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Studies on Tetrahydroisoquinolines. VII.[1] Synthesis of Homoaporphine *via* a *p*-Quinol Acetate; Total Synthesis of (±)-Kreysigine[2]

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Acid treatment (conc. H_2SO_4–Ac_2O) of a *p*-quinol acetate (VIII) derived from phenolic (±)-1-phenethylisoquinoline (III) by means of Pb $(OAc)_4$ oxidation was found to afford readily (±)-O-acetylhomoaporphine (I). Consequently, synthesis of (±)-kreysigine (II) was accomplished *via* the corresponding *p*-quinol acetate (XV).

In a proceeding paper,[1] we described a new method for aporphine synthesis, in which generation of *p*-quinol acetate and its treatment with acid were crucial steps. In order to amplify the applicability of the method, we attempted to synthesize a model compound (I)[4] having homoaporphine skeleton and found that I was readily formed. Hence total synthesis of (±)-kreysigine (II),[4–6] an alkaloid from *Kreysigia multiflora*, was carried out by its application.

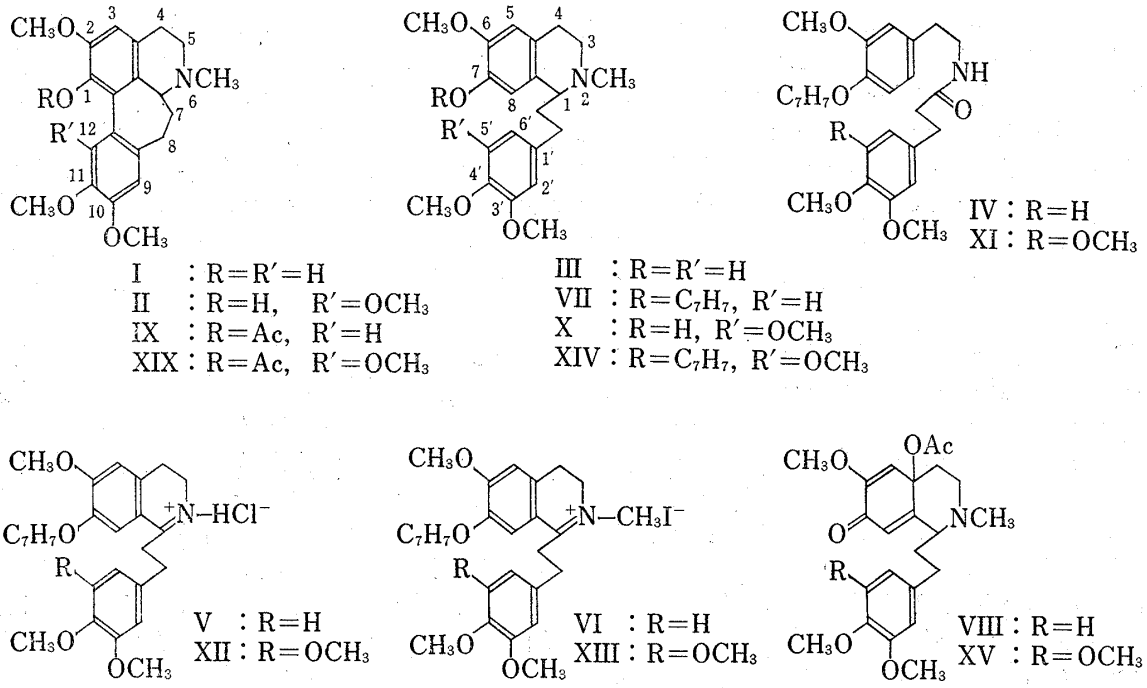

Chart 1

1) Part VI: O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 1302 (1974).
2) The preliminary communication of this work appeared in O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, **1972**, 740.
3) Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
4) T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 1923.
5) A. Battersby, R.B. Bradbury, R.B. Herbert, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 450.
6) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **36**, 3733 (1971).

