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Studies on the Syntheses of Heterocyclic Compounds. CDLXXXIII.[1] Synthesis of Homoaporphine and Attempts to Synthesize C-Noraporphine by Pschorr Reaction

Tetsuji Kametani, Takuo Nakano, Chizuko Seino, Shiroshi Shibuya, Keiichiro Fukumoto,[2a] T.R. Govindachari, K. Nagarajan, B.R. Pai, and P.S. Subramaniani[2b]

Pharmaceutical Institute, Tohoku University[2a] and Department of Chemistry, Presidency College[2b]

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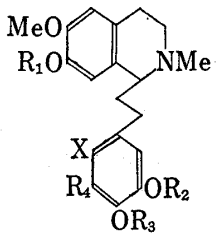
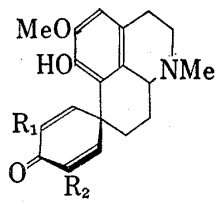
Photolysis of the diazonium salt derived from 1-(2-amino-4-hydroxy-5-methoxyphenethyl)-7-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (V) gave, 1,11-dihydroxy-2,10-dimethoxyhomoaporphine (IX), which was identical with the rearranged product of kreysiginone (VII) by acid. The same reaction of 1-(2-aminophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXI) gave an abnormal product, 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline (XXV), in addition to the deamination product (XXII) and the phenolic isoquinoline (XXIII).

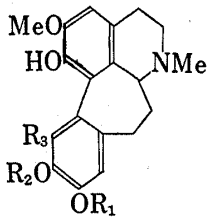
Previously, we reported that phenol oxidation of the diphenolic isoquinoline (I) gave kreysiginone (VII) and its spiro isomer (VIII), which on acidic treatment afforded the 1, 11-dihydroxy-2,10-dimethoxy- (IX) and 1,10-dihydroxy-2,11-dimethoxyhomoaporphine (X), respectively.[3,4] Since the structures (IX and X) of both homoaporphines were assigned tentatively by the spectroscopic method using mainly nuclear magnetic resonance (NMR) spectra, the reinvestigation of the structures was carried out by the synthesis of the homoaporphines by a photo-Pschorr reaction developed in our laboratory.[5] Herein we wish to report the suggested structures (IX and X) to be correct, and, moreover, examined a synthetic approach of C-noraporphine (XIII) by a similar reaction.



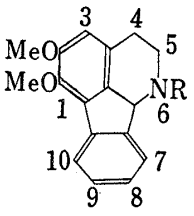
	R_1	R_2	R_3	R_4	X
I	H	Me	H	H	H
II	H	H	Me	OMe	H
III	H	H	Me	H	H
IV	H	Me	Me	OMe	N_2^+
V	H	Me	H	H	NH_2
VI	$CH_2C_6H_5$	Me	$CH_2C_6H_5$	H	NH_2



