

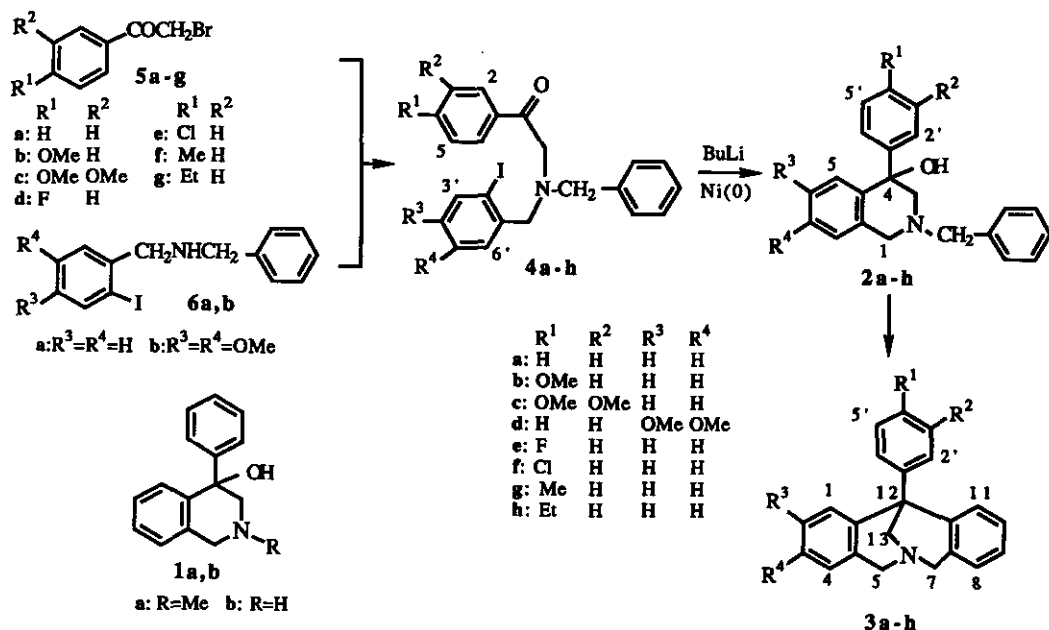
A NEW SYNTHESIS OF 7,12-DIHYDRO-12-PHENYL-5H-6,12-METHANODIBENZ[C,F]-AZOCINES VIA N-BENZYL-1,2,3,4-TETRAHYDRO-4-PHENYLISOQUINOLIN-4-OLS

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Abstracts- 7,12-Dihydro-12-phenyl-5H-6,12-methanodibenz[C,F]azocine derivatives were prepared from N-benzyl-1,2,3,4-tetrahydro-4-phenylisoquinolin-4-ols by an intramolecular Friedel-Crafts reaction.

We have recently reported the convenient synthesis of 1,2,3,4-tetrahydro-N-methyl-4-phenylisoquinolin-4-ol(PI-OH)(1a) and its derivatives by an intramolecular Barbier reaction with BuLi^{1,2} and by an insertion reaction with zerovalent nickel^{1,3} of phenacylamine derivatives. The isoquinolin-4-ol(1a) was also found to have a strong and selective noradrenaline potentiating activity.^{4,5} In order to study the structure-activity relationships of PI-OH analogues, the synthesis of a secondary amine(1b) was attempted by debenylation of an N-benzylisoquinolin-4-ol(2a) with AlCl₃ according to the method reported by Murakami.⁶ The structure of the product was found to be not 1b but 7,12-dihydro-12-phenyl-5H-6,12-methanodibenz[C,F]azocine(3a). This result indicates that the intramolecular Friedel-Crafts reaction in the treatment of 2a with AlCl₃ predominates over the N-debenzylation reaction because of the reactive hydroxy group at a double benzylic position. Although the preparation of dibenz[C,F]azocines(3) via N,N-dibenzylaminoacetaldehyde dialkyl acetals was reported by Takayama,⁷ the reaction of isoquinolin-4-ols(2) with acids should offer a new method for the preparation of 3.



