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Studies on the Syntheses of Heterocyclic Compounds. DLXVIII.[1] Catalytic Hydrogenation of (±)-Kreysiginone

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Catalytic hydrogenation of the isomeric homoproaporphines (**5a** and **5b**) and the deuterated dienones (**6a** and **6b**) in the presence of platinum catalyst afforded the same mixture of cyclohexanols (**7a** and **7b**). In contrast, reduction of hydrochloride of **5a** on palladium-charcoal provided the cyclohexanone (**8a**) while that of **5b** gave a mixture of the cyclohexanone (**8b**) and the cyclohexenone (**9**).

In a previous study involving the homoproaporphine alkaloid kreysiginone, we described the synthesis and separation of two isomeric homoproaporphines (**5a** and **5b**), obtained by phenolic oxidation of diphenolic phenethylisoquinoline.[3] Since hydrogenation experiments have been shown to be very useful in establishing the configuration of reduced morphinandienones,[4] we now report the results of hydrogenating two dienones (**5a** and **5b**) in the presence of platinum and palladium catalysts.

Catalytic hydrogenation of either of the isomeric dienones (**5a** and **5b**) in methanol in the presence of platinum oxide afforded a mixture of the cyclohexanols (**7a** and **7b**), which were easily separated by recrystallization. The nuclear magnetic resonance (NMR) spectrum of the cyclohexanol (**7a** or **7b**), mp 196—198°, showed the signal assigned to aliphatic OMe group at 3.42 ppm, but no olefinic proton. The structure of cyclohexanol (**7a** or **7b**) was supported by the other physical data.

Another cyclohexanol (**7a** or **7b**) was characterised as its hydrochloride, mp 257—259° (decomp.), and in the NMR spectrum of the free base (**7a** or **7b**), an aliphatic OMe signal was observed at 3.42 ppm.

On the other hand, catalytic hydrogenation of dienone (**5b**) under the same conditions as in case of **5a** gave a mixture, which was separated into two cyclohexanols (**7a** and **7b**) by the same treatment as in case of **5a**. Both compounds were identical with the authentic samples (**7a** and **7b**) obtained from **5a**.

In view of this conversion of both dienones (**5a** and **5b**) into a mixture of the same cyclohexanols (**7a** and **7b**) and based on the previous study[5] regarding configuration of the homoproaporphine, the relative configuration between C_{6a}–hydrogen and C_{3a}–C_9 bond of a cyclohexadienone system of **5a** should be *trans*, and those of **5b** *cis*. Therefore, the platinum catalyst would abstract a hydrogen on the C_{6a}–position to give a common intermediate (**5c**) from the dienones (**5a** and **5b**), which was hydrogenated to afford the same products (**7a** and **7b**). Similar results were reported by us.[6] Namely the treatment of the optical active proto-

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[1] Part DLXVII: T. Kametani, M. Takemura, K. Fukumoto, T. Terui, and A. Kozuka, *Heterocycles*, **2**, 433 (1974).

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[3] T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Commun.*, **1967**, 878; *idem*, *J. Org. Chem.*, 33, 690 (1968).

[4] L.J. Haynes, G.E.M. Husbands, and K.L. Stuart, *J. Chem. Soc.* (*C*), **1968**, 951.

[5] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1970**, 382.

[6] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), **1968**, 191; T. Kametani, M. Ihara, and K. Shima, *J. Chem. Soc.* (*C*), **1968**, 1619.

berberines and 1-benzylisoquinolines under the condition of catalytic hydrogenation on platinum catalyst afforded the corresponding racemic products.

