In one run, the product of m.p. 256° (decomp.), which have the satisfactory analytical figures for XVI was obtained. This compound was heated with 6*N* HCl on a water bath for 30 min. to give the higher melting isomer obtained above, therefore, this compound may be unstable form of XVI.

Boron Trifluoride Complex of 1,2-Dimethylbenzimidazole 3-Oxide (XVII)——To a solution of I (I′, 0.40 g., 2.0 mmole) in $CHCl_3$ (5.0 ml.) was added BF_3–ether (0.50 ml., 3.9 mmole) dropwise with stirring at room temperature, and the solution was allowed to stand for 30 min. In a few minutes, colorless crystals separated from the resulting turbid solution. The mixture was cooled and filtered to give the complex as colorless crystals (0.45 g.). Recrystallization from acetone to give the complex as colorless crystals (0.45 g.). Recrystallization from acetone to give colorless prisms, m.p. 206～208°. *Anal.* Calcd. for $C_9H_{10}ON_2 \cdot BF_3$: C, 46.99; H, 4.39; N, 12.18. Found: C, 47.17; H, 4.27; N, 12.12.

The authors express their gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this Laboratory, for their helpful guidance and encouragement. Thanks are also due to the members of the Physical Chemistry Department for the spectral measurements, to the members of the Analysis Room for the elemental analysis, and to Mr. S. Hashimoto for his technical assistance.

Summary

Deoxygenation of 1,2-dimethylbenzimidazole 3-oxide (I) proceeded by treatment with phosphorus trichloride, sulfur dioxide, sodium hydrogensulfite and sodium borohydride besides by catalytic reduction with Raney nickel. The methyl group at C-2 of I seemed less reactive than that of the parent base and did not condense with benzaldehyde, *p*-dimethylaminonitrosobenzene or *p*-nitrobenzenediazonium chloride. However, I reacted with dimethyl oxalate in the presence of alkali to give 2-methoxalylmethyl-1-methylbenzimidazole 3-oxide in good yield. The reactions of I with acetic anhydride, benzoyl chloride, phosphoryl chloride, tosyl chloride, tosyl chloride-pyridine, potassium cyanide-benzoyl chloride, methyl cyanoacetate-acetic anhydride, phenyl isocyanate, phenyl isocyanide and isoamyl nitrite-sodium amide were examined. By these reactions, 2-substituted methyl-1-methylbenzimidazole and/or 6-substituted 1,2-dimethylbenzimidazole were obtained. As a co-ordination compound, the boron trifluoride complex of I was obtained.

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UDC 547.945.1.04 : 615.711.7

167. Zen-ichi Horii, Takushi Kurihara, Shigeo Yamamoto, Ming-Ching Hsü, Chuzo Iwata, Ichiya Ninomiya, and Yasumitsu Tamura: Studies on Ergot Alkaloids and Related Compounds. XIII.*1 Syntheses and Stereochemistries of 4-Methyl-1,2,3,-4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylic Acids.

(*Faculty of Pharmaceutical Sciences, Osaka University**2)

In the preceding paper*1, ethyl *anti*-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (I) and ethyl *trans-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (III) have been prepared as simplified analogues of lysergic acid and shown to possess a marked oxytocic activity. In view of this result, it appears of

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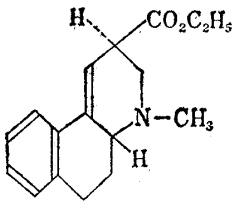
*1 Part XII: This Bulletin, **13**, 420 (1965).

*2 Toneyama, Toyonaka, Osaka (堀井善一, 栗原拓史, 山本重雄, 徐 明 郷, 岩田宙造, 二宮一弥, 田村恭光).

