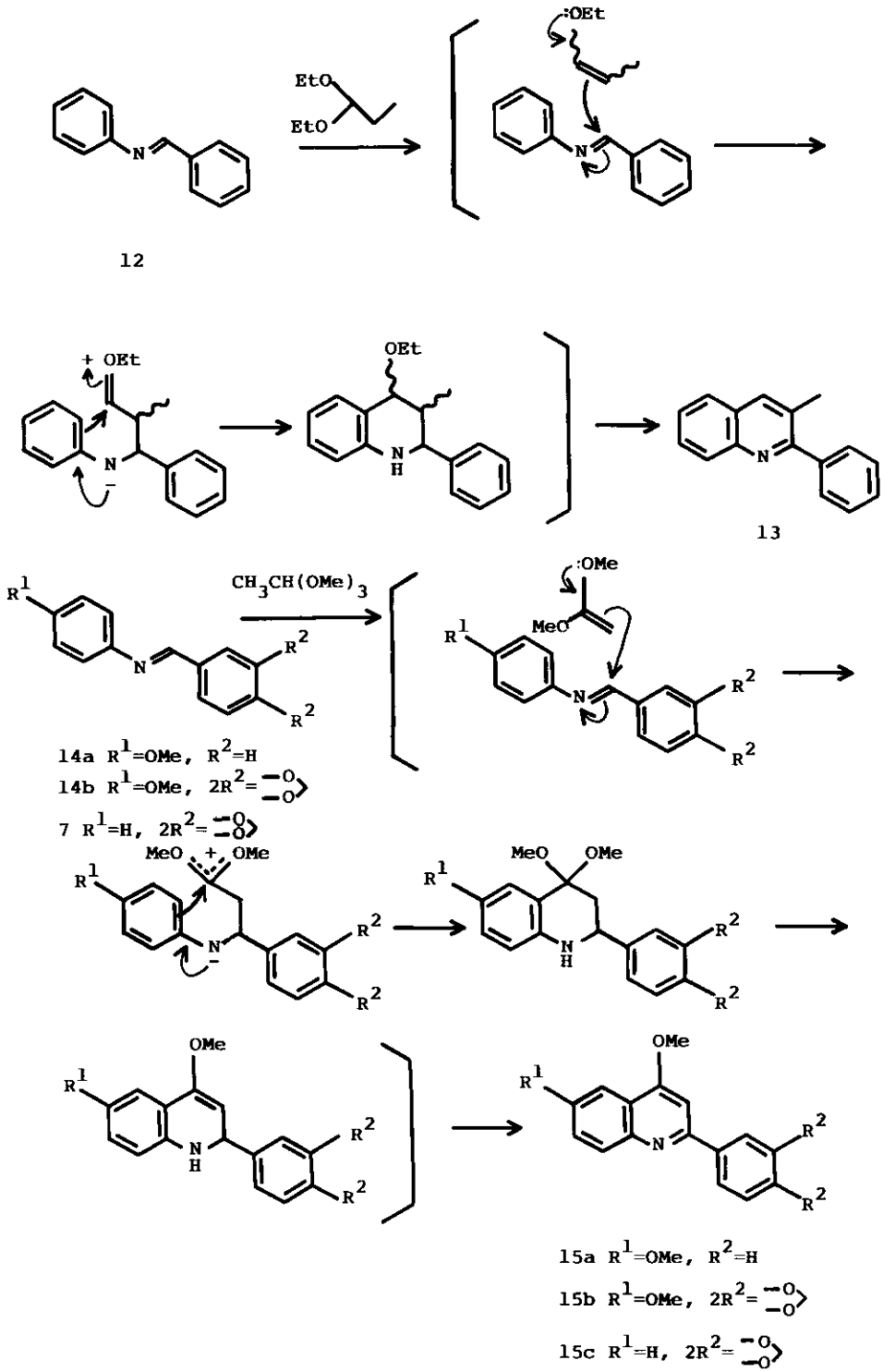


9 10 11

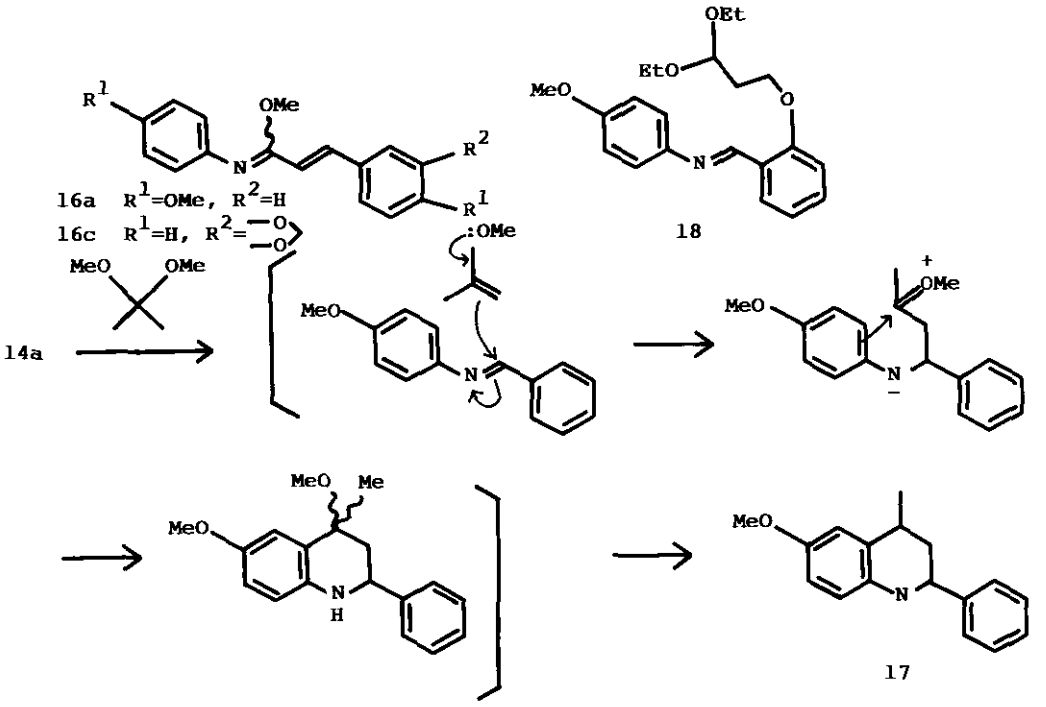
Scheme 1

prepared from aniline and corresponding cinnamaldehyde[6] (Scheme 1). Furthermore, in order to extend the utility of Lewis acid catalyzed [4+2]cycloaddition reaction, we first examined the reaction of the Schiff base and acetal or orthoester which are more stable and available than the corresponding vinyl ether or ketene acetal. The Schiff base **12** was treated with 1,1-diethoxypropane in the presence of stannic chloride to provide quinoline compounds **13**[7] in 11.8% yield. Treatment of **14a** with trimethyl orthoacetate produced a small amount of **15a**[8] with major adduct **16a**. Similar reaction of **14b**[9] and **7** with trimethyl orthoacetate afforded **15b** and graveolinine (**15c**)[10] in low yields. And the reaction of **14a** with 2,2-dimethoxypropane was tried to give the cyclized product **17**[11] (Scheme 2). Some chemists have reported[12] the acid catalyzed [4+2]cycloaddition reaction of the Schiff bases and olefin or acetylene derivatives having electron-donating groups, for example *ethyl vinyl sulfide*, *ethoxyacetylene*, and some enamines. Consideration of olefin substitution effects on the cycloaddition led to the conclusion that one substituent including hetero atom is effective enough to activate the nucleophilicity and the electrophilicity of the dienophile as shown in Scheme 2. Two geminal substituents including hetero atoms enhances the nucleophilicity, but depress the electrophilicity since two hetero atoms stabilize the resulting cationic intermediate. We also examined an intramolecular [4+2]cycloaddition of the iminoacetal **18** in the presence of stannic chloride, but none of the desired cycloadduct was obtained at all.