Scheme 1

This paper describes a new synthesis of dibenz[c,f]azocine derivatives(3) via N-benzyltetrahydroisoquinolin-4-ols(2) by an intramolecular Friedel-Crafts reaction.

The key intermediates(2a-h) were prepared by both methods using an intramolecular Barbier reaction with BuLi^{1,2} and using an insertion reaction with zerovalent nickel^{1,3} from N-benzyl-N-(2-iodobenzyl)phenacylamines(4a-h), which were obtained from the corresponding phenacyl bromides(5a-g) and N-benzyl-2-iodobenzylamines(6a,b) in good yields(Scheme 1 and Table III). The reaction of phenacylamines(4a-h) with BuLi gave higher yields of isoquinolin-4-ols(2a-h) than those with zerovalent nickel(Table I). These results are consistent with those of the reaction of N-methylphenacylamine derivatives with BuLi and zerovalent nickel reported in the previous papers.^{1,3}

Isoquinolin-4-ol(2a) was treated with AlCl₃ in benzene at room temperature to give a cyclization product(3a) in 83% yield. Reaction of other isoquinolin-4-ols(2e-h) with AlCl₃ also gave good yields of the dibenz[c,f]azocines(3e-h)(Table II). The debenzylolation products of 2a and 2e-h were not isolated in these reactions. The reaction of a methoxy derivative of isoquinolin-4-ol(2a) with AlCl₃ was predicted to give a cleaved product of the methyl ether. In fact, the reaction of 2d with AlCl₃ gave only a poor yield of 3d

Table I. Yields and Physical Data for Isoquinolin-4-ols(2c-h)^a

No	Yield(%)		mp(°C)	Formula	Elemental Analysis		
	Calcd (Found)				C	H	N
	BuLi	Ni(O)					
2c	74	37	181-182	C ₂₄ H ₂₅ NO ₃ ·HCl	69.98 (69.74)	6.36 (6.56)	3.40 (3.36)
2d	71	51	182-184	C ₂₄ H ₂₅ NO ₃ ·HCl	69.98 (70.14)	6.36 (6.39)	3.40 (3.39)
2e	80	31	205-209	C ₂₂ H ₂₀ NOF·HCl	71.44 (71.20)	5.72 (5.39)	3.89 (3.97)
2f	73	15	215-219	C ₂₂ H ₂₀ NOCl·HCl	68.40 (68.36)	5.48 (5.42)	3.63 (3.58)
2g	77	32	201-203	C ₂₃ H ₂₃ NO·HCl	75.50 (75.14)	6.61 (6.67)	3.83 (3.72)
2h	86	33	195-198	C ₂₄ H ₂₅ NO·HCl·1/4H ₂ O	74.98 (75.20)	6.95 (6.84)	3.64 (3.53)

a. Ref. 1 for 2a,b.

Table II. Yields and Physical Data for Dibenz[c,f]azocines(3a-h)

No	Yield (%)			mp(°C)	Formula	Elemental Analysis		
	Calcd (Found)					C	H	N
	AlCl ₃	85%H ₂ SO ₄	CF ₃ SO ₃ H					
3a	83	78	----	140-145	C ₂₂ H ₁₉ N	88.85 (89.06)	6.44 (6.45)	4.71 (4.63)
3b	----	21	57	165-166.5	C ₂₃ H ₂₁ NO·HCl ·3/2H ₂ O	70.67 (70.84)	6.45 (6.32)	3.58 (3.31)
3c	----	96	----	170-175	C ₂₄ H ₂₃ NO ₂ ·HCl ·1/3H ₂ O	72.08 (71.98)	6.22 (6.10)	3.50 (3.46)
3d	4	43	----	212-214	C ₂₄ H ₂₃ NO ₂ ·HCl ·1/3H ₂ O	72.08 (71.96)	6.22 (5.83)	3.50 (3.60)
3e	80	----	----	199-205	C ₂₂ H ₁₈ NF·HCl	75.10 (74.86)	5.44 (5.16)	3.98 (3.97)
3f	82	----	----	131-132	C ₂₂ H ₁₈ NCl	79.63 (79.71)	5.47 (5.46)	4.22 (4.16)
3g	47	----	----	190-191.5	C ₂₃ H ₂₁ N·HCl	79.41 (79.08)	6.37 (6.38)	4.03 (4.05)
3h	57	----	----	167-169	C ₂₄ H ₂₃ N·HCl ·1/3H ₂ O	77.71 (77.87)	6.79 (6.70)	3.78 (3.60)