(±)-1-Homoveratryl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (III) as the starting material for a required *p*-quinol acetate was obtained in the following manner. Namely, 4-benzyloxy-3-methoxy-phenethylamine and the acid chloride derived from 3,4-dimethoxydihydrocinnamic acid[7] by thionyl chloride were subjected to Schotten-Baumann reaction to leave the amide (IV), mp 127—128°, heating of which with phosphoryl chloride ($POCl_3$) in anhydrous toluene caused ring-closure to furnish 3,4-dihydroisoquinoline hydrochloride (V), mp 174—175°. The free base was reacted with methyl iodide (CH_3I) in hot benzene to afford methiodide (VI), mp 185—186.5°, whose sodium borohydride ($NaBH_4$) reduction in methanol (CH_3OH) gave (±)-tetrahydroisoquinoline (VII) quantitatively. On debenzylation of the benzyloxy base with palladium on carbon in acetic acid (AcOH) including conc. hydrochloric acid (HCl), (±)-1-homoveratryl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (III) was produced as an oil.

Lead tetraacetate [$Pb(OAc)_4$] oxidation of the base (III) in AcOH led to an amorphous substance, which was undoubtedly *p*-quinol acetate (VIII) as revealed by characteristic infrared (IR) bands at 1745, and 1670, 1650 and 1630 (shoulder) cm^{-1} for acetoxyl group and conjugated dienone grouping, respectively. Treatment of the crude *p*-quinol acetate (VIII) with conc. sulfuric acid (H_2SO_4) in acetic anhydride (Ac_2O) at room temperature furnished an amorphous substance, which was subjected to silicic acid column chromatography. Elution with chloroform ($CHCl_3$): CH_3OH (200: 1—100: 1) gave white crystals, mp 154—159°, in 16% yield. When recrystallized its melting point raised to 163—164°. Its molecular formula agreed well with $C_{23}H_{27}O_5N$ (mol. wt.=397.45) as supported by elemental analysis and mass spectrum [*m/e*: 397 (M^+)]. Furthermore the presence of aromatic acetoxy group was exhibited by IR band at 1755 cm^{-1} and its nuclear magnetic resonance (NMR) spectrum showed three proton singlet at δ 2.07 for an acetoxy, three proton singlet at δ 2.38 for a N-methyl, and six proton singlet at δ 3.81 for two methoxy groups, and three proton each singlet at δ 6.70, 6.72 and 6.86 for three aromatic protons. All these data and especially the presence of uncoupled three aromatic protons strongly suggested its correct structure as (±)-1-acetoxy-2,10,11-trimethoxy-homoaporphine (IX). Furthermore, hydrolysis of (±)-IX with 4N HCl in CH_3OH at 80° gave phenolic (±)-homoaporphine (I), mp 199—200°, the mp and NMR spectral data of which were identical with those published[4] for an authentic sample.

Thus it was proved that homoaporphine skeleton could readily be constructed *via p*-quinol acetate.

For the purpose of developing the above method, a synthesis of (±)-kreysigine (II) was undertaken and the starting material, phenolic (±)-1-trimethoxyphenethylisoquinoline (X),[8,9] was prepared as follows. Namely methyl 3,4,5-trimethoxydihydrocinnamate was heated with phenethylamine to give N-(4-benzyloxy-3-methoxyphenethyl)-3′,4′,5′-trimethoxyphenylpropionamide (XI), mp 102—104°, cyclization of which was effected by the action of $POCl_3$ in anhydrous toluene to give 3,4-dihydroisoquinoline hydrochloride (XII), mp 203—205°. Reaction of the free base with CH_3I gave methiodide (XIII), mp 184—185.5°, whose reduction with $NaBH_4$ yielded (±)-tetrahydroisoquinoline (XIV) as an oil. Finally, debenzylation of the base by hydrogenolysis gave phenolic (±)-tetrahydroisoquinoline (X) as an oil.