VII : R_1=H, R_2=OMe
VIII : R_1=OMe, R_2=H



	R_1	R_2	R_3
IX	Me	H	H
X	H	Me	H
XI	Me	Me	OH
XII	Me	Me	OMe



XIII : R=H
XXV : R=Ac

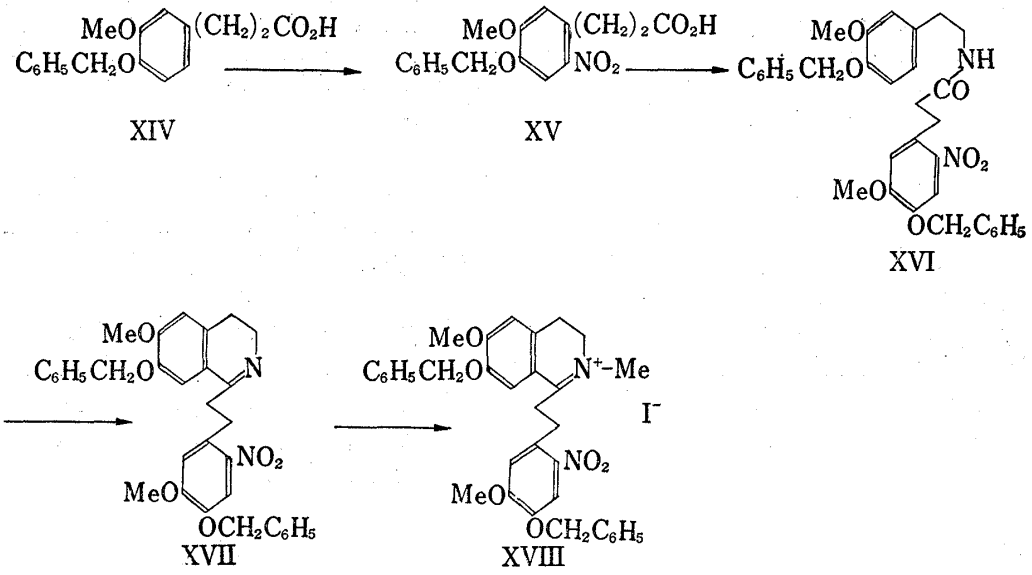
Chart 1

1) Part CDLXXXII: T. Kametani, T. Kohno, R. Charubala, S. Shibuya, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1488 (1972).
2) Location: *a*) *Aobayama, Sendai*; *b*) *Madras, India.*
3) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).
4) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1968**, 1003.
5) T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 1923.

We have not obtained fruitful result for synthesizing the homoaporphine by a classic Pschorr reaction,[6] and only one example of the homoaporphine synthesis without application of the rearrangement was carried out by Battersby;[7] phenol oxidation of autumnaline (II) gave 1,12-dihydroxy-2,10,11-trimethoxyhomoaporphine (XI). However, the expected homoaporphine (X) could not be obtained from homoorientaline (III) by this method.

Recently, we reported a new way of synthesizing kreysigine[8] (XII), and homoaporphine alkaloid from *Kreysigia multiflora*,[9] from the diazotized phenethylisoquinoline (IV) by photolytic cyclization.[5] This method was applied to the synthesis of the homoaporphines (IX and X) from the aminoisoquinoline (V), which was prepared as follows.

Nitration of the phenylpropionic acid derivative (XIV) gave the 2 nitrophenylpropionic acid (XV), which was fused with 4-benzyloxy-3-methoxyphenethylamine to afford the corresponding amide (XVI). A Bischler–Napieralski reaction of the above amide furnished the 3,4-dihydroisoquinoline (XVII), the methiodide (XVIII) of which was reduced with zinc and hydrochloric acid to give the aminoisoquinoline (VI). Debenzylation of VI by ethanolic hydrochloric acid afforded the starting phenolic aminoisoquinoline (V).



XIV XV XVI XVII XVIII

Chart 2

The diazotization of V, followed by the irradiation of the resulting diazonium salts with a Hanovia 450 W mercury lamp enclosed in a pyrex filter, afforded the homoaporphine, which was identical perfectly with the product (IX) derived from kreysiginone (VII) in spectroscopic methods. Thus, we confirmed that kreysiginone (VII) rearranged to 1,11-dihydroxy-2,10-dimethoxyhomoaporphine (IX) and that the structures (IX and X) tentatively assigned by NMR spectroscopy to the homoaporphines were correct.[4]

Secondly, the synthesis of C-noraporphine (XIII) was examined by Pschorr and photo-Pschorr reaction as follows. The aminoisoquinoline (XXI), which was synthesized by methylation of 2′-nitroisoquinoline[10] (XIX) with methyl iodide, followed by reduction of XX with zinc dust and sulfuric acid, was diazotized and the resulting diazonium salt was decomposed at 70° without metallic catalyst to give the deamination product (XXII), the phenolic base

6) T. Kametani, K. Fukumoto, F. Satoh, and Yagi, *J. Chem. Soc.* (*C*), **1968**, 3084.
7) A.R. Battersby, E. McDonald, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 934.
8) T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *J. Chem. Soc.* (*C*), **1969**, 1295.
9) A.R. Battersby, R.B. Bradbury, R.B. Herbert, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 450.
10) S. Rajagopalan, *Proc. Indian. Acad. Sci.*, **14A**, 126 (1941).

