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Total Synthesis of the Alkaloid (±)-Dendrobine[1]

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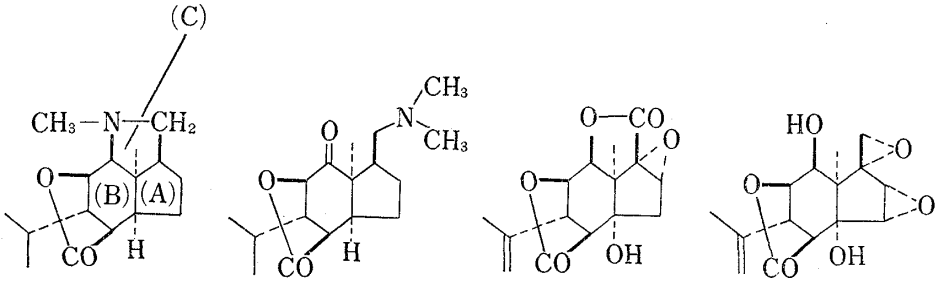
Total synthesis of (±)-dendrobine has been completed. The ketol (**19**) was derived to the keto-nitrile (**21**). Hydrogenation of (**21**) gave the compound (**5**). Treatment of (**5**) with Br_2, followed by dehydrobromination provided the enone (**6**). After ketalization, the compound (**5**) was hydrolyzed and deketalization of the product gave the keto-lactone (**8**). The compound (**8**) was derived to the keto-lactam (**9**) which was successively treated with iso-PrMgBr, $KHSO_4$, I_2-AcOAg–AcOH–H_2O, KOH–MeOH–H_2O, and CrO_3–pyridine to afford the enone (**10**) and (**55**). Hydrocyanation of (**10**) with Et_2AlCN[3] gave three isomeric cyano-ketones (**11**), (**56**), and (**57**). Hydrolysis of the cyano-ketone (**11**) with H_2SO_4–AcOH, followed by methylation afforded the keto-ester (**60**). Reduction of (**60**) with $NaBH_4$ gave the hydroxy-ester (**61**). Hydrolysis of (**61**) with KOH, followed by acidification yielded (±)-oxodendrobine (**13**). Reduction of (**13**) by the Borch's method[4] gave (±)-dendrobine (**1**).

Dendrobine was first isolated from the Chinese drug "Chin-Shih-Hu" (*Dendrobium nobile* Lindl.) by Suzuki, *et al.*,[5] in 1932 and they also revealed its molecular formula and the presence of an N-methyl group and a lactone function. Until 1963, there had been, however, no report concerning this alkaloid and then the complete structure of dendrobine (**1**) was disclosed independently by three groups[6] in 1964. A more recent examination of the genus *Dendrobium* has shown that the widespread *Dendrobium nobile* Lindl. contains not only dendrobine but another alkaloids, nobiline (**2**),[6a,b,7] dendroxine,[8] dendramine,[9] and dendrine,[10] and their structures have been established. Since the skeletal structure of these alkaloids is unique and is closely related to that of picrotoxinin (**3**)[11] and tutin (**4**),[12] which possess a very powerful neurophilic activity, there has been some interest[13,14] in the synthesis of a representative

1) A preliminary communication of this work appeared in *J. Chem. Soc., Chem. Commun.*, **1972** (22), 1252.
2) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) W. Nagata, M. Yoshioka, and S. Hirai, *J. Am. Chem. Soc.*, **94**, 4635 (1972); W. Nagata, M. Yoshioka, and M. Murakami, *ibid.*, **94**, 4644 (1972); *idem*, *ibid.*, **94**, 4654 (1972); W. Nagata, M. Yoshioka, and T. Terasawa, *ibid.*, **94**, 4672 (1972).
4) R.B. Herbert and C.J. Moody, *Chem. Commun.*, **1970**, 121; R.F. Borch, *Tetrahedron Letters*, **1968**, 61.
5) H. Suzuki, I. Keimatsu, and K. Ito, *Yakugaku Zasshi*, **52**, 1049 (1932); *idem*, *ibid.*, **54**, 801 (1934).
6) *a*) T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **12**, 506 (1964); *b*) S. Yamamura and Y. Hirata, *Tetrahedron Letters*, **1964**, 79; *idem*, *Nippon Kagaku Zasshi*, **85**, 377 (1964); *c*) Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konida, J. Matsumoto, E. Katarao, and J. Nakano, *Yakugaku Zasshi*, **83**, 1184 (1963); *idem.*, *Tetrahedron*, **20**, 2007 (1964); Y. Inubushi, Y. Sasaki, Y. Tsuda, and J. Nakano, *Tetrahedron Letters*, **1965**, 1519.
7) T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 745 (1965).
8) T. Okamoto, M. Natsume, T. Onaka, F. Uchimaru, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **14**, 672 (1966).
9) Y. Inubushi, Y. Tsuda, and E. Katarao, *Chem. Pharm. Bull.* (Tokyo), **14**, 668 (1966).
10) *a*) Y. Inubushi and J. Nakano, *Tetrahedron Letters*, **1965**, 2733; *b*) I. Granelli and K. Leander, *Acta Chem. Scand.*, **24**, 1108 (1970).
11) H. Conroy, *J. Am. Chem. Soc.*, **73**, 1889 (1951); B.M. Craven, *Tetrahedron Letters*, **1960**, 21.
12) T. Okuda and T. Yoshida, *Tetrahedron Letters*, **1965**, 2137.
13) Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada, and Y. Hirata, *Tetrahedron*, **27**, 5157 (1971).
14) K. Yamamoto, I. Kawasaki, and T. Kaneko, *Tetrahedron Letters*, **1970**, 4859.

of these alkaloids, dendrobine. However, the complication of asymmetry (seven centers) has prevented a successful synthesis.[15] We have reported a complete synthesis of (±)-dendrobine in a preliminary communication[1] and we wish to give here a full detail of the synthesis of this alkaloid.

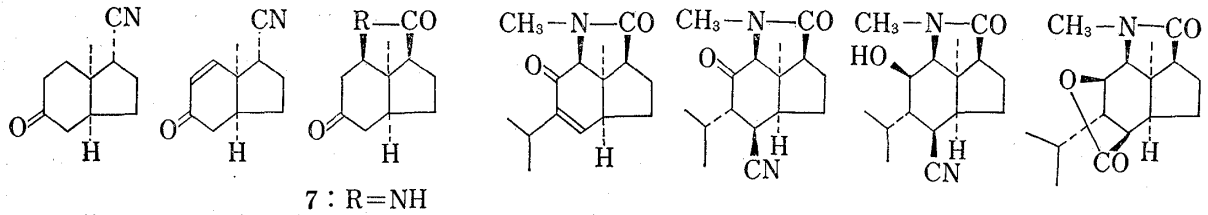


1 2 3 4

Chart 1

The Synthetic Planning

The feature of the dendrobine molecule is the *cis*-hydroindan unit (A, B ring), the N-methylpyrrolidine ring (C ring), the γ-lactone ring, and the isopropyl unit. In the design of the synthetic scheme of dendrobine, sufficient attention must be paid to stereochemical problems. The *cis*-hydroindan derivative such as the compound (**15**) in Chart 3, which possesses the appropriate functions at the suitable positions for the subsequent reactions, will be adequate for the starting material of this synthesis because the stereochemical control of reactions for the formation of the pyrrolidine ring and for the functionalization of this basic skeleton would be expected. Under these considerations, the following synthetic scheme was elaborated. Thus, the compound (**5**) which is prepared from the compound (**14**) and has a cyano group at C_1 and a carbonyl function at C_5, may be expected to give the enone by dehydrogenation. Hydrolysis of the cyano group of **6** to the amide, followed by intramolecular Michael type addition will provide the keto-lactam (**7**). If the expected addition is unsuccessful, the N-methyl-lactam (**9**) will be obtained from the compound (**6**) *via* the lactone (**8**) which is derived from the corresponding carboxylic acid by a Michael type addition. The successive treatment of **9** with the Grignard reagent, dehydration and oxidation will provide the compound (**10**). It is reasonable to assume that application of the hydrocyanation reaction to the compound (**10**) may generate the cyano-ketone (**11**) in which the cyano group and the isopropyl group are both in the more stable equatorial conformation. Reduction of the ketone group of **11** will solely result in one isomer (**12**) in which the stereochemistry of hydroxyl group serves the present purpose, and hydrolysis of the cyano group, followed by the lactonization may yield (±)-oxodendrobine (**13**). Then, we will be able to arrive at the target molecule by selective reduction of the lactam carbonyl function of **13**.



5 6 7 : R=NH, 8 : R=O, 9 : R=N—CH3 10 11 12 13

Chart 2

15) Most recently, Hirata, *et al.*, have reported a complete synthesis of (±)-dendrobine through their original synthetic scheme in *J. Am. Chem. Soc.*, **94**, 8278 (1972).

Synthesis of 1β-Cyano-8α-methyl-*cis*-hexahydroindan-5-one (18) and 1α-Cyano-8α-methyl-*cis*-hexahydroindan-5-one (5)[16]

We can find many excellent methods for the preparation of *cis*-hydroindan derivatives substituted at C_1 in the literature; for instance, the methods employing an intramolecular Michael type addition by Barton, *et al.*,[17] Johnson, *et al.*,[18] and Hirata, *et al.*;[13] the route through catalytic hydrogenation of hydroindan-3-ene derivatives by Ireland, *et al.*;[19] the method using an intramolecular aldol condensation reaction of dialdehyde derivatives by Kaneko, *et al.*[14]

On the basis of the facts[20,21] that tetrahydroindan series compounds afford the *cis*-fused hexahydroindan derivatives on catalytic hydrogenation and that neither the position of the unsaturation nor the type of angular substituents can be utilized to control the steric course of catalytic hydrogenation, we tried to obtain the *cis*-fused hexahydroindan derivative from the tetrahydroindan derivative. The diketone (**14**) obtained by the Boyce's procedure[21] was hydrogenated over catalyst to give the hexahydroindanedione (**15**) which was monoketalized with the limited amount of ethylene glycol. It was confirmed by gas liquid chromatography (GLC) examination that the reaction product contains the monoketal (**16**: ν_{CO} 1725 cm^{-1}) above 99% together with a small amount of the starting material and the diketalized compound. The compound (**16**), without any purification, was treated with $NaHSO_3$–NaCN, dehydrated with thionyl chloride–pyridine and then deketalized with 5% HCl to provide the α,β-unsaturated nitrile (**17**) in 10—40% overall yield. Catalytic hydrogenation of **17** afforded 1β-cyano-8α-methyl-*cis*-hexahydroindan-5-one (**18**), mp 83—84°. The *trans* relationship of C_1-CN and C_8-CH_3 in **18** serves for the present purpose but the yield of the α,β-unsaturated nitrile (**17**) from the monoketal (**16**) was poor and irregular. We, therefore, explored an alternative route.