The (±)-phenethylisoquinoline (X) was subjected to $Pb(OAc)_4$ oxidation in AcOH to furnish an amorphous substance, which had characteristic IR bands at 1740 and 1670, 1640 and 1630 (shoulder) cm^{-1} due to acetoxy group and conjugated dienone grouping suggesting that it was composed largely of *p*-quinol acetate (XV). Immediate treatment of the crude *p*-quinol acetate with conc. H_2SO_4 in Ac_2O gave an amorphous substance, which was purified using silicic acid column chromatography. The first eluate with $CHCl_3$ afforded a crystalline

7) J. Iwao and K. Tomino, *Yakugaku Zasshi*, **74**, 814 (1956).
8) A. Brossi, J. Van Burik, and S. Teitel, *Helv. Chim. Acta*, **51**, 1965 (1968).
9) M.A. Schwartz, B.F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973).

indoline derivative, mp 145—146°. In its NMR spectrum chemical shifts due to two acetoxy (δ 2.25 and 2.28), an N-methyl (δ 2.79) and a methoxy (δ 3.76) groups, and one aromatic proton (δ 6.74) were observed. Moreover, two methylene protons which coupled with each other at δ 2.95 and 3.30 (J=7.5 Hz) were present and the molecular weight was 279 in mass spectral measurement. Accordingly the structure of indoline could be assigned as 6,7-diacetoxy-or 4,6-diacetoxy-5-methoxy-2-methylindoline [(XVI) or (XVII)]. Of these two the former was preferred, because its formation was reasonably considered as derived from *o*-quinol acetate (XVIII) existed in the crude so-called *p*-quinol acetate (XV), although the mechanistic details for its formation was not assured.

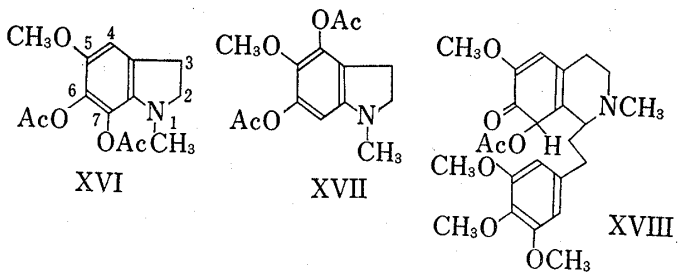

Chart 2

The second eluate with $CHCl_3$–CH_3OH (100: 1—50: 1) gave an amorphous substance, which was further purified using preparative thin-layer chromatography (TLC) to produce (±)-O-acetylkreysigine (XIX), mp 128.5—129°, in 18% yield. Among others the presence of two aromatic protons (δ 6.58 and 6.77) without any coupling in its NMR spectrum accounted for ring-closure to homoaporphine skeleton.

Hydrolysis of the (±)-O-acetylkreysigine (XIX) with 4N HCl in CH_3OH afforded (±)-kreysigine (II),[4–6] mp 185.5—186.5°, in 56% yield. Identity with an authentic sample was given by comparison of their IR and NMR spectra.

Thus we developed a new method for synthesis of homoaporphine skeleton. Especially synthesis of (±)-kreysigine (II) *via* a *p*-quinol acetate would be worthy for some comment; first in the starting phenolic (±)-phenethylisoquinoline (X) there was no need for functionalization, second the yield was comparatively high and third the principle used was considered presumably as a possible biosynthetic pathway.

