STUDIES ON FRIEDEL-CRAFTS ACYLATION OF N-ACETYLHOMOVERATRYLAMINE AND PREPARATION OF 1-SUBSTITUTED 3,4-DIHYDRO-6,7-DIMETHOXYISOQUINOLINES

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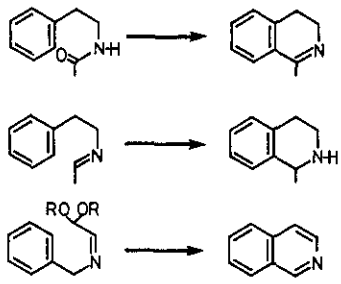
Abstract--- Friedel-Crafts acylation of N-acetylhomoveratrylamine in a molar ratio of 1:2:3 of 1, $AlCl_3$ and the appropriate acid chloride using nitrobenzene as solvent gave the corresponding 2-acyl derivatives 2a-l in good yields. Subsequent treatment of 2 in boiling 1N-hydrochloric acid afforded a variety of 1-substituted 3,4-dihydro-6,7-dimethoxyisoquinolines 3a-j in almost quantitative yields. The dihydroisoquinolines 3h-j having carboxyalkyl groups at C_1-position were further converted to the benzo[a]-quinolizine analogues 6h-j.

Many procedures for the construction of isoquinoline nucleus have been developed due to their pharmacological activities and the basic skeleton of the alkaloids. The well-known and representative reaction sequences leading to the isoquinoline ring system, such as the Bischler-Napieralski,[1] Pictet-Spengler[2] or Pomeranz-Fritsch[3] reaction, consist of the intramolecular reaction between an electron-rich aromatic ring carbon and an electrophilic center on the side-chain attached to N-atom of the phenethylamine or benzylamine unit (Scheme I). On the contrary, the reaction sequence via the intermolecular, electrophilic acylation of the same type of the N-β-phenethylamides as substrates for the Bischler-Napieralski reaction may also provide an alternative route to the isoquinoline ring formation. Thus, we studied the acylation reactions of the acetamide 1 under the Friedel-Crafts conditions, which have not often been employed for the compounds containing alkylamide side chain,[4] compared with those of well known acetanilide.[5]

RESULTS AND DISCUSSION

First, in order to find the suitable solvent system, the amide 1 was treated with AcCl in the presence of $AlCl_3$ in various solvents. The Table 1 shows the results of the acetylations employed



Scheme I

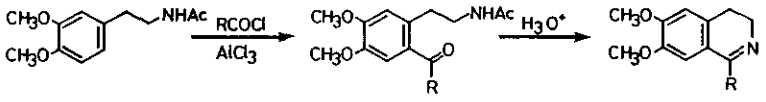
Table 1: Acetylation of 1 with AcCl in the presence of $AlCl_3$.

solvent	yield[a] of 2a
CS_2	9%
CCl_4	11%
$CHCl_3$	58%
CH_2Cl_2	65% (81%)[b]
$ClCH_2CH_2Cl$	68% (83%)[b]
CH_3NO_2	67%
$C_6H_5NO_2$	100%

[a] Averages of three runs of the reaction.
[b] Yield after stirring for 24 h.

in a molar ratio of 1:2:3 of 1, $AlCl_3$ and AcCl in the appropriate solvent (2 ml to 1 mmol of the amide 1) at 30±1°C for 2 h. CCl_4 and CS_2, which are most frequently used solvents in the Friedel-Crafts reaction,[6] were found to be not effective in the present case, probably due to less solubility of the starting amide 1 as well as its complex with $AlCl_3$ separated from the solution by addition of $AlCl_3$. This complex formation was also observed at the beginning of the reaction attempted in $CHCl_3$, CH_2Cl_2 and $ClCH_2CH_2Cl$. The separated oily mass disappeared within 30 min ∿ 1 h. In CH_2Cl_2, 65% of 1 was converted to 2a after 2 h and 68% in $ClCH_2CH_2Cl$. However, the longer reaction time did not much improve the yields of 2a. Even after 24 h, the yield was not more than 81-83%. Next, CH_3NO_2 and $C_6H_5NO_2$[6a] were examined. It is known that CH_3NO_2 or $C_6H_5NO_2$ with $AlCl_3$ forms a 1:1 molar complex which works as an efficient and quite soluble catalyst.[6b] In the present case, both solvents afforded the homogeneous conditions, and the former solvent gave 2a in 67% yield comparable to that on the above CH_2Cl_2 or $ClCH_2CH_2Cl$ system. On the other hand, the acetylation in $C_6H_5NO_2$ solution proceeded smoothly to give 2a almost quantitatively. Nitrobenzene was therefore chosen as solvent. The reaction temperature is another important term in the Friedel-Crafts reaction. Bulky acylating agents may need the drastic conditions more than those for AcCl. The higher tempereture than 40°C, however, caused the lower yield. Thus the acylation of 1 with various acid chlorides was performed at 35±1°C for 3 h in the same ratio 1:2:3[7] of 1, $AlCl_3$ and RCOCl as that of the above acetylation to give each type of the acylation products, acetophenones 2a,f,g, benzophenone 2b, deoxybenzoin 2c,d, chalcone 2e and keto-esters 2h-j. The results are summerized in Table II. The acetophenone 2a has been prepared by three step reaction sequences via the acetylation of 3a, which was obtained by the Bischler-Napieralski reaction of 1, followed by acid treatment of the resultant N-acetyl-1-methylenetetrahydroisoquinoline.[8-10] The chalcone 2e, whose chloro derivatives have been reported as synthetic precursors to pharmacologically active isoquinoline derivatives,[8,9,11] was also obtained quantitatively by base catalyzed condensation of 2a with benzaldehyde. In the acylation of 1 with the acid chlorides of the monomethyl esters of succinic acid, glutamic acid and adipic acid, each reaction mixture was worked up being neutralized prior to steam distillation in order to avoid hydrolysis of the ester groups, and gave the keto-esters 2h-j in good yields (77-82%). Acetic anhydride and succinic anhydride did not