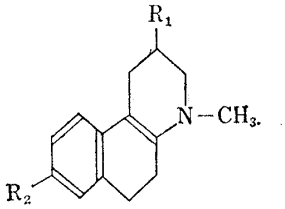
interest to examine the pharmacological properties of their stereoisomers. The investigation was undertaken to prepare stereoisomers of Ⅲ. Theoretically, four stereoisomers are possible for a plain structure represented by Ⅲ. Three isomers of them, *i.e.* the *trans-anti* (Ⅲ), the *cis-anti* (Ⅳ) and the *cis-syn* (Ⅴ), have now been prepared by the reduction of ethyl 4-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (Ⅱ)*[1], and their stereochemistries are established. Some derivatives of Ⅲ, Ⅳ and Ⅴ in which C_2-ethoxycarbonyl group was replaced by carboxyl, diethylcarbamoyl, hydroxymethyl and methyl groups have also been prepared. The *cis* or *trans* designation in this paper refers to the relationship of the hydrogens in the C_{4a}- and C_{10b}-positions, and the *syn* or *anti* designation refers to that in the C_2- and C_{4a}-positions.

Preparation

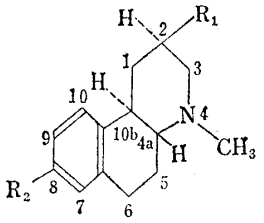
Catalytic hydrogenation of the enamine (Ⅱ) over platinum oxide in ethanol gave a mixture of the *cis-syn* ester (Ⅴ) and the *cis-anti* ester (Ⅳ) in the ratio of 9:1, shown by vapor phase chromatography (v.p.c.). The structures of Ⅳ and Ⅴ were discussed afterwards in the section of stereochemistry. Reduction of Ⅱ with sodium borohydride in ethanol yielded a mixture of the known *trans-anti* ester (Ⅲ)*[1] and the *cis-anti* ester (Ⅳ) in the ratio of 7:3 by v.p.c. When the sodium borohydride reduction of Ⅱ was carried out in tetrahydrofuran in the presence of acetic acid,[1] a mixture of Ⅲ, Ⅳ and Ⅴ was obtained in the ratio of 0.2:4.7:5.1 by v.p.c.



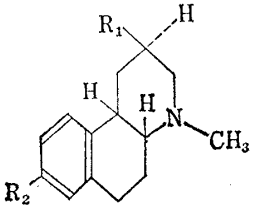
I



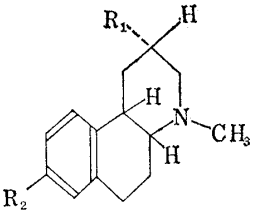
II : $R_1=CO_2C_2H_5$, $R_2=H$
IIa : $R_1=CO_2C_2H_5$, $R_2=OCH_3$



III : $R_1=CO_2C_2H_5$, $R_2=H$
IIIa : $R_1=CO_2C_2H_5$, $R_2=OCH_3$
VI : $R_1=CO_2H$, $R_2=H$
IX : $R_1=CH_2OH$, $R_2=H$
XII : $R_1=CON(C_2H_5)_2$, $R_2=H$



IV : $R_1=CO_2C_2H_5$, $R_2=H$
IVa : $R_1=CO_2C_2H_5$, $R_2=OCH_3$
VII : $R_1=CO_2H$, $R_2=H$
X : $R_1=CH_2OH$, $R_2=H$
XIII : $R_1=CON(C_2H_5)_2$, $R_2=H$



V : $R_1=CO_2C_2H_5$, $R_2=H$
Va : $R_1=CO_2C_2H_5$, $R_2=OCH_3$
VIII : $R_1=CO_2H$, $R_2=H$
XI : $R_1=CH_2OH$, $R_2=H$
XIV : $R_1=CON(C_2H_5)_2$, $R_2=H$

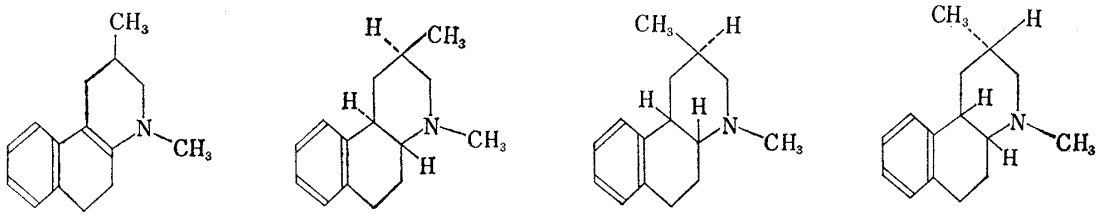
Chart 1.*[3]

*[3] These projections were depicted according to the reference 10). Hydrogens at C_{10b} in Ⅳ and Ⅴ show equatorial and axial configuration respectively with respect to the piperidine ring.