with ambiguous products. Thus, the isoquinolin-4-ol(2a) was tried to treat with 85% H_2SO_4 ⁸ to give a desired product(3a) in 78% yield. The treatment of the methoxy compounds (2b-d) in the same way as 2a afforded methoxyazocines(3b-c). As the yield of 3b from 2b was low, 2b was cyclized with CF_3SO_3H and the azocine(3b) was obtained in 57% yield. The structures of the dibenz[c,f]azocines(3a-h) were confirmed by their physical properties (Table II) and ¹H-nmr spectra(Table IV). In the ¹H-nmr spectra of 3a-c and 3e-h, the methylene protons at C-5 and C-7 showed same chemical shifts but the protons of C-5 in 3d were in higher field than those of C-7, which were assigned by determination of its 2D-NOESY spectrum.

EXPERIMENTAL

All melting points are given as uncorrected values. Ir spectra were taken with a Perkin-Elmer 1720 infrared fourier transform spectrophotometer and are given in cm^{-1} . High-resolution mass spectra were recorded on a JEOL JMS-D 300 spectrometer. ¹H- And ¹³C-nmr spectra were recorded on a JEOL JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as a standard and are given in δ values.

4-Methylphenacyl Bromide(5f) A solution of benzyltrimethylammonium tribromide⁹(5.13 g, 13.2 mmol) in CH_2Cl_2 -MeOH(5:2) (50 ml) was added to a solution of 4'-methylacetophenone (1.60 g, 11.94 mmol) in CH_2Cl_2 -MeOH(5:2) (20 ml) and was stirred for 2 h at room temperature. The mixture was evaporated in vacuo and H_2O (50 ml) was added to the residue. The mixture was extracted with ether(50 ml x 3). The extract was washed with H_2O , dried over $MgSO_4$ and evaporated to give 5f as colorless crystals(2.49 g, 98%), mp 41-44°C. ¹H-Nmr:7.86 (2H,d,J=8 Hz, H-2 and H-6), 7.26(2H,d,J=8 Hz,H-3 and H-5), 4.42(2H,s, CH_2) 2.40 (3H,s, CH_3). Ir(KBr):1694 (C=O). Ms(m/z)(M⁺):Calcd for C_9H_9OBr :211.9838. Found:211.9861. Phenacyl bromide(5g) was prepared in the same way as 5f. Phenacyl bromides(5a,b and 5e) were commercially available, and 5c³ and 5d¹ have been reported by us.

4-Ethylphenacyl Bromide(5g) A colorless oil(99%). ¹H-Nmr: 7.90(2H,d,J=8.5 Hz,H-2 and H-6), 7.30(2H,d,J=8.5 Hz,H-3 and H-5), 4.43(2H,s, CH_2Br), 2.71(2H,q,J=7.5 Hz, CH_2CH_3), 1.26 (3H,t,J=7.5 Hz, CH_2CH_3). Ir(KBr): 1678(C=O). Ms(m/z)(M⁺): Calcd for $C_{10}H_{11}OBr$: 225.9992.

Found: 225.9982.

N-Benzyl-2-iodo-4,5-dimethoxybenzylamine(6b) 2-Iodo-4,5-dimethoxybenzaldehyde(5.85 g, 20.0 mmol) and 6.5N HCl-MeOH(6 ml, 39 mmol) were added to a solution of benzylamine(12.9 g, 120 mmol) in absolute MeOH(25 ml) and NaBH₃CN(0.88 g, 13.5 mmol) was added. The mixture was stirred for 48 h at room temperature. The precipitates formed were filtered and the filtrate was acidified with conc. HCl and evaporated. H₂O(100 ml) was added to the residue and the mixture was washed with ether, basified with powdered KOH and extracted with CHCl₃. The extract was dried over MgSO₄ and evaporated to give a crude product. This was purified by flash chromatography on SiO₂ with CHCl₃-MeOH(10:1) to give **6a** as a pale yellow oil(5.32 g, 69%), which was converted to the hydrochloride as colorless needles (from MeOH), mp 176-177.5 °C. ¹H-Nmr(free base): 7.22(1H,s,H-3), 6.94(1H,s,H-6), 3.85 and 3.86(each 3H,s, 2xOCH₃), 3.77 and 3.81(each 2H,s, 2xCH₂), 1.74(1H, br s, NH). Anal. Calcd for C₁₆H₁₈NI·HCl: C, 45.79; H, 4.56; N, 3.34. Found: C, 45.64; H, 4.58; N, 3.28.