react with 1 under the conditions, but when 1, $AlCl_3$ and Ac_2O were used in a ratio of 1:4:3 moles, 2a was obtained in 51% yield. Treatment of each 2 in boiling diluted hydrochloric acid, on spontaneous ring closure between the carbonyl group and the formed amino group, gave the 1-substituted dihydroisoquinolines 3 in good yields(Scheme II, Table 2). 3a-e have previously been prepared by the Bischler-Napieralski reaction,[8-10,12-15] or its modification.[16]



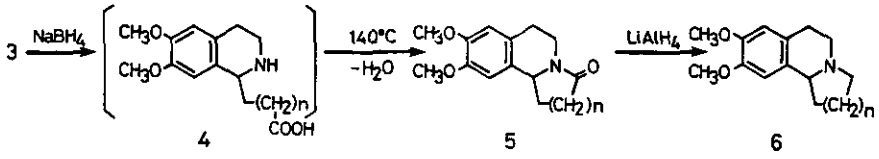
1 2 3

Scheme II

Table 2: Friedel-Crafts Acylation of 1 and Hydrolysis of Products 2 to Dihydroisoquinolines 3.

		Product	
	R	2, yield(%)	3, yield(%)
a:	$-CH_3$	92	96
b:	$-C_6H_5$	86	93
c:	$-CH_2C_6H_5$	86	99
d:	$-CH_2C_6H_2$-2-Br,3,4-$(OCH_3)_2$	88	90
e:	$-CH=CH-C_6H_5$	82	90
f:	$-CH_2CH_2CH_3$	88	92
g:	$-CH_2CH_2C_6H_5$	62	93
h:	$-CH_2CH_2COOCH_3$ for 2	82	
	$-CH_2CH_2COOH$ for 3		93
i:	$-CH_2CH_2CH_2COOCH_3$ for 2	79	
	$-CH_2CH_2CH_2COOH$ for 3		97
j:	$-CH_2CH_2CH_2CH_2COOCH_3$ for 2	77	
	$-CH_2CH_2CH_2CH_2COOH$ for 3		98

Ester groups of 2h-j were also hydrolyzed under the conditions. Products 3h-j with carboxyalkyl groups at C_1-position carbon can further be converted to benzo[a]quinolizine skeleton or its analogues, essentially according to the Pecherer's scheme.[4] $NaBH_4$ reduction of 3h, followed by neutralization and dryness in vacuo, afforded the crude amino acid(4h), which was heated in boiling xylene for 24 h (see Experimental) to give the lactam 5h in 82% yield. Similarly, 3i,j gave the lactams 5i(71%) and 5j(79%), respectively. Successive treatment of 5 with $LiAlH_4$ in boiling dry THF furnished the tricyclic isoquinoline derivatives 6h-j in good yields (Scheme III).



4 5 6

h: n=1
i: n=2
j: n=3

	5	6
h	82%	91%
i	71%	82%
j	79%	92%

Scheme III

EXPERIMENTAL

Melting points were determined on a Laboratory Devices Meltemp, and are uncorrected. Boiling points are uncorrected. Infrared (ir) spectra were recorded on a Hitachi Perkin-Elmer Model 125 spectrophotometer. ^{1}H Nmr spectra were run on $CDCl_3$ solution, unless otherwise noted, with Me_4Si as an internal standard (δ=0 ppm) and resistered on a 90 M Hz Hitachi R-22 spectrometer. Preparative thin layer chromatography (TLC) was run on Merck silica gel PF-254 (No.7749).