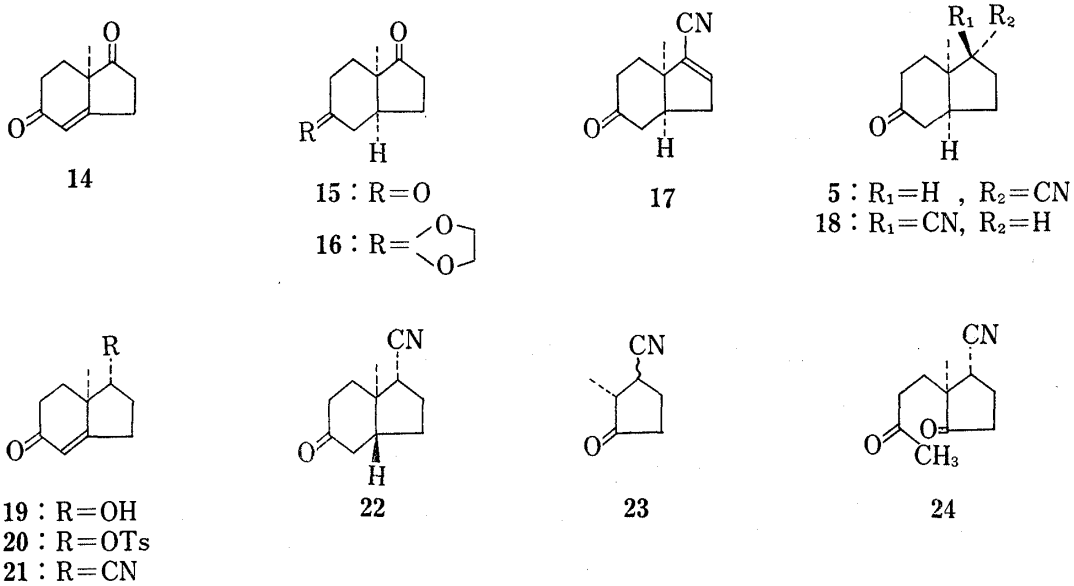


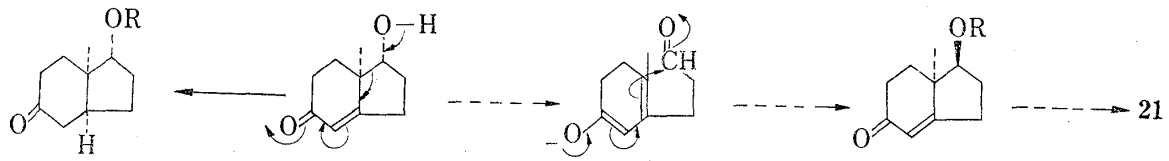
Chart 3

The ketol (**19**)[21] which was obtained from the diketone (**14**) by reduction with $NaBH_4$, was derived to its tosylate (**20**) and then treated with NaCN in DMSO to give the keto-nitrile

16) The relative configuration of the cyano function at C_1 and the methyl group at C_8 will be stated later.
17) D.H.R. Barton, A. Da S. Campos-Neves, and A.I. Scott, *J. Chem. Soc.*, **1957**, 2698.
18) W.S. Johnson, S. Shulman, K.L. Williamson, and R. Rappo, *J. Org. Chem.*, **27**, 2015 (1962).
19) M. Chykovsky and R.E. Ireland, *J. Org. Chem.*, **28**, 748 (1963).
20) W.G. Dauben, J.W. McFarland, and J.B. Rogan, *J. Org. Chem.*, **26**, 297 (1961).
21) C.B.C. Boyce and J.C. Whitehurst, *J. Chem. Soc.*, **1960**, 4547. *cf.* W. Acklin, V. Prelog, and A.P. Prieto, *Helv. Chim. Acta*, **41**, 1416 (1958).

(**21**) over 80% yield. Alternatively, the Michael adduct (**24**) obtained from the compound (**23**)[22] and methyl vinyl ketone, was treated with *p*-TsOH in benzene to give the compound (**21**) in good yield, and in this reaction, the acid catalyst was essential. It is presumed that the substitution reaction of the α-oriented O-tosyl group of the compound (**20**) under the S_N2 reaction condition will afford the nitrile in which the cyano group is oriented in β. Contrary to this presumption, the compound (**20**) was substituted under this reaction condition without inversion. This result may be rationalized by assuming the following reaction course. Thus, the ketol (**19**) is first subjected to the retro-aldol and then the aldol condensation reaction to give the ketol (**19a**) in which the configuration of hydroxyl group is opposite to that of the original hydroxyl group, and the resulting ketol is then derived to its tosylate (**20a**) and is subjected to the S_N2 reaction to provide the keto-nitrile (**21**) (Chart 4). This reaction path, however, was ruled out by the following observation. Thus, the tosylate (**26**) of the known compound, 1α-hydroxy-8α-methyl-*cis*-hexahydroindan-5-one (**25**),[21] which was obtained from the ketol (**19**) by catalytic hydrogenation, was proved to be identical with the tosylate (**26**) derived from the compound (**19**) by tosylation, followed by catalytic hydrogenation. Details of this substitution reaction process of the tosylate (**20**) to the nitrile (**21**) remain still equivocal.

Catalytic hydrogenation of the keto-nitrile (**21**) in MeOH under the presence of 5% Pd-$SrCO_3$ catalyst[23] provided a mixture of the *trans* isomer (**22**) and the *cis* isomer (**5**) in a ratio of 2.7: 97.3 as judged by GLC criterion. Recrystallization of this mixture from a mixed solvent of ether–*n*-hexane (4: 1) gave the pure *cis* isomer (**5**) over 93% yield. Thus, the readily available keto-nitrile (**5**) was employed for the present synthesis. In catalytic hydrogenation of the keto-nitrile (**21**), the *trans*/*cis* ratio was observed as 21.2/78.8, when the 5% Pd-C catalyst is employed.



25 : R=H
26 : R=Ts

19

19a : R=H
20a : R=Ts

Chart 4

Synthesis of 1α-Cyano-8α-methyl-*cis*-hexahydroind-6-en-5-one (6)

The following reactions were carried out with the intention of introduction a double bond at the C_6-C_7 position of the keto-nitrile (**5**).

Formylation of the compound (**5**) with $H\cdot COOC_2H_5$-CH_3ONa gave the thermodynamically controlled reaction product,[24] the C_6-formyl derivative (**27**), in 41% yield. Oxidation of the compound (**27**) with DDQ afforded the enone (**28**) which was then refluxed in dil. H_2SO_4 to give the keto-lactone (**8**: *vide infra*). This synthetic route of the keto-lactone, however, is rather impractical because the yield of DDQ oxidation product was poor (below 18%). Next, treatment of the compound (**5**) with two molar equivalents of bromine, followed by heating of the product in HOAc–NaOAc underwent the rearrangement reaction[25] to provide a mixture of two diketone (**29**) and (**30**), in a 1/4 ratio. Methylation of the compound (**30**)

22) I.N. Nazarov and S. I. Zav'yalov, *Zh. Obshch. Khim.*, **24**, 466 (1954); *C.A.* **49**, 6139^f.
23) R. Mozingo, *Organic Syntheses*, **26**, 77 (1946).
24) R.O. Clinton, R.L. Clarke, F.W. Stonner, A.J. Manson, K.F. Jennings, and D.K. Phillips, *J. Org. Chem.*, **27**, 2800 (1962).
25) *a*) F.G. Bordwell and K.M. Wellman, *J. Org. Chem.*, **28**, 1347 (1963); *idem*, *ibid.*, **31**, 351 (1966); *b*) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

with BF_3·ether–MeOH furnished two α,β-unsaturated ketones, (**31**: 4.42 τ, d., J=4 Hz, C_4-H) and (**32**: 4.63 τ, s., C_7-H) in a 1: 1 ratio. An attempt to obtain the tricylcic compound (**33**) from the compound (**32**) by hydrolysis of the cyano group, followed by an intramolecular Michael type addition was unsuccessful.

Sodium borohydride reduction of the compound (**31**) and treatment of the resulting alcohol (**34**) with $POCl_3$–pyridine or TsCl–pyridine gave the chloride (**35**) which was hydrolyzed with dil. HCl to afford the chloro-ketone (**36**). Dehydrochlorination of the compound (**36**) by the Mattox-Kendall's procedure[26] gave the desired enone (**6**). This synthetic route, however, was not satisfactory because this route involves many steps and the overall yield of the compound (**6**) from the compound (**31**) was poor (30%). Then, another path was explored. Treatment of the compound (**5**) with one molar equivalent of bromine, followed by heating with LiBr-Li_2CO_3 in DMF and chromatographic separation of the product afforded two enones, (**21**) and (**6**), in a ratio of 3—4: 1. This synthetic route for obtaining the enone (**6**) was superior to the previously mentioned routes in the following respects. Thus, this synthetic path is rather simple and the compound (**21**) can be reutilized by converting it to the compound (**5**) through catalytic hydrogenation. In the present synthesis, the enone (**6**) was therefore prepared exclusively by means of this synthetic procedure.

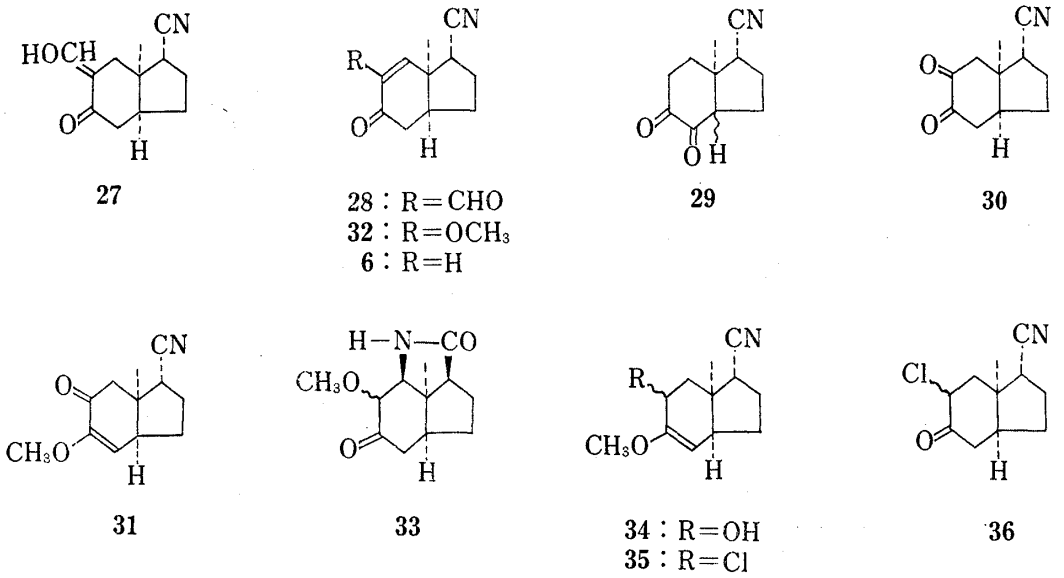


Chart 5

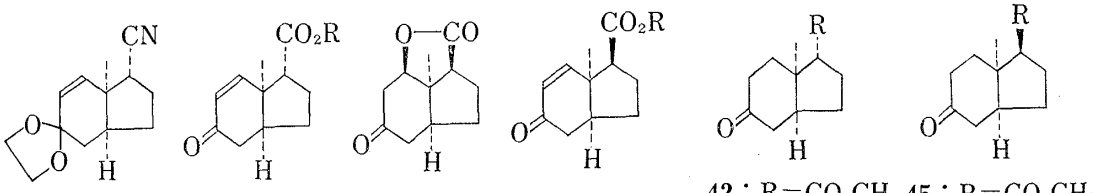
Synthesis of the Keto-lactone (8) and Relative Configuration of C_1-CN and C_8-CH_3 of the Keto-nitrile (18) and (5)

The compound (**6**) was derived to its ethylene ketal derivative (**37**), the cyano group of which was then hydrolyzed with alkaline and the ethylene ketal group of the resulting acid was hydrolyzed with acid to give the keto-acid (**38**: ν_{max} 1700 and 1670 cm^{-1}) and the keto-lactone (**8**: ν_{max} 1768 and 1721 cm^{-1}). When refluxed the keto-acid (**38**) in ethylene glycol with 25% H_2SO_4, the lactonization reaction took place to afford the keto-lactone (**8**). The overall yield of the keto-lactone (**8**) from the compound (**6**) was above 55%. The fact that the keto-acid (**40**) corresponding to the keto-lactone (**8**) is not isolated from the hydrolysis product of the compound (**37**), suggests a *trans* relationship of the C_1-COOH function and the C_8-CH_3 group of the compound (**40**) because the intramolecular Michael addition causing lactonization is favorable under such stereochemical environment. Consequently, the stereochemical relationship of C_1-COOH and C_8-CH_3 of the keto-acid (**38**) is supposed to be *cis*.

26) V.R. Mattox and E.C. Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948).

The relative configurations of C_1-CN and C_8-CH_3 of the keto-nitrile (**5**) and (**18**: *vide ante*) were defined chemically by the following experiments. The keto-acid (**38**) was derived to the keto-amide (**44**) *via* the ester (**39**), (**42**), and the saturated keto-acid (**43**). Dehydration of the keto-amide (**44**) gave the saturated keto-nitrile (**5**) which was identical with the keto-nitrile derived from the compound (**21**: *vide ante*) by catalytic hydrogenation. From this result, the relative configuration of C_1-CN and C_8-CH_3 of the compound (**5**) should be *cis*. On the other hand, treatment of the keto-lactone (**8**) with K_2CO_3-CH_3I in MeOH gave the ester (**41**) which was derived to the saturated keto-nitrile (**18**) *via* the keto-ester (**45**), the saturated keto-acid (**46**) and the amide (**47**). The keto-nitrile (**18**) was identical with the keto-nitrile from the α,β-unsaturated nitrile (**17**: *vide ante*) by catalytic hydrogenation, indicating that the relative configuration of C_1-CN and C_8-CH_3 of the compound (**18**) should be *trans*.

