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Studies on Tetrahydroisoquinolines. VIII.[1] Lead Tetraacetate Oxidation of 1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline and Its 1-Substituted Derivatives

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Lead tetraacetate oxidation of 1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinolines (VIIIa—d) in methylene chloride was found to form readily 4-acetoxy-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinolines (XIVa—d) in moderate yield.

Previously we demonstrated that acid treatment of 10-acetoxy-$\Delta^{5,6,8,9}$-hexahydro-6-methoxy-2-methyl-7-oxoisoquinolines (*p*-quinol acetates) (I) derived from 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinolines (II) by means of their lead tetraacetate [$Pb(OAc)_4$] oxidation caused a facile rearrangement giving their corresponding 4,7-diacetoxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinolines (4,7-diacetates) (III),[3] which were highly reactive toward various nucleophiles[4–6] at C-4 position. Moreover, similar *p*-quinol acetate (IV) or (V) having an activated benzyl or phenethyl group at C-1 position was shown to suffer intramolecular Michael type reaction followed by 1,2-shift to give readily aporphine[7] or homoaporphine[1] skeleton, which was converted into (±)-thaliporphine (VI)[8] or (±)-kreysigine (VII).[9]

Presence of a methoxy adjacent to a phenolic hydroxy group in these reaction seemed of great significance. Especially, in the formation of III a methoxy group at C-6 position in the original *p*-quinol acetates (I) constituted vinyl ether system preventing acetoxy group migration to C-5 position. Therefore, we were interested in the behavior to $Pb(OAc)_4$ oxidation of 1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinolines (VIII) which had isomeric patterns with respect to hydroxy and methoxy group as compared to corypalline series (II) and the oxidation of these bases (VIII) was first perfomed.

The synthesis of 1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (VIIIa)[10] and of (±)-1-methyl-,[11] (±)-1-phenyl-[12] and (±)-1-benzyl-[13] 1,2,3,4-tetrahydro-6-hydroxy-7-

1) Part VII: O. Hoshino, T. Toshioka, K. Ohyama, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 1307 (1974).
2) Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
3) B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue, and T. Toshioka, *Chem. Pharm. Bull.* (Tokyo), **19**, 2138 (1971).
4) B. Umezawa, O. Hoshino, and Y. Yamanashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2154 (1971).
5) O. Hoshino, Y. Yamanashi, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2161 (1971).
6) O. Hoshino, Y. Yamanashi, T. Toshioka, and B. Umezawa, *Chem. Pharm. Buli.* (Tokyo), **19**, 2166 (1971).
7) O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, **1971**, 1533; *idem*, *Chem. Pharm. Bull.* (Tokyo), **22**, 1302 (1974).
8) M. Shamma, R.J. Shine, and B.S. Dudock, *Tetrahedron*, **23**, 2887 (1967); T. Kametani, S. Shibuya, and S. Kano, *J. Chem. Soc. Perkin I*, **1973**, 1212; S.M. Kupchan and P.F. O'Brien, *J. C. S. Chem. Commun.*, **1973**, 915.
9) A.R. Battersby, R.B. Bradbery, R.B. Herbert, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 450; T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 1923; T. Kametani, Y. Satoh, S. Shibuya, M. Koizumi, and K. Fukumoto, *J. Org. Chem.*, **36**, 3733 (1971).
10) J.M. Bobbitt, D.N. Roy, A. Marchand, and C.W. Allen, *J. Org. Chem.*, **32**, 2225 (1967).
11) J.M. Bobbitt, A.S. Steinfeld, K.H. Weisgraber, and S. Dutta, *J. Org. Chem.*, **34**, 2478 (1969).
12) T. Kametani and M. Shio, *J. Heterocyclic Chem.*, **2**, 222 (1965).
13) A. Brossi, A.I. Rachlin, and S. Teitel, *J. Heterocyclic Chem.*, **4**, 417 (1967).