1) J. A. Marshall, W. S. Johnson : J. Org. Chem., **28**, 421 (1963).

Refluxing with 10% hydrochloric acid converted Ⅲ, Ⅳ and Ⅴ into the corresponding acids (Ⅵ, Ⅶ and Ⅷ). Esterification of Ⅵ, Ⅶ and Ⅷ by Fischer method gave the starting esters (Ⅲ, Ⅳ and Ⅴ) respectively, which showed no change in the configuration at C_2 during hydrolysis. These esters (Ⅲ, Ⅳ and Ⅴ) on reduction with lithium aluminum hydride in ether gave the alcohols (Ⅸ, Ⅹ and Ⅺ). Treatment of these acids (Ⅵ, Ⅶ and Ⅷ) with sulfur trioxide-dimethylformamide complex and diethylamine according to the method of Garbrecht[2] gave the corresponding diethylamides (Ⅻ, ⅩⅢ and XIV).

Three isomers (XVI, XVII and XVIII) of 2,4-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline were obtained by reduction of 2,4-dimethyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (XV) as shown in Chart 2. The structures of XVI, XVII and XVIII were determined in direct comparison with the corresponding authentic samples derived from Ⅸ, Ⅹ and Ⅺ by tosylation followed by lithium aluminum hydride reduction.[3]



XV XVI XVII XVIII

Chart 2.

TABLE I. Reduction of 2,4-Dimethyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (XV)

Reducing agent	Yield (%)	Products ratio (%)[a]		
		XVI	XVII	XVIII
PtO_2–H_2 in EtOH	86		35	65
$NaBH_4$ in MeOH	70	86	14	
B_2H_6	73	83	17	
Li in liq. NH_3	79	65	35	
$HClO_4$ salt-$NaBH_4$	89	88	12	

a) The ratio was obtained by vapor phase chromatography.

Condensation of 6-methoxy-2-tetralone with ethyl 2-(bromomethyl)acrylate and methylamine according to the method of Grob[4] gave ethyl 4-methyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (Ⅱa) in 53% yield. Dihydro derivatives (Ⅲa, Ⅳa and Ⅴa) were obtained from Ⅱa by catalytic hydrogenation or sodium borohydride reduction in tetrahydrofuran and also in acetic acid,[1] respectively, as in the case of Ⅱ.

Stereochemistry

It is possible to assume that the catalytic hydrogenation of the enamine (Ⅱ) will predominantly lead to *cis* addition of hydrogens to the tetra-substituted double bond.[5] Both hydrogenation products (Ⅳ and Ⅴ) should therefore have *cis* configuration at B/C ring juncture. This was supported by the following chemical transformations. When

2) W. L. Garbrecht : J. Org. Chem., **24**, 368 (1956).
3) E. Shreier : Helv. Chim. Acta, **41**, 1984 (1958).
4) C. A. Grob, E. Renk : *Ibid.*, **44**, 1531 (1961).
5) A. Nelson, J. E. Ladbury : J. Am. Chem. Soc., **80**, 6633 (1958). R. P. Linstead, W. E. Doering : *Ibid.*, **64**, 1985 (1942).

the *trans-anti* acid (Ⅵ) was treated with acetic anhydride according to the method of Stoll,[6] the *trans*-methylene lactam (XIX) was obtained. On the other hand, the *cis-anti* acid (Ⅶ) and the *cis-syn* acid (Ⅷ) were converted by the same treatment as above into the *cis* methylene lactam (XX) shown in Chart 3.