It has been reported that the stereochemical relationship of the C_1-substituent and the C_8-CH_3 group of the *cis*-hydroindan derivatives[14] and that of the C_2-substituent and the C_3-CH_3 group of the pyrrolidine derivatives[27] are inferred from the chemical shift of the methyl signal in their nuclear magnetic resonance (NMR) spectra. Thus, the methyl signal of the *cis*-derivatives is observed at higher field than that of the corresponding *trans* derivatives. The same relationship was observed in our compounds as shown in Table I.



37 38 : R=H, 39 : R=CH_3 8 40 : R=H, 41 : R=CH_3 42 : R=CO_2CH_3, 43 : R=CO_2H, 44 : R=$CONH_2$, 5 : R=CN 45 : R=CO_2CH_3, 46 : R=CO_2H, 47 : R=$CONH_2$, 18 : R=CN

Chart 6

Table I. Chemical Shift of C_8-Methyl Group

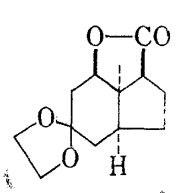
cis-series	**39**	**42**	**43**	**44**	**5**
C_8-CH_3 : τ	8.84	8.95	8.86	8.84	8.65
trans-series	**41**	**45**	**46**	**47**	**18**
C_8-CH_3 : τ	8.62	8.58	8.55	8.58	8.62

Synthesis of (±)-Dendrobine (1)

When heated in 30% aq. methylamine under the presence of methylamine hydrochloride at 180—190° in a sealed tube,[28] the lactone (**8**) or the ketal-lactone (**48**) provided the keto-lactam (**9**: ν_{max} 1723 and 1677 cm^{-1}) over 80% yield. The Grignard reaction of the keto-lactam (**9**) with isopropyl magnesium bromide in ether at room temperature or at boiling temperature did not occur because of liberating the enolate as a precipitate but this reaction did work at −70°——60° to give a mixture of the alcohol (**49**) and the starting material (**9**). The pure alcohol (**49**) was obtained by fractional crystallization of the reaction product, and the reaction of the mother liquor removed the alcohol (**49**) with isopropyl magnesium bromide at the same temperature above was repeated 4 or 5 times[29] to afford the desired alcohol (**49**) over 80% as the total yield.

27) A.B. Mauger, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 2019 (1966); *cf.* N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., 1964, p. 24.
28) Y. Inubushi, M. Kitano, and T. Ibuka, *Chem. Pharm. Bull.* (Tokyo), **19**, 1820 (1971).
29) J.E. McMurry, *J. Am. Chem. Soc.*, **90**, 6821 (1968).

Dehydration of the alcohol (**49**) by treatment with alumina-pyridine,[30] thionyl chloride-pyridine or phosphorous oxychloride-pyridine was unsuccessful but on heating with $KHSO_4$,[31] dehydration occurred to give three kinds of olefins (**50**) in an almost quantitative yield and a ratio of these olefins was 1/1/1 as judged from the NMR spectrum. Because of the lability, this olefin mixture, without further purification, was treated with I_2-CH_3COOAg in AcOH[32] and chromatographic separation of the product through a silica gel column provided two kinds of O-acetyl allyl alcohols: the compound (**51**: ν_{max} 1732 and 1675 cm^{-1}; τ: 4.37, d., J=2.4 Hz, C_7-H; 6.51, d., J=2.4 Hz, C_{7a}-H; 7.93, s., $OCOCH_3$; 5.30, diffused s., C_5-H) and the compound (**53**; ν_{max} 1728 and 1667 cm^{-1}; 4.21, q., J_A=1.2 Hz, J_B=3.0 Hz, C_7-H; 6.33, q., J_A=3 Hz, J_B=1.2 Hz, C_{7a}-H; 7.97, s., $OCOCH_3$; 4.54, d., J=2 Hz, C_5-H) in 5 and 15% yield, respectively, together with the starting olefin mixture. Repetition of this reaction with the recovered olefins gave another crop of O-acetyl allyl alcohols. The total yields of (**51**) and (**53**) were 10 and 20%, respectively. The examples that treatment of the trisubstituted olefins with I_2-CH_3COOAg gives the O-acetyl allyl alcohols, have been reported.[33]



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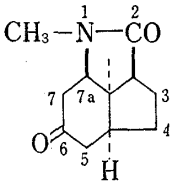

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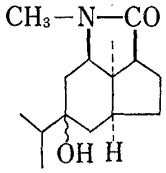

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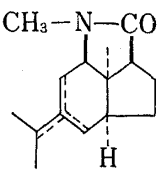

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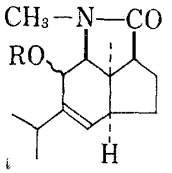
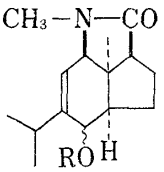
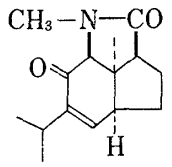


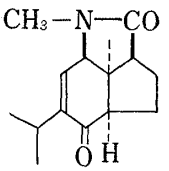
51 : R=Ac
52 : R=H



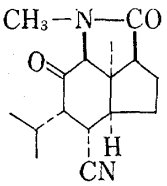
53 : R=Ac
54 : R=H



10



55



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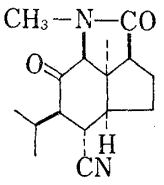
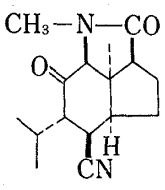


57



11

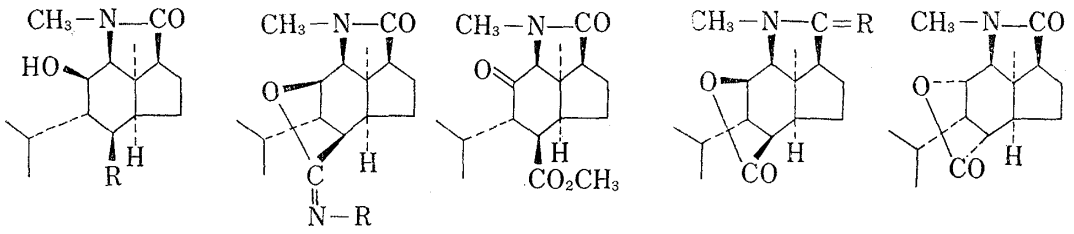
Chart 7

Hydrolysis of the acetate (**51**) with aq. MeOH–KOH gave the alcohol (**52**) which was then oxidized with CrO_3-pyridine complex[34] to afford the enone [**10**: ν_{max} 1671 cm^{-1} (lactam and α,β-unsaturated CO); τ: 3.39, q., J_A=1.5 Hz, J_B=5 Hz, C_5-H; 6.43, s., C_{7a}-H]. On the other hand, the same treatment of the acetate (**53**) gave the enone [**55**: ν_{max} 1672 cm^{-1} (lactam and α,β-unsaturated CO); τ: 3.54, q., J_A=4 Hz, J_B=1 Hz, C_7-H; 6.18, q., J_A=1 Hz, J_B=4 Hz, C_{7a}-H]. All trials for the transformation of the enone (**55**) to the enone (**10**) were unsuccessful.

30) E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).
31) H.H. Inhoffen, H. Siemer, and K.D. Möhle, *Ann.*, **585**, 126 (1954).
32) R.B. Woodward and F.V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 209 (1958); L. Birckenbach, J. Goubeau, and E. Berninger, *Ber.*, **65**, 1339 (1932).
33) L. Magoni and V. Davinola, *Tetrahedron Letters*, **1969**, 5235.
34) J.C. Collins, W.W. Hess, and F.J. Frank, *Tetrahedron Letters*, **1968**, 3368.

The hydrocyanation reaction of the enone (**10**) with KCN-DMF-NH_4Cl was tried. Under the reaction condition at room temperature or at 100° for 24 hr, the enone (**10**) was recovered unchanged but under the condition at 190° for 20 hr in a sealed tube, the reaction took place to give three kinds of cyano-ketones. Thus, chromatographic separation of the reaction product through a silica gel column afforded the cyano-ketone (**56**: mp 199—200°; τ: 6.64, q., J_A=1 Hz, J_B=4.5 Hz, C_5-H), the cyano-ketone (**57**: mp 123°; τ: 7.01, q., J_A=5.5 Hz, J_B=9 Hz, C_5-H) and the cyano-ketone (**11**: mp 133°; τ: 6.78, q., J_A=3.5 Hz, J_B=10 Hz, C_5-H) in 28, 8 and 20% yield, respectively, with the recovery of 36% of starting material. Then, the hydrocyanation reaction using a new reagent, diethylaluminum cyanide which had been developed by Nagata, *et al.*,[3] was applied to the enone (**10**). In this case, the reaction proceeded at room temperature and a considerable reduction in time was brought about. The yields of the cyano-ketones, (**56**), (**57**), and (**11**) were 18, 20, and 29%, respectively, with the recovery of 17% of starting material. These three cyano-ketones are correlated by isomerization reaction as follows. Treatment of the compound (**57**) with NaOMe in benzene gave the compound (**56**) in 80% yield and on treatment with NaOMe in MeOH, the compound (**56**) was isomerized to the compound (**11**) in 20% yield.

The conformations of the C_5-CN function and the C_6-isopropyl group of the cyano-ketones, (**56**), (**57**) and (**11**) were assigned on the basis of the following results.



12 : R=CN
61 : R=CO_2CH_3

58 : R=H
59 : R=Ts

60

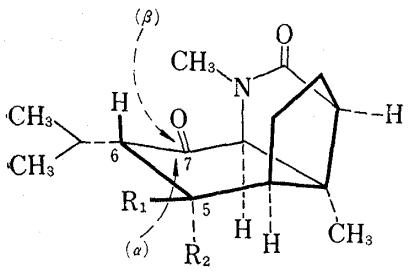
13 : R=O
1 : R=H_2

62

Chart 8

The NMR spectrum of the compound (**11**) revealed a signal due to the C_5-H at 6.78 τ as a quartet, J=3.5 and 10 Hz, indicating that the C_5-H is axial and the C_5-CN group, therefore, is equatorial. Reduction of the compound (**11**) with $NaBH_4$ proceeded stereoselectively to give the hydroxy-nitrile (**12**) alone. Treatment of the compound (**12**) with basic alumina gave the oily imino-lactone (**58**) over 90% yield which on treatment with TsCl-pyridine provided quantitatively the N-tosylate (**59**). When refluxed in dioxane with 5% NaOH for 1.5 hr, the N-tosylate (**59**) gave (±)-oxodendrobine (**13**: mp 183—184°, ν_{max} 1779 and 1674 cm^{-1}; τ: 5.26, q., J_A=3.5 Hz, J_B=5 Hz, C_7-H; 6.73, d., J=3.5 Hz, C_{7a}-H), the stereochemistry of which had been established.[6] Since the configuration of the isopropyl group seems to be unchanged during $NaBH_4$ reduction process, the above mentioned experimental result indicates that the B ring of the compound (**11**) is a chair form, the C_5-CN group is β-equatorial and the C_6-isopropyl group is α-equatorial.