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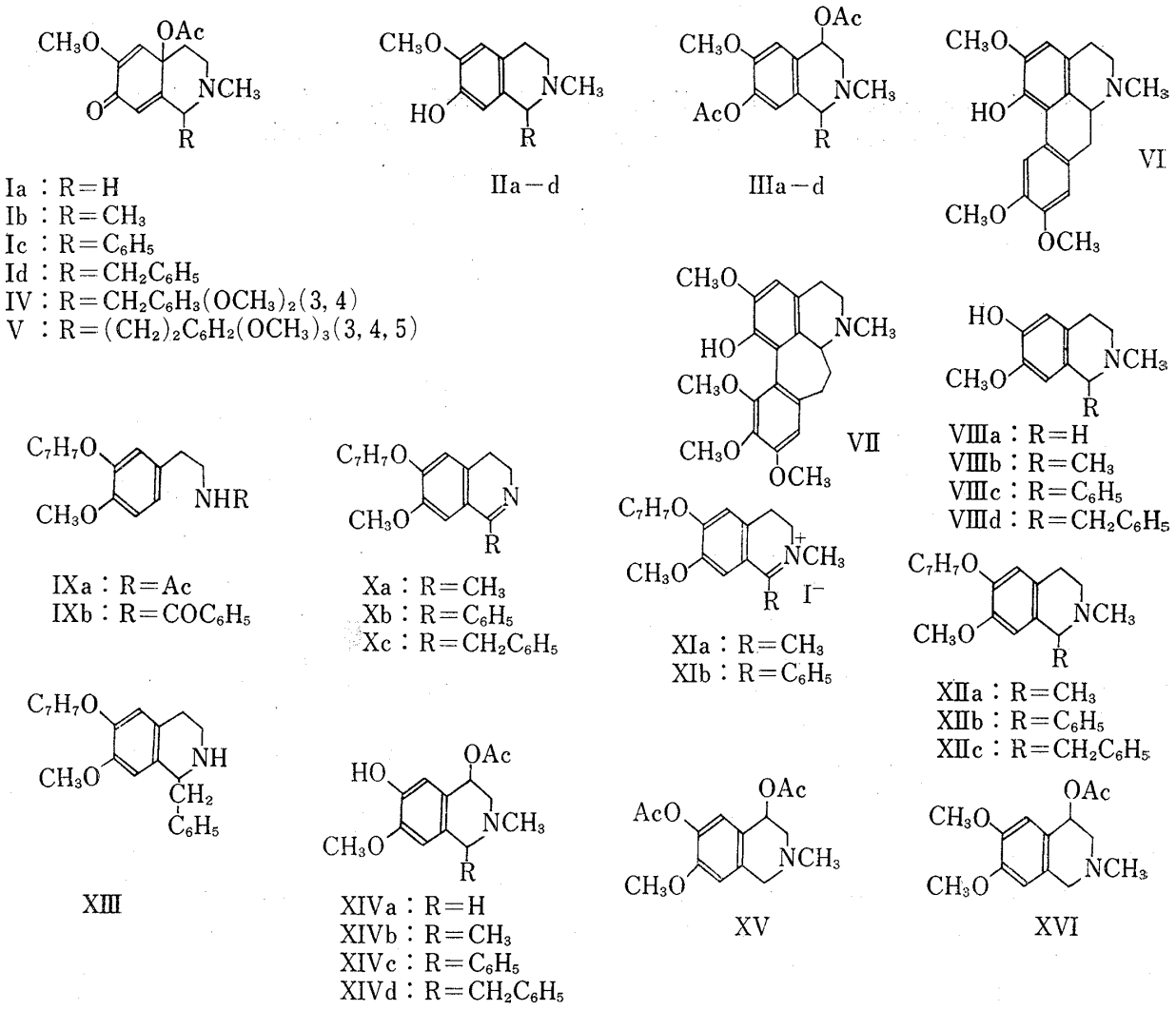

Chart 1

methoxy-2-methylisoquinoline [(VIIIb), (VIIIc) and (VIIId)] was achieved as follows. Namely, VIIIa was prepared according to the method of Bobbitt and his coworkers.[10] For the preparation of VIIIb, β-(3-benzyloxy-4-methoxyphenyl)ethylacetamide (IXa)[14] was cyclized with phosphoryl chloride (Bischler-Napieralski reaction) to produce the 3,4-dihydroisoquinoline (Xa), methylation of which with methyl iodide gave the methiodide (XIa). The methiodide (XIa) was reduced with sodium borohydride ($NaBH_4$) to yield the tetrahydroisoquinoline (XIIa), whose debenzylation by hydrogenolysis gave (±)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-1,2-dimethylisoquinoline (VIIIb), mp 144.5—147°, as pale yellow prisms. Similar sequence of reactions on β-(3-benzyloxy-4-methoxyphenyl)ethylbenzamide (IXb)[12] furnished (±)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methyl-1-phenylisoquinoline (VIIIc),[12] mp 152.5—154°, as colorless needles. As to the formation of VIIId, the 3,4-dihydroisoquinoline hydrochloride (Xc·HCl) was reduced with $NaBH_4$ to afford the tetrahydroisoquinoline (XIII), which was subjected to the Eschweiler-Clark reaction giving the 2-methyltetrahydroisoquinoline (XIIc). Similar debenzylation of XIIc led to (±)-1-benzyl-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (VIIId),[13] mp 161—162°, as pale yellow needles.