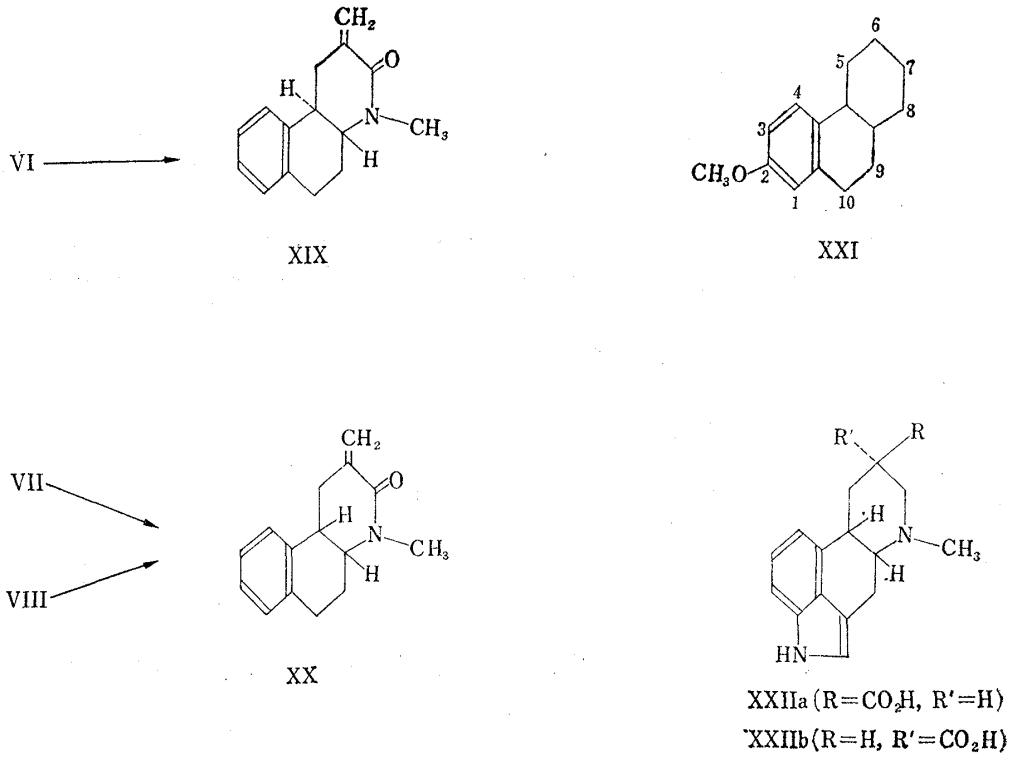


Chart 3.

Further proofs for their stereochemistries were obtained by nuclear magnetic resonance (NMR) spectra*4 and pKa*5 values. As shown in Fig. 1, the signal of aromatic protons of Ⅴ showed a sharp singlet at 2.92τ, while those of Ⅲ and Ⅳ showed a multiplet signal at 2.76~2.99τ.

Recently Nagata[7] has reported on NMR spectra of A-ring aromatic octahydrophenanthrene series (XXI) that strong deshielding of the aromatic C_4-proton is caused by the steric effect of the equatorial C_5-proton, and the degree of this deshielding was closely related to the interatomic distance between the two protons. Inspection of Dreiding model on these three esters (Ⅲ, Ⅳ and Ⅴ) clearly shows that two protons at C_1- and C_{10}-positions in Ⅲ and Ⅳ are in the very close position as in the case of octahydrophenanthrenes. Thus, the multiplet signal of the aromatic protons in Ⅲ and Ⅳ can be interpreted to be caused by an abnormal proximity between two protons at C_1 and C_{10}, which breaks the equivalency of aromatic protons in Ⅴ giving the singlet signal. The same results were obtained on alcohols (Ⅸ, Ⅹ and Ⅺ) and methyl derivatives (XVI, XVII and XVIII) as listed in Table Ⅱ.