Next, the conformations of the C_5-CN function and the C_6-isopropyl group of the compound (**56**) were assigned as follows. Since the NMR spectrum of the compound (**56**) revealed the signal due to a proton geminal to the CN function at 6.64 τ as a quartet, J=1 and 4.5 Hz, the conformation of the C_5-H is equatorial and that of the C_5-CN function is therefore axial. On reduction of the cyano-ketone (**11**) and the keto-ester (**60**: *vide infra*) with $NaBH_4$, these compounds gave an alcohol alone, respectively. The stereochemical outcome of this reduction is illustrated by steric-approach control of the metal hydride ion to the ketone function. Thus, the hydride ion approaches to the ketone group from the less hindered side, the α-side of the molecule, to provide one of two epimeric alcohols in which the hydroxyl group is oriented

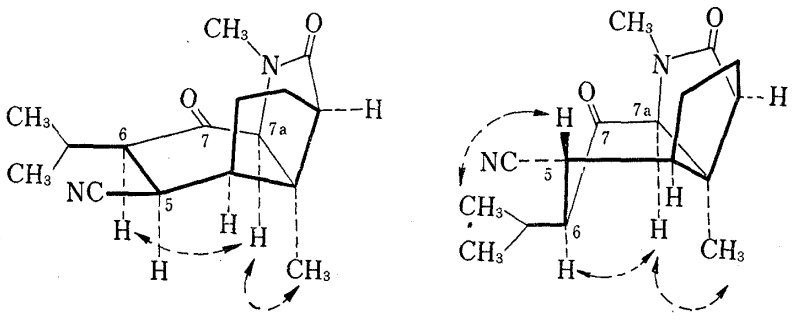


11 : R_1=CN , R_2=H
56 : R_1=H , R_2=CN
60 : R_1=CO_2CH_3, R_2=H

Chart 9

in β (see Chart 9). On the other hand, reduction of the cyano-ketone (**56**) with $NaBH_4$ gave a mixture of two epimeric alcohols. Since the conformation of the C_5-CN function of the cyano-ketone (**56**) is axial and the metal hydride ion attack to the C_7 carbonyl function from the α side is somewhat sterically hindered by the axial C_5-CN function which is situated in 1,3-diaxial relationship with the metal hydride ion approaching to the ketone function, the hydride attack will be accessible from both α and β side to give a mixture of two epimeric alcohols.Hydrolysis of the mixture of epimeric alcohols with KOH, followed by heating with dil. HCl provided (±)-oxodendrobine (**13**) and its isomer (**62**) in 25 and 50% yield, respectively. The formation of (±)-oxodendrobine (**13**) from the keto-nitrile (**56**) is rationalized by assuming that the carboxyl group derived from the cyano function epimerizes to the β side during hydrolysis process and the β-oriented carboxyl group then formed a lactone ring with the hydroxyl group oriented in β. From these observations, the ring B is a chair form, the C_5-CN is α-axial and the C_6-isopropyl group is α-equatorial in the cyano-ketone (**56**).

Finally, the stereochemistry of the cyano-ketone (**57**) is now discussed. The NMR spectrum of the compound (**57**) showed a signal due to a proton geminal to the C_5-CN group at 7.01 τ as a quartet, J=5.5 and 9.0 Hz. Judging from the coupling constants, the C_5-H and the C_6-H are both axial and consequently, the C_5-CN and the C_6-isopropyl group are both equatorial. Since the stereochemistry of the cyano-ketone (**11**) has been established as that the conformations of the C_5-CN and the C_6-isopropyl group are both equatorial and the B ring is a chair form, the B ring of the cyano-ketone (**57**) should be a boat form. This conclusion is also substantiated by the fact that treatment of the compound (**57**) with NaOMe causes the ring-flip of the B ring and epimerization of the C_6-isopropyl group to give the cyano-ketone (**56**). The two formulas, (**57-A**) and (**57-B**), for the cyano-ketone (**57**) are considered feasible to satisfy the above steric requirements. In the formula (**57-A**), the CN function and the isopropyl group are both β-equatorial, whereas in the formula (**57-B**), the CN function is α-equatorial and the isopropyl group is β-equatorial. In order to determine which is reasonable for the cyano-ketone (**57**), (**57-A**) or (**57-B**), an attempt was made to use the nuclear Overhauser effects. The nuclear Overhauser effects above 10% were observed between the following protons; (1) C_{7a}-H-C_6-H, (2) C_{7a}-H- the angular Me, and (3) C_5-H-Me of the isopropyl group but no enhancement was observed between C_5-H and the angular methyl group. From these observations, the formula (**57-B**) is preferred to the formula (**57-A**) because in the formula (**57-A**), the nuclear Overhauser effects (1) and (2) will be observed but no effect of (3) will be expected and the enhancement between C_5-H and the angular methyl group should be observed (see Chart 10).



57−A 57−B

Chart 10

(±)-Oxodendrobine (**13**) required for the subsequent synthetic steps was mainly obtained from the cyano-ketone (**11**) through the following route. Thus, hydrolysis of the cyano-ketone (**11**) with H_2SO_4-AcOH, followed by methylation with diazomethane gave the keto-ester (**60**) in 50% yield which was identical with the keto-ester[6c] derived from natural dendrobine. Reduction of the compound (**60**) with $NaBH_4$ proceeded stereoselectively to give the hydroxy-ester (**61**) alone in 90% yield, in which the hydroxyl group is β-equatorial. After hydrolysis of the compound (**61**) with KOH, the reaction mixture was acidified with dil. HCl to give quantitatively (±)-oxodendrobine (**13**). Treatment of the compound (**13**) with triethyloxonium fluoroborate, followed by reduction with $NaBH_4$[4] provided (±)-dendrobine (**1**), mp 131—132°, which was identical with natural dendrobine in all respects except specific rotation.

Since dendrobine has been transformed to nobiline (**2**) by Okamoto, *et al.*[7] and dendrine[10a] has been derived from dendrobine by Granelli, *et al.*,[10b] the present synthesis amounts to the completion of syntheses of these alkaloids.

Experimental

All melting points were measured on a Yanagimoto Melting Point Apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPS-2U Spectrometer in $CHCl_3$. All NMR spectra were taken on a Varian Associates A-60 Spectrometer at 60 Mc. and/or HA-100 D Spectrometer at 100 Mc in $CDCl_3$ using tetramethylsilane as an internal standard, and chemical shifts were reported in τ values. Abbreviation used for multiplicity of signals were: s., singlet; d., doublet; t., triplet; q., quartet; m., multiplet. Mass spectra were recorded on a Hitachi-RMU-6D Mass Spectrometer equipped with a direct inlet system operating at 80 eV, an ion acceleration voltage at 1.8 KV and evaporating temperature at 150—180°. Thin-layer chromatography (TLC) was performed on Kieselgel G nach Stahl and developed by $CHCl_3$–acetone (4: 1) or on Aluminium Oxyd G nach Stahl and developed by $CHCl_3$ or $CHCl_3$–acetone (4: 1). Column chromatography was performed on silica gel (Mallinckrodt Silicic Acid, 100 mesh) or alumina (Aluminium Oxyd G, Brockmann, Activity, II—III). GLC was carried out on a 10% SE-30 column (stainless steel, 1 m×3 mm i.d., on 60—80 mesh chromosorb WNAW) at 150—200° or a 15% Reoplex 400 column (stainless steel, 2 m×3 mm i.d., on 60—80 mesh chromosorb WNAW) at 150—200° with a Hitachi Gas Chromatograph Model 063 equipped with a hydrogen flame ionization detector. Nitrogen or helium gas was used as a carrier gas. (30 ml/min). Unless otherwise stated, the extracts were dried over anhydrous $MgSO_4$.

The Monoketal (16)——To a solution of 1.66 g of the hexahydroindanedione (**15**) in 50 ml of benzene were added 682 mg of ethylene glycol (1.05 molar equivalent) and 200 mg of *p*-toluenesulfonic acid. The reaction mixture was refluxed for 5 hr, while water was separated with a Dean-Stark type apparatus. After cooling, the mixture was made alkaline with 3% NH_4OH and evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ solution was washed with water, dried, and evaporated to give 1.8 g of colorless oil. It was confirmed by GLC that the oil contains the monoketal (**16**) above 99% along with a small amount of the compound (**15**) and the diketalized compound. The monoketal (**16**) showed the following spectral data. IR ν_{max} cm^{-1}: 1726 (five membered CO); NMR τ: 6.07 (4H, s., ethylene ketal) and 8.95 (3H, s., CH_3); Mass Spectrum *m/e*: 210 (M^+).

The α,β-Unsaturated Nitrile (17)——To a mixture of 1.5 g of the monoketal (**16**), 32 ml of water, 4 g of $NaHCO_3$ and 6 g of KCN was added 20 ml of MeOH, and the reaction mixture was allowed to stand at room temperature for 15 hr under stirring. The reaction mixture was then extracted with $CHCl_3$ and the extract was washed with water, dried and evaporated to leave 1.6 g of colorless oil. A mixture of 1.6 g of this oil, 3 ml of pyridine and 1 ml of $SOCl_2$ was allowed to stand at room temperature for 15 hr. Pyridine and excess $SOCl_2$ were removed *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to afford 1.4 g of colorless oil, which without further purification, was dissolved in 10 ml of a mixed solvent, MeOH–H_2O (10/1). To this solution was added little by little 0.5 g of $NaBH_4$ at 0° under stirring and after the completion of addition of $NaBH_4$, stirring was further continued for 30 min. Removal of the solvent *in vacuo* left the residue which was extracted with $CHCl_3$. The extract was treated as usual to give 1.2 g of colorless oil. To a solution of 1.2 g of the oil in 3 ml of MeOH was added 1 ml of 5% HCl and the mixture was refluxed for 30 min. After cooling, MeOH was evaporated under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 400 mg of colorless oil. This oil in $CHCl_3$ was chromatographed on silica gel column (50×1 cm i.d.) and elution with the same solvent gave 180 mg of the α,β-unsaturated nitrile (**17**) as a colorless oil, bp 90° (2×10^{-4} mmHg); IR ν_{max} cm^{-1}: 2250 (CN), 1714 (CO) and 1625 (C=C); NMR τ: 3.39 (1H, t, $J=2$ Hz., C_2–H), and 8.65 (3H, s., CH_3); Mass Spectrum *m/e*: 175 (M^+). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.58; H, 7.61; N, 7.92. The molecular weight of this oil was supported by the M^+ peak

in the mass spectrum and the homogenity was certified by a single peak in GLC (15% Reoplex 400, column temperature 180°, retention time: 18 min).

1β-Cyano-8α-methyl-*cis*-hexahydroindan-5-one (18)——To a solution of 20 mg of the α,β-unsaturated nitrile (**17**) in 5 ml of MeOH was added 10 mg of 10% Pd-C catalyst and the solution was hydrogenated with hydrogen under atmospheric pressure. After 10 min, no hydrogen had been absorbed and the catalyst was removed by filtration and the filtrate was evaporated to leave the residue which was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. On trituration with ether, the residue crystallized and several recrystallizations gave 19 mg of the compound (**18**) as colorless prisms, mp 83—84°. IR ν_{max} cm^{-1}: 2250 (CN) and 1710 (CO). *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.33; H, 8.43; N, 7.92.

The Tosylate (20)——To a solution of 35 g of the ketol (**19**) in 120 ml of pyridine was added little by little 40 g of *p*-toluenesulfonyl chloride and the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into 200 ml of ice-water and when stirred the mixture, the tosylate precipitated. The tosylate was collected by filtration and washed with water. The crude tosylate was dissolved in 200 ml of $CHCl_3$ and the $CHCl_3$ solution was successively washed with 5% HCl and water, dried and evaporated. The residue was recrystallized from ether gave 51 g of the tosylate (**20**) as colorless prisms, mp 109—110° (80% yield). IR ν_{max} cm^{-1}: 1665 (CO), 1600 (aromatic ring), 1367 and 1176 (SO_2); NMR τ: 4.24 (1H, t., J=2 Hz, C_4–H), 5.58 (1H, t., J=8 Hz, C_1–H), 7.53 (3H, s., CH_3 on aromatic ring), and 8.80 (3H, s., angular CH_3). *Anal.* Calcd. for $C_{17}H_{20}O_4S$: C, 63.72; H, 6.29. Found: C, 63.58; H, 6.44.

The Keto-nitrile (21)——To a solution of 44 g of the dried tosylate (**20**) in 140 ml of anhydrous dimethylsulfoxide (distilled three times with calcium hydride) was added 10.12 g of NaCN and the mixture was stirred for 3 hr at room temperature. The reaction mixture was then poured into 500 ml of ice-water and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The residue in ether was chromatographed on an alumina column (10×10 cm) and elution with the same solvent gave a crystalline mass. Recrystallizations from ether afforded 19 g of the keto-nitrile (**21**) as colorless needles, mp 71—73° (80% yield). IR ν_{max} cm^{-1}: 1668 (CO) and 2250 (CN); NMR τ: 4.22 (1H, t., J=2 Hz, C_4–H) and 8.65 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.15; H, 7.60; N, 7.76.

The Michael Adduct (24)——To a solution of 300 mg of the compound (**23**) in 3 ml of anhydrous MeOH were added 300 mg of methyl vinyl ketone and 0.5 ml of triethylamine and the mixture was kept on standing overnight and then heated at 50° for 3 hr under stirring and nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was extracted with ether. The ether extract was washed with water, dried and evaporated to leave 400 mg of colorless oil. This oil in $CHCl_3$ was chromatographed on a silica gel column (30×1.6 cm) and elution with the same solvent gave 230 mg of the Michael adduct (**24**) as colorless oil. IR ν_{max} cm^{-1}: 1743 (five membered CO.), 1715 (acetyl) and 2260 (CN); NMR τ: 7.83 (3H, s., $COCH_3$), 8.82 (3H, s., CH_3); Mass Spectrum *m/e*: 193 (M^+).