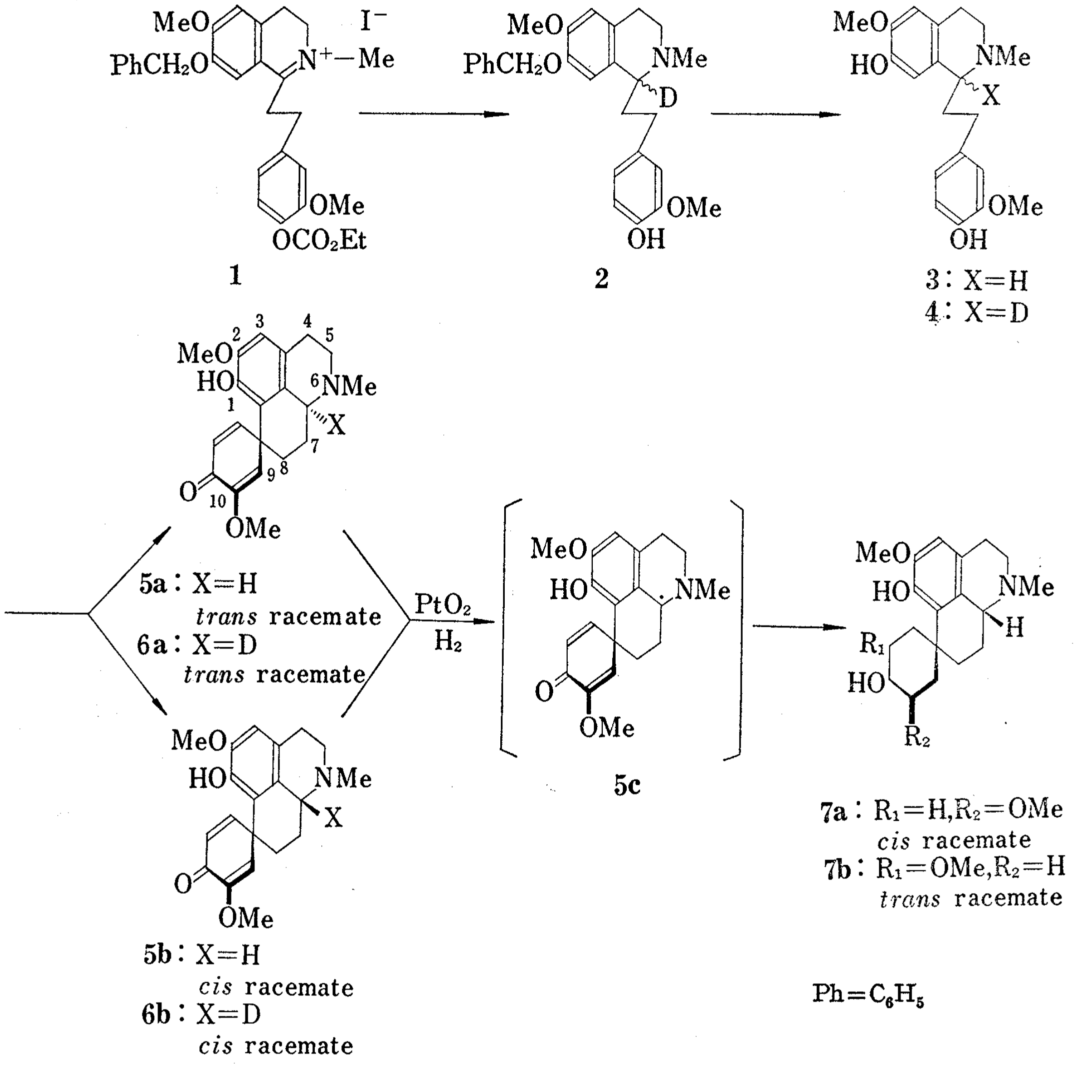

Chart 1

In order to explain this phenomena, the deuterated dienones (**6a** and **6b**) at the C_6-position were synthesized and then hydrogenated on platinum oxide. Reduction of the dihydroisoquinoline methiodide[3] (**1**) with sodium borodeuteride gave the [1-D]-1,2,3,4-tetrahydroisoquinoline (**2**), whose debenzylation with concentrated hydrochloric acid afforded the diphenolic phenethylisoquinoline (**4**). This was converted into dienones (**6a** and **6b**) by phenolic oxidation.

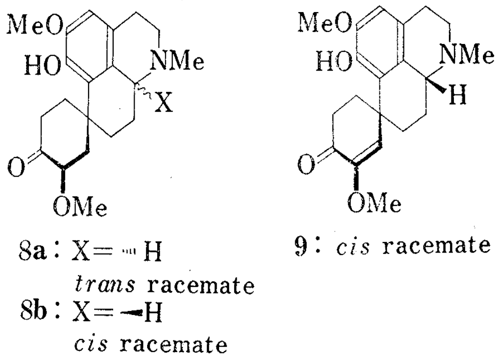

Chart 2

Hydrogenation of the deuterated dienones (**6a** and **6b**) on platinum oxide gave the same cyclohexanols (**7a** and **7b**). It was therefore revealed that both dienones were ruptured homolytically to give a common intermediate (**5c**), which was reduced to afford the same products (**7a** and **7b**).