Reaction of 1 with AcCl and $AlCl_3$ using verious solvent systems. To a stirred mixture of 1(223 mg, 1 mmol) and AcCl(236 mg, 3 mmol) in the appropriate dry solvent(2 ml) in an ice-water bath was added freshly powdered $AlCl_3$(267 mg, 2 mmol). The mixture was then warmed in an oil bath at 30±1°C for 2 h. Each reaction mixture was poured into ice-water, and extracted with $CHCl_3$. The extracts were washed with diluted NaOH solution and water, and dried over Na_2SO_4. Evaporation of the solvents gave the residue, whose ^{1}H nmr spectra displayed peaks at δ 1.92(s) and 1.90(s) due to N-acetyl protons of 1 and 2a, respectively. Judging from the intensities of both peaks, the ratio of 1 and 2a was determined. The reaction mixture in $C_6H_5NO_2$ was treated with ice-water, and subjected to steam distillation. The residue was extracted with $CHCl_3$ and further worked up as described above.

A method for the preparation of N-(2-acyl-4,5-dimethoxyphenethyl)acetamides 2. To a stirred solution of 1(1.00 g, 4.48 mmol), the appropriate acid chloride(13.44 mmol) and dry $C_6H_5NO_2$(10 ml) in a flask fitted with cotton wool tube in an ice-water bath was added freshly powdered $AlCl_3$(1.20 g, 8.94 mmol). The mixture was warmed in an oil bath at 35±1°C for 2.5 h, and poured into ice-water(100 ml). a) for 2a-g: After removal of $C_6H_5NO_2$ by steam distillation, the residue was cooled and extracted with $CHCl_3$. The extracts were washed with diluted NaOH solution and water, and dried over Na_2SO_4. Evaporation of the solvent and crystallization afforded the crude product as follows. b) for 2h-j: The organic layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were thoroughly washed with water until the washings became neutral to litmus paper. After addition of water(100 ml) the mixture was subjected to steam distillation and then worked up as described above.

N-(2-Acetyl-4,5-dimethoxyphenethyl)acetamide 2a. The crude crystalline product (1.90 g, 92%), mp 120-123°C, was recrystallized from benzene to afford an analytical sample of 2a, mp 124-125°C, (Lit.[8] mp 124°C, Lit.[9] mp 123-125°C, Lit.[10] mp 126-127°C). *Ir(nujol) 3320, 1670, 1630 cm^{-1}; ^{1}H nmr* δ 1.90(3H, s, $NCOCH_3$), 2.59(3H, s, $ArCOCH_3$), 3.02(2H, t J=6Hz, CH_2CH_2N), 3.48, 3.55(each 1H, t J=6 Hz, CH_2N), 3.92 (6H, s, 2×OCH_3), 6.55(1H, br, NH), 6.76, 7.19(each 1H, s, Ar-H). Anal. calc for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.24; H, 7.12; N, 5.18.

N-(2-Benzoyl-4,5-dimethoxyphenethyl)acetamide 2b. The oily residue was treated with benzene-ether to give crystals(1.20 g, 86%), mp 117-119°C, whose recrystallization from benzene gave a pure sample of 2b, mp 119-120°C. Ir(nujol) 3340, 1645, 1640 cm^{-1}; ^{1}H nmr δ 1.93(3H, s, $N-COCH_3$), 2.84

(2H, t J=6Hz, $C\underline{H}_2CH_2N$), 3.49, 3.55(each 1H, t J=6Hz, CH_2N), 3.78, 3.95(each 3H, s, $2\times OCH_3$), 6.82, 6.86(each 1H, s, Ar-H), 6.95(1H, br, NH), 7.3-7.9(5H, m, Ar-H). Anal.calc for $C_{19}H_{21}O_4N$; C, 69.70; H, 6.47; N, 4.28. Found: C, 69.83; H, 6.50; N, 4.42.

N-(4,5-Dimethoxy-2-phenylacetylphenethyl)acetamide 2c. Crystallization of the residue from ether-benzene afforded 2c(1.31 g, 86%), mp 111-115°C, which on recrystallization from benzene gave a pure sample of 2c, mp 120-121°C. Ir(nujol) 3320, 1660, 1640 cm^{-1}; ^1H nmr δ 1.88(3H, s, $N-COCH_3$), 2.89 (2H, t J=6Hz, $C\underline{H}_2CH_2N$), 3.41, 3.48(each 1H, t J=6Hz, CH_2N), 3.87, 3.90(each 3H, s, $2\times OCH_3$), 4.20(2H, s, $ArC\underline{H}_2CO$), 6.46(1H, br, NH), 6.48(1H, s, Ar-H), 7.1-7.5(6H, m, Ar-H). Anal. calc for $C_{20}H_{23}O_4N$; C, 70.36; H, 6.79; N, 4.10. Found: C, 70.62; H, 6.74; N, 3.86.

N-[2-(2-Bromo-4,5-dimethoxyphenylacetyl)-4,5-dimethoxyphenethyl]acetamide 2d. Crystallization of the crude product from benzene-ether gave 2d(1.90 g, 88%), mp 134-142°C. Recrystallization from benzene afforded an analytical sample, mp 143-146°C. Ir(nujol) 3310, 1700, 1680, 1600 cm^{-1}; ^1H nmr δ 1.88(3H, s, $N-COCH_3$), 2.96(2H, t J=6Hz, $C\underline{H}_2CH_2N$), 3.46, 3.53(each 1H, t J=6Hz, CH_2N), 3.85, 3.87(each 3H, s, $2\times OCH_3$), 3.93(6H, s, $2\times OCH_3$), 4.30(2H, s, $ArC\underline{H}_2CO$), 6.49(1H, br, NH), 6.77, 6.78, 7.06, 7.31(4H, each s, Ar-H). Anal.calc for $C_{22}H_{26}O_6NBr$: C, 55.01; H, 5.45; N, 2.91; Br, 16.63. Found: C, 55.29; H, 5.36; N, 2.82; Br, 16.63.

