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Studies on the Syntheses of Heterocyclic Compounds. DCCIX.[1] A Synthetic Approach to Kesselringine

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Phenolic oxidation of 1,2,3,4-tetrahydro-6,7-dihydroxy-1-(4-hydroxy-3-methoxyphenethyl)-2-methylisoquinoline (**14**) with ferric chloride gave the homoproaporphine (**15**), isolated as the corresponding diacetate (**16**), which would be a key intermediate to kesselringine (**6**) from chemical and biogenetic points of view.

Keywords——synthetic approach to kesselringine; kesselringine; phenol oxidation; homoproaporphine; a key intermediate to kesselringine

Previously we have reported that a phenol oxidation of the diphenolic isoquinoline (**1**) gave kreysiginone (**2**)[3,4] whose acidic treatment afforded the enone (**3**)[5] that was reduced to the cyclohexanone (**4**) and cyclohexanols (**5**).[6]

Our product (**5**) is closely similar to an alkaloid kesselringine (**6**),[7] and, therefore, we have tried to accomplish a total synthesis of **6** along with our method. Here we wish to report a synthesis of the homoproaporphine (**15**) which seems to be a key intermediate from chemical and biogenetical points of view.

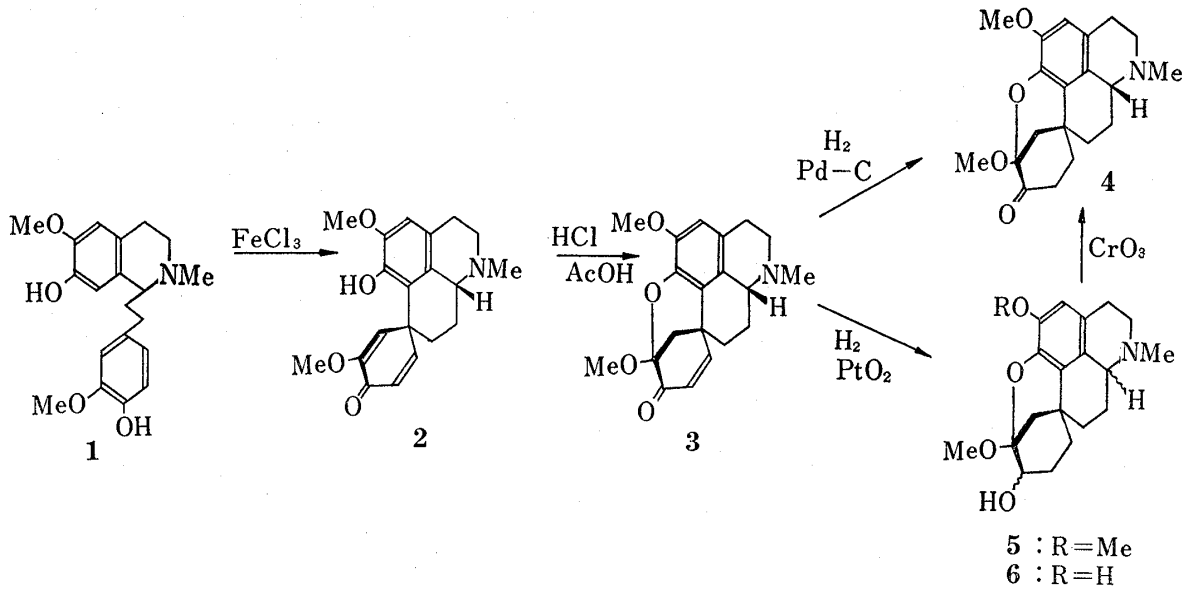

Chart 1

1) Part DCCVIII: T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and T. Nakamura, *Yakugaku Zasshi*, **97**, 519 (1977).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Comm.*, **1967**, 878.
4) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).
5) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *Chem. Comm.*, **1967**, 1103; *J. Chem. Soc.* (*C*), **1968**, 1003.
6) T. Kametani, K. Fukumoto, F. Satoh, K. Kigasawa, and H. Sugi, *Heterocycles*, **3**, 921 (1975).
7) M.K. Jusupov, *Chim. Rastitel. Vecěstv, Taškent*, **1972**, 19.