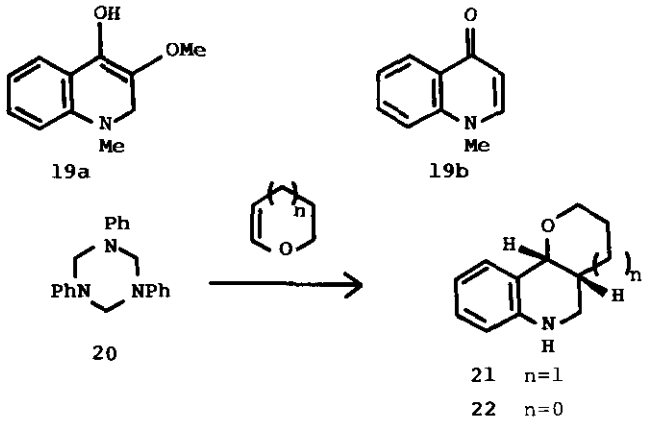
Secondly we planned to synthesize an unsubstituted quinoline compound at C-2 position, since all the compounds which we have synthesized possessed the substituents at C-2 position because of stability and reactivity of the Schiff bases. And in naturally occurring quinoline alkaloids, compounds unsubstituted at C-2 are known such as echinine[13a] (**19a**) and echinopsine[13b] (**19b**). Unsubstituted quinoline compounds at C-2 position have already been synthesized by Shono,[14] via Lewis acid catalized [4+2]cycloaddition reaction using N-methoxymethylaniline derivatives, prepared from N-methylaniline derivatives by anodic oxidation, with enol ethers. We sought for easy method to synthesize the quinoline ring unsubstituted at C-2 position and found that [4+2]cycloaddition using s-triazine derivative, well suited as a diene, with enol ethers provided the desired compounds. s-Triazine derivative **19**,[15] easily prepared from aniline and paraformaldehyde, was treated with 2,3-dihydrofuran and 3,4-dihydro-2H-pyran to give the corresponding fused quinolines **21** and **22** (Scheme 3).


:OEt
EtO
EtO
N
12
+ OEt
OEt
N
H
13
$CH_3CH(OMe)_3$
:OMe
MeO
R^1
R^2
14a R^1=OMe, R^2=H
14b R^1=OMe, $2R^2$=
7 R^1=H, $2R^2$=
MeO + OMe
15a R^1=OMe, R^2=H
15b R^1=OMe, $2R^2$=
15c R^1=H, $2R^2$=

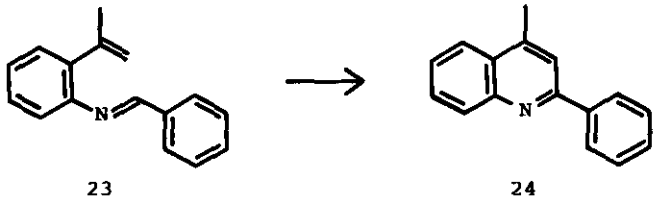
Scheme 2-1



Scheme 2-2



Scheme 3



Scheme 4

Finally we attempted the electrocyclic reaction of the Schiff base **23** in the presence of boron trifluoride etherate or stannic chloride to give the dehydrogenated quinoline **24**[16] in 25.3% or 20.2% yields (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Hitachi 260-10 spectrophotometer, nmr spectra with JEOL-PMX-60 and JEOL JNM-FX-100 spectrometers, and mass spectra with JEOL JMS-OISG-2 and JEOL JMS D-300 mass spectrometers.

2-(2-Furyl)-6-methoxyquinoline (3). —— To a stirred solution of the Schiff base **1** (3.37 g, 16.7 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 (100 ml) was added a solution of ethyl vinyl ether (2.16 g, 31 mmol) in dry CH_2Cl_2 (50 ml). After stirring for 48 h at room temperature, the reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give the residue, which was purified with column chromatography. Elution of benzene afforded a solid, recrystallization of which from Et_2O-hexane gave **3** (413 mg, 11.0%) as yellowish plates, mp 96 ℃; IR ν_{max}^{KBr} cm^{-1}: 1612. NMR (CCl_4) δ 3.80 (3H, s, OMe), 6.50 (1H, dd, J = 3 Hz, 1.5 Hz, ArH), 6.84 (1H, d, J = 3 Hz, ArH), 7.17 - 8.00 (6H, m, 6 x ArH). MS Calcd for $C_{14}H_{11}NO_2$ m/z 225.0790 (M^+). Found m/z 225.0798 (M^+).