N-[4,5-Dimethoxy-2-(3-phenylpropenoyl)phenethyl]acetamide 2e. Treatment of the crude product with benzene-ether gave yellow crystals 2e(1.30 g, 82%), mp 118-120°C, which on recrystallization from benzene afforded an analytical sample, mp 121-122°C. Ir(nujol) 3320, 1660, 1620 cm^{-1}; ^1H nmr δ 1.93(3H, s, $N-COCH_3$), 2.91(2H, t J=6Hz, $C\underline{H}_2CH_2N$), 3.52, 3.59(each 1H, t J=6Hz, CH_2N), 3.92, 3.96 (each 3H, s, $2\times OCH_3$), 6.87, 7.10(each 1H, s, Ar-H), 7.20(1H, br, NH), 7.1-7.8(7H, m, olefinic and Ar-H). Anal.calc for $C_{21}H_{23}O_4N$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.46; H, 6.57; N, 3.90.

N-(2-n-Butyryl-4,5-dimethoxyphenethyl)acetamide 2f. The residue was crystallized from benzene-ether to give crystals of 2f(1.16 g, 88%), mp 109-110°C. Ir(nujol) 3420, 1680, 1640 cm^{-1}; ^1H nmr δ 1.00(3H, t J=7Hz, CH_3), 1.74(2H, sex J=7Hz, $COCH_2C\underline{H}_2CH_3$), 1.91(3H, s, $N-COCH_3$), 2.88(2H, t J=7Hz, $C\underline{H}_2CH_3$), 2.92(2H, t J=6Hz, $C\underline{H}_2CH_2N$), 3.47, 3.54(each 1H, t J=6Hz, CH_2N), 3.92(6H, s, $2\times OCH_3$), 6.77, 7.13(each 1H, s, Ar-H), 6.79(1H, br, NH). Anal.calc for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.38; H, 7.97; N, 4.64.

1-[2-(2-Acetamidoethyl)-4,5-dimethoxyphenyl]-3-phenyl-1-propanone 2g. Crystallization of the crude product from MeOH afforded 2g(1.29 g, 81%), mp 120-121°C. Recrystallization from the same solvent gave a pure sample, mp 121-122°C. Ir(nujol) 3340, 1680, 1645 cm^{-1}; ^1H nmr δ 1.91(3H, s, $N-COCH_3$), 2.89(2H, t J=6Hz, CH_2CH_2N), 3.11, 3.16, 3.49(each 2H, each t J=6Hz, $COCH_2C\underline{H}_2$, $COC\underline{H}_2CH_2$, CH_2N), 3.84, 3.91(each 3H, s, $2\times OCH_3$), 6.63(1H, br, NH), 6.75, 7.03(each 1H, s, Ar-H), 7.26(5H, br s, Ar-H). Anal.calc for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.07; N, 3.94. Found: C, 70.99; H, 7.06; N, 3.93.

Methyl 4-[2-(2-Acetamidoethyl)-4,5-dimethoxyphenyl]-4-oxobutyrate 2h. Crystallization of the crude product from benzene-ether gave 2h (1.24 g, 82%), mp 125-128°C. Recrystallization from benzene

provided a pure sample, mp 127-128°C. Ir(nujol) 3320, 1720, 1670, 1640 cm^{-1}; ^1H nmr δ 1.87(3H, s, N-$COCH_3$), 2.76, 3.27(each 2H, t J=7Hz, $CH_2CH_2COOCH_3$), 2.97(2H, t J=6Hz, CH_2CH_2N), 3.47, 3.54 (each 1H, t J=6Hz, CH_2N), 3.74(3H, s, $COOCH_3$), 3.98(6H, s, 2×OCH_3), 6.70(1H, br, NH), 6.80, 7.22(each 1H, s, Ar-H). Anal.calc for $C_{17}H_{23}O_6N$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.61; H, 6.81; N, 4.34.