(XXIII) and the abnormal product which was characterized as oxalate. In the latter compound the microanalysis and mass spectrometry revealed the molecular formula $C_{17}H_{17}O_2N$, and ultraviolet (UV) spectrum showed the presence of 3,4-dihydroisoquinoline system. In the NMR (δ) spectrum, two O-methyl resonances were shown but not N-methyl resonance. Moreover, two methylene groups resonanced at 2.75 and 3.82 ppm as distorted triplets, and the methine proton could not be observed. The aromatic protons were observed at 6.78 corresponding to two protons as a singlet and at 7.5 equivalent to five protons as a broad signal. These data revealed the product to the 3,4-dihydroisoquinoline (XXV), which was proved by direct comparison with the authentic sample[11] by spectroscopic method and melting point determination.

The elimination of N-methyl group in this reaction was shown in Chart 3. The photolysis of the diazonium salt of the aminoisoquinoline (XXI) after decomposition of an excess of nitrous acid by urea gave the 3,4-dihydroisoquinoline (XXV) in low yield after purification by column chromatography.

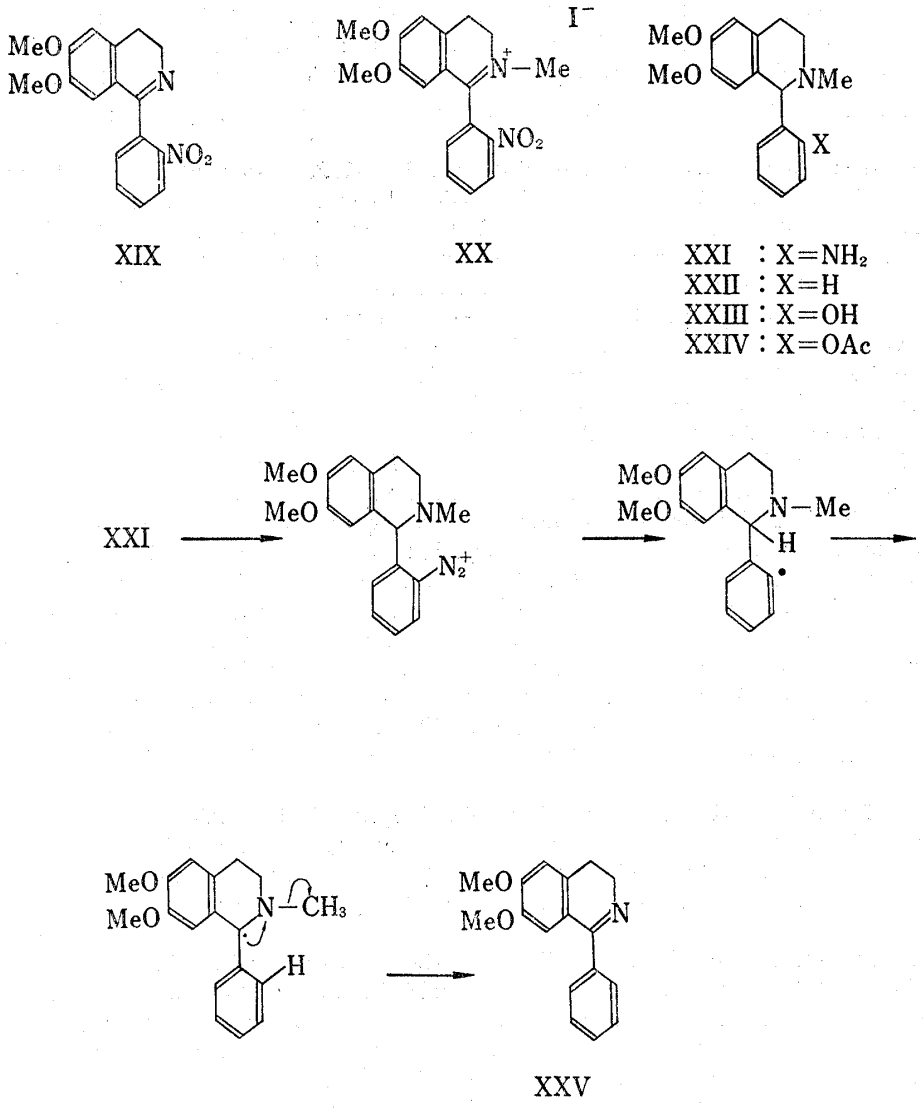


Chart 3

Thus, the homoaporphine was synthesized by Pschorr reaction which has been applied to a synthesis of the aporphine and an abnormal reaction was observed in case of the Pschorr reaction of 2′-amino-1-phenylisoquinoline.

11) S. Sugasawa, *Yakugaku Zasshi*, **55**, 224 (1935).

Experimental[12]

4-Benzyloxy-5-methoxy-2-nitrophenylpropionic Acid (XV)——To a solution of 30 g of 4-benzyloxy-3-methoxyphenylpropionic acid[13] (XIV) in 200 ml of AcOH was added dropwise 40 ml of conc. HNO_3 (*d*: 1.42) during 0.5 hr with stirring under cooling, and the mixture was stirred at room temperature for 1 hr and poured into an excess of ice–H_2O. The separated crystals were collected and recrystallized from MeOH to give 20 g of the nitrophenylpropionic acid (XV) as pale yellow prisms, mp 138—140°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O), 1328 (NO_2). *Anal.