The benzylamine(**6a**) was reported in our previous paper.¹

General Procedure for Preparation of N-Benzyl-N-(2-iodobenzyl)phenacylamines This is exemplified by the preparation of **4c**. A solution of the benzylamine(**6a**)(1.640 g, 5.11 mmol) in dioxane(15 ml) was added to a solution of phenacyl bromide(**5c**)(686 mg, 2.64 mmol) in dioxane(15 ml). The mixture was stirred for 5 h at room temperature. The colorless precipitates(866 mg) of the hydrobromide of **6a** formed were filtered and the filtrate was evaporated to give a crude oil(1.513 g). This was purified by flash chromatography on SiO₂ with CHCl₃-benzene(2:1) to give **4c** as an oil(1.204 g, 91%). The spectral data for **4c** thus obtained are shown in Table III.

Other N-benzylphenacylamines(**4d-h**) were prepared in the same way as **4c**(Table III).

General Procedure for Reaction of N-Benzyl-N-(2-iodobenzyl)phenacylamines with BuLi

This is exemplified by the reaction of **4c** with BuLi. BuLi(1.6 M sol. in hexane, 0.41 ml, 0.65 mmol) was added to a solution of the phenacylamine(**4c**)(252 mg, 0.50 mmol) in dry THF (4 ml) by a syringe at -78 °C under N₂ and the mixture was stirred for 10 min at -78 °C. H₂O(20 ml) was added and the mixture was extracted with ether(20 ml x 3). The extract was dried over MgSO₄ and evaporated to give an oil(195 mg). This was subjected to preparative tlc on SiO₂ with CHCl₃. The fraction of R_f 0.04-0.24 gave **2c** as a pale brown oil(141 mg,