Catalytic hydrogenation of dienone (**5a**) hydrochloride in the presence of 10% palladium–charcoal afforded a cyclohexanone (**8a**), whose infrared (IR) spectrum showed the carbonyl absorption at 1720 cm^{-1}. The NMR spectrum revealed an aliphatic OMe resonance at 3.43 ppm as a singlet and no peak due to olefinic proton was observed.

However, the same treatment of dienone (**5b**) gave a mixture of cyclohexanone (**8b**) and cyclohexenone (**9**). The latter compound was isolated as leaves, mp 198—200° (decomp.), whose IR spectrum was in good accord with a cyclohexenone system. The NMR spectrum showed the signals at 3.62 (olefinic OMe) and 5.90 ppm (olefinic proton) as singlets.

On the basis of the above results, it was revealed that the homoproaporphine derivative is absorbed on the platinum catalyst and then the proton at C_{6a}–position is ruptured homolytically to afford the intermediatl (**5c**), which is then hydrogenated to the cyclohexanol (**7a** and **7b**).

Experimental

Melting points are uncorrected and IR and NMR spectra were measured on a type Hitachi-215 recording photometer and JNM-NH-60 (60 Mc) with tetramethylsilane as internal standard, respectively. Mass spectra were taken with a Hitachi RMU-7 spectrometer.

7-Benzyloxy-[1-D]-1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (2)——To a stirred suspension of 13 g of 7-benzyloxy-1-(4-ethoxycarbonyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline methiodide (1)[3] in 60 ml of ethanol was added in portions 0.5 g of sodium borodeuteride at 0° during 30 min. After the stirring had been continued for 30 min at room temperature, 20 ml of 20% sodium hydroxide solution was added to the reaction mixture and then it was refluxed for 30 min. Evaporation of the ethanol gave a residue, to which was added 50 ml of water and 2 g of ammonium chloride and the resulting mixture was extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to leave the tetrahydroisoquinoline (2) as a pale brown caramel, NMR ($CDCl_3$) δ: 2.52 (3H, s, $NC\underline{H}_3$), 3.94 and 3.97 (each 3H, s, $2\times OC\underline{H}_3$), 5.23 (2H, s, $OC\underline{H}_2C_6H_5$), 5.90 (1H, broad, OH), 6.60—7.00 (5H, m, Ar$\underline{H}$), 7.30—7.60 (5H, m, $OCH_2C_6\underline{H}_5$), which was identical with those of 7-benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline except C_1–H resonance, Mass Spectrum *m/e*: 434 (M^+). This was converted into the hydrochloride in a usual manner and recrystallized from methanol to give needles (7.5 g), mp 236—238° (decomp.). *Anal.* Calcd. for $C_{27}H_{30}O_4ND\cdot HCl$: N, 2.95. Found: N, 2.98.

[1-D]-1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (4)——A mixture of 7.5 g of tetrahydroisoquinoline (2) hydrochloride, 60 ml of concentrated hydrochloric acid and 60 ml of ethanol was refluxed for 2 hr. Evaporation of the ethanol and water gave 6.5 g of dihydroxyisoquinoline (4) hydrochloride, NMR ($CDCl_3$) (free base) δ: 2.55 (3H, s, $NC\underline{H}_3$), 3.95 (6H, s, $2\times OC\underline{H}_3$), 6.08 (2H, s, $2\times O\underline{H}$), 6.70—7.05 (5H, m, Ar$\underline{H}$). This was used for the following reaction without purification.

Phenolic Oxidation of 4——A solution of 26 g of ferric chloride in 200 ml of water was added to a stirred solution of 6.1 g of dihydroxyisoquinoline hydrochloride in 150 ml of water during 5 min. After the stirring had been continued for 5 hr, the reaction mixture was basified with 28% ammonia and extracted with 1.5 liters of chloroform. The chloroform extract was washed with water, dried over Na_2SO_4, and evaporated to give 5.5 g of a brownish gum, which was chromatographed on 70 g of silica gel using chloroform containing 2% methanol as an eluent with inspection by thin–layer chromatography.