6-Methoxy-2-(2-thienyl)quinoline (4). —— The same procedure as above using the Schiff base **2** (5.57 g, 25.6 mmol) and ethyl vinyl ether (3.69 g, 51.3 mmol) afforded **4** (2.33 g, 37.6%) as colorless needles, mp 140 ℃ (Et_2O-hexane) (lit.[2] mp 137.5 - 138 ℃); IR ν_{max}^{KBr} cm^{-1}: 1615. NMR ($DCDl_3$) δ 3.93 (3H, s, OMe), 7.00 - 8.15 (8H, m, 8 x ArH). MS m/z 241 (M^+).

Dubamine (8). —— The same procedure as above using the Schiff base **7** (2.4 g, 10.7 mmol) and ethyl vinyl ether (1.53 g, 21.3 mmol) afforded **8** (27 mg, 1%, as colorless needles, mp 95 ℃ (hexane) (lit.[4] mp 96 - 97 ℃). The spectral data were identical with those reported.[5a]

2-(3,4-Dimethoxyphenylethenyl)quinoline (10). —— A mixture of coniferaldehyde[6]

and aniline in benzene was stirred with Na_2SO_4 for 48 h at room temperature. The reaction mixture was filtered and the filtrate was evaporated to give **9** as a solid. The Schiff base **9** (500 mg, 1.8 mmol) without purification was treated by the same procedure as above to afford **10** (380 mg, 49.9%), mp 114 ℃ (lit.[5b] mp 111 - 113 ℃), the spectral data of which were identical with those reported.[5a]

3-Methyl-2-phenylquinoline (13). —— To a stirred solution of the Schiff base **12** (1.0 g, 5.5 mmol) and 1,1-diethoxypropane (1.33 g, 11 mmol) in CH_2Cl_2 (50 ml) was stirred for 24 h at room temperature in the presence of 3 drops of $BF_3 \cdot Et_2O$. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated. The residue was column chromatographed on silica gel. Elution with benzene gave a solid, which was recrystallized from Et_2O-hexane to afford **13** (142 mg, 11.8%) as colorless needles, mp 48 - 49 ℃ (lit.[7] mp 48 - 49 ℃); NMR (CCl_4) δ 2.45 (3H, s, CH_3), 7.17 - 8.26 (10H, m, 10 x ArH). MS m/z 219 (M^+).

Reaction of the Schiff base (14a) with the orthoester. —— A mixture of **14a** (2.11 g, 10 mmol) and trimethyl orthoacetate (2.4 g, 20 mmol) in CH_2Cl_2 (40 ml) was stirred for 3 h at room temperature in the presence of a catalytic amount of $BF_3 \cdot Et_2O$. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated. The residue was separated by column chromatography on silica gel. Elution with benzene afforded **16a** (1.27 g, 48%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR (CCl_4) δ 3.71 and 3.90 (each 3H, each s, 2 x OMe), 6.43 (1H, d, J=16.5 Hz, C_2-H), 6.80 (4H, s, 4 x ArH), 7.27 (5H, s, 5 x ArH), 7.38 (1H, d, J=16.5 Hz, C_3-H). MS m/z 267 (M^+). Mild hydrolysis of **16** with $KHSO_4$ in aqueous THF gave methyl cinnamate and p-anisidine, both of which were identical with authentic samples. Further elution of benzene-AcOEt (20:1 v/v) afforded a solid, which was recrystallized from Et_2O-hexane to give **15a** (130 mg, 5%) as colorless needles, mp 112 - 113 ℃. IR ν_{max}^{KBr} cm^{-1}: 1620. NMR (CCl_4) δ 3.90 and 4.00 (each 3H, each s, 2 x OMe), 7.10 - 8.30 (9H, m, 9 x ArH). MS Calcd for $C_{17}H_{15}NO_2$ m/z 265.1101 (M^+). Found m/z 265.1099 (M^+).