Experimental[10]

N-(4-Benzyloxy-3-methoxyphenethyl)-3′,4′-dimethoxyphenylpropionamide (IV)——A mixture of 3,4-dimethoxydihydrocinnamic acid[7] (7.26 g) and $SOCl_2$ (35.5 g) was refluxed for 1 hr. On removal of excess $SOCl_2$ under reduced pressure, the whole was dissolved in anhydrous ether. To an ice-cold, stirred solution of 4-benzyloxy-3-methoxyphenethylamine in ether (prepared from the oxalate of the amine (10 g), 5% KOH (200 ml) and ether (200 ml)] was added dropwise the above solution of acid chloride over a period of 70 min and stirring was continued for further 30 min at the same temperature and for additional 30 min at room temp. Ether was removed under reduced pressure without any warming and the product was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with 5% HCl and brine and dried. Usual work-up gave amide (IV) (11 g, 74%), mp 119—125°, as light brown crystals. When recrystallized from benzene–*n*-hexane the mp was raised to 123—126° (9.7 g, 65%). Recrystallization yielded an analytical sample, mp 127—128°. *Anal.* Calcd. for $C_{27}H_{31}O_5N$: C, 72.14; H, 6.95; N, 3.12. Found: C, 71.97; H, 6.93; N, 3.43. NMR δ: 2.37 (2H, t, J=7.5 Hz, $COCH_2CH_2$–), 2.65 (2H, t, J=7.5 Hz, $-CH_2CH_2NH$–), 2.86 (2H, t, J=7.5 Hz, $-CO-CH_2CH_2$–), 3.82 (9H, s, $OCH_3\times3$), 5.10 (2H, s, $ArCH_2O$–), 7.38 (5H, m, $C_6H_5CH_2O$–). IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1640 (C=O).

7-Benzyloxy-1-homoveratryl-6-methoxy-3,4-dihydroisoquinoline Hydrochloride (V)——A mixture of amide (IV) (8 g) and $POCl_3$ (8 ml) in anhydrous toluene (40 ml) was refluxed at 120—125° (bath temp.) for

10) 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-4H-100 spectrometer in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard. Following abbreviations were used: s; singlet, bs; broad singlet, t; triplet, dt; defused triplet, m; multiplet, AB q; AB quartet. Mass spectra were measured with a Hitachi Model RMU-6E mass spectrometer. IR spectra were run on a Hitachi Model 225 infrared spectrometer. Preparative TLC was performed over Silica gel GF_{254} (Merck).

1 hr. Yellow crystalline hydrochloride which precipitated on concentration of the reaction mixture was filtered up, washed well with petroleum ether and weighed 8.05 g (95%, mp 132—139°). Recrystallization from iso-PrOH gave light yellow needles (V) (6.05 g, 71%), mp 170—173°. Further recrystallization furnished an analytical sample, mp 174—175°. *Anal.* Calcd. for $C_{27}H_{30}O_4NCl$: C, 69.29; H, 6.46; N, 2.99. Found: C, 68.83; N, 6.56; N, 2.82. IR ν_{max}^{KBr} cm^{-1}: 1650, 1565 (C=NH). Free base, NMR δ: 2.58 (2H, t, J=7.5 Hz, C-4 H), 2.85 (4H, bs, C-1 CH_2CH_2–), 3.62 (2H, t, J=7.5 Hz, C-3 H), 3.80 (6H, s, $OCH_3\times2$), 3.88 (3H, s, OCH_3), 5.08 (2H, s, $ArCH_2O$–), 6.71 (2H, s, aromatic H), 6.74 (2H, AB q, J=12 Hz, J=8 Hz, C-5′ H, and C-6′ H), 7.01 (1H, s, aromatic H), 7.35 (5H, m, $C_6H_5CH_2O$–).