The attempted oxidation of the base (VIIIa) revealed that cold benzene[15] or acetic acid (AcOH)[3] was inadequate as a solvent, because too many spots were detected on thin-layer

14) E. Späth, A. Orechoff, and F. Kuffner, *Chem. Ber.*, **67**, 1214 (1934).
15) Similar reaction of VIIIa in hot benzene gave the 4-acetoxytetrahydroisoquinoline (XIVa) in 31.7% yield.

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chromatography (TLC) and that long reaction time was undesirable. Hence, the reaction was conducted in a large volume of ice-cooled anhydrous methylene chloride (CH_2Cl_2) employing 1.0 to 1.4 eq of $Pb(OAc)_4$ in order to minimize the formation of by-product. Moreover, the oxidant was added in one portion and the reaction was stopped within 5 min to avoid any unnecessary contact of the reactant and the reagent.

Thus the base (VIIIa) was oxidized with 1.03 eq of the oxidant in CH_2Cl_2 to give, after purification through alumina (Activity II—III, Merck) column chromatography, a brown oil (XIVa) in 54.3% yield, which showed a single infrared (IR) absorption band due to carbonyl group at 1720 cm^{-1} excluding a *p*-quinol acetate structure. Moreover, a phenolic hydroxy group was present in the molecule as noted by IR band at 3540 cm^{-1} and the band at 1720 cm^{-1} would be due to an aliphatic acetoxy group, which should be bonded to C-1, C-3 or C-4 position if the ring remained intact. Acetylation of the oily base (XIVa) gave a crystalline diacetate (XV), mp 119—119.5°, whose elemental analysis confirmed the molecular formula as $C_{15}H_{19}O_5N$ pointing out that one acetoxy group was introduced into the original base (VIIIa). When compared nuclear magnetic resonance (NMR) spectrum of the diacetate (XV) with that of 4,7-diacetate (IIIa), both NCH_3 resonance signals were observed at almost identical position (δ 2.45 and δ 2.46) indicating that there was no change in the vicinity of the group. Therefore, possibility of the presence of the acetoxy group at C-1 or C-3 was excluded. Moreover, absence of one proton singlet due to methine bearing acetoxy group evidenced that the group was not substituted at C-1. In reality, methine proton resonance signal appeared at δ 5.88 as triplet (J=3.8 Hz). Accordingly, acetoxy group must be present at C-4 and the oily base was assigned as 4-acetoxy-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (XIVa).

Furthermore, the structure was firmly established as follows. Namely, methylation of the oily base (XIVa) with diazomethane afforded the dimethoxy base, mp 89—92°, which was identical with an authentic sample of 4-acetoxy-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XVI)[3] (mp 90—91.5°) by comparison of each spectral data (IR and NMR) and by mixed fusion.

Thus $Pb(OAc)_4$ oxidation of VIIIa was proved to produce directly the corresponding 4-acetoxy compound (XIVa).