The starting triphenolic phenethylisoquinoline (**14**) was prepared in the following steps which are outlined in Chart 2. A fusion of 3,4-dibenzyloxyphenethylamine (**7**)[8] with 4-hydroxy-3-methoxyphenylpropionic acid (**8**)[4] at 160—180° gave, in 75% yield, the amide (**9**), mp 109—110°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 3450 (NH) and 1650 (>CO), whose phenolic hydroxyl group was protected by ethoxycarbonylation with methyl chlorocarbonate and triethylamine in cold chloroform to afford the nonphenolic amide (**10**), mp 110—111°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1760 (OCO_2Me) and 1660 (>CO). Bisphler-Napieralski reaction of the amide (**10**) with phosphoryl chloride in boiling benzene gave the 3,4-dihydroisoquinoline (**11**) as an oil, which was immediately converted into the methiodide (**12**), mp 197—198° (decomp.), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (OCO_2Me) and 1620 (>C=$\overset{+}{N}$<), in 72% yield, by treatment with methyl iodide in methanol. Reduction of the methiodide (**12**) with sodium borohydride gave, in 82% yield, the phenolic 1,2,3,4-tetrahydro-2-methylisoquinoline (**13**), $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), $\delta(CDCl_3)$ 2.42 (3H, s, NMe), was characterized as oxalate, mp 138—139°. Debenzylation of **13** was carried out under a current of hydrogen on palladium charcoal in methanol in the presence of hydrochloric acid at room temperature to afford the starting triphenolic isoquinoline (**14**) hydrochloride as a colorless syrup.

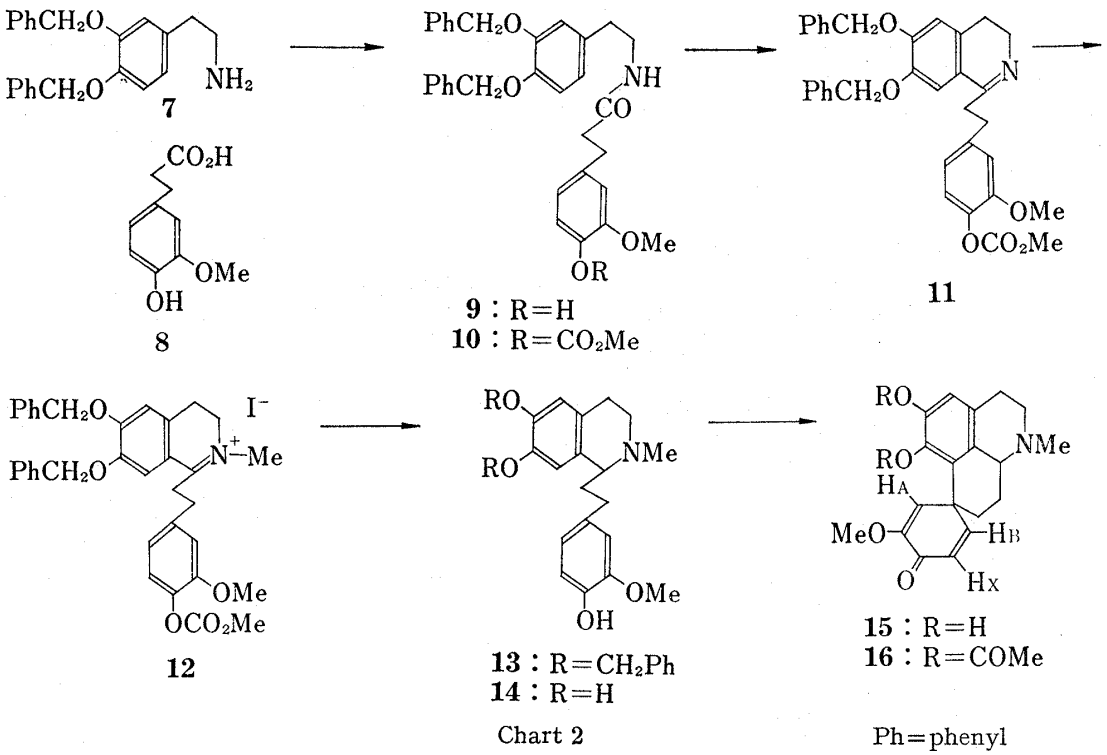

Chart 2 Ph=phenyl

The oxidation of the triphenolic phenethylisoquinoline (**14**) hydrochloride to the homoproaporphine (**15**) was investigated under several conditions by using inorganic reagents, the best procedure being the one in which one molar equivalent of the isoquinoline (**14**) hydrochloride was treated with 8 moles of ferric chloride hexahydrate in water at room temperature for 3 hr in a current of nitrogen. Since the product (**15**) was very unstable in the air, the dienone (**15**) was isolated as the corresponding diacetate (**16**) by acetylation with acetic anhydride in the presence of aqueous ammonium acetate and characterized as its methiodide, mp 235—238° (decomp.) The infrared (IR) spectrum ($CHCl_3$) of the product showed the typical α-methoxylated cross-conjugated dienone absorption[4] at 1660, 1635 and 1605 cm^{-1} in addition to acetoxyl absorption at 1760 cm^{-1} and nuclear magnetic reso-