Methyl 5-[2-(2-Acetamidoethyl)-4,5-dimethoxyphenyl]-5-oxovalerate 2i. Crystallization of the crude product from benzene-ether gave crystals of 2i (1.24 g, 79%), mp 92-97°C. Recryctallization from benzene afforded an analytical sample, mp 108-109°C(Lit.[4] mp 104-105°C). Ir(nujol) 3320, 1720, 1670, 1640 cm^{-1}; ^1H nmr δ 1.93(3H, s, N-$COCH_3$), 2.06(2H, quint J=7Hz, $CH_2CH_2CH_2$), 2.46(2H, t J=7Hz, CH_2COOCH_3), 2.98(2H, t J=6Hz, CH_2CH_2N), 3.02(2H, t J=7Hz, Ar$COCH_2$), 3.48, 3.55(each 1H, t J=6Hz, CH_2N), 3.71(3H, s, $COOCH_3$), 3.93(6H, s, 2×OCH_3), 6.82(1H, br, NH), 6.84, 7.24(each 1H, s, Ar-H). The ^1H nmr spectral data were essentially identical with those reported by Pecherer.[4] Anal.calc for $C_{18}H_{25}O_6N$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.38; H, 7.08; N, 4.00.

Methyl 6-[2-(2-Acetamidoethyl)-4,5-dimethoxyphenyl]-6-oxohexanoate 2j. Crystallization of the crude product from benzene-ether gave 2j(1.26 g, 77%), mp 100-103°C. Recryatallization from benzene afforded a pure sample, mp 105-106°C. Ir(nujol) 3320, 1720, 1670, 1640 cm^{-1}; ^1H nmr δ 1.86(4H, m, $CH_2CH_2CH_2CH_2$), 1.91(3H, s, N-$COCH_3$), 2.38(2H, t J=7Hz, CH_2COOCH_3), 2.94(2H, t J=6Hz, CH_2CH_2N), 2.94(2H, t J=7Hz, Ar$COCH_2$), 3.52(each 1H, t J=6Hz, CH_2N), 3.70(3H, s, $COOCH_3$), 3.94(6H, s, 2×OCH_3), 6.78 (1H, br, NH), 6.82, 7.17(each 1H, s, Ar-H). Anal.calc for $C_{19}H_{27}O_6N$: C, 62.25; H, 7.45; N, 3.83. Found: C, 62.28; H, 7.31; N, 3.74.

Acetylation of 1 with acetic anhydride under Friedel-Crafts conditions. To a stirred mixture of the amide 1(500 mg, 2.24 mmol), Ac_2O(682 mg, 6.72 mmol) and $C_6H_5NO_2$(2 ml) was added $AlCl_3$(1.20 g, 8.94 mmol). The mixture was stirred at 35±1°C for 2.5 h, and then worked up as described above. Crystallization of the crude product from benzene-ether afforded 2a(300 mg, 51%), mp 124-125°C.

Reaction of 2a with benzaldehyde in the presence of NaOH. A mixture of 2a(133 mg, 0.5 mmol), benzaldehyde(60 mg, 0.57 mmol) and NaOH(30 mg) in 95% EtOH(1 ml) was stirred at room temperature. After 1 h, water(10 ml) was added. Yellow crystals separated were collected by suction filtration, dried and amounted to 170 mg, mp 121-122°C, which was identical in all respects with the chalcone 2e.

Preparation of 3 from 2.

Method a): 3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline 3a. A mixture of 1N-HCl(5 ml) and 2a (150 mg) was heated to reflux with stirring for 18 h. The mixture was basified with 2N-NaOH and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline solid(112 mg, 96%), mp 101-102°C. Recrystallization from ether-petroleum ether afforded an analytical sample, mp 104-105°C(Lit.[8,12] mp 108°C, Lit.[15] mp 104-105°C). Ir(nujol) 1620, 1600, 1570, 1510 cm^{-1}; ^1H nmr δ 2.39(3H, s, CH_3), 2.64(2H, t, J=7Hz, C_4-H), 3.71(2H, t, J=7 Hz, C_3-H), 3.96(6H, s, 2×OCH_3), 6.80, 7.11(each 1H, s, Ar-H). These spectral data were identical

with those of an authentic sample prepared by reaction of 1 with $POCl_3$.[10] Anal.calc for $C_{12}H_{13}O_2N$; C, 70.91; H, 6.45; N, 6.89. Found: C, 71.13; H, 6.22; N, 6.91.

3,4-Dihydro-6,7-dimethoxy-1-phenylisoquinoline 3b. 2b(500 mg) in 1N-HCl(12 ml) was heated for 18 h, and worked up by the method a) to give 3b(380 mg, 93%), mp 110-118°C. An analytical sample was prepared by recrystallization from EtOH and melted at 120-122°C(Lit.[13] mp 120.5-121.5° C, Lit.[15] mp 120-122°C). Ir(nujol) 1641, 1600, 1540, 1510 cm^{-1}; ^1H nmr δ 2.74(2H, dd J=9, 7Hz, C_4-H), 3.76, 3.97(each 3H, s, 2×OCH_3), 3.85(2H, dd J=9, 7Hz, C_3-H), 6.82, 6.83(each 1H, s, Ar-H), 7.3-7.7(5H, m, Ar-H). Anal.calc for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.28. Found: C, 76.30; H, 6.45; N, 5.20.