Evaporation of an appropriate fraction gave 3.2 g of the crude dienone (**6a** and **6b**) which was triturated with benzene to give a dienone (**6a**). Recrystallization from chloroform–benzene gave prisms (530 mg; 10%), mp 194—195° (decomp.), IR (KBr) cm^{-1}: 1658 (C=O), 1635 and 1608 (C=C), NMR ($CDCl_3$) δ: 2.46 (3H, s, $NC\underline{H}_3$), 3.58 (3H, s, olefinic $OC\underline{H}_3$), 3.79 (3H, s, aromatic $OC\underline{H}_3$), 5.95 (1H, d, J=2.5 Hz, C_9–H), 6.26 (1H, d, J=10 Hz, C_{12}–H), 6.49 (1H, s, C_3–H), 6.82 (1H, d, d, J=10 and 2.5 Hz, C_{13}–H), which were identical with those of **5a** except C_{6a}–H resonance, Mass Spectrum *m/e*: 342 (M^+), 340 (M^+-2), 314 (M^+-28), 299 (M^+-43). *Anal.* Calcd. for $C_{20}H_{22}O_4ND$: C, 70.15; H, 6.78; N, 4.09. Found: C, 70.25; H, 6.72; N, 4.10.

On the other hand, by addition of hexane to the mother liquor from which the dienone (**6a**) had been removed, the other dienone (**6b**) was separated as a brownish solid, the recrystallization of which from methanol gave prisms (590 mg; 11%), mp 208—210° (decomp.), IR ($CHCl_3$) cm^{-1}: 1656 (C=O), 1630 and 1604 (C=C), NMR ($CDCl_3$) δ: 2.42 (3H, s, $NC\underline{H}_3$), 3.63 (3H, s, olefinic $OC\underline{H}_3$), 3.76 (3H, s, aromatic $OC\underline{H}_3$), 5.78 (1H, d, J=2.5 Hz, C_9–H), 6.14 (1H, d, J=10 Hz, C_{12}–H), 6.48 (1H, s, C_3–H), 6.91 (1H, d, d, J=10 and 2.5 Hz, C_{13}–H), which were identical with those of **5b** except C_{6a}–H resonance, Mass Spectrum *m/e*: 342 (M^+), 340 (M^+-2), 314 ($M-28$), 299 (M^+-43). *Anal.* Calcd. for $C_{20}H_{22}O_4ND$: C, 70.15; H, 6.78; N, 4.09. Found: C, 69.93; H, 6.79; N, 4.01.

Hydrogenation of Dienone on Platinum Oxide——The reaction was performed under the condition shown in Table I and the general procedure was described as follows. The catalyst (PtO_2) in methanol was shaken with hydrogen for about 30 min and then the dienone was added. The resulting mixture was shaken at room temperature and atmospheric pressure. After filtration and removal of methanol, the residue was triturated with benzene to give crystals, the recrystallization of which from methanol or chloroform–benzene afforded the cyclohexanol derivative (**7a** or **7b**) as prisms, mp 196—198° (decomp.), NMR ($CDCl_3$) δ: 2.42 (3H, s, $NC\underline{H}_3$), 3.42 (3H, s, aliphatic $OC\underline{H}_3$), 3.60 (1H, broad, C_{6a}–H), 3.85 (3H, s, aromatic $OC\underline{H}_3$), 6.48 (1H, s, C_3–H), Mass Spectrum *m/e*: 347 (M^+), 346 (M^+-1), 304 (M^+-43). *Anal.* Calcd. for $C_{20}H_{29}O_4N$: C, 69.13; H, 8.41; N, 4.03. Found: C, 68.89; H, 8.44; N, 3.77.