The Keto-nitrile (21)——To a solution of 200 mg of the Michael adduct (**24**) in 50 ml of anhydrous benzene was added 15 mg of *p*-toluenesulfonic acid and the mixture was heated for three days while water was separated with a Dean-Stark type apparatus. After cooling, the solvent was evaporated and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was successively washed with 5% NaOH, 5% HCl and water, dried and evaporated. Recrystallization of the residue from ether gave 150 mg of the keto-nitrile (**21**) as colorless needles, mp 71—73°. *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.62; H, 7.34; N, 7.99.

1α-Tosyloxy-8α-methyl-*cis*-hexahydroindan-5-one (26)——a) From 1α-Hydroxy-8α-methyl-*cis*-hexahydroindan-5-one (**25**)[21]: To a solution of 2.0 g of the compound (**25**) in 10 ml of anhydrous pyridine was added 2.3 g of *p*-toluenesulfonyl chloride under stirring and the mixture was allowed to stand for 3 days at room temperature. Pyridine was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed successively with 5% HCl, 5% NaOH, water, dried and evaporated. Recrystallization of the residue from a mixed solvent of ether–acetone gave 1.99 g of the tosylate (**26**) as colorless prisms, mp 106—109°. IR ν_{max} cm^{-1}: 1714 (CO), 1358 and 1170 (SO_2). *Anal.* Calcd. for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88. Found: C, 63.54; H, 7.16.

b) From the Tosylate (**20**) of the Ketol (**19**): To a solution of 140 mg of the tosylate (**20**) in 20 ml of MeOH were added 50 mg of PtO_2 and 3 drops of 10% HCl. Hydrogenation was performed at room temperature and atmospheric pressure. When hydrogen uptake had ceased after 1 hr, the catalyst was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to leave the residue which was dissolved in $CHCl_3$. The $CHCl_3$ solution was dried and evaporated. Recrystallization of the residue from a mixed solvent of ether–acetone gave 14 mg of the tosylate (**26**), mp 106—109°. A sample of the tosylate (**26**) prepared through the b) route was identical in all respects with a sample from the a) route.

1α-Cyano-8α-methyl-*cis*-hexahydroindan-5-one (5) and 1α-Cyano-8α-methyl-*trans*-hexahydroindan-5-one (22)——A solution of 175 mg of the keto-nitrile (**21**) in 5 ml of MeOH was hydrogenated at room temperature and atmospheric pressure in the presence of 30 mg of 5% Pd-$SrCO_3$ catalyst. The hydrogen uptake ceased in 5 min when the sample had absorbed 26 ml of hydrogen. The solution was acidified with dil. HCl and filtered. The filtrate was concentrated under reduced pressure and the residue was extracted with $CHCl_3$.

The extract was washed with water, dried and evaporated to leave 180 mg of a colorless oil which was dissolved in a mixed solvent of ether–*n*-hexane (4: 1). When the solution was kept on standing, crystals deposited. Recrystallizations from ether–*n*-hexane (4: 1) gave 165 mg of the compound (**5**) as colorless prisms, mp 76°. IR ν_{max} cm^{-1}: 1714 (CO) and 2260 (CN); NMR τ: 8.65 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.75; H, 8.51; N, 7.86. GLC: column; 15% Reoplex 400, column temperature, 180°; retention time, 23.5 min. The compound (**5**) was removed as extensive as possible from the solution above and the solvent was removed under reduced pressure. The oily residue in $CHCl_3$ was chromatographed on a silica gel column (30×1.0 cm) and elution with the same solvent, the compound (**22**) was obtained from the earlier eluate. Trituration of the eluate with ether gave a crystalline mass and recrystallization from ether afforded 9 mg of the compound (**22**) as colorless prisms, mp 88—90°. IR ν_{max} cm^{-1}: 1706 (CO) and 2250 (CN); NMR τ: 8.81 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{15}ON$; C, 74.54; H, 8.53; N, 7.90. Found: C, 74.27; H, 8.59; N, 7.73. GLC: column; 15% Reoplex 400; column temperature 180°; retention time, 26.5 min.

1α-Cyano-6-formyl-8α-methyl-*cis*-hexahydroindan-5-one (**27**)——A solution of 2.7 g of the compound (**5**) in 20 ml of dry benzene was added to 2.0 g (2.5 molar equivalents) of NaOMe. To this mixture was added dropwise 10 ml of ethyl formate under stirring and stirring was continued for further 4 hr at room temperature. The reaction mixture was extracted with 3% NaOH and the alkaline extract was made acidic with 3.5% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave 3.09 g of a red oil. Trituration of the oil with ether gave a crystalline mass which was recrystallized from ether to give 1.31 g of the compound (**27**) as colorless prisms, mp 70—78° (41% yield). When exposed to air, the colorless crystals turned to red. IR ν_{max} cm^{-1}: 2250 (CN), 1658 (CO) and 1596 (C=C); NMR τ: 2.37 (1H, s., HO–CH=C<), 8.73 (3H, s., CH_3). *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 69.69; H, 7.09.

1α-Cyano-6-formyl-8α-methyl-*cis*-hexahydroind-6-en-5-one (**28**)——To a solution of 205 mg of the compound (**27**) in 7 ml of dry dioxane was added a solution of 227 mg of DDQ in 3 ml of dry dioxane under stirring at room temperature. Stirring was continued for 30 min and the deposited hydroquinone derivative was removed by filtration. The filtrate was concentrated under reduced pressure. The residue in $CHCl_3$ was chromatographed on a silica gel column (9×1.5 cm) and the column was eluted with the same solvent. The eluate was recrystallized from a mixed solvent of ether–acetone (5: 1) to give 37 mg of the compound (**28**) as colorless flakes, mp 98—103° (18% yield). IR ν_{max} cm^{-1}: 2250 (CN), 1689 (CO) and 1615 (C–C); NMR τ: −0.04 (1H, s., –CHO), 2.74 (1H, s., C_7–H) and 8.46 (3H, s., CH_3). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.64; H, 6.41; N, 6.75.

The Cyano-diketone (29) and (30)——To a solution of 3.0 g of the compound (**5**) in 30 ml of AcOH was added dropwise a solution of 5.44 g of Br_2 (2.05 molar equivalents) in 22.5 ml of AcOH under stirring. After 30 min, the brown color of reaction mixture faded away. To this solution was added 8.37 g of freshly fused NaOAc and the mixture was heated at 115° for 2 hr. After cooling, AcOH was evaporated under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. The residue was dissolved in ether and the ether solution was extracted with 5% NaOH. The aqueous 5% NaOH layer was made acidic with dil. HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to give 3.5 g of acidic portion as an oil. The oil showed one spot on the silica gel TLC but was not homogeneous by GLC criterion. To a solution of 3.5 g of the above acidic portion in 200 ml of benzene were added 30 ml of ethylene glycol and 500 mg of *p*-toluenesulfonic acid and the mixture was refluxed for 15 hr while water was separated with a Dean-Stark apparatus. After cooling, the solvent was evaporated under reduced pressure. The residue was made alkaline by addition of 5% NaOH solution and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave an oily residue. The residue was mixed with a small amount of acetone and on standing the diketal of the cyano-diketone (**30**) crystallized as colorless prisms, mp 132°, yield 1.9 g. *Anal.* Calcd. for $C_{15}H_{21}O_4N$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.75; H, 7.77; N, 5.09.

The mother liquor from which the diketal of the compound (**30**) was removed as extensive as possible, was concentrated. A mixed solvent of acetone–ether (1: 2) was added to the residue and on standing, crystals separated out from the above solution. Recrystallization of crystals collected by filtration gave 450 mg of the diketal of the compound (**29**) as colorless prisms, mp 132°. *Anal.* Calcd. for $C_{15}H_{21}O_4N$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.37; H, 7.80; N, 4.93. To a solution of 100 mg of the diketal of the compound (**30**) in 6 ml of acetone was added 1 ml of 5% HCl and the mixture was refluxed for 20 hr. After cooling, the solvent was removed by distillation and the residue was extracted with ether. The ether extract was extracted with 2% NaOH solution. The aqueous alkaline layer was made acidic with 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. The residue was recrystallized from ether to give 52 mg of the cyano-diketone (**30**) as colorless needles, mp 95—97°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.80; H, 6.94; N, 7.29.

To a solution of 50 mg of the diketal of the compound (**29**) in 3 ml of acetone was added 0.5 ml of 5% HCl and the mixture was refluxed for 20 hr. The same treatment of the reaction mixture as noted above, gave a crystalline mass which was recrystallized from ether to afford 27 mg of the cyano-diketone (**29**) as colorless prisms, mp 164°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.99; H,

6.95; N, 7.19.

1α-Cyano-5-methoxy-8α-methyl-*cis*-hexahydroind-4-en-6-one (31) and 1α-Cyano-6-methoxy-8α-methyl-*cis*-hexahydroind-6-en-5-one (32)——To a solution of 50 mg of the cyano-diketone (30) in 20 ml of MeOH was added 1 ml of BF_3·ether and the mixture was refluxed for 6 hr. After cooling, the solvent was removed by distillation under reduced pressure and the residue was mixed with 10 ml of water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave 60 mg of a yellow oil. To this oil was added a small amount of ether and on standing, crystals separated out and was collected by filtration. Recrystallization from ether gave 25 mg of the compound (31) as colorless needles, mp 139°. IR ν_{max} cm^{-1}: 2260 (CN), 1689 (CO), and 1632 (C=C). NMR τ: 4.42 (1H, d., J=4 Hz, C_4–H) and 8.63 (3H, s., CH_3). *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.99; H, 7.35; N, 6.87. The mother liquor from which the compound (31) was removed as extensive as possible, was chromatographed on a silica gel column (20×1 cm) and elution with $CHCl_3$ yielded 28 mg of the compound (32) as colorless oil. IR ν_{max} cm^{-1}: 2260 (CN), 1690 (CO), and 1630 (C=C). NMR τ: 4.63 (1H, s., C_7–H) and 8.52 (3H, s., CH_3). The homogeneity of this oil was checked by TLC but because of its lability, no further datum was obtained.

1α-Cyano-5-methoxy-6ξ-chloro-8α-methyl-*cis*-hexahydroind-4-ene (35)——To a solution of 100 mg of the compound (31) in 4.5 ml of a mixed solvent of MeOH–H_2O (8: 1) was added little by little 70 mg of $NaBH_4$ and the mixture was stirred for 3 hr. MeOH was removed by distillation under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave 101 mg of a colorless oil. The oil was dissolved in 2 ml of pyridine, and 0.3 ml of $POCl_3$ was added to the solution at 5°. The mixture was allowed to stand for 34 hr, poured into ice-water and extracted with ether. The ether extract was successively washed with 5% HCl, water, dried and evaporated. Recrystallization of the residue from ether gave 58 mg of the compound (35) as colorless needles, mp 125—130°. IR ν_{max} cm^{-1}: 2250 (CN) and 1658 (C=C). *Anal.* Calcd. for $C_{12}H_{16}ONCl$: C, 63.85; H, 7.15; Cl, 15.71. Found: C, 64.03; H, 7.14; Cl, 15.75.

1α-Cyano-6ξ-chloro-8α-methyl-*cis*-hexahydroindan-5-one (36)——To a solution of 15 mg of the compound (35) in 3 ml of MeOH was added 0.8 ml of conc. HCl and the mixture was allowed to stand for 1 hr at room temperature. The mixture was diluted with 10 ml of water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. Recrystallization of the residue from ether furnished 11 mg of the compound (36) as colorless plates, mp 97—100°. IR ν_{max} cm^{-1}: 2250 (CN) and 1732 (CO). *Anal.* Calcd. for $C_{11}H_{14}ONCl$: C, 62.41; H, 6.67; Cl, 16.74. Found: C, 62.64; H, 6.59; Cl, 16.52.