* Calcd. for $C_{17}H_{17}O_6N$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.41; H, 5.13; N, 4.42.

N-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-5-methoxy-2-nitrophenylpropionamide (XVI)——A mixture of 5.4 g of 4-benzyloxy-3-methoxyphenethylamine and 7.1 g of 2-nitrophenylpropionic acid (XV) was heated at 175—180° for 1.5 hr and the cooled mixture was recrystallized from MeOH to give 8.7 g of the amide (XVI) as colorless needles, mp 165—167°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3400 (NH), 1660 (C=O), 1328 (NO_2). *Anal.* Calcd. for $C_{33}H_{34}O_7N_2$: C, 69.46; H, 6.01; N, 4.91. Found: C, 69.17; H, 5.82; N, 4.84.

7-Benzyloxy-1-(4-benzyloxy-5-methoxy-2-nitrophenethyl)-3,4-dihydro-6-methoxyisoquinoline (XVII)——A mixture of 614 mg of the amide (XVI), 1 ml of $POCl_3$ and 20 ml of anhyd. $CHCl_3$ was refluxed for 1 hr, and the solvent and reagent were distilled off *in vacuo* to give 510 mg of the 3,4-dihydroisoquinoline (XVII) hydrochloride as pale yellow needles (from MeOH), mp 205—207°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1648 ($>C=\overset{+}{N}$). *Anal.* Calcd. for $C_{33}H_{32}O_6N_2 \cdot HCl$: C, 67.28; H, 5.65; N, 4.72. Found: C, 67.45; H, 5.77; N, 4.90. The free base (XVII) gave the methiodide (XVIII) as pale yellow needles (from MeOH), mp 193—195.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625 ($>C=\overset{+}{N}$). *Anal.* Calcd. for $C_{34}H_{35}O_6N_2I$: C, 58.79; H, 5.08; N, 4.03. Found: C, 58.43; H, 5.19; N, 4.39.