NMR spectra of 8-methoxy esters (Ⅲa, Ⅳa and Ⅴa), which could be interpreted as follows, confirms the above stereochemical consideration in Fig. 2. The C_{10}-proton signal occurs as a doublet (J_{ortho} = 8.4 c.p.s.) and the lines are somewhat broadened

*4 NMR spectra were measured in $CDCl_3$ at 60 Mc.p.s. and tetramethylsilane as internal standard, using Hitachi Perkin-Elmer H-60 type Spectrometer.

*5 Three isomeric acids as well as alcohols were dissolved in excess 0.0401N hydrochloric acid in 80% methyl cellosolve and titrated automatically with 0.243N sodium hydroxide in the same solvent.

6) A. Stoll, A. Hofmann, F. Troxler: Helv. Chim. Acta, **32**, 506 (1951).
7) W. Nagata, T. Terasawa, K. Tori: J. Am. Chem. Soc., **86**, 3746 (1964).

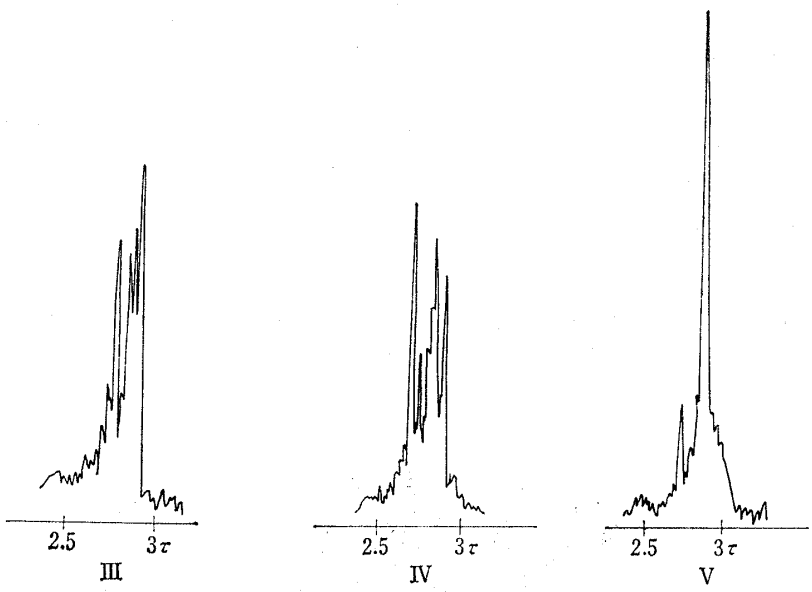


Fig. 1. Nuclear Magnetic Resonance Spectra of III, IV and V measured in $CDCl_3$ at 60 Mc.p.s.

Table II. Nuclear Magnetic Resonance on Aromatic Part ($CDCl_3$, 60 Mc.p.s.)

Compound No.	τ-Value	Shape
III, IX, XVI	2.76~2.99	multiplet
IV, X, XVII	2.78~2.98	〃
V, XI, XVIII	2.91~2.93	singlet

due to the small para-coupling.[8] The C_9-proton resonance is split by J_{ortho} = 8.4 c.p.s. and J_{meta} = 3.3 c.p.s. The C_7-proton is coupled to other two protons with J value of 3.3 c.p.s. and 0~1 c.p.s. As shown in Fig. 2, the C_{10}-proton signals of IIIa and IVa occur at lower field than that of Va, indicating the abnormally proximate disposition of C_{10}- and C_1-protons in IIIa and IVa.

The configuration of C_2-substituent was determined by pKa data, as shown in Table III, indicating that there are no prominent differences in their pKa values between two *cis*-isomers (VII and VIII or X and XI). It has been known that in amino acid the spatial vicinity of the carboxyl group to the amino group affects remarkably on acidity of the carboxyl group and basicity of the amino group due to the formation of hydrogen bonding.[9] Therefore, the C_2-substituents of both *cis*-isomers should have the equatorial configuration. And all those evidences support the suggestion that the compounds IV and V have the conformation IVA and VA, compound III has IIIA (Fig. 3).