1α-Cyano-8α-methyl-*cis*-hexahydroind-6-en-5-one (6)——To a solution of 40 mg of the chloro-ketone (36) in 1.5 ml of AcOH was added 50 mg of 2,4-dinitrophenylhydrazine and the mixture was heated at 95° for 10 min. After cooling, the mixture was allowed to stand at room temperature for 2 hr and poured into ice-water. The precipitate was collected by filtration and the crude hydrazone in $CHCl_3$ was chromatographed on a silica gel column (10×1.0 cm) and the column was eluted with the same solvent. Recrystallization of the eluate from ether–acetone (2: 1) gave 52 mg of 2,4-dinitrophenylhydrazone of the compound (6), mp 234—235° (88% yield). To a solution of 52 mg of the above hydrazone in 5 ml of 50% AcOH was added 0.5 ml of pyruvic acid and the mixture was heated at 95° for 3 hr. After cooling, the reaction mixture was neutralized with 5% Na_2CO_3 solution and extracted with ether. The ether extract was washed with water, dried and evaporated. Recrystallization of the residue from ether afforded 19 mg of the compound (6), mp 89°. IR ν_{max} cm^{-1}: 2250 (CN) and 1678 (CO); NMR τ: 3.49 (1H, d.d., J_A=10 Hz, J_B=1 Hz, C_7–H), 4.04 (1H, d., J=10 Hz, C_6–H), 7.09 (1H, t., J=6 Hz, C_1–H) and 8.53 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.50; H, 7.51; N, 8.09.

1α-Cyano-8α-methyl-*cis*-hexahydroind-6-en-5-one (6) and 1α-Cyano-8α-methylhexahydroind-9(4)-en-5-one (21)——To a solution of 25 g of the cyano-ketone (5) in 400 ml of $CHCl_3$ was added dropwise a solution of 25 g of Br_2 in 50 ml of $CHCl_3$ under stirring. After the completion of dropping of the bromine solution, stirring was continued for further 30 min. The reaction mixture was washed with water, dried and evaporated under reduced pressure. To a solution of the oily residue in 120 ml of DMF were added 46 g of LiBr and 46 g of Li_2CO_3 under stirring. The reaction mixture was heated at 140° and nitrogen atmosphere for 3 hr under stirring. After cooling, the mixture was made acidic with dil. HCl and extracted with a mixed solvent of ether–$CHCl_3$ (3: 1) and the organic layer was washed with water, dried and evaporated. The residue in $CHCl_3$ was chromatographed on a silica gel column (60×5.5 cm) and the column was eluted with the same solvent. Recrystallization of the earlier eluate from ether gave 5.1 g of the compound (6) as colorless prisms, mp 89°, which was identified with an authentic sample by comparison of IR spectra and mixture melting point determination. Recrystallization of the later eluate from ether afforded 17 g of the compound (21) as colorless needles, mp 71—73°, which was identified with an authentic sample by comparison of IR spectra and mixture melting point determination.

1α-Carboxy-8α-methyl-*cis*-hexahydroind-6-en-5-one (38) and the Keto-lactone (8)——To a solution of 730 mg of the compound (6) in 20 ml of dry benzene were added 8 ml of ethylene glycol and 35 mg of *p*-toluenesulfonic acid, and the mixture was refluxed for 10 hr while water was separated with a Dean-Stark apparatus. After cooling, 3 g of KOH was added to the mixture and the solvent was removed by distillation under reduced pressure. To the residue was added 5 ml of ethylene glycol and 1.5 ml of water and the

mixture was refluxed for 7 hr at nitrogen atmosphere. After cooling, the mixture was acidified with dil. HCl and heated at 100° for 5 min, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave 900 mg of a reddish oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (40×1.5 cm) and the column was eluted with the same solvent. Recrystallization of the earlier eluate from ether gave 180 mg of the compound (**8**) as colorless prisms, mp 95°. IR ν_{max} cm^{-1}: 1766 (γ-lactone), 1719 (ketone); NMR τ: 5.33 (1H, t., J=3 Hz, –O–CH<), and 8.65 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.84; H, 7.23. Recrystallization of the later eluate from a mixed solvent of MeOH–ether (3: 1) afforded 560 mg of the compound (**38**) as colorless prisms, mp 150—152°. IR ν_{max} cm^{-1}: 1700 (COOH), and 1670 (α,β-unsaturated CO). NMR τ: 3.27 (1H, d., J=10 Hz, C_7–H), 4.07 (1H, d., J=10 Hz, C_6–H), and 8.73 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.31; H, 7.43.

1α-Methoxycarbonyl-8α-methyl-*cis*-hexahydroind-6-en-5-one (**39**)——To a solution of 250 mg of the compound (**38**) in 30 ml of MeOH was added a solution of diazomethane in ether and the mixture was allowed to stand for 10 min at room temperature. Excess diazomethane was decomposed with AcOH and the solution was made alkaline with 5% NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. The oily residue in benzene was chromatographed on an alumina column (10× 1.5 cm) and elution with ether gave 264 mg of the compound (**39**) as a colorless oil. IR ν_{max} cm^{-1}: 1724 (CO_2-Me), and 1672 (α,β-unsaturated CO); NMR τ: 3.35 (1H, d., J=10 Hz, C_7–H), 4.11 (1H, d., J=10 Hz, C_6–H), 6.28 (3H, s., OCH_3) and 8.84 (3H, s., CH_3); Mass Spectrum m/e: 208 (M^+).

1α-Methoxycarbonyl-8α-methyl-*cis*-hexahydroindan-5-one (**42**)——A solution of 232 mg of the compound (**39**) in 10 ml of MeOH was added to 100 mg of 5% Pd-C catalyst and stirred at room temperature and atmospheric pressure in the presence of hydrogen. The reaction stopped in 5 min and the solvent was evaporated under reduced pressure after catalyst had been removed by filtration. The residue was extracted with $CHCl_3$ and the extract was washed with water, dried and evaporated to leave 229 mg of the compound (**42**) as a colorless oil. bp 95° (2×10^{-4} mmHg); IR ν_{max} cm^{-1}: 1719 (COOMe) and 1711 (CO); NMR τ: 6.30 (3H, s., OCH_3) and 8.95 (3H, s., CH_3); Mass Spectrum m/e: 210 (M^+). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.92.

1α-Carboxy-8α-methyl-*cis*-hexahydroindan-5-one (**43**)——To a solution of 169 mg of the compound (**42**) in 10 ml of 50%–MeOH was added 481 mg of KOH and the mixture was refluxed for 30 min. The solvent was removed under reduced pressure and the residue was acidified by addition of 5% HCl and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. Recrystallization of the residue from ether furnished 55 mg of the compound (**43**) as colorless prisms, mp 116.5—118°. IR ν_{max} cm^{-1}: 1704 (COOH and CO); NMR τ: 8.86 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.19; H, 8.26.

The Keto-amide (**44**)——To a solution of 380 mg of the compound (**43**) in 10 ml of dry benzene was added 1 ml of $SOCl_2$ under ice cooling and the mixture was allowed to stand overnight at 5°. The solvent and excess $SOCl_2$ were removed under reduced pressure. To the residue was added 20 ml of dry benzene and ammonia was bubbled into the solution. After evaporation of the solvent under reduced pressure, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 2% Na_2CO_3 solution, water, dried and evaporated. The residue in $CHCl_3$ was chromatographed on a silica gel column (11×1 cm) and eluted with the same solvent. The eluate was recrystallized from a mixed solvent of acetone–ether to give 70 mg of the compound (**44**) as colorless prisms, mp 136—138°. IR ν_{max} cm^{-1}: 3500—3200 (NH_2), 1708 (CO) and 1678 ($CONH_2$); NMR τ: 3.75—4.50 (2H, broad, NH_2) and 8.84 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{17}O_2N\cdot 1/3H_2O$: C, 65.64; H, 8.85; N, 6.96. Found: C, 65.78; H, 8.57; N, 6.97.

1α-Cyano-8α-methyl-*cis*-hexahydroindan-5-one (**5**)——To a solution of 35 mg of the compound (**44**) in 2.5 ml of dry pyridine was added 120 mg of *p*-toluenesulfonyl chloride and the mixture was allowed to stand overnight at room temperature. Pyridine was removed by distillation under reduced pressure and the residue was washed successively with 5% HCl, 5% Na_2CO_3, water, and dried. Evaporation of the solvent left a solid mass which was recrystallized from ether to give 27 mg of the compound (**5**) as colorless prisms, mp 76.5—77.5°. A sample was identified with a sample of the compound (**5**) synthesized formerly by comparison of IR spectra and mixture melting point determination.

1β-Methoxycarbonyl-8α-methyl-*cis*-hexahydroind-6-en-5-one (**42**)——To a solution of 2 g of the keto-lactam (**8**) in 10 ml of MeOH were added 1.3 g of K_2CO_3 and 20 ml of CH_3I and the mixture was refluxed for 4 hr. The solvent was removed by distillation under reduced pressure and the residue was made acidic with 1% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated. The oily residue in $CHCl_3$ was chromatographed on a silica gel column (20×2 cm) and eluted with the same solvent to give 2.01 g of a colorless oil (**42**). IR ν_{max} cm^{-1}: 1723 (COOMe) and 1672 (α,β-unsaturated CO); NMR τ: 3.31 (1H, d.d., J_A=1.5 Hz, J_B=10 Hz, C_7–H), 4.05 (1H, d., J=10 Hz, C_6–H), 6.26 (3H, s., OCH_3) and 8.62 (3H, s., CH_3); Mass Spectrum m/e: 208 (M^+).

1β-Methoxycarbonyl-8α-methyl-*cis*-hexahydroindan-5-one (**45**)——A solution of 900 mg of the compound (**41**) in 20 ml of MeOH was added to 100 mg of 10% Pd-C catalyst and stirred in the presence of hydrogen. The reaction stopped in 30 min and catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to leave 900 mg of an oil. This oil in benzene was chromatographed on

an alumina column (10×1 cm) and elution with ether gave 895 mg of the keto-ester (**45**) as colorless oil, bp 85° (2×10^{-4} mmHg). IR ν_{max} cm^{-1}: 1719 (CO and $COOCH_3$); NMR τ: 6.30 (3H, s., OCH_3) and 8.58 (3H, s., CH_3); Mass Spectrum *m/e*: 210 (M^+). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 67.94; H, 8.74.

1β-Carboxy-8α-methyl-*cis*-hexahydroindan-5-one (46)——To a solution of 700 mg of the keto-ester (**45**) in 20 ml of 50% MeOH was added 560 mg of KOH and the mixture was refluxed for 1 hr. The solvent was evaporated under reduced pressure. The residue was extracted with ether and the remaining aqueous alkaline solution was made acidic with 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. Recrystallization of the residue from ether gave 550 mg of the keto-acid (**46**) as colorless needles, mp 122°. IR ν_{max} cm^{-1}: 1704 (CO and COOH); NMR τ: 8.55 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.46; H, 8.14.

The Keto-amide (47)——To a solution of 500 mg of the keto-acid (**46**) in 5 ml of dry benzene was added 2 ml of $SOCl_2$ at 0° and the mixture was allowed to stand overnight. Excess $SOCl_2$ and benzene were removed by distillation and the oily residue was dissolved in 10 ml of dry benzene and ammonia was bubbled into the solution. The solvent was removed by distillation under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed twice with 5% Na_2CO_3, water and dried. Evaporation of the solvent gave the residue which in $CHCl_3$ was chromatographed on a silica gel column (5×1.5 cm) and eluted with the same solvent. Recrystallization of the eluate from a mixed solvent of acetone–ether (1: 1) gave 120 mg of the keto-amide (**47**) as colorless prisms, mp 149°. IR ν_{max} cm^{-1}: 3500—3200 (NH_2), 1704 (CO) and 1677 ($CONH_2$); NMR τ: 8.58 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.37; H, 8.72; N, 6.93.

1β-Cyano-8α-methyl-*cis*-hexahydroindan-5-one (18)——To a solution of 30 mg of the keto-amide (**47**) in 1.5 ml of pyridine was added 150 mg of *p*-toluenesulfonyl chloride at 0° and the mixture was allowed to stand for 15 hr. Excess pyridine was removed by distillation and the residue was extracted with ether. The ether extract was washed with 5% NaOH, 5% HCl, water, and dried. Evaporation of the solvent left the residue which in $CHCl_3$ was chromatographed on a silica gel column (10×0.8 cm) and eluted with $CHCl_3$. Recrystallization of the eluate from ether gave 15 mg of the keto-nitrile (**18**) as colorless prisms, mp 85°. IR ν_{max} cm^{-1}: 2250 (CN) and 1712 (CO); NMR τ: 8.62 (3H, s., CH_3). *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.32; H, 8.68; N, 7.97.