7-Benzyloxy-1-homoveratryl-6-methoxy-2-methyl-3,4-dihydroisoquinolinium Iodide (VI)——Neutralization of hydrochloride (V) (2.0 g) with conc. NH_4OH, extraction with $CHCl_3$ and usual work-up gave free base as an oil. A solution of the base and CH_3I (5 ml) in benzene (20 ml) was warmed at 55° (bath temp.) for 40 min. Concentration of the reaction mixture under reduced pressure gave methiodide (VI) (2.1 g, 88%), mp 180—183.5°. Recrystallization from CH_3OH–C_2H_5OH gave yellow prisms (1.88 g, 78%), mp 184—186°. Further recrystallization yielded an analytical sample, mp 185—186.5°. *Anal.* Calcd. for $C_{28}H_{32}O_4NI$: C, 58.64; H, 5.62; N, 2.44. Found: C, 58.31; H, 5.66; N, 2.52. NMR δ: 3.58 (3H, s, $=\overset{+}{N}(I^-)-CH_3$), 3.73 (6H, s, $OCH_3\times2$), 3.93 (3H, s, OCH_3), 5.06 (2H, s, $ArCH_2O$–), 6.57 (2H, AB q, J=23 Hz, J=8 Hz, C-5′ and C-6′ H), 6.68, 6.89, 7.12 (each 1H, s, aromatic H), 7.30 (5H m, $C_6H_5CH_2O$–). IR ν_{max}^{KBr} cm^{-1}: 1625, 1560 ($C=\overset{+}{N}(I^-)CH_3$).

(±)-7-Benzyloxy-1-homoveratryl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII)——To a stirred suspension of methiodide (VI) (3 g) in CH_3OH (80 ml) was added $NaBH_4$ (1 g) with occasional ice-cooling over a period of 30 min, when a clear solution was slowly resulted. On additional 1 hr's agitation at room temp., removal of the solvent under reduced pressure and addition of water, the product was taken up in ether. Usual work-up gave (±)-tetrahydroisoquinoline (VII) (2.39 g, quantitative) as a brown oil. NMR δ: 2.41 (3H, s, NCH_3), 3.32 (1H, t, J=7 Hz, $=CHCH_2$–), 3.80 (9H, s, $OCH_3\times3$), 5.03 (2H, s, $ArCH_2O$–), 6.55 (2H, s, aromatic H), 6.64 (1H, s, aromatic H), 7.30 (5H, m, $C_6H_5CH_2O$–). Picrolonate: yellow needles, mp 144—145° (C_2H_5OH). *Anal.* Calcd. for $C_{38}H_{41}O_9N_5$: C, 64.12; H, 5.81; N, 9.84. Found: C, 64.16; H, 5.65; N, 9.91.

(±)-1-Homoveratryl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (III)——A mixture of benzyloxy base (VII) (1.2 g), 2% $PdCl_2$ (3.2 ml) and active carbon (360 mg) in AcOH (60 ml) was shaken in a hydrogen atmosphere for about 1 hr. Catalyst was filtered off and the solvent was removed under reduced pressure. To the residue was added water and after basification with conc. NH_4OH the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave phenolic (±)-base (III) (818 mg, 85%) as a brown oil. NMR δ: 2.42 (3H, s, NCH_3), 3.35 (1H, t, J=7 Hz, $=CHCH_2$–), 3.78 (9H, s, $OCH_3\times3$), 6.51, 6.64 (each 1H, s, aromatic H), 6.71 (3H, bs, aromatic H). III was used in the following reaction without purification.

(±)-1-Acetoxy-2,10,11-trimethoxyhomoaporphine (IX)——To a stirred solution of phenolic (±)-base (III) (960 mg) in AcOH (15 ml) was added Pb $(OAc)_4$ (1.7 g) in one portion under ice-cooling and stirring was continued for 40 min. On addition of water to the reaction mixture and basification with $NaHCO_3$ (powder), the product was taken up in $CHCl_3$. Treating usually of the $CHCl_3$ layer left an amorphous product (VIII) (595 mg). IR ν_{max}[11] cm^{-1}: 1745 (OAc), 1670, 1650, 1630 (shoulder) (dienone). To an ice-cold solution of the product (VIII) in Ac_2O (6 ml) was added dropwise a mixture of conc. H_2SO_4 (300 mg) in Ac_2O (1 ml) with stirring over a period of 5 min and the agitation was continued for 1 hr at room temp. The reaction mixture was poured into ice water and the whole was washed with ether. The aqueous layer was basified with $NaHCO_3$ (powder) and extracted with $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave an amorphous mass (410 mg), which was chromatographed over silicic acid (12 g). Elution with $CHCl_3$–CH_3OH (200: 1—100: 1) furnished white crystalline (±)-homoaporphine (IX) (171 mg, 16%), mp 154—159°, whose recrystallization from benzene–*n*-hexane left colorless needles (132 mg, 12%), mp 161—163°. Further recrystallization gave an analytical sample, mp 163—164°. *Anal.* Calcd. for $C_{23}H_{27}O_5N$ (mol. wt.=397.45): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.41; H, 6.87; N, 3.40. NMR δ: 2.07 (3H, s, OAc), 2.38 (3H, s, NCH_3), 3.81 (6H, s, $OCH_3\times2$), 3.88 (3H, s, OCH_3), 6.70, 7.74, 6.86 (each 1H, s, aromatic H). IR ν_{max}[11] cm^{-1}: 1755 (OAc), 1602 (C=C). Mass Spectrum *m/e*: 397 (M^+).