8) A. Baxter, L.T. Allan, and G.A. Swan, *J. Chem. Soc.*, **1965**, 3645.

nance (NMR) spectrum (δ in $CDCl_3$) revealed three olefinic protons on the dienone ring system as ABX pattern at 5.85 (d, J=2.5 Hz), 6.31 (d, J=10 Hz) and 7.11 (dd, J=10 and 2.5 Hz) along with an aromatic proton at 7.02 as a singlet and an enolic O-methyl resonance at 3.68. These data well support the product to have the structure **16**.

Thus we have prepared a nice intermediate (**15**) to kesselringine (**6**), and the dienone (**15**) or its biogenetic equivalent would be transformed into **6** in nature by a similar mechanism as shown in Chart 1.

Experimental

All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus. IR spectra were measured with a Hitachi 215 grating spectrophotometer and NMR spectra were taken with a JEOL PMX-60 spectrometer with Me_4Si as an internal standard.

N-(3,4-Dibenzyloxyphenethyl)-4-hydroxy-3-methoxyphenylpropionamide (**9**)——A mixture of 3,4-dibenzyloxyphenethylamine (**7**)[8] (10.0 g, 30 mmole) and 4-hydroxy-3-methoxyphenylpropionic acid (**8**)[4] (5.9 g, 30 mmole) was heated at 160° for 20 min and then at 180° for 1 hr in a current of nitrogen. After cooling, the reaction mixture was taken in chloroform. The extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate aqueous solution and water, dried over Na_2SO_4 and evaporated *in vacuo* to give the amide (**9**) (11.5 g, 75%) as colorless prisms, mp 109—110°, after recrystallization from benzene–*n*-hexane, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (–OH), 3450 (>NH) and 1650 (>CO), NMR ($CDCl_3$) ppm: 2.10—3.12 (6H, m, $3\times CH_2$), 3.20—3.63 (2H, m, $CH_2C\underline{H}_2N$), 3.85 (3H, s, OMe), 5.13 (4H, s, $2\times OC\underline{H}_2C_6H_5$), 5.44 (1H, broad, NH), 6.33—7.02 (6H, m, ArH) and 7.16—7.58 (10H, m, $2\times OCH_2C_6\underline{H}_5$), *Anal.* Calcd. for $C_{32}H_{33}O_5N$: C, 75.12; H, 6.50; N, 2.74. Found: C, 75.05; H, 6.55; N, 2.78.

N-(3,4-Dibenzyloxyphenethyl)-3-methoxy-4-methoxycarbonyloxyphenylpropionamide (**10**)——To a stirred solution of the amide (**9**) (7.0 g, 13.7 mmole) and triethylamine (1.7 g, 16.5 mmole) in chloroform (50 ml) was added dropwise methyl chlorocarbonate (1.6 g, 16.5 mmole) under cooling, and the reaction mixture was further stirred for 1 hr at room temperature. After the reaction the mixture was washed with 10% hydrochloric acid and water and dried over Na_2SO_4. Evaporation of the solvent under a reduced pressure gave the nonphenolic amide (**10**) (6.5 g, 84%) as colorless needles, mp 110—111°, from benzene–*n*-hexane, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (>NH), 1760 (–OCO_2Me) and 1660 (>CO), NMR ($CDCl_3$) ppm: 2.10—3.15 (6H, m, $3\times CH_2$), 3.20—3.65 (2H, m, $CH_2C\underline{H}_2N$), 3.81 (3H, s, OMe), 3.88 (3H, s, OMe), 5.13 (4H, s, $2\times OC\underline{H}_2$-$C_6H_5$), 5.58 (1H, m, NH), 6.48—7.14 (6H, m, ArH) and 7.16—7.60 (10H, m, $2\times OCH_2C_6\underline{H}_5$). *Anal.* Calcd. for $C_{34}H_{35}O_7N$: C, 71.69; H, 6.19; N, 2.46. Found: C, 71.76; H, 6.33; N, 2.38.