For the purpose of exploring the scope of the present reaction, similar oxidation of 1-substituted derivatives was carried out. 1-Methyl base (VIIIb) was oxidized with the oxidant (1.1 eq) to produce a diastereomeric mixture of (±)-4-acetoxy-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-1,2-dimethylisoquinoline (XIVb) [NMR δ: 5.78—5.95 (1H, m, C-4 H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1725 (aliphatic OAc)] as an oil in 53.6% yield, which was converted into a methiodide of 4,6-diacetate, mp 235—237° (decomp.). When similarly treated with the oxidant

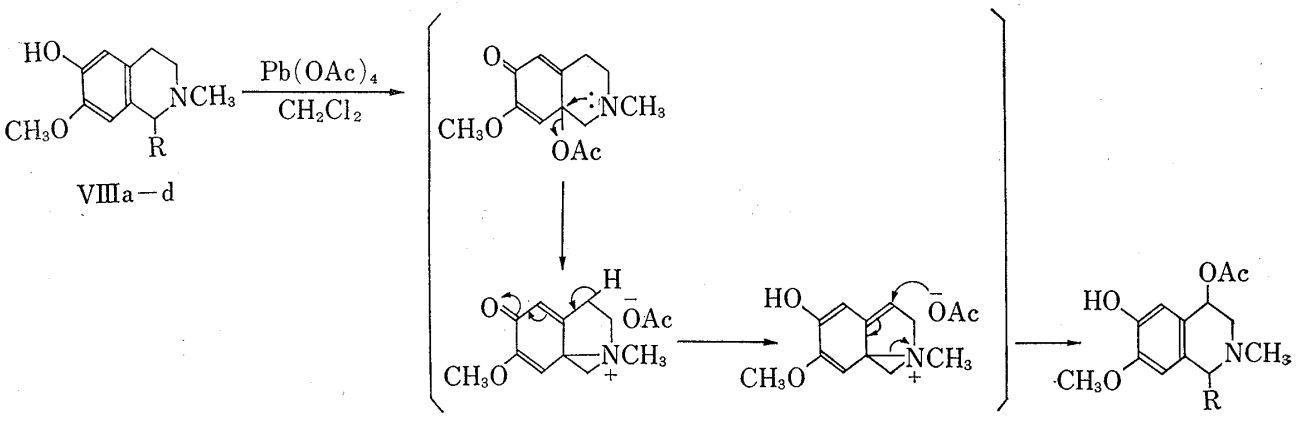

Chart 2

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(1.1 or 1.4 eq), 1-phenyl (VIIIc) or 1-benzyl base (VIIId) afforded a diastereomeric mixture of the corresponding (±)-1-phenyl- or (±)-1-benzyl-4-acetoxy-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline [(XIVc) or (XIVd)] [NMR δ: 5.92 and 6.03—6.25 (1H, m, C-4 H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1720 (aliphatic OAc) or NMR δ: 5.82, 5.96 (1H, each m, C-4 H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1720 (aliphatic OAc)] as each oil in 47.5 or 42.6% yield, respectively. Each of them was converted into a methiodide of the corresponding 4,6-diacetate [mp 230—233° (decomp.) or mp 204—208° (decomp.)]. In the case of 1-substituted base (VIIIb—d), when measured by NCH_3 resonance peak area in products (XIVb—d), XIVb and XIVc consisted of two diastereoisomers of a ratio of 1: 1.4, and XIVd 1: 2.5, respectively.

Thus it was proved that $Pb(OAc)_4$ oxidation of 6-hydroxy-7-methoxy bases (VIIIa—d) produced not *p*-quinol acetates but 4-acetoxy bases (XIVa—d) directly, regardless of substituted groups at C-1 position in the original bases (VIIIa—d). These, when compared in the case of 7-hydroxy-6-methoxy bases (II),[3] deserved attention from both mechanistic and synthetic viewpoint and the reaction pathway could be visualized by the following argument.

Participation of tertiary nitrogen atom in the oxidation process, as depicted in Chart 2, would give rise to an intermediate with bicyclo[3,1,0] system,[16] which must be unstable enough to change instantaneously to 4-acetoxy bases (XIVa—d) through enolization followed by ring opening coupled with attack of acetoxy group at C-4 position.

Furthermore, the finding that 4-acetoxyisoquinolines (XIVa—d) were readily formed from the corresponding phenolic bases (VIIIa—d) appeared to imply a simple and useful method[17] for the synthesis of isopavine alkaloid.

Experimental[18]

1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (VIIIa)——The base (VIIIa) was prepared according to the same procedure as described by Bobbitt and his coworkers.[10] The hydrochloride (VIIIa·HCl), mp 270—280° (lit.[10] mp 276—280°); the free base (VIIIa), mp 163—165° (lit.[10] mp 164—165°). NMR δ (acetone-d_6): 2.32 (3H, s, NCH_3), 3.39 (2H, s, C–1 H), 3.78 (3H, s, OCH_3), 6.57, 6.62 (each 1H, s, aromatic H).