The Keto-lactam (9)——To a solution of 100 mg of the keto-lactone (**8**) in 10 ml of dry benzene were added 3 ml of ethylene glycol and 25 mg of *p*-toluenesulfonic acid and the mixture was refluxed for 8 hr while water was separated with a Dean-Stark apparatus. The solvent was removed by distillation under reduced pressure, and the residue was made alkaline with 5% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. To a solution of the oily residue in 12 ml of dioxane were added 2 ml of 30% aqueous CH_3NH_2, 600 mg of $CH_3NH_2\cdot HCl$ and 2 ml of water and the mixture was heated at 180—190° in a sealed tube for 45 hr. Dioxane was removed by distillation under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. Recrystallization of the residue from ether afforded 90 mg of the keto-lactam (**9**) as colorless prisms, mp 105°. IR ν_{max} cm^{-1}: 1723 (CO) and 1677 (lactam CO); NMR τ: 6.35 (1H, t., J=3.5 Hz, C_{7a}–H), 7.30 (3H, s., N–CH_3) and 8.66 (3H, s., CH_3); Mass Spectrum *m/e*: 207 (M^+). *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.41; H, 8.31; N, 6.80.

The Alcohol (49)——To the Grignard reagent which was prepared from 36.4 g of iso-propyl bromide (8 molar equivalents), 7.3 g of magnesium (8 molar equivalents), and 5 mg of I_2 in 200 ml of ether, was added a solution of 8 g of the keto-lactam (**9**) in 50 ml of dry tetrahydrofuran and 100 ml of ether at −70°——−60°. After addition of the solution of keto-lactam had completed, the reaction temperature was raised to room temperature. The reaction mixture was made acidic with 5% HCl and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. Fractional recrystallization of the residue from a mixed solvent of ether–tetrahydrofuran (1: 1) furnished 1.65 g of the alcohol (**49**). The same Grignard reaction as above was carried out with the mother liquor removed the crystalline alcohol. These treatments were repeated 4—5 times. Recrystallization of the collected alcohol from a mixed solvent of $CHCl_3$–ether (1: 5) gave 7.18 g of the alcohol (**49**) as colorless prisms, mp 153°. IR ν_{max} cm^{-1}: 3400 (OH) and 1664 (lactam CO); NMR τ: 6.56 (1H, t., J=3.5 Hz, C_{7a}–H), 7.15 (3H, s., N–CH_3), 8.75 (3H, s., angular CH_3) and 9.02 (6H, d., J=6 Hz, iso-propyl). *Anal.* Calcd. for $C_{15}H_{25}O_2N$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.53; H, 10.11; N, 5.57.

The Olefin Mixture (50)——A mixture of 700 mg of the alcohol (**49**) and 2.6 g of freshly fused and pulverized $KHSO_4$ was heated in an oil bath (bath temperature 190°) for 5 min. After cooling, the mixture was added to 10 ml of water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated. The oily residue in benzene was chromatographed on an alumina column and elution with ether gave 609 mg of the olefin mixture (**50**) as a slightly yellow oil. A ratio of three kinds of olefins was estimated by the relative intensity of angular methyl. NMR τ: 8.75/8.77/8.79=1: 1: 1. Because of the lability on standing, this olefin mixture was used immediately for the subsequent reaction without further purification.

The Acetyl Allyl Alcohols, (51) and (53)——To a solution of 400 mg of the olefin mixture (**50**) in 40 ml

of AcOH was added 500 mg of I_2 and the mixture was stirred for 20 min at nitrogen atmosphere and after addition of 608 mg of AgOAc, the mixture was stirred for 30 min and then 0.5 ml of water was added. The mixture was stirred for 24 hr at room temperature. To this mixture was added 200 ml of ether and the mixture was filtered. The filtrate was made alkaline with ammonia and the ether layer was separated, and the aqueous layer was extracted with ether. The ether layer and the ether extracts were combined and washed successively with 5% Na_2CO_3, 5% $NaHSO_3$, water and dried. Evaporation of ether left an oily residue which in $CHCl_3$ was chromatographed on a silica gel column (35×1.5 cm) and eluted with the same solvent. From the earlier eluate, 75 mg of the olefin mixture (**50**) was recovered. Continued elution of the column with $CHCl_3$ gave 20 mg of the acetate of allyl alcohol (**51**) as a colorless oil. All attempts to crystallize this oil were failed. IR ν_{max} cm^{-1}: 1732 ($OCOCH_3$) and 1675 (lactam CO); NMR τ: 4.30 (1H, diffused s., C_5–H), 4.37 (1H, d., J=2.4 Hz, C_7–H), 6.51 (1H, d., J=2.4 Hz, C_{7a}–H), 7.19 (3H, s., N–CH_3), 7.93 (3H, s., $OCOCH_3$), 8.70 (3H, s., angular CH_3), 8.98 and 9.01 (each 3H, d., J=7 Hz, iso-propyl); Mass Spectrum *m/e*: 291 (M^+). From the later eluate, the acetate of allyl alcohol (**53**) was obtained as a colorless oil in a yield of 60 mg. IR ν_{max} cm^{-1}: 1728 ($OCOCH_3$) and 1667 (lactam CO); NMR τ: 4.21 (1H, q., J_A=1.2 Hz, J_B=3 Hz, C_7–H), 4.54 (1H, d., J=2 Hz, C_5–H), 6.33 (1H, q., J_A=1.2 Hz, J_B=3 Hz, C_{7a}–H), 7.10 (3H, s., N–CH_3), 7.97 (3H, s., $OCOCH_3$) and 8.62 (3H, s., angular CH_3), 8.94 and 8.99 (each 3H, d., J=7 Hz, iso-propyl); Mass Spectrum *m/e*: 291 (M^+).

The Allyl Alcohol (54)——To a solution of 20 mg of the acetate (**53**) in 4 ml of MeOH was added 2 ml of 5% NaOH and the mixture was refluxed for 2 hr. The solvent was removed by distillation under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and evaporated to leave 21 mg of colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (10× 1 cm) and elution with the same solvent gave a solid mass. Recrystallization from ether gave 12 mg of the allyl alcohol (**54**) as colorless needles, mp 146°. IR ν_{max} cm^{-1}: 3450 (OH) and 1663 (lactam CO); NMR τ: 4.39 (1H, q., J_A=1.2 Hz, J_B=3 Hz, C_7–H), 5.76 (1H, d., J=2.7 Hz, C_5–H), 6.34 (1H, q., J_A=1.2 Hz, J_B= 3 Hz, C_{7a}–H), 7.14 (3H, s., N–CH_3), 8.56 (3H, s., angular CH_3), 8.90 and 8.94 (each 3H, d., J=6.5 Hz, iso-propyl). *Anal.* Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.06; H, 9.54; N, 5.56.

The Allyl Alcohol (52)——A solution of 13 mg of the acetate (**51**) in 3 ml of MeOH was added to a solution of 1.5 ml of 5% NaOH and the mixture was refluxed for 2 hr. MeOH was removed under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave 12 mg of colorless oil. This oil in $CHCl_3$ was chromatographed on a silica gel column (5× 1 cm) and eluted with the same solvent to give a solid mass. Recrystallization from ether afforded 8 mg of the allyl alcohol (**52**) as colorless prisms, mp 130°. IR ν_{max} cm^{-1}: 3450 (OH) and 1667 (lactam CO); NMR τ: 4.50 (1H, diffused s., C_5–H), 5.61 (1H, d., J=3 Hz, C_7–H), 6.41 (1H, d., J=3 Hz, C_{7a}–H), 7.23 (3H, s., N–CH_3), 8.62 (3H, s., angular CH_3), 8.92 and 8.95 (each 3H, d., J=7 Hz, iso-propyl). *Anal.* Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.12; H, 9.09; N, 5.56.

The Enone (10)——To a solution of 18 mg of the alcohol (**52**) in 5 ml of CH_2Cl_2 was added 120 mg of Collins CrO_3–pyridine complex and the mixture was stirred for 2 hr at room temperature. The reaction mixture was filtered and the precipitate was washed with CH_2Cl_2 several times. The filtrate and the washings were combined, washed successively with 5% $NaHSO_3$, 5% NH_4OH, 5% HCl, water and dried. Evaporation of the solvent left 18 mg of yellow oil. This oil in $CHCl_3$ was chromatographed on a silica gel column (10×0.7 cm) and elution with the same solvent gave 8 mg of the enone (**10**) as colorless oil. IR ν_{max} cm^{-1}: 1617 (lactam and α,β-unsaturated CO); NMR τ: 3.39 (1H, q., J_A=1.5 Hz, J_B=5 Hz, C_5–H), 6.43 (1H, s., C_{7a}–H), 7.23 (3H, s., N–CH_3), 8.66 (3H, s., angular CH_3), 8.94 and 9.01 (each 3H, d., J=6.5 Hz, iso-propyl); Mass Spectrum *m/e*: 247 (M^+) and 111 (base peak).

The Enone (55)——By the procedure described for the enone (**10**), 64 mg of the alcohol (**54**) was treated with 390 mg of Collins CrO_3–pyridine complex. The reaction product was chromatographed on a silica gel column (20×1 cm) and elution with $CHCl_3$ left a solid mass which crystallized on trituration with ether. Recrystallization from a mixed solvent of ether–*n*-hexane (1: 1) afforded 25 mg of the enone (**55**) as colorless prisms, mp 83°. IR ν_{max} cm^{-1}: 1672 (lactam and α,β-unsaturated CO); NMR τ: 3.54 (1H, q., J_A=1 Hz, J_B=4 Hz, C_7–H), 6.18 (1H, q., J_A=1 Hz, J_B=4 Hz, C_{7a}–H), 7.09 (3H, s., N–CH_3), 8.63 (3H, s., angular CH_3), 8.93 and 8.97 (each 3H, d., J=6.5 Hz, iso-propyl). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.94; H, 8.86; N, 5.70.

The Cyano-ketones, (56), (57), and (11)——To a solution of 215 mg of the enone (**10**) in 5 ml of dry benzene was added 4.5 ml of toluene solution of Et_2AlCN (1.05 mmole of Et_2AlCN in 1 ml toluene) and the mixture was stirred at nitrogen atmosphere and room temperature for 3 hr. The reaction mixture was made alkaline with 2N NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated to leave 227 mg of colorless oil. This oil in $CHCl_3$ was chromatographed on a silica gel column (20×1.7 cm). Elution with $CHCl_3$ gave the following four major fractions which are shown in the order of easiness of readsorption; (1) 37 mg of the enone (**10**), (2) 40 mg of the cyano-ketone (**56**), (3) 45 mg of the cyano-ketone (**57**), (4) 65 mg of the cyano-ketone (**11**). The cyano-ketone (**56**) was recrystallized from acetone to give colorless needles, mp 199—200°. IR ν_{max} cm^{-1}: 2260 (CN), 1721 and 1686; NMR τ: 6.37 (1H, s., C_{7a}–H), 6.64 (1H, q., J_A=1 Hz, J_B=4.5 Hz, C_5–H), 7.28 (3H, s., N–CH_3), 8.51 (3H, s., angular CH_3) and 9.04 (6H, d., J=6 Hz, iso-propyl). *Anal.* Calcd. for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.96;

H, 8.16; N, 9.98. The cyano-ketone (**57**) was recrystallized from a mixed solvent of acetone–ether (1: 1) to give colorless prisms, mp 123°. IR ν_{max} cm^{-1}: 2250, 1720 and 1683; NMR τ: 6.39 (1H, s., C_{7a}–H), 7.01 (1H, q., J_A=5.5 Hz, J_B=9 Hz, C_5–H), 7.12 (3H, s., N–CH_3), 8.43 (3H, s., angular CH_3), 8.89 and 8.96 (each 3H, d., J=7 Hz, iso-propyl). *Anal.* Calcd. for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.90; H, 8.07; N, 10.24. The cyano-ketone (**11**) was recrystallized from a mixed solvent of acetone–ether (1: 1) to give colorless prisms, mp 133°. IR ν_{max} cm^{-1}: 2250, 1720 and 1683; NMR τ: 6.78 (1H, q., J_A=3.5 Hz, J_B=10 Hz, C_5–H), 7.06 (3H, s., N–CH_3), 6.60 (1H, s., C_{7a}–H), 8.56 (3H, s., angular CH_3), 8.84 and 8.97 (each 3H, d., J=7 Hz, iso-propyl). *Anal.* Calcd. for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.81; H, 8.27; N, 9.99.