1-(2-Amino-4-benzyloxy-5-methoxyphenethyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (VI)——Zinc powder (37 g) was added in portions to a mixture of 6.4 g of the methiodide (XVIII), 125 ml of AcOH, 125 ml of conc. HCl, and 31 ml of H_2O with stirring at 0—2°, and the mixture was stirred for 5 hr at 0—2°. An excess of zinc was filtered off, and the filtrate was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over K_2CO_3, and evaporated *in vacuo* to give 5.4 g of a brown viscous syrup, which was purified on 100 g of silica gel by elution with $CHCl_3$–MeOH (v/v 99:1) to give 4.2 g of the 1,2,3,4-tetrahydroisoquinoline (VI) as a pale brown viscous syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300 (NH_2). NMR (in $CDCl_3$) ppm: 2.40 (3H, s, N-C$\underline{H}_3$), 3.78 (3H, s, OC$\underline{H}_3$), 3.82 (3H, s, OC$\underline{H}_3$), 5.07 (4H, s, 2×OC$\underline{H}_2$C$_6$H$_5$), 6.24 (1H, s, 3′-H), 6.56 (3H, s, Ar-H), 7.35 (10H, s, 2×OCH$_2$C$_6$$\underline{H}_5$).

Debenzylation of VI——A mixture of 2 g of the aminoisoquinoline (VI), 20 ml of conc. HCl, and 20 ml of EtOH was refluxed for 3 hr, and the excess of reagent and solvent were distilled off *in vacuo* to give 1.33 g of the phenolic aminoisoquinoline (V), which was used immediately without purification.

1,2,3,4-Tetrahydro-1,11-dihydroxy-2,10-dimethoxy-6-methylhomoaporphine (IX)——To a stirred solution of 1.28 g of the aminoisoquinoline (V) in 35 ml of 5% H_2SO_4 was added dropwise 3 ml of 10% $NaNO_2$ at 0° and the stirring was continued for 1 hr at 0°. This solution was diluted to 1 liter with H_2O and irradiated with a Hanovia 450 W mercury lamp in the presence of a pyrex filter for 4.5 hr at 5—10° with stirring. The reaction mixture was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over K_2CO_3, and distilled to leave 410 mg of a brown gum, which was chromatographed on 10 g of silica gel. The $CHCl_3$–MeOH (96:4 v/v) eluate gave 43.8 mg of the homoaporphine (IX) as colorless needles, mp 185—187°. The IR [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3505 (OH)], UV [λ_{max}^{MeOH} mμ: 264, 291] and NMR [in $(CD_3)_2SO$] ppm: 6.63 (1H, s, C_3-H), 6.78 (1H, s, C_9-H), 6.88 (1H, s, C_{12}-H)] spectra of which were identical with those of the sample prepared from kreysigninone (VII).[4]

3,4-Dihydro-6,7-dimethoxy-1-(2-nitrophenyl)isoquinoline Methiodide (XX)——A mixture of 0.5 g of 3,4-dihydroisoquinoline (XIX),[11] 5.4 ml of $CHCl_3$, and an excess of MeI was left overnight at room temperature. Evaporation of the solvent yielded 0.7 g of a yellow solid, which was recrystallized from MeOH to give yellow needles, mp 194°. *Anal.* Calcd. for $C_{18}H_{19}O_4N_2I$: C, 47.59; H, 4.22. Found: C, 47.90; H, 4.41.

1-(2-Aminophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXI)——To a solution of 1 g of the methiodide (XX) in a mixture of 40 ml of 4N H_2SO_4 and 2 ml of MeOH was added in portions 4 g of zinc dust under stirring. The mixture was heated on a water-bath under stirring for 1 hr. A further 10 ml of H_2SO_4 was added towards the end. The resulting solution was filtered from the excess of zinc and the residue was washed with H_2O. The combined solution was basified with 28% NH_4OH and extracted with ether. The extract was washed with saturated NaCl solution and dried over Na_2SO_4. Evaporation of the solvent afforded 0.6 g of the 2′-aminoisoquinoline (XXI), mp 145—146° (from EtOH). *Anal.* Calcd. for $C_{18}H_{22}O_2N_2$: C, 72.45; H, 7.43; N, 9.39. Found: C 72.48; H, 7.54; N, 9.47.