Reaction of the Schiff base (14b) with the orthoester. —— The same procedure as above using the Schiff base (**14b**) and trimethyl orthoacetate gave **15b** as colorless needles. **15b:** Yield 1%, mp 130 ℃. IR ν_{max}^{KBr} cm^{-1}: 1635. NMR ($CDCl_3$) δ 3.93 and 4.10 (each 3H, each s, 2 x OMe), 6.02 (2H, s, CH_2), 6.76 - 8.07 (7H, m, 7

x ArH). MS Calcd for $C_{18}H_{15}NO_4$ m/z 309.1000 (M^+). Found m/z 309.0990 (M^+).

Reaction of the Schiff base (7) with the orthoester. —— The same procedure as above using the Schiff base (7) and trimethyl orthoacetate gave graveolinine (15c) and **16c**. **15c**: Yield 4%, mp 118 - 119 ℃ (lit.[10] 115 - 116 ℃). NMR (CCl_4) δ 4.10 (3H, s, OMe), 6.05 (2H, s, CH_2), 6.83 - 8.30 (8H, m, 8 x ArH). MS m/z 279 (M^+). **16c**: 20%, yellowish oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. NMR (CCl_4) δ 3.98 (3H, s, OMe), 5.98 (2H, s, CH_2), 6.27 (1H, d, J=17 Hz, C_2-H), 6.80 - 7.60 (9H, m, 8 x ArH and C_3-H). MS m/z 281 (M^+). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.77; H, 5.39; N, 4.84.

6-Methoxy-4-methyl-2-phenylquinoline (17). —— To a stirred solution of **14a** (422 mg, 2 mmol) and 2,2-dimethoxypropane (312 mg, 3 mmol) in CH_2Cl_2 (30 ml) was added a catalytic amount of $BF_3 \cdot Et_2O$ and the resulting solution was stirred for 48 h at room temperature. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated to give the residue, which was purified with column chromatography on silica gel. Elution of benzene afforded a solid, recrystallization of which from Et_2O-hexane gave **17** (125 mg, 25%) as colorless needles, mp 129 - 130 ℃ (lit.[11] 128℃); NMR (CCl_4) δ 2.67 (3H, s, CH_3), 3.93 (3H, s, OMe), 7.10 - 7.73 (6H, m, 6 x ArH), 7.95 - 8.27 (3H, m, 3 x ArH). MS m/z 249 (M^+).

2-(3,3-Diethoxypropyloxy)benzylidene-p-anisidine (18). —— To a stirred solution of salicylaldehyde (2.09 ml, 20 mmol) in dry DMF (50 ml) was added NaH (830 mg, 20 mmol) under ice-cooling. After stirring for 10 min at 0 ℃, 1-chloro-3,3-diethoxypropane (3.35 ml, 20 mmol) in dry DMF (5 ml) was added. The reaction mixture was stirred for 24 h at room temperature followed by reflux for 1 h, which was poured into ice-water and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give the residue, which was purified by column chromatography on silica gel to give 2-(3,3-diethoxypropyloxy)-benzaldehyde (323 mg, 6.4%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1680. NMR ($CDCl_3$) δ 1.20 (6H, t, J = 7 Hz, 2 x CH_3), 2.15 (2H, q, J = 6 Hz, CH_2), 3.24 - 3.90 (4H, m, 2 x CH_2), 4.18 (2H, t, J = 6 Hz, CH_2), 4.78 (1H, t, J = 6 Hz, CH), 6.80 - 7.95 (4H, m, 4 x ArH), 10.58 (1H, s, CHO). MS Calcd for $C_{14}H_{20}O_4$ m/z 252.1362 (M^+). Found m/z 252.1372 (M^+).