(±)1-Hydroxy-2,10,11-trimethoxyhomoaporphine (I)——A solution of (±)-acetylhomoaporphine (IX) (200 mg) and 4N HCl (20 ml) in CH_3OH (20 ml) was heated for 1.5 hr at 80° (bath temp.). On removal of the solvent under reduced pressure and dilution with water, the whole was basified with $NaHCO_3$ (powder) and the product was taken up in $CHCl_3$. Usual treatment of the $CHCl_3$ layer left a greasy solid, whose trituration with *n*-hexane gave phenolic (±)-homoaporphine (I), (147 mg, 80%), mp 199—200° (lit.[4] mp 195—196°). Its NMR spectrum was identical with that published[4] for an authentic sample.

Methyl 3,4,5-Trimethoxydihydrocinnamate——A mixture of acid (9.5 g) and conc. H_2SO_4 (1.5 ml) in

11) IR spectra were taken with a Hitachi Model 215 spectrometer in $CHCl_3$ solution.

CH_3OH (50 ml) was refluxed for 4 hr at 95° (bath temp.). On removal of the solvent, ice water was added to the residue and the product was taken up in ether. The ether layer was washed with saturated $NaHCO_3$ and treating usually gave colorless crystalline ester (8.9 g, 89%), mp 45—46°, whose recrystallization from *n*-hexane yielded colorless plates, mp 45—46°. *Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.17. Found: C, 61.54; H, 7.17. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O).

N-(4-Benzyloxy-3-methoxyphenethyl)-3′,4′,5′-trimethoxyphenylpropionamide (XI)——A mixture of 4-benzyloxy-3-methoxyphenethylamine [prepared from oxalate of the amine (5 g) and 10% KOH (40 ml)] and methyl dihydrocinnamate (3.63 g) was heated at 160° (bath temp.) for 6.5 hr. During the reaction, CH_3OH formed was slowly distilled off under reduced pressure. When cooled, the reaction mixture was dissolved in $CHCl_3$ and rinsed successively with 5% HCl and brine. Usual treatment of the $CHCl_3$ layer left amide (XI) (6.1 g, 88%), mp 95—99°, whose recrystallization from benzene–*n*-hexane yielded colorless needles (5.5 g, 80%), mp 102—104° (lit.[8] mp 97—99°).

7-Benzyloxy-6-methoxy-1-(3′,4′,5′-trimethoxyphenethyl)-3,4-dihydroisoquinoline Hydrochloride (XII)——A mixture of amide (XI) (3.9 g), $POCl_3$ (4 ml) and anhydrous toluene (20 ml) was refluxed gently at 115—120° (bath temp.) for 1.5 hr. When cooled, orange yellow crystals precipitated was filtered up and washed well with petroleum ether. The crystalline hydrochloride had mp 146—155° and weighed 3.98 g (98%). Recrystallization from iso-PrOH–CH_3OH gave hydrochloride (XII) (3.1 g, 77%), as yellow scales. When further recrystallized its mp raised to 203—205° (lit.[8] mp 209—211°).