Table III. Yields and Ms, Ir and ¹H-Nmr Spectral Data for Phenacylamines(4c-h)^a

No	Yield (%)	Formula	Ms(m/z)(M ⁺) Calcd(Found)	Ir(KBr) (cm ⁻¹)	¹ H-Nmr(CDCl ₃) δ
4c	91	C ₂₄ H ₂₄ NO ₃ I	501.0800 (501.0793)	1683	7.85 and 7.82(each 1H,dd,J=8 and 2 Hz,H-3' and 6'),6.93(1H,ddd,J=8, 8 and 2 Hz,H-4'), 6.79(1H,d,J=8 Hz,H-5),3.91 and 3.86(each 2H, s,2xCH ₂),3.92(3H,s,OCH ₃),3.89(5H,s,CH ₂ and OCH ₃)
4d	80	C ₂₄ H ₂₄ NO ₃ I	501.0800 (501.0790)	1691	7.79(2H,d,J=7 Hz,H-2 and 6'),7.38(2H,dd,J=7 and 7 Hz,H-3 and 5),7.34-7.21(5H,m,C ₆ H ₅), 7.17(1H,s,H-3'),7.03(1H,s,H-6'),3.90,3.82, and 3.80(each 2H,s,3XCH ₂),3.83 and 3.75(each 3H,s,OCH ₃)
4e	83	C ₂₂ H ₁₉ NOFI	459.0494 (459.0453)	1687	7.82(1H,m,H-3'),7.80(2H,dd,J=9 and 5.5 Hz,H-2 and 6'),7.47(1H,dd,J=7.5 and 2 Hz,H-6'), 7.37-7.23(5H,m,C ₆ H ₅),7.02(2H,dd,J=9 and 9 Hz,H-3 and 5),6.93(1H,ddd,J=8, 7 and 2 Hz, H-4'),3.88, 3.85 and 3.84(each 2H,s,3xCH ₂)
4f	77	C ₂₂ H ₁₉ NOClI	474.0121 ^b (474.0081)	1690	7.81(1H,d,J=8 Hz,H-3'),7.70(2H,d,J=8 Hz,H-2 and 6'),7.45(1H,d,J=7 Hz,H-6'),7.35-7.23(5H, m,C ₆ H ₅),7.27(2H,d,J=8 Hz,H-3 and 5),6.93(1H, ddd,J=8, 7 and 1 Hz,H-4'),3.87 and 3.83(4H and 2H,s,3XCH ₂)
4g	75	C ₂₃ H ₂₂ NOI	453.0592 (453.0598)	1688	7.81(1H,dd,J=8 and 1 Hz,H-3'),7.71(2H,d,J= 8 Hz,H-2 and 6'),7.55(1H,dd,J=8 and 1.5 Hz, H-6'),7.18(2H,d,J=8 Hz,H-3 and 5),6.93(1H, ddd,J=8, 7 and 1.5 Hz,H-4'),3.93,3.91,3.88 (each 2H,s,3XCH ₂),2.38(3H,s,CH ₃)
4h	85	C ₂₄ H ₂₄ NOI	469.0902 (469.0875)	1689	7.81(1H,dd,J=8 and 1 Hz,H-3'),7.74(2H,J=8 Hz,H-2 and 6'),7.53(1H,dd,J=7.5 and 2 Hz,H-6'),7.20(2H,d,J=8 Hz,H-3 and 5),6.93(1H,ddd, J=8, 7.5 and 2 Hz,H-4'),3.92,3.91 and 3.88 (each 2H,s,3XCH ₂),2.67(2H,q,J=7.5 Hz, CH ₂ CH ₃),1.23(3H,t,J=7.5 Hz,CH ₂ CH ₃)

a. Ref. 1 for 4a,b. b. M-1.

74%). This was converted to the hydrochloride as colorless cubes (from EtOH-acetone), mp 181-182°C (decomp.). The physical and spectral data for 2c are shown in Tables I and IV.

Reactions of other phenacylamines (4d-h) with BuLi were carried out in the same way as 4c. The physical and spectral data for the products (2d-h) are summarized in Tables I and IV.

General Procedure for Reaction of N-Benzyl-N-(2-iodobenzyl)phenacylamines with Zerovalent Nickel

This is exemplified by the reaction of 4c with zerovalent nickel.^{1,3} Ph₃P (2.503 g, 9.12 mmol), NiCl₂ (580 mg, 4.47 mmol), and Zn (297 mg, 4.54 mmol) were placed in a two-necked flask. The flask was evacuated and filled with N₂. Dry oxygen-free DMF (35 ml) was added through a syringe. The mixture was stirred at 60°C for 5 min. A solution of 4c (1.072 g, 2.14 mmol) in dry oxygen-free DMF (5 ml) was added and the mixture was stirred for 10 h at 60°C. Then, the mixture was acidified with 2% HCl and washed with ether. The aqueous layer was basified with 25% NH₄OH and extracted with CHCl₃ (50 ml x 4). The extract was dried over MgSO₄ and evaporated to give a crude product (850 mg). This was subjected to preparative TLC on Al₂O₃ with benzene-CHCl₃ (5:1) to give the isoquinolin-4-ol (2c) as a pale yellow oil (298 mg, 37%). This was identical with 2c prepared with BuLi as described above by comparison of their ¹H-NMR spectra.

Reactions of other phenacylamines (4d-h) with zerovalent nickel were carried out in the same way as 4c.