6-Benzyloxy-3,4-dihydro-7-methoxy-1-methylisoquinoline (Xa)——A mixture of the acetamide (IXa)[14] (3 g) and $POCl_3$ (10 ml) in anhydrous $CHCl_3$ (18 ml) was gently heated under reflux for 2 hr. To a residue obtained on removal of the solvent under reduced pressure was added conc. NH_4OH until basified and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over anhydrous K_2CO_3. Removal of the solvent gave 2.77 g (98.2%, mp 97—101°) of the 3,4-dihydroisoquinoline (Xa), which was recrystallized from n-hexane to afford 2.07 g (73.4%, mp 99—101°) of colorless needles (Xa) and an analytical sample had mp 100.5—101.5°. *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.14; H, 6.78; N, 5.02. NMR δ: 2.35 (3H, s, C–1 CH_3), 2.56 (2H, t, J=7.5 Hz, C–4 H), 3.60 (2H, t, J=7.5 Hz, C–3 H), 3.90 (3H, s, OCH_3), 5.18 (2H, s, $OCH_2C_6H_5$), 6.72, 7.12 (each 1H, s, aromatic H), 7.40 (5H, m, C_6H_5). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 1570 (C=N).

6-Benzyloxy-3,4-dihydro-7-methoxy-1,2-dimethylisoquinolinium Iodide (XIa)——To a solution of the 3,4-dihydro base (Xa) (3.5 g) in CH_3OH (30 ml) was added CH_3I (20 ml) and the whole was gently warmed on a water bath for 10 min. On addition of another 10 ml of CH_3I, refluxing was continued for further 1 hr. Condensation of the mixture gave 5.15 g [97.8%, mp 202—219° (decomp.)] of the methiodide (XIa), which was recrystallized from CH_3OH to yield 4.55 g [86.3%, mp 221.5—226.5° (decomp.)] of light yellow needles (XIa) and an analytical sample had mp 231—234° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_2NI$: C, 53.95; H, 5.24; N, 3.31. Found: C, 54.18; H, 5.34; N, 3.38.

(±)-6-Benzyloxy-1,2,3,4-tetrahydro-7-methoxy-1,2-dimethylisoquinoline (XIIa)——To an ice-cooled, stirred suspension of the methiodide (XIa) (662 mg) in CH_3OH (50 ml) was added in portions $NaBH_4$ (0.3 g)

16) J.M. Bobbitt, H. Yagi, S. Shibuya, and J.T. Stock, *J. Org. Chem.*, **36**, 3006 (1971).
17) O. Hoshino, M. Taga, and B. Umezawa, *Heterocycles*, **1**, 223 (1971).
18) All melting points were uncorrected and measured on a Büchi melting point measuring apparatus. NMR spectra were taken with a Japan Electron Optics Labs. Model JNR-4-100 spectrometer in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard, unless otherwise noted. Following abbreviations were used; s: singlet; d: doublet; dd: double doublet; t: triplet; q: quartet; m: multiplet. IR spectra were run on a Hitachi Model 215 infrared spectrometer. Column chromatography was performed over alumina (Activity II—III, Merck) with CH_2Cl_2 as eluting solvent, unless otherwise noted.

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and stirring was continued at room tempt. for 30 min. To a residue obtained on removal of the solvent under reduced pressure was added H_2O and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over anhydrous K_2CO_3. Removal of the solvent gave 480 mg (quantitative, mp 73—75.5°) of the tetrahydroisoquinoline (XIIa), which was recrystallized from *n*-hexane to yield 430 mg (92.5%, mp 77—78.5°) of colorless needles (XIIa) and an analytical sample had mp 78—78.5°. *Anal.* Calcd. for $C_{19}H_{23}O_2N$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.82; H, 7.84; N, 4.76. NMR δ: 1.35 (3H, d, J=7.0 Hz, C-1 CH_3), 2.45 (3H, s, NCH_3), 3.54 (1H, q, J=7.0 Hz, C-1 H), 3.85 (3H, s, OCH_3), 5.11 (2H, s, $OCH_2C_6H_5$), 6.64 (2H, s, aromatic H).