7-Benzyloxy-6-methoxy-1-(3′,4′,5′-trimethoxyphenethyl)-methyl-3,4-dihydroisoquinolinium Iodide (XIII)——A solution of the base [prepared from hydrochloride (XII) (6.7 g)] and CH_3I (14 ml) in C_2H_5OH (34 ml) was warmed at 53—55° (bath temp.) for 40 min. Concentration of the reaction mixture under reduced pressure gave yellow crystalline methiodide (XIII) (7.6 g, 94%), mp 181.5—184°, whose recrystallization from C_2H_5OH–CH_3OH furnished yellow prisms (XIII) (6.9 g, 85%), mp 184—185.5°, (lit.[8] mp 159—161°). *Anal.* Calcd. for $C_{29}H_{34}O_5NI$: C, 57.91; H, 5.70; N, 2.33. Found: C, 58.12; H, 5.67; N, 2.65. NMR δ: 3.75 (6H, s), 3.77 (6H, s), 3.99 (3H, s) ($OCH_3\times4$, NCH_3), 5.15 (2H, s, $ArCH_2O$–), 6.38 (2H, s, C-2′, 6′ H), 6.89, 7.16 (each 1H, s, aromatic H), 7.36 (5H, m, $C_6H_5CH_2O$–). IR ν_{max}^{KBr} cm^{-1}: 1630, 1565 ($C=\overset{+}{N}CH_3$).

(±)-7-Benzyloxy-6-methoxy-1-(3′,4′,5′-trimethoxyphenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (XIV)——To a sitrred suspension of methiodide (XIII) (2.5 g) in CH_3OH (70 ml) was added $NaBH_4$ (800 mg) with occasional ice-cooling, when the suspension gradually went to a clear solution. On additional 1 hr's agitation at room temp. and removal of the solvent under reduced pressure, water was added to the residue and the product was taken up in ether. Usual treatment of the ether layer left a pale yellow oily (±)-base (XIV) (2.03 g, quantitative). NMR δ: 1.98 (2H, defused q, $=CH-CH_2CH_2$–), 2.48 (3H, s, NCH_3), 3.43 (1H, dt, $=CHCH_2$–), 3.84 (9H, s, $OCH_3\times3$), 3.87 (3H, s, OCH_3), 5.11 (2H, s, $ArCH_2O$–), 6.38 (2H, s, C-2′, 6′ H), 6.62, 6.63 (each 1H, s, aromatic H), 7.35 (5H, m, $C_6H_5CH_2O$–). Picrolonate: mp 166—167° (C_2H_5OH–CH_3OH). *Anal.* Calcd. for $C_{39}H_{43}O_{10}N_5$: C, 63.15; H, 5.85; N, 9.44. Found: C, 63.10; H, 5.79; N, 9.35.

(±)-7-Hydroxy-6-methoxy-1-(3′,4′,5′-trimethoxyphenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (X)——To a solution of (±)-benzyloxy isoquinoline (XIV) (2 g) in AcOH (100 ml), 2% $PdCl_2$ (4.8 ml) and active carbon (540 mg) were added and the whole was shaken in a hydrogen atmosphere. Hydrogen up-take ceased in about 1.5 hr. On removal of catalyst and of the solvent under reduced pressure, water was added to the residue and the product was taken up in $CHCl_3$ after basification with conc. NH_4OH. Usual work-up of the $CHCl_3$ layer left phenolic (±)-base (X) (1.57 g, 94%) as a yellow oil. NMR δ: 2.50 (3H, s, NCH_3), 3.45 (1H, dt, $=CHCH_2$–), 3.85 (s, OCH_3), 3.87 (9H, s, $OCH_3\times3$), 6.45 (2H, s, C-2′, 6′ H), 6.60, 6.72 (each 1H, aromatic H). IR ν_{max}[11] cm^{-1}: 3540 (OH). Styphnate: yellow crystals, mp 167—168.5° (C_2H_5OH). *Anal.* Calcd. for $C_{28}H_{32}O_{13}N_4$: C, 53.16; H, 5.15; N, 8.85. Found: C, 53.26; H, 5.15; N, 8.80. Phenolic (±)-base (X) was used in the following reaction without purification.