General Procedure for Reaction of N-Benzyl-1,2,3,4-tetrahydro-4-phenylisoquinolin-4-ols with AlCl₃

This is exemplified by the reaction of 2a. AlCl₃ (129 mg, 0.97 mmol) was added to a solution of 2a (76 mg, 0.24 mmol) in benzene (2 ml). The mixture was stirred for 30 min at room temperature. H₂O (30 ml) was added and the mixture was basified with powdered Na₂CO₃. The mixture was extracted with benzene (30 ml x 3). The extract was washed with brine, dried over MgSO₄ and evaporated *in vacuo* to give a crude product (80 mg). This was subjected to preparative TLC on SiO₂ with benzene-EtOH (10:1) to give 3a as colorless needles (59 mg, 83%), mp 140-145°C (from MeOH) (lit.,⁷ mp 138-139°C). ¹³C-NMR: 144.30 (s, C-1'), 143.13 (s, C-11a and 12a), 135.57 (s, C-4a and 7a), 129.26 (d, C-1 and 11), 126.20 (d, C-4'), 61.00 (t, C-13), 57.70 (t, C-5 and 7), 44.76 (s, C-12). The physical and ¹H-NMR spectral data are shown in Tables II and IV.

Reactions of other isoquinolin-4-ols (2d-h) were carried out in the same way as 2a. The physical and spectral data for the products (3d-h) are summarized in Tables II and IV.

Table IV. $^1\text{H-Nmr}$ Spectral Data for Isoquinolin-4-ols(2c-h)^a and Azocines(3a-h)

2c	6.85(1H,d,J=2 Hz,H-2'), 6.80(1H,d,J=8.5 Hz,H-5'), 3.94 and 3.56(each 1H,d,J=15 Hz, CH ₂ -1), 3.88 and 3.85(each 3H,s,2XOCH ₃), 3.94 and 3.56(each 1H,d,J=13 Hz,NCH ₂ Ph), 3.03 and 2.79(each 1H,d,J=12 Hz,CH ₂ -3)
2d	7.34(5H,s,NCH ₂ Ph), 6.52(1H,s,H-8), 6.42(1H,s,H-5), 3.85 and 3.47(each 1H,d,J=15 Hz,CH ₂ -1), 3.83 and 3.62(each 3H,s,2XOCH ₃), 3.78 and 3.68(each 1H,d,J=13 Hz, NCH ₂ Ph), 3.02 and 2.73(each 1H,d,J=12 Hz,CH ₂ -3)
2e	7.39(2H,dd,J=9 and 5.5 Hz,H-2' and 6'), 6.99(2H,dd,J=9 and 9 Hz,H-3' and 5'), 3.93 and 3.56(each 1H,d,J=15 Hz,CH ₂ -1), 3.73(2H,s,NCH ₂ Ph), 2.99 and 2.74(each 1H,d,J=12 Hz,CH ₂ -3)
2f	6.92(1H,dd,J=7.5 and 1.5 Hz,H-5), 3.93 and 3.56(each 1H,d,J=15 Hz,CH ₂ -1), 3.73 (2H,s,NCH ₂ Ph), 2.98 and 2.73(each 1H,d,J=12 Hz,CH ₂ -3)
2g	3.94 and 3.54(each 1H,d,J=15 Hz,CH ₂ -1), 3.73(2H,s,NCH ₂ Ph),3.02 and 2.76(each 1H,d, J=12 Hz,CH ₂ -3), 2.34(3H,s,CH ₃)
2h	7.34 and 7.16(each 2H,d,J=8 Hz,H-2' and 6', and H-3' and 5'), 6.97(1H,dd,J=7 and 2 Hz,H-5), 3.95 and 3.56(each 1H,d,J=15 Hz,CH ₂ -1), 3.74(2H,s,NCH ₂ Ph),3.03 and 2.77 (each 1H,d,J=12 Hz,CH ₂ -3), 2.65(2H,q,J=7.5 Hz,CH ₂ CH ₃), 1.25(3H,t,J=7.5 Hz,CH ₂ CH ₃)
3a	4.72 and 3.96(each 2H,d,J=17.5 Hz,CH ₂ -5 and 7), 3.34(2H,s,CH ₂ -13)
3b	7.32(2H,d,J=9 Hz,H-2' and 6'), 6.87(2H,d,J=9 Hz,H-3' and 5'), 4.71 and 3.95(each 2H,d,J=17 Hz,CH ₂ -5 and 7), 3.82(3H,s,OCH ₃), 3.31(2H,s,CH ₂ -13)
3c	6.91(1H,d,J=2 Hz,H-2'), 6.84(1H,d,J=8.5 Hz,H-5'), 4.72 and 3.96(each 2H,d,J=18 Hz, CH ₂ -5 and 7), 3.92 and 3.90(each 3H,s,2XOCH ₃), 3.34(2H,s,CH ₂ -13)
3d	7.46-7.28(5H,m,C ₆ H ₅ -12), 7.12-7.03(4H,m,H-8, 9, 10 and 11), 6.76(1H,s,H-1), 6.51 (1H,s,H-4), 4.79 and 4.07(each 1H,d,J=17 Hz,CH ₂ -7), 4.70 and 3.92(each 1H,d,J=16.5 Hz,CH ₂ -5), 3.81(3H,s,OCH ₃ -3), 3.71(3H,s,OCH ₃ -2), 3.35(2H,s,CH ₂ -13)
3e	7.38(2H,dd,J=9 and 5.5 Hz,H-2' and 6'), 4.71 and 3.96(each 2H,d,J=17.5 Hz,CH ₂ -5 and 7), 3.30(2H,s,CH ₂ -13)
3f	7.37 and 7.28(each 2H,d,J=9 Hz,H-2' and 6', and H-3' and 5'), 4.70 and 3.94(each 2H,d,J=18 Hz,CH ₂ -5 and 7), 3.30(2H,s,CH ₂ -13)
3g	7.30 and 7.14(each 2H,d,J=8 Hz,H-2' and 6', and H-3' and 5'), 4.70 and 3.99(each 2H,d,J=17.5 Hz,CH ₂ -5 and 7), 3.30(2H,s,CH ₂ -13), 2.67(3H,s,CH ₃)
3h	7.32 and 7.16(each 2H,d,J=8 Hz,H-2' and 6', and H-3' and 5'), 4.69 and 3.94(each 2H,d,J=18 Hz,CH ₂ -5 and 7), 3.31(2H,s,CH ₂ -13), 2.67(2H,q,J=7.5 Hz,CH ₂ CH ₃), 1.27 (3H,t,J=7.5 Hz,CH ₂ CH ₃)