(±)-1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-1,2-dimethylisoquinoline (VIIIb)——A mixture of the tetrahydro base (XIIa) (2.5 g), 2% $PdCl_2$ (3 ml) and active carbon (0.29 g) in AcOH (150 ml) was shaken in an atmosphere of H_2 at room tempt. until H_2 uptake ceased (it required about 75 min). On filtration of the catalyst, the solvent was removed under reduced pressure giving a white solid, which was basified with conc. NH_4OH under ice-cooling. The free base was extracted with $CHCl_3$–iso-PrOH (5: 1). Usual work-up of the extract gave 1.55 g (88.8%. mp 141—144°) of the 6-hydroxy base (VIIIb), which was recrystallized from benzene to afford 1.22 g (70.2%, mp 144.5—146°) of pale yellow prisms (VIIIb) and an analytical sample had mp 144.5—147°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.43; H, 8.21; N, 6.74. NMR δ: 1.38 (3H, d, J=7.0 Hz, C-1 CH_3), 2.47 (3H, s, NCH_3), 3.57 (1H, q, J=7.0 Hz, C-1 H), 3.80 (3H, s, OCH_3), 6.54, 6.58 (each 1H, s, aromatic H). $IR_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH).

6-Benzyloxy-3,4-dihydro-7-methoxy-1-phenylisoquinoline (Xb)——A mixture of the amide (IXb) (2.5 g), mp 144—145° (lit.[12] mp 143—144°), and $POCl_3$ (10 ml) in anhydrous benzene (80 ml) was gently heated under reflux for 1.5 hr. An oily residue obtained on removal of the solvent under reduced pressure was washed several times with ether to give a crystalline mass, which was recrystallized from iso-PrOH yielding 2.03 g [77.2%, mp 200—202° (lit.[12] mp 161—165°)] of the hydrochloride (Xb·HCl). It was basified with conc. NH_4OH yielding the free base, which was repeatedly recrystallized from *n*-hexane–benzene to afford mp 145—146° (lit.[12] mp 143—145°) of colorless fine needles (Xb). NMR δ: 2.62 (2H, t, J=7.0 Hz, C-4 H), 3.67 (3H, s, OCH_3), 3.78 (2H, t, J=7.0 Hz, C-3 H), 5.17 (2H, s, $OCH_2C_6H_5$), 6.80, 6.83 (each 1H, s, aromatic H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (C=N).

6-Benzyloxy-3,4-dihydro-7-methoxy-2-methyl-1-phenylisoquinolinium Iodide (XIb)——The hydrochloride (Xb·HCl) (5.49 g) was basified with conc. NH_4OH under ice-cooling and the free base was extracted with $CHCl_3$. Usual work-up of the extract gave 4.97 g of the free base as a colorless solid. A mixture of the base (Xb) (4.97 g) and CH_3I (30 ml) in CH_3OH (100 ml) was gently refluxed for 8 hr. The same treatment as noted above gave 5.50 g (70.7%, mp 194—201°) of the methiodide (XIb), which was recrystallized from CH_3OH giving 5.17 g [66.5%, mp 197.5—201° (lit.[12] mp 186—187°)] of yellow needles (XIb) and an analytical sample had mp 198—201°. *Anal.* Calcd. for $C_{24}H_{24}O_2NI$: C, 59.39; H, 4.98; N, 2.89. Found: C, 59.04; H, 5.05; N, 2.93.

(±)-1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-2-methyl-1-phenylisoquinoline (VIIIc)——A mixture of the 6-benzyloxy base (XIIb), mp 114—115° (lit.[12] mp 114—115°), 2% $PdCl_2$ (2.5 ml) and active carbon (0.27 g) in AcOH (300 ml) was shaken in an atmosphere of H_2 at room tempt. until H_2 uptake ceased (it required about 50 min). The catalyst was filtered off and the solvent was removed under reduced pressure to give an oily residue, which was basified with conc. NH_4OH under ice-cooling. The product was taken up in $CHCl_3$–iso-PrOH (5: 1). Usual work-up of the extract gave 2.24 g (99%, mp 130—154°) of the 6-hydroxyisoquinoline (VIIIc), which was recrystallized from benzene to give 1.87 g [82.8%, mp 150—154° (lit.[12] mp 152°)] of colorless needles (VIIIc).