Method b): 1-Benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline 3c. 2c(319 mg) in 1N-HCl(8 ml) was heated for 18 h in the same manner as described for a). The solvent was evaporated without basifying and the residue was crystallized from water to give HCl salt of 3c(341 mg, 99%), mp 160-175°C. Recrystallization from EtOH gave the pure hydrochloride, mp 173-178°C(Lit.[15] mp 176-176°C). Ir(nujol) 1650, 1605, 1573, 1511 cm^{-1}; ^1H nmr ($DMSOD_6$-D_2O) δ 3.18(2H, t, J=8Hz, C_4-H), 3.89, 3.99 (each 3H, s, 2×OCH_3), 4.00(2H, t J=8Hz, C_3-H), 7.18, 7.58(each 1H, s, Ar-H), 7.3-7.7(6H, m, Ar-H). Anal.calc for $C_{18}H_{20}O_2NCl$: C, 68.03; H, 6.34; N, 4.41; Cl, 11.16. Found: C, 68.01; H,6.31; N, 4.32; Cl, 11.07.

1-(2-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline 3d. 2d (480 mg) in 1N-HCl(8 ml) and EtOH(10 ml) was heated for 18 h, and HCl salt 3d (410 mg, 90%), mp 171-180°C, was obtained by the method b). Recrystallization from $CHCl_3$-ether afforded a sample, mp 224-225°C (Lit.[14] oxalate mp 192-193°C). Ir(nujol)(HCl salt) 1673, 1642, 1600, 1565, 1512 cm^{-1}; ^1H nmr (free base) δ 2.70(2H, dd J=8, 7Hz, C_4-H), 3.78, 3.85, 3.89(3H, 6H, 3H, each s, 4×OCH_3), 3.81(2H, dd J=8, 7Hz, C_3-H), 4.15 (2H, s, benzylic H), 6.70, 6.88, 7.02, 7.04(each 1H, s, Ar-H). Anal. calc for $C_{20}H_{23}O_4NBrCl$: C, 52.59; H, 5.08; N, 3.07. Found: C, 52.43; H, 5.13; N, 2.93.

3,4-Dihydro-4,5-dimethoxy-1-(2-stylyl)isoquinoline 3e. 2e(240 mg) in 1N-HCl(6 ml) and EtOH(5 ml) was heated for 18 h. A crystalline solid(201 mg, 90%), mp 170-176°C, of HCl salt of 3e was obtained by the method b). Recrystallization from EtOH-petroleum ether gave an analytical sample, mp 175- 176°C(Lit.[16] mp 176-177.5°C). Ir(nujol) 1638, 1602, 1552 cm^{-1}; ^1H nmr ($CDCl_3$-$DMSOD_6$-D_2O) δ 3.04(2H, t J=8Hz, C_4-H), 3.90(2H, t J=8Hz, C_3-H), 4.02, 4.06(each 6H, s, 2×OCH_3), 6.99(1H, s, Ar-H), 7.2-8.0(6H, m, Ar-H), 7.58, 8.41(each 1H, d J=16Hz, olefinic H). Anal. calc for $C_{19}H_{20}O_2NCl$: C, 69.19; H, 6.11; N, 4.25; Cl, 10.75. Found: C; 69.45; H, 6.21; N, 4.23; Cl, 10.84.

3,4-Dihydro-6,7-dimethoxy-1-n-propylisoquinoline 3f. 2f(400 mg) was treated in boiling 1N-HCl (10 ml) for 18 h, and work-up by the method a) gave an oily product, which was distilled to afford a pure sample of 3f(294 mg, 93%), bp 122-124°C/0.1 mmHg. Ir(neat) 1625, 1605, 1573, 1512 cm^{-1}; ^1H nmr δ 0.95(3H, t J=7Hz, CH_3), 1.65(2H, sex J=7Hz, CH_2CH3), 2.53(2H, dd J=8, 7Hz, C_4-H), 2.64(2H, t J=7Hz, $CH_2CH_2CH_3$), 3.58(2H, dd J=8, 7Hz, C_3-H), 3.87(6H, s, 2×OCH_3), 6.66, 6.99(each 1H, s, Ar-H). Anal.calc for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.08; N, 6.01.

3,4-Dihydro-6,7-dimethoxy-1-(2-phenylethyl)isoquinoline 3g. 2g (200 mg) was heated in 1N-HCl(5 ml) and EtOH(1 ml) for 18 h. Work-up by the method a) gave a crystalline solid(155 mg, 93%), mp 91-92 °C, of 3g. Recrystallization from ether afforded a pure sample, mp 94~95°C. Ir(nujol) 1630, 1602, 1578, 1513 cm^{-1}; ^1H nmr δ 2.60(2H, dd J=7, 8Hz, C_4-H), 3.02(4H, s, $C_6H_5\underline{CH_2}\underline{CH_2}$), 3.67(2H, dd J=8, 7Hz, C_3-H), 3.76 3.92(each 3H, s, 2×OCH_3), 6.72, 7.00(each 1H, s, Ar-H), 7.1-7.4(5H, br s, Ar-H). Anal.calc for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.31; H, 7.17; N, 4.72.