12) IR and UV spectra were taken with a type EPI-3 and EPS-3 Hitachi recording spectrometers, respectively. Mass spectra were measured with a Hitachi RMU-7 mass spectrometer, and NMR spectra were taken with a Hitachi A-20 with tetramethylsilane as internal standard.

13) R.E. Harmon and B.L. Jensen, *J. Heterocyclic Chem.*, 7, 1077 (1970).

Pschorr Reaction of 1-(2-Aminophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXI) (a) Thermal Decomposition of the Diazonium Salt of XXI: A solution of 2.0 g of the aminoisoquinoline (XXI) in 180 ml of 5% H_2SO_4 was diazotized with 25 ml of 10% $NaNO_2$ at 0° with stirring and the stirring was continued for 1 hr at 0—1°. The resulting mixture was gradually warmed to 70° and stirred for a further 1 hr at the same temperature. After being cooled to room temperature, this was washed with benzene, basified with 10% NH_4OH, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and distilled to leave 2.5 g of a brown gum, which was chromatographed on 30 g of silica gel using $CHCl_3$ [fractions F_1 1—37 (each 25 ml), monitored by IR and UV spectra], $CHCl_3$–MeOH (99.5: 0.5 v/v; fractions F_1 38—55), $CHCl_3$–MeOH (99:1 v/v; fractions F_1 56—65), and $CHCl_3$–MeOH (97:3 v/v; fractions F_1 66—69) as eluants.

Fractions F_1 9—26 were combined and evaporated to leave 360 mg of a reddish viscous oil, which was recrystallized from EtOH to give 155 mg of 1,2,3,4-tetrahydro-1-(2-hydroxyphenyl)-6,7-dimethoxy-2-methylisoquinoline (XXIII) as pale brown plates, mp 146—147°. NMR (in $CDCl_3$) ppm: 2.38 (3H, s, NCH_3), 3.55, 3.76 (6H, each s, OCH_3), 4.30 (1H, s, 1-H), 6.12 (1H, s, 8-H), 6.50 (1H, s, 5-H), 6.60—7.20 (4H, m, ArH). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.24; H, 7.02; N, 4.69. Found: C, 72.29; H, 6.97; N, 4.80. A mixture of 40 mg of the hydroxy derivative (XXIII), 0.1 ml of Ac_2O, and 3 drops of pyridine was stirred overnight at room temperature and then poured into 10 ml of H_2O. The resulting mixture was stirred for a further 10 hr at the same temperature. After an addition of 20 ml of H_2O, the mixture was extracted with 50 ml of $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated to afford 30 mg of 1-(2-acetoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXIV) as a yellow gum. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (C=O). NMR (in $CDCl_3$) ppm: 2.17, 2.20 (6H, each s, NCH_3, $COCH_3$), 3.53, 3.78 (6H, each s, OCH_3), 4.33 (1H, s, 1-H), 6,13 (1H, s, 8-H), 6,50 (1H, s, 5-H), 6.58—7.30 (4H, m, ArH), which was recrystallized from EtOH–hexane to give pale yellow prisms, mp 142.5—143.5°. Mass Spectrum *m/e*: 341 (M^+), 299 (M^+-42). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79. Found: C, 70.60; H, 7.06.

Fractions F_1 30—37 were combined and evaporated to leave 90 mg of a yellow gum, which was again chromatographed on 5 g of alumina and eluted successively with benzene [fractions (each 6 ml) 1—50] and benzene–$CHCl_3$ (9:1 v/v; fractions 51—68), benzene–$CHCl_3$ (1:1 v/v; fractions 69—82), and $CHCl_3$ (fractions 83—88). Fraction 2 was extracted with 20 ml of ether and the extract was evaporated to leave a pale red gum, the crystallization of which from hexane yielded 2 mg of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline (XXII) as pale orange granules, mp 79—80° (lit.,[14] 81—82°). Mass Spectrum (*m/e*): 283 (M^+). *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.32; H, 7.42; N, 4.95. Found: C, 76.08; H, 7.66; N, 5.05. Fractions 3—29 were collected and chromatographed on 4 g of silicic acid eluting with $CHCl_3$ (fractions 1—63) and $CHCl_3$–MeOH (99:1 v/v; fractions 64—67). Among the above eluants, fractions 19—63 gave 13 mg of the 3,4-dihydroisoquinoline (XXV) as a pale yellow oil, which was identical with the following sample.