(±)-1-Benzyl-6-benzyloxy-1,2,3,4-tetrahydro-7-methoxyisoquinoline (XIII)——To a water-cooled, stirred solution of the hydrochloride of 3,4-dihydroisoquinoline (Xc) (4.74 g), mp 204—206.5° (lit.[13] mp 204—205°) in CH_3OH (160 ml) was added in portions $NaBH_4$ (1 g) during 8 min and stirring was continued at room tempt. for 1.5 hr. To a residue obtained on removal of the solvent under reduced pressure was added H_2O and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over anhydrous K_2CO_3. Usual work-up of the extract produced 4.21 g (98%, mp 102—105°) of the tetrahydro base (XIII), which was recrystallized from *n*-hexane–benzene to give 3.86 g (89.5%, mp 103—104.5°) of colorless needles (XIII) and an analytical sample had mp 103.5—104.5°. *Anal.* Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.53; H, 6.99; N, 4.05. NMR δ: 3.81 (3H, s, OCH_3), 4.19 (1H, dd, J=5, 7.5 Hz, C-1 H).

(±)-1-Benzyl-6-benzyloxy-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (XIIc)——A mixture of the tetrahydro base (XIII) (3.5 g), 35% formalin (10.5 ml) and 97% HCOOH (10 ml) was heated on a water bath for 6 hr. To a residue obtained on removal of the solvent under reduced pressure was added 5% KOH (50 ml) under ice-cooling and the product was taken up in $CHCl_3$. Usual work-up of the extract gave 3.48 g (96%, mp 67.5—75°) of the 2-methylisoquinoline (XIIc), which was recrystallized from n-hexane to afford 3.10 g (83%, mp 66—68°) of yellow needles (XIIc) and an analytical sample exhibited mp 68—69°. *Anal.* Calcd. for $C_{25}H_{27}O_2N$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.33; H, 7.21; N, 3.66. NMR δ: 2.51 (3H, s, NCH_3), 3.51 (3H, s, OCH_3), 3.75 (1H, dd, J=5, 7.5 Hz, C-1 H), 5.07 (2H, s, $OCH_2C_6H_5$), 6.02, 6.61 (each 1H, s, aromatic H).

(±)-1-Benzyl-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline (VIIId)——A mixture of

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the 6-benzyloxy base (XIIc) (3.24 g), 2% $PdCl_2$ (2.7 ml) and active carbon (0.29 g) in AcOH (250 ml) was shaken in an atmosphere of H_2 at room tempt. until H_2 uptake ceased (it required about 50 min). After filtration of the catalyst, a residue obtained on removal of the solvent under reduced pressure was basified with conc. NH_4OH and the product was taken up in $CHCl_3$. Usual work-up of the exttact afforded 2.27 g (93%, mp 158—161°) of the 6-hydroxyisoquinoline (VIIId), which was recrystallized from iso-PrOH yielding 2.05 g [83%, mp 161—163° (lit.[13] mp 157—158°)] of pale yellow needles (VIIId).

General Procedure for the Reaction of VIII with $Pb(OAc)_4$——To an ice-cooled, stirred solution of the 6-hydroxyisoquinoline (VIIIa—d) was added in one portion $Pb(OAc)_4$ and stirring was continued for 5 min. The whole was washed with conc. NH_4OH and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure (below 30°) gave an oil, which was chromatographed.

1) XIVa: VIIIa (414 mg, 2.15 mmoles), $Pb(OAc)_4$ (980 mg, 2.20 mmoles) and CH_2Cl_2 (120 ml) were used. Chromatography of an oil over alumina (16 g) gave 292 mg (54.2%) of an oil (XIVa) [NMR δ: 2.04 (3H, s, OAc), 2.43 (3H, s, NCH_3), 5.82 (1H, t, $J=3.8$ Hz, C-4 H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 1720 (aliphatic OAc)], a part (205 mg) of which was acetylated with Ac_2O (0.6 ml) and pyridine (3 ml) at room tempt. for 3 days. To a residue obtained on condensation of the solvent under reduced pressure was added H_2O and the mixture was basified with $NaHCO_3$ (solid). The product was taken up in $CHCl_3$. Usual work-up of the extract gave 213 mg of an oil, which was chromatographed over silicic acid (Mallinckrodt) (4 g). Elution with $CHCl_3$ afforded 104.7 mg of colorless oil, which was crystallized from *n*-hexane to yield 82.7 mg (34.5%, mp 118—119.5°) of colorless needles (XV). On further recrystallization from *n*-hexane, the mp raised to 119—119.5°. *Anal.* Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.35; H, 6.52; N, 4.74. NMR δ: 2.08, 2.25 (each 3H, s, OAc $\times$2), 2.45 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 5.88 (1H, t, $J=3.8$ Hz, C-4 H). 6.62, 7.02 (each 1H, s, aromatic H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (aromatic OAc), 1720 (aliphatic OAc).