a. Ref. 1 for 2a,b.

General Procedure for Reaction of N-Benzyl-1,2,3,4-tetrahydro-4-phenylisoquinolin-4-ols with 85% H₂SO₄ This is exemplified by the reaction of 2a. The hydrochloride(52.9 mg, 0.15 mmol) of 2a was suspended in 85% H₂SO₄(1 ml) and was stirred for 30 min under ice-cooling. The reaction mixture was poured into ice-water(30 ml) and basified with powdered Na₂CO₃. The mixture was extracted with CHCl₃(50 ml x 3). The extract was washed with H₂O, dried over MgSO₄, and evaporated to give a crude product(63 mg). This was purified by preparative tlc on SiO₂ with benzene-EtOH(10:1) to give colorless crystals(34.8 mg, 78%), mp 139-142°C. This was identical with a sample of 3a prepared with AlCl₃ as described above by comparison of their ¹H-nmr spectra and by a mixed melting point test.

Reaction of other N-benzylisoquinolin-4-ols(2b-d) with 85% H₂SO₄ was carried out in the same way as 2a. The physical and ¹H-nmr spectral data for the products(3b-d) are shown in Tables II and IV.

Reaction of N-Benzyl-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)isoquinolin-4-ol(2b) with CF₃SO₃H The free base(86.1 mg, 0.26 mmol) of 2b was dissolved in CF₃SO₃H(3 ml) under ice-cooling. The solution was stirred at room temperature overnight. The reaction mixture was poured into ice-water(20 ml) and basified with 25% NH₄OH. The mixture was extracted with CHCl₃(20 ml x 4). The extract was dried over MgSO₄ and evaporated to give an oil (82.7 mg). This was subjected to preparative tlc on SiO₂ with benzene-EtOH(10:1) to give 3b as a pale yellow oil(45.7 mg, 57%). Ms(m/z)(M⁺):Calcd for C₂₃H₂₁NO:327.1622. Found:327.1622. This oily product was converted to the hydrochloride as colorless needles (from MeOH), mp 165-166.5°C. This was identical with the hydrochloride of 3b prepared with 85% H₂SO₄ by comparison of the ¹H-nmr spectra of their free bases.

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