Fractions F_1 38—45 were evaporated to leave 148 mg of a yellow gum, which was purified by preparative TLC on silica gel using ether to give 67.5 mg of the above 3,4-dihydroisoquinoline (XXV) as prisms, mp 119.5—120° (lit.,[11] mp 120—121°), which was also characterized as its oxalate, mp 186—187° (from EtOH–ether). NMR (in $CDCl_3$) (free base) ppm: 3.72, 3.94 (3H, s, OCH_3), 6.68, (2H, s, 5 and 8-H), 7.32—7.70 (5H, m, ArH). UV λ_{max}^{MeOH} mμ: (free base) 313, 283 (ε 5400, 5200). Mass Spectrum *m/e*: 267 (M^+), 266, 252, 236. *Anal.* Calcd. for $C_{17}H_{17}O_2N \cdot C_2H_2O_4$: C, 63.86; H, 5.36; N, 3.92. Found: C, 64.05; H, 5.78; N, 4.04.

(b) Photolysis of the Diazonium Salt of XXI: To a solution of 2.0 g of the aminoisoquinoline (XXI) in 180 ml of 5% H_2SO_4 was added dropwise a solution of 25 ml of 10% $NaNO_2$ during 20 min at 0—3°, and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of HNO_2 with 2.45 g of NH_2CONH_2, followed by dilution to 1 liter with H_2O, the mixture was irradiated by a Hanovia 450 W mercury lamp with a pyrex filter at 4—16° for 4.5 hr. The reaction mixture was basified with conc. NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to afford 2.1 g of a dark red gum, which was chromatographed on 50 g of silica gel using $CHCl_3$ [fractions (each 25 ml) 1—61], $CHCl_3$–MeOH (99:1 v/v; fractions 62—74), $CHCl_3$–MeOH (97:3 v/v; fractions 75—101), and $CHCl_3$–MeOH (95:5 v/v; fractions 102—112) as eluants (monitored by IR and UV spectra).

Fractions 18—41 were evaporated to leave 142 mg of a reddish viscous oil, which was recrystallized from EtOH to give 60 mg of 1,2,3,4-tetrahydro-1-(2-hydroxyphenyl)-6,7-dimethoxy-2-methylisoquinoline (XXIII) as pale brown plates, mp 146—147°, which were identical with the above authentic sample.

Fractions 53—72 gave 200 mg of a dark brown gum, which was again chromatographed on 10 g of silicic acid with $CHCl_3$ [fractions (each 10 ml) 1—51] and $CHCl_3$–MeOH [99.5:0.5 v/v; fractions 52—64]. Fractions 9—12 were treated as usual and purified by preparative TLC on silica gel in ether to give 10 mg of a pale brown oil, which was recrystallized from hexane to give 2 mg of the isoquinoline (XXII) as pale orange granules, mp 79—80°, which was identical with the above authentic sample. Fractions 19—36 left 32.5 mg of a pale yellow oil, which was extracted with ether. The extract was evaporated to leave 18 mg of a pale yellow oil, which was purified by preparative TLC on silica gel using ether to afford 15 mg of a pale yellow

14) T. Kametani and M. Shio, *J. Heterocyclic Chem.*, **2**, 222 (1965).

oil, which was again chromatographed on 1 g of alumina with benzene. The fractions (each 5 ml) 4—11 gave 5 mg of the above 3,4-dihydroisoquinoline (XXV) which was identical with the above authentic sample.

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