6,7-Dibenzyloxy-3,4-dihydro-(3-methoxy-4-methoxycarbonyloxyphenethyl)isoquinoline Methiodide (**12**)——A mixture of the amide (**10**) (5.7 g, 10 mmole), phosphoryl chloride (4.6 g) and dry benzene (50 ml) was refluxed for 2 hr and concentrated *in vacuo* to leave a viscous syrup which was washed with ether. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent under a reduced pressure gave the 3,4-dihydroisoquinoline (**11**) (5.0 g) as a pale brown viscous syrup, which was treated with methyl iodide (10 ml) in methanol (10 ml) at room temperature overnight. The reaction mixture was concentrated *in vacuo* to give the methiodide (**12**) (5.0 g, 72%) as pale yellow needles, mp 197—198° (decomp.), from methanol, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (–OCO_2Me) and 1620 (>C=$\overset{+}{N}$<). *Anal.* Calcd. for $C_{35}H_{36}O_6NI$: C, 60.60; H, 5.23; N, 2.02. Found: C, 60.68; H, 5.39; N, 2.00.

6,7-Dibenzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxyphenethyl)-2-methylisoquinoline (**13**)——To a suspension of the above methiodide (**12**) (4.5 g, 6.5 mmole) in methanol (100 ml) was added in portions sodium borohydride (1.0 g) with stirring under cooling. The stirring was continued for 30 min at room temperature, and then the mixture was refluxed for 1 hr. After removal of the solvent by distillation, the resulting residue was treated with saturated ammonium chloride aqueous solution and extracted with chloroform. The extract was washed with saturated ammonium chloride aqueous solution, dried over Na_2SO_4 and evaporated *in vacuo* to give the tetrahydroisoquinoline (**13**) as a pale yellow viscous syrup, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (–OH) and 2780 (–NMe), NMR ($CDCl_3$) ppm: 1.71—2.18 (2H, m, $CH_2C\underline{H}_2CH$), 2.42 (3H, s, NMe), 2.30—3.12 (6H, m, $3\times CH_2$), 3.30—3.50 (1H, m, C_1–H), 3.80 (3H, s, OMe), 5.11 (4H, s, $2\times OC\underline{H}_2C_6H_5$), 6.34—6.90 (5H, m, ArH) and 7.03—7.60 (10H, m, $2\times OCH_2C_6\underline{H}_5$). Recrystallization of the oxalate from methanol-ether afforded colorless needles (3.2 g, 82%), mp 138—139°. *Anal.* Calcd. for $C_{33}H_{35}O_4N\cdot C_2H_2O_4$: C, 70.10; H, 6.22; N, 2.34. Found: C, 69.87; H, 6.30; N, 2.23.

1,2,3,4-Tetrahydro-6,7-dihydroxy-1-(4-hydroxy-3-methoxyphenethyl)-2-methylisoquinoline (**14**)——A mixture of the above tetrahydroisoquinoline (**13**) (2.6 g, 5 mmole), 10% palladium charcoal (250 mg) and concentrated hydrochloric acid (0.5 ml) in methanol (50 ml) was shaken in a current of hydrogen at room temperature and at atmospheric pressure. After absorption of the calculated amount of hydrogen, catalyst was filtered off and the solvent was evaporated *in vacuo* to give the triphenolic isoquinoline (**14**) hydrochloride as a colorless viscous syrup, IR ν_{max}^{film} cm^{-1}: 3540 (–OH), NMR (D_2O) ppm: 2.82 (3H, s, NMe), 3.78 (3H, s, OMe)

and 6.52—6.88 (5H, m, ArH).

Phenol Oxidation of 14——A solution of the triphenolic isoquinoline (**14**) (2.5 g, 7 mmole) in water (100 ml) was added dropwise to a solution of ferric chloride hexahydrate (15 g, 55 mmole) in water (100 ml) with stirring at room temperature during 10 min in a current of nitrogen, and then the stirring had been continued for more 3 hr. The reaction mixture was neutralized with 28% ammonia, and to this solution was added an excess of acetic anhydride and ammonium acetate. After standing overnight, the reaction mixture was basified with 28% ammonia and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a brown syrup (1.0 g), which was chromatographed on silica gel (30 g) using chloroform containing 2% methanol as the eluent to give the homoproaporphine (**16**) (15 mg) as a colorless syrup, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 ($OCOCH_3$), 1660 (>CO), 1635 (C=C) and 1605 (C=C), NMR ($CDCl_3$) ppm: 2.03 (3H, s, OCOMe), 2.23 (3H, s, OCOMe), 2.52 (3H, s, NMe), 3.68 (3H, s, OMe), 5.85 (1H, d, J=2.5 Hz, H_A), 6.31 (1H, d, J=10 Hz, Hx), 7.02 (1H, s, ArH) and 7.11 (1H, dd, J=2.5 and 10 Hz, H_B). The methiodide was recrystallized from methanol to give pale yellow needles, mp 235—238° (decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_6NI$: C, 52.08; H, 5.10. Found: C, 51.62; H, 4.82.

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