3,4-Dihydro-6,7-dimethoxyisoquinoline-1-propionic acid 3h. 2h(2.00 g) was heated in 1N-HCl(24 ml) for 18 h. Evaporation of water left the crude HCl salt of 3h(1.70 g, 93%), mp 170~180°C. Recrystallization from EtOH-ether gave an analytical sample, mp 185-186°C. Ir(nujol) 3430, 3250~2000, 1720 cm^{-1}; ^1H nmr ($CDCl_3$-$DMSOD_6$) δ 2.85(2H, t J=7Hz, $\underline{CH_2}COOH$), 3.06(2H, t J=8Hz, C_4-H), 3.29 (2H, t J=7Hz, $\underline{CH_2}CH_2COOH$), 3.82(2H, t J=8Hz, C_3-H), 3.97, 4.00(each 3H, s, 2×OCH_3), 7.12, 7.53 (each 1H, s, Ar-H). Anal.calc for $C_{14}H_{18}O_4NCl$: C, 56.11; H, 6.05; N, 4.67; Cl, 11.86. Found: C, 56.00; H, 6.14; N, 4.42; Cl, 11.58.

3,4-Dihydro-6,7-dimethoxyisoquinoline-1-butyric acid 3i. 2i(2.00 g) was heated in 1N-HCl(25 ml) for 18 h. Concentration of water gave a crystalline solid of 3i(1.79 g, 97 %), mp 195-200°C. Recrystallization from EtOH gave an analytical sample, mp 202~204°C(Lit.[4] mp 258-261°C). Ir(nujol) 3430, 3200~1800, 1750 cm^{-1}; ^1H nmr($CDCl_3$-$DMSOD_6$) δ 2.00(2H, quint J=7Hz, $C_{3'}$-H), 2.50(2H, t J=7Hz, $C_{2'}$-H), 3.18(2H, t J=8Hz, C_4-H), 3.27(2H, t J=7 Hz, $C_{4'}$-H), 3.83(2H, t J=7Hz, C_3-H), 3.94, 3.99(each 3H, s, 2×OCH_3), 7.14, 7.62(each 1H, s, Ar-H). Anal.calc for $C_{15}H_{20}O_4NCl$: C, 57.43; H, 6.25; N, 4.46; Cl, 11.30. Found: C, 57.24; H, 6.31; N, 4.47; Cl, 11.08.

3,4-Dihydro-6,7-dimethoxyisoquinoline-1-valeric acid 3j. 2j(1.80 g) was heated in 1N-HCl(24 ml) for 18 h, and concentration of the reaction mixture afforded crystals(1.69 g, 98%), mp 168-172°C. Recrystallization from EtOH furnished an analytical sample for 3j, mp 179-180°C. Ir (nujol) 3460, 3350~1800, 1730 cm^{-1}; ^1H nmr ($CDCl_3$-$DMSOD_6$) δ 1.5-2.1(4H, m, $C_{3',4'}$-H), 2.35(2H, t J=7Hz, $C_{2'}$-H), 3.08(2H, t J=8Hz, C_4-H), 3.27(2H, t J=7Hz, $C_{5'}$-H), 3.85(2H, t J=8Hz, C_3-H), 3.98, 4.03(6H, each s, 2×OCH_3), 7.07, 7.42(each 1H, s, Ar-H). Anal.calc for $C_{16}H_{22}O_4NCl$: C, 58.64; H, 6.77; N, 4.23; Cl, 10.82. Found: C, 58.64; H, 6.61; N, 4.16; Cl, 10.76.

Preparation of 5 from 3h-j:.

1,2,3,5,6,10b-Hexahydro-8,9-dimethoxypyrrolo[2,1-a]isoquinolin-3-one 5h. To a stirred solution of the hydrochloride 3h(1.1 g, 3.5 mmol)in MeOH (25 ml)was added $NaBH_4$(0.34 g, 9.0 mmol), and the mixture was allowed to stir at room temperature over night. After addition of water(40 ml), the solution was neutralized with diluted HCl solution to pH 6.8-7.0. Water was then evaporated, and the residue was dried on P_2O_5 in a vacuum desiccator. This dry mixture was powdered and heated in boiling xylene(50 ml) using a Dean-Stark water separator for 24 h. Precipitates and the solvent were removed to give an oily residue, which on crystallization from ether afforded 5h(750 mg, 82%),

mp 98-99°C. Ir(nujol) 1670 cm^{-1}; ^1H nmr δ 1.6-2.0(2H, m, C_1-H), 2.4-3.2(5H, m, $C_{2,5^{\beta},6}$-H), 3.87(6H, s, 2×OCH_3), 4.31(1H, m, $C_5\alpha$-H), 4.73(1H, br t J=8Hz, C_{10b}-H), 6.57, 6.65(each 1H, s, Ar-H). Anal.calc for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.14; H, 6.90; N, 5.74.