(±)-O-Acetylkreysigine (XIX)——To a stirred solution of phenolic (±)-base (X) (1.3 g) in AcOH (20 ml) was added $Pb(OAc)_4$ (2.8 g) in one portion with ice-cooling and stirring was continued for 30 min. On addition of water to the reaction mixture, the whole was basified with $NaHCO_3$ (powder) and extracted with $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave amorphous *p*-quinol acetate (XV) (1.33 g). To a well stirred solution of the crude *p*-quinol acetate (XV) in Ac_2O (12 ml) was added a solution of conc. H_2SO_4 (700 mg) in Ac_2O (2 ml) over a period of 5 min and the whole was stirred at room temp. for 1 hr. The reaction mixture was poured into ice-water and washed with ether. On basification of the aqueous layer with $NaHCO_3$ (powder), the product was taken up in $CHCl_3$. Usual treatment of the $CHCl_3$ layer gave an amorphous solid (1.03 g), which was chromatographed over silicic acid (31 g). Elution with $CHCl_3$ afforded 6,7-diacetoxy-5-methoxy-1-methylindoline (XVI) (15 mg, 1.5%), mp 145—146° (benzene–*n*-hexane). NMR δ: 2.25, 2.28 (each 3H, s, $OAc\times2$), 2.79 (3H, s, NCH_3), 2.95 (2H, t, J=7.5 Hz, C-3 H), 3.30 (2H, t, J=7.5 Hz, C-2 H), 3.76 (3H, s, OCH_3), 6.74 (1H, s, aromatic H). IR ν_{max}[11] cm^{-1}: 1770 (OAc). Mass Spectrum *m/e*: 279 (M^+), 237 (M^+-42), 195, 180 (base peak). Eluate with $CHCl_3$–CH_3OH (200: 1—100: 1) was subjected to preparative TLC using $CHCl_3$–CH_3OH (12: 1) to give (±)-O-acetylkreysigine (XIX) (262 mg, 18%), mp 125—128°, when recrystallized from benzene–*n*-hexane. Further recrystallization gave an analytical sample, mp 128.5—129°. *Anal.* Calcd. for $C_{24}H_{29}O_6N$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.50; H, 6.86; N, 3.56. NMR δ: 2.05

(3H, s, OAc), 2.48 (3H, s, NCH_3), 3.57, 3.85, 3.89, 3.90 (each 3H, s, $OCH_3 \times 4$), 6.58, 6.77 (each 1H, s, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1760 (OAc).

(±)-Kreysigine (II)——A solution of O-acetylkreysigine (XIX) (80 mg) and 4N HCl (8 ml) in CH_3OH (8 ml) was heated for 1.5 hr at 80° (bath temp.). On removal of the solvent under reduced pressure and addition of water to the residue, the whole was basified with $NaHCO_3$ (powder) and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer left a crystalline mass (66 mg), which was chromatographed on preparative TLC using $CHCl_3$–CH_3OH (8: 1) to furnish (±)-kreysigine (II) (40 mg, 56%), mp 172—176°, whose recrystallization from benzene–*n*-hexane yielded colorless crystals, mp 185.5—186.5° (lit.[5] mp 188°). Its IR and NMR spectral data were identical in all respects with that of an authentic sample. NMR δ: 2.42 (3H, s, NCH_3), 3.64, 3.88 (each 3H, s, $OCH_3 \times 2$), 3.90 (6H, s, $OCH_3 \times 2$), 6.65, 6.69 (each 1H, s, aromatic H). IR ν_{max}[11] cm^{-1}: 3540 (OH). Mass Spectrum *m/e*: 385 (M^+), 368 (M^+-17).

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