A mixture of the above aldehyde (100 mg, 0.40 mmol) and p-anisidine (49 mg, 0.40 mmol) in benzene (5 ml) was warmed to give a suspension. Removal of the solvent and water in vacuo afforded **18** as a yellowish oil (137 mg, 95.8%). IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1610. NMR ($CDCl_3$) δ 1.20 (6H, t, J = 7 Hz, 2 x CH_3), 2.13 (2H, q, J = 6 Hz, CH_2), 3.78 (3H, s, OMe), 4.11 (2H, t, J = 6 Hz, CH_2), 4.73 (1H, t, J = 6 Hz, CH), 6.70 - 7.60 (7H, m, 7 x ArH), 8.20 (1H, dd, J = 7 Hz, 2 Hz, ArH), 9.00 (1H, s, CHN). MS Calcd for $C_{21}H_{27}NO_4$ m/z 257.1940 (M^+). Found m/z 357.1915 (M^+).

3,4,4aβ,5,6,10bβ-Hexahydro-2H-pyrano[3,2-c]quinoline (21). —— To a stirred solution of s-triazine[15] (**19**) (1.575 g, 5.0 mmol) in dry CH_2Cl_2 (50 ml) was added $TiCl_4$ (1.66 ml, 15 mmol) under ice-cooling. After stirring for 10 min at the same temperature, 3,4-dihydro-2H-pyran (2.73 ml, 30 mmol) was added dropwise to the reaction mixture and the resulting mixture was stirred for 4 h at 0 ℃. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with the brine, dried over Na_2SO_4, and evaporated to give the residue, which was purified by column chromatography on silica gel to afford a solid. Recrystallization from Et_2O-hexane gave **21** (656 mg) in 25% yield as colorless needles (mp 82 - 83 ℃). IR ν_{max}^{KBr} cm^{-1}: 3340. NMR ($CDCl_3$) δ 1.20 - 2.25 (5H, m, 2 x CH_2 and CH), 2.73 - 4.00 (5H, m, 2 x CH_2 and NH), 4.40 (1H, d, J = 3 Hz, CH), 6.22 - 7.20 (4H, m, 4 x ArH). MS m/z 189 (M^+). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.28; H, 8.11; N, 7.32.

2,3,3aβ,4,5,9bβ-Hexahydrofuro[3,2-c]quinoline (22). —— Yield 16.8%, mp 103 ℃ (Et_2O-hexane). IR ν_{max}^{KBr} cm^{-1}: 3350. NMR ($CDCl_3$) δ 1.40 - 3.30 (5H, m, 2 x CH_2 and CH), 3.50 - 4.03 (3H, m, CH_2, and NH), 4.53 (1H, d, J = 4 Hz, CH), 6.37 - 7.40 (4H, m, 4 x ArH). MS m/z 175 (M^+). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.57; H, 7.45; N, 7.97.

4-Methyl-2-phenylquinoline (24). —— The Schiff base (**23**), which was prepared by refluxing of o-isopropenylaniline with benzaldehyde in benzene in the presence of Na_2SO_4, was pure enough for using in the next reaction without purification. NMR (CCl_4) δ 2.11 (3H, s, CH_3), 5.00 (2H, d, J = 7 Hz, C=CH_2), 6.71 - 8.00 (9H, m, 9 x ArH), 8.30 (1H, s, N=CH). A solution of the Schiff base (**23**) (2.0 g, 9.0 mmol) in dry benzene (30 ml) was heated under reflux in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ for 48 h. The reaction mixture was washed with saturated $NaHCO_3$

solution, dried over Na_2SO_4, and evaporated to give the residue, which was purified by column chromatography to afford **24** (500 mg, 25.3%) as colorless needles, mp 61 - 62 ℃ (lit.[16] 64 - 64.5 ℃). NMR (CCl_4) δ 2.43 (3H, s, CH_3), 7.12 - 7.77 (7H, m, 7 x ArH), 8.00 - 8.50 (3H, m, 3 x ArH). MS m/z 219 (M^+). The same reaction using $SnCl_4$ in dry CH_2Cl_2 at 0 ℃ gaved **24** in 20.2% yield.

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