The Cyano-ketones, (56), (57), and (11) by Treatment of the Enone (11) with KCN-NH_4Cl——To a solution of 23 mg of the enone (**10**) in 3 ml of DMF were added 40 mg of KCN, 35 mg of NH_4Cl and 0.5 ml of water and the mixture was heated at 185—190° for 20 hr in a sealed tube. After cooling, the reaction mixture was made alkaline with 5% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and evaporated to leave 31 mg of colorless oil. This oil in $CHCl_3$ was chromatographed on a silica gel column (10×1 cm) and elution with the same solvent gave four major fractions as described in the Et_2AlCN procedure; (1) 9 mg of the enone (**10**), (2) 7 mg of the cyano-ketone (**56**), (3) 2 mg of the cyano-ketone (**57**), and (4) 5 mg of the cyano-ketone (**11**). These samples were identified with the sample obtained from the Et_2AlCN procedure, respectively, by comparison of TLC (Kiesel gel G), IR spectra and mixture melting point determinations.

The Equilibrium Reaction of the Cyano-ketone (57) with NaOMe——To a solution of 10 mg of the cyano-ketone (**57**) in 2 ml of dry benzene was added 20 mg of NaOMe and the mixture was allowed to stand for 72 hr under stirring and at room temperature. The solvent was removed under reduced pressure and the residue was made acidic by addition of 5% HCl under ice-cooling and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The residue was recrystallized from a mixed solvent of acetone–ether (1: 1) to give 8 mg of the cyano-ketone (**56**) as colorless needles, mp 199—200°. A sample was identified with an authentic sample of the compound (**56**) by comparison of TLC (Kiesel gel G), IR spectra and mixture melting point determinations. The TLC examination of the mother liquor removed the crystalline cyano-ketone (**56**) revealed the presence of the cyano ketones (**56**) and (**57**) but the cyano-ketone (**11**) was not detected.

The Equilibrium Reaction of the Cyano-ketone (56) with NaOMe——To a solution of 10 mg of the cyano-ketone (**56**) in 1 ml of anhydrous MeOH was added 20 mg of NaOMe and the mixture was warmed at 40—50° for 5 hr under bubbling nitrogen into the mixture. By the treatment described in the equilibrium reaction of the cyano-ketone (**57**), 6 mg of a yellow oil was obtained. This oil in $CHCl_3$ was chromatographed on a silica gel column (15×0.7 cm) and eluted with the same solvent. From the earlier eluate, 1 mg of the cyano-ketone (**56**) was recovered. A sample was identified with an authentic sample of the cyano-ketone (**56**) by comparison of IR spectra. The later eluate was recrystallized from a mixed solvent of acetone–ether (1: 1) to give 2 mg of the cyano-ketone (**11**) as colorless prisms, mp 133°. A sample was identified with an authentic sample of the cyano-ketone (**11**) by comparison of IR spectra and mixture melting point determination.

(±)-Oxodendrobine (13) and Its Isomer (62)——To a solution of 60 mg of the cyano-ketone (**56**) in 5 ml of MeOH was added little by little 30 mg of $NaBH_4$ under stirring. The mixture was stirred for further 30 min, and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ and the extract was washed with water, dried and evaporated to leave 61 mg of colorless oil. This oil, without further purification, was dissolved in 2 ml of ethylene glycol, and 100 mg of KOH, 0.5 ml of water and 1 drop of NH_2–$NH_2 \cdot H_2O$ were added to the solution. The mixture was heated at 180° for 5 hr and was made acidic with dil. HCl after cooling, and extracted with AcOEt. The extract was dried and evaporated. The residue in 3 ml of MeOH was added to 3 ml of 5% HCl and the mixture was refluxed for 2 hr. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The oily residue in $CHCl_3$ was chromatographed on a silica gel column (20× 1 cm) and eluted with the same solvent. From the earlier eluate, the crude (±)-oxodendrobine (**13**) was obtained as crystals. Recrystallization from ether gave 14 mg of (±)-oxodendrobine (**13**) as colorless needles, mp 183—184°. IR ν_{max} cm^{-1}: 1779 (lactone CO) and 1674 (lactam CO); NMR τ: 5.26 (1H, q., J_A=3.5 Hz, J_B=5 Hz, C_7–H), 6.73 (1H, d., J=3.5 Hz, C_{7a}–H), 7.15 (3H, s., N–CH_3), 8.58 (3H, s., angular CH_3) and 8.97 (6H, d., J=6 Hz, iso-propyl). *Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.04; H, 8.28; N, 5.03.

Continued elution of the chromatographic column with $CHCl_3$ gave the crude isomeric lactone (**62**) of (±)-oxodendrobine as crystals. Recrystallization from ether afforded 30 mg of the pure isomeric lactone (**62**) as colorless, needles, mp 182°. IR ν_{max} cm^{-1}: 1787, 1765 (lactone CO) and 1679 (lactam CO); NMR τ: 5.16 (1H, q., J_A=0.7 Hz, J_B=4 Hz, C_7–H), 6.38 (1H, d., J=4 Hz, C_{7a}–H), 7.19 (3H, s., N–CH_3), 8.70 (3H, s., angular CH_3), 9.01 and 9.08 (each 3H, d., J=6 Hz, iso-propyl). *Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.00; H, 8.23; N, 5.19.

The Hydroxy-nitrile (12)——To a solution of 51 mg of the cyano-ketone (**11**) in 6 ml of MeOH and 0.3 ml of water was added little by little 20 mg of $NaBH_4$ at 0° and the mixture was stirred for 30 min. The mixture

was made acidic with 5% HCl, concentrated under reduced pressure, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residue was recrystallized from a mixed solvent of acetone–ether (1: 1) to give 41 mg of the hydroxy-nitrile (**12**), mp 184—185°. IR ν_{max} cm^{-1}: 3400 (OH), 2260 (CN) and 1673 (CO); NMR τ: 6.25 (1H, q., J_A=2.7 Hz, J_B=10.5 Hz, C_7–H), 6.47 (1H, d., J=2.7 Hz, C_{7a}-H), 7.02 (3H, s., N–CH_3), 8.22 (3H, s., angular CH_3) and 8.88 (6H, d., J=7 Hz, iso-propyl). *Anal.* Calcd. for $C_{16}H_{24}O_2N_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.34; H, 8.83; N, 10.00.

The Imino-lactone (58)——A solution of 35 mg of the hydroxy-nitrile (**12**) in $CHCl_3$ was passed through an alumina column (Merck, Aluminium Oxide, Akt. II—III, 10×0.5 cm) two times. Evaporation of $CHCl_3$ left 35 mg of the imino-lactone (**58**) as colorless oil. IR ν_{max} cm^{-1}: 1673 (C=N) and lactam CO; NMR τ: 4.90 (1H, broad s., NH), 5.40 (1H, q., J_A=3 Hz, J_B=5 Hz, C_7–H), 6.78 (1H, d., J=3 Hz, C_{7a}–H), 7.17 (3H, s., N–CH_3), 8.59 (3H, s., angular CH_3) and 8.98 (6H, d., J=6 Hz, iso-propyl); Mass Spectrum *m/e*: 276 (M^+).

The N-Tosylate of Imino-lactone (58)——To a solution of 30 mg of the imino-lactone (**58**) in 5 ml of dry pyridine was added 80 mg of *p*-toluenesulfonyl chloride at 0° and under stirring for 16 hr. The mixture was poured into 5 ml of ice-water and stirred for 30 min. The mixture was extracted with $CHCl_3$. The extract was successively washed with 5% HCl, 5% $NaHCO_3$, water and dried. Evaporation of the solvent left 62 mg of the N-tosylate of imino-lactone (**58**) as colorless oil. IR ν_{max} cm^{-1}: 1675 (CO) and 1643 (C=N); NMR τ: 5.14 (1H, q., J_A=3 Hz, J_B=5 Hz, C_7–H), 6.79 (1H, d., J=3 Hz, C_{7a}–H), 7.21 (3H, s., N–CH_3), 7.57 (3H, s., tosyl CH_3), 8.64 (3H, s., angular CH_3) and 8.99 (6H, d., J=6 Hz, iso-propyl); Mass Spectrum *m/e*: 430 (M^+).

(±)-Oxodendrobine (13)——To a solution of 40 mg of the N-tosylate (**59**) in 3 ml of dioxane was added 4 ml of 5% NaOH and the mixture was refluxed for 1.5 hr. The solvent was removed under reduced pressure. The residue was mixed with a small amount of water and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The oily residue in $CHCl_3$ was chromatographed on a silica gel column (10×1 cm) and eluted with the same solvent. The eluate was recrystallized from ether to give 7 mg of (±)-oxodendrobine (**13**) as colorless needles, mp 183—184°. A sample was identified with an authentic sample of (±)-oxodendrobine synthesized formerly.

The Keto-ester (60)——To a solution of 130 mg of the cyano-ketone (**11**) in 1 ml of AcOH was added 6 ml of 20% H_2SO_4 and the mixture was heated at 100—105° under stirring for 40 hr. After cooling, AcOH was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. To the residue in 10 ml of MeOH was added excess diazomethane in ether and the mixture was allowed to stand at room temperature for 30 min. Excess diazomethane was decomposed with AcOH and the solvent was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was washed with water, dried and evaporated. The residue in $CHCl_3$ was chromatographed on a silica gel column (10×1 cm) and eluted with the same solvent. Recrystallization of the eluate from ether provided 60 mg of the keto-ester (**60**) as colorless prisms, mp 145—146°. IR ν_{max} cm^{-1}: 1722 (CO_2Me) and 1678 (lactam CO); NMR τ: 6.26 (3H, s., OCH_3), 6.61 (1H, s., C_{7a}-H), 6.99 (3H, s., N–CH_3), 8.50 (3H, s., angular CH_3), 9.01 and 9.08 (each 3H, d., J=6.5 Hz, iso-propyl). *Anal.* Calcd. for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.38; H, 7.92; N, 4.66.

The Hydroxy-ester (61)——To a solution of 50 mg of the keto-ester (**60**) in 10 ml of MeOH and 0.4 ml of water was added 25 mg of $NaBH_4$ for 1 hr at 0° and under stirring. The reaction mixture was acidified with 5% HCl and the solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ and the extract was treated in the usual way. Recrystallization of the crude product from a mixed solvent of acetone–ether (1: 1) afforded 40 mg of the hydroxy-ester (**61**) as colorless prisms, mp 170—171°. IR ν_{max} cm^{-1}: 3400 (OH), 1723 (CO_2Me) and 1669 (lactam CO); NMR τ: 6.16 (1H, q., J_A=3 Hz, J_B=10 Hz, C_7–H), 6.67 (1H, d., J=3 Hz, C_{7a}–H), 7.01 (3H, s., N–CH_3), 8.72 (3H, s., angular CH_3), 8.88 and 9.03 (each 3H, d., J=7 Hz, iso-propyl). *Anal.* Calcd. for $C_{17}H_{27}O_4N$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.78; H, 8.51; N, 4.48.

(±)-Oxodendrobine from the Hydroxy-ester (61)——To a solution of 30 mg of the hydroxy-ester (**61**) in 3 ml of MeOH was added a solution of 65 mg of KOH in 1 ml of water, and the mixture was refluxed for 1 hr. After cooling, the reaction mixture was made acidic with 5% HCl and refluxed for 2.5 hr. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave the crystalline mass. Recrystallization from ether gave 19 mg of (±)-oxodendrobine (**13**) as colorless needles, mp 183—184°. A sample was identified with an authentic sample synthesized formerly.

(±)-Dendrobine (1)——To a solution of 32 mg of (±)-oxodendrobine (**13**) in 6 ml of dry CH_2Cl_2 was added 65 mg of $BF_4^-\cdot Et_3O^+$ (3 molar equivalents) at room temperature and the mixture was stirred for 24 hr. The solvent was removed under reduced pressure and the residue was dissolved in 5 ml of absolute alcohol and 20 mg of $NaBH_4$ was added to the solution under stirring. Stirring was continued for 24 hr and the solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ and the extract was washed with water, dried, and evaporated to leave 27 mg of colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (10×1 cm) and eluted with the same solvent. From the earlier eluate, 18 mg of (±)-oxodendrobine (**13**) was recovered. Continued elution afforded the oily eluate which was recrystallized from ether–*n*-hexane (1: 2) to give 4 mg of (±)-dendrobine (**1**) as colorless needles, mp 131—132°.

IR ν_{max} cm^{-1}: 1768 (γ-lactone); NMR τ: 5.16 (1H, q., $J_A=3$ Hz, $J_B=5$ Hz, C_7–H), 7.50 (3H, s., N–CH_3), 8.62 (3H, s., angular CH_3) and 9.04 (6H, d., $J=5.5$ Hz, iso-propyl). A sample was proved to be identical with an authentic sample of natural dendrobine in terms of TLC (Kiesel gel G nach Stahl), IR and NMR spectra.

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