1,2,3,6,7,11b-Hexahydro-9,10-dimethoxy-4H-benzo[a]quinolizin-4-one 5i. In the same manner as noted for 5h, the reaction of the hydrochloride 3i(1.5 g, 4.67 mmol) with $NaBH_4$ (0.45 g, 11.9 mmol), followed by neutralization and treatment with boiling xylene(50 ml) for 24 h gave an oil. Crystallization from ether gave 5i(880 mg, 71%), mp 84-90°C (heating[4] for 5 h resulted in the 49% yield of 5i). Recrystallization from ether afforded an analytical sample, mp 88-90°C (Lit.[4] mp 89-90°C), of 5i. Ir(nujol) 1650 cm^{-1}; ^1H nmr δ 1.5-2.1(4H, m, $C_{1,2}$-H), 2.2-3.1(5H, m, $C_{3,6^{\beta},7}$-H), 3.86(6H, s, 2×OCH_3), 4.60(1H, dd J=10, 4Hz, C_{11b}-H), 4.88(1H, m, $C_6\beta$-H), 6.62, 6.68(each 1H, s, Ar-H). Anal calc for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.21; H, 7.30; N, 5.22.

1,2,3,4,5,7,8,12b-Octahydro-10,11-dimethoxyazepino[2,1-a]isoquinolin-5-one 5j. Reaction of 3j (1.6 g, 4.8 mmol) and $NaBH_4$(0.4 g, 1.1 mmol) in MeOH(30 ml), followed by treatment of the resultant amino acid with boiling xylene(50 ml) for 24 h provided crystals(1.04 g, 79%), mp 120-123°C. Recrystallization from ether gave a pure sample of 5j, mp 123-124°C. Ir(nujol) 1653 cm^{-1}; ^1H nmr δ 1.4- 2.2(6H, m, $C_{1,2,3}$-H), 2.5-2.9(4H, m, $C_{4,8}$-H), 3.87(6H, s, 2×OCH_3), 3.51(1H, dt J=13, 6, 6Hz, $C_7\beta$-H), 4.02(1H, dt J=13, 6, 6Hz, $C_7\alpha$-H), 4.78(1H, d J=9Hz, C_{12b}-H), 6.61, 6.63 (each 1H, s, Ar-H). Anal calc for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.61; H, 7.76; N, 4.92.

Preparation of 6 from 5:

1,2,3,5,6,10b-Hexahydro-8,9-dimethoxypyrrolo[2,1-a]isoquinoline 6h. To a stirred suspension of $LiAlH_4$(120 mg) in boiling dry THF(10 ml), a solution of 5h (250 mg) in dry THF(5 ml) was added dropwise. After heating for 3 h, the cooling mixture was treated with water(0.5 ml) and one drop of 2N-NaOH. The resultant precipitates were filtered off. The solvent was evaporated to leave an oil, whose crystallization from ether gave 6h(212 mg, 91%), mp 86-88°C. Recrystallization from ether-petroleum ether gave an analytical sample, mp 89°C. ^1H nmr δ 1.5-2.1(4H, m, $C_{1,2}$-H), 2.1-3.2 (7H, m, $C_{3,5,6,10b}$-H), 3.91(6H, s, 2×OCH_3), 6.57, 6.65(each 1H, s, Ar-H). Anal.calc for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.15; H, 8.24; N, 5.98.

1,2,3,6,7,11b-Hexahydro-9,10-dimethoxy-4H-benzo[a]quinolizine 6i. In the same manner as noted for 6h, 5i(140 mg) in THF(10 ml) was treated with $LiAlH_4$(100 mg). A crude oily product was purified by silica gel TLC developed with 10% MeOH-CH_2Cl_2 to give 6i(108 mg, 82%). ^1H Nmr δ 1.1-2.1(6H, m, $C_{1,2,3}$-H), 2.1-3.4(7H, m, $C_{4,6,7,11b}$-H), 3.86(6H, s, 2×OCH_3), 6.62, 6.74(each 1H, s, Ar-H). The methiodide was crystallized from MeOH and melted at 238-240°C. Anal.calc for $C_{16}H_{24}O_2NI$: C, 49.37; H, 6.21; N, 3.60; I, 33.00. Found: C, 49.53; H, 6.22; N, 3.37; I, 32.87. The hydrochloride melted at 220-224°C(Lit.[4] mp 222-225°C).

1,2,3,4,5,7,8,12b-Octahydro-10,11-dimethoxyazepino[2,1-a]isoquinoline 6j. Reduction of 5j(300 mg)

with $LiAlH_4$(130 mg) in dry THF(10 ml) gave the crude product, which was purified by preparative TLC on silica gel in the manner described for 6i to give an oil, 6j(262 mg, 92%). ^1H nmr δ 1.4-2.2(6H, m, $C_{1,2,3,4}$-H), 2.5-3.2(7H, m, $C_{5,7,8,12b}$-H), 3.89(6H, s, 2×OCH_3), 6.58, 6.65(each 1H, s, Ar-H). The methiodide melted at 208-209°C. Anal calc for $C_{17}H_{26}O_2NI$: C, 50.63; H, 6.25; N, 3.47; I, 31.47. Found; C, 50.67; H, 6.38; N, 3.18; I, 31.46.

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