On the other hand, the caramel obtained by evaporation of the mother liquor, from which cyclohexanol (**7a** or **7b**) had been removed, was converted into hydrochloride in a usual manner to give a solid. Recrystallization from ethanol gave the other cyclohexanol (**7a** or **7b**) hydrochloride as prisms, mp 257—259° (decomp.), NMR ($CDCl_3$) (free base) δ: 2.43 (3H, s, $NC\underline{H}_3$), 3.42 (3H, s, aliphtaic $OC\underline{H}_3$), 3.60 (1H, broad, C_{6a}–H), 3.86 (3H, s, aromatic $OC\underline{H}_3$), 6.48 (1H, s, C_3–H), Mass Spectrum *m/e*: 347 (M^+), 346 (M^+-1), 304 (M^+-43). *Anal.* Calcd. for $C_{20}H_{29}O_4N \cdot HCl \cdot H_2O$: C, 59.77; H, 8.03; N, 3.49. Found: C, 59.94; H, 7.84; N, 3.56.

Table I. Hydrogenation of Dienones on Platinum Oxide

	Dienone (mg)	Catalyst PtO_2 (mg)	Methanol (ml)	Reaction time (hr)	Yield: mg (%)	
					7a	**7b**
5a	200	100	25	20	40(19.6)	10(4.4)
5b	250	100	40	20	50(19.7)	20(7.1)
6a	210	100	50	80	75(35.0)	15(6.4)
6b	215	100	20	51	80(36.7)	35(14.5)

Hydrogenation of Dienone (5a) on 10% Palladium-Charcoal——A suspension of 150 mg of dienone (**5a**) hydrochloride, 500 mg of freshly prepared 10% Pd–C and 50 ml of ethanol was shaken in a current of hydrogen at room temperature and atmospheric pressure for 74 hr. After filtration and removal of the solvent, the residue was basified with 10% ammonium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave 140 mg of a pale yellow caramel. This was chromatographed on 5.0 g of silica gel using chloroform containing 2% methanol as an eluent to give 50 mg of the cyclohexanone (**8a**) as a plae yellowish caramel, IR ($CHCl_3$) cm^{-1}: 3525 (OH) and 1720 (C=O), NMR ($CDCl_3$) δ: 2.43 (3H, s, $NC\underline{H}_3$), 3.43 (3H, s, aliphatic $OC\underline{H}_3$), 3.80 (3H, s, aromatic $OC\underline{H}_3$), 6.53 (1H, s, C_3–H), Mass Spectrum *m/e*: 345 (M^+), 344 (M^+-1), 302 (M^+-43).

Hydrogenation of Dienone (5b) on 10% Palladium-Charcoal——A suspension of 200 mg of dienone (**5b**) hydrochloride, 500 mg of freshly prepared 10% Pd–C and 40 ml of ethanol was shaken in a current of hydrogen at room temperature and atmospheric pressure for 89 hr. After filtration and removal of the solvent, the residue was treated in the same way as dienone (**5a**) to give 180 mg of a pale yellow caramel, which was triturated with methanol to give crystals. Recrystallization from methanol afforded 70 mg of the cyclohexenone (**9**) as plates, mp 198—200° (decomp.), IR (KBr) cm^{-1}: 1672 (C=O) and 1620 (C=C), NMR ($CDCl_3$) δ: 2.45 (3H, s, $NC\underline{H}_3$), 3.62 (3H, s, olefinic $OC\underline{H}_3$), 3.90 (3H, s, aromatic $OC\underline{H}_3$), 5.90 (1H, s, C_9–H), 6.15 (1H, broad OH), 6.55 (1H, s, C_3–H). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.96; H, 7.34; N, 3.91.

On the other hand, evaporation of the methanolic mother liquor, from which cyclohexanone (**9**) had been removed, gave the residue, which was chromatographed on 2 g of silica gel using chloroform containing 2% methanol as an eluent to afford 10 mg of cyclohexanone (**8b**) as a caramel, IR ($CHCl_3$) cm^{-1}: 3525 (OH) and 1722 (C=O), NMR ($CDCl_3$) δ: 2.40 (3H, s, $NC\underline{H}_3$), 3.44 (3H, s, aliphatic $OC\underline{H}_3$), 3.84 (3H, s, aromatic $OC\underline{H}_3$), 6.50 (1H, s, C_3–H), the spectral data of which were not identical with those of **8a** from dienone (**5a**), Mass Spectrum *m/e*: 345 (M^+), 344 (M^+-1), 302 (M^+-43).

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