2) XIVb: VIIIb (207 mg, 1 mmole), $Pb(OAc)_4$ (490 mg, 1.1 mmole) and CH_2Cl_2 (60 ml) were used. Chromatography of an oil over alumina (8 g) gave 142 mg (53.6%) of an oil (XIVb). NMR δ: 1.25, 1.45 [3H, each d, $J=7$ Hz, C-1 CH_3 (1: 1.4)], 2.05 (3H, s, OAc), 2.50, 2.65 [3H, each s, NCH_3 (1: 1.4)]. 3.86 (3H, s, OCH_3), 5.78—5.95 (1H, m, C-4 H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1725 (aliphatic OAc). Acetylation of the oil (XIVb) gave an oil, which was converted into the methiodide, mp 235—237° (decomp.) (95% C_2H_5OH). *Anal.* Calcd. for $C_{17}H_{24}O_5NI$: C, 45.45; H, 5.38; N, 3.12. Found: C, 45.54; H, 5.53; N, 3.26.

3) XIVc: VIIIc (107.6 mg, 0.4 mmole), $Pb(OAc)_4$ (195 mg, 0.44 mmole) and CH_2Cl_2 (20 ml) were used. Chromatography of an oil over alumina (4 g) gave 56 mg (47.5%) of an oil (XIVc). NMR δ: 2.11 (3H, s, OAc), 2.18, 2.22 (3H, each s, NCH_3 (1: 1.4)], 3.54, 3.58 [3H, each s, OCH_3 (1: 1.4)], 4.09, 4.45 (1H, each s, C-1 H (1: 1.4)]. Acetylation of the oil (XIVc) gave an oil, which was converted into the methiodide, mp 230—233° (decomp.) (95% C_2H_5OH). *Anal.* Calcd. for $C_{22}H_{26}O_5NI$: C, 51.67; H, 5.12; N, 2.74. Found: C, 51.58; H, 4.96; N, 2.88.

4) XIVd: VIIId (425 mg, 1.67 mmoles), $Pb(OAc)_4$ (975 mg, 2.2 mmoles) and CH_2Cl_2 (120 ml) were used. Chromatography of an oil over alumina (16 g) gave 199 mg (42.6%) of an oil (XIVd). NMR δ: 2.04, 2.09 [3H, each s, OAc (2.5: 1)], 2.57, 2.63 [3H, each s, NCH_3 (1: 2.5)], 3.42, 3.47 [3H, each s, OCH_3 (2.5: 1)], 5.82, 5.96 [1H, each m, C-4 H (2.5: 1)]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1720 (aliphatic OAc). Acetylation of the oil (XIVd) produced an oil, which was converted into the methiodide, mp 204—208° (decomp.) (iso-PrOH). *Anal.* Calcd. for $C_{23}H_{28}O_5NI \cdot \frac{1}{2}H_2O$: C, 51.78; H, 5.39; N, 2.62. Found: C, 51.75; H, 5.27; N, 2.38.

Methylation of XIVa——A solution of the 4-acetoxy base (XIVa) (192 mg) and CH_2N_2 in CH_3OH (2 ml) was kept in a refrigerator for 12 hr. Removal of the solvent gave 154.6 mg of an oil, which was chromatographed over silicic acid (Mallincrodt) (6.4 g). Elution with $CHCl_3$ afforded 66.4 mg (32.8%) of an oil (XVI), which was crystallized from n-hexane to yield 37.5 mg (18.5%, mp 88—91.5°) of colorless needles (XVI). Recrystallization from the same solvent furnished 30.4 mg (15%, mp 89—92°) of the 6,7-dimethoxyisoquinoline (XVI), which was identical with an authentic sample (lit.[3] mp 90—91.5°) in all respects.

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