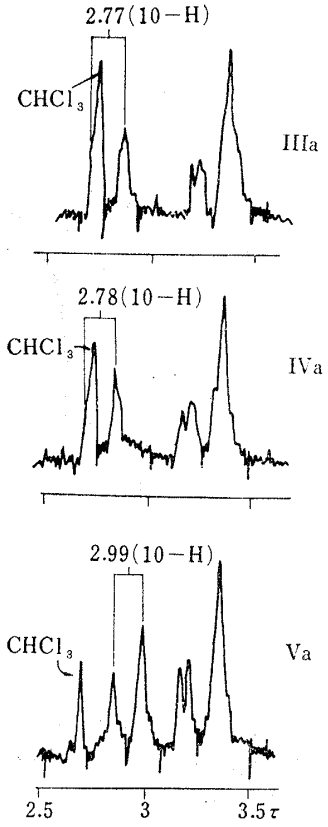


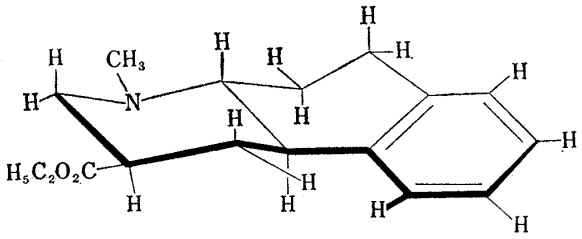
Fig. 2. Nuclear Magnetic Resonance measured in $CDCl_3$ at 60 Mc.p.s.

8) N. S. Bhacca, D. H. Williams: "Application of NMR spectroscopy in organic chemistry" 1964, p. 97. Holden-Day, Inc., San Francisco.
9) J. B. Stenlake: Chem. & Ind., **1953**, 1089.

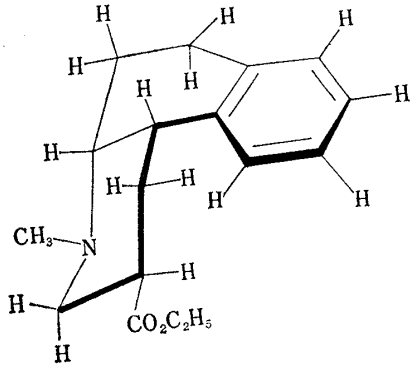
Table Ⅲ. pKa-Value[a] of the Compounds (Ⅵ~Ⅺ)

Compounds	pK_1	pK_2
Ⅵ (*trans-anti*)	4.70	8.20
Ⅶ (*cis-anti*)	4.86	8.40
Ⅷ (*cis-syn*)	4.86	8.44
Ⅸ (*trans-anti*)		7.85
Ⅹ (*cis-anti*)		8.10
Ⅺ (*cis-syn*)		8.25

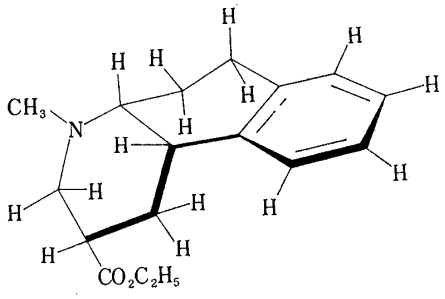
a) Determined in 80% Methylcellosolve, using Metrohm Automatic Titrator Model E364.



IIIA



IVA



VA

Fig. 3.

Upon refluxing Ⅳ with 20% sodium ethoxide in ethanol,[10] the compound (Ⅳ) was isomerized to Ⅴ in 53% yield, while Ⅴ was recovered almost unchanged. Therefore, the *cis-syn* ester (Ⅴ) should be thermodynamically more stable than the *cis-anti* ester (Ⅳ), and this result is in good agreement with the Barton's report[11] stating that, of the two possible conformations for dihydro- and dihydro-*iso*-lysergic acid-Ⅱ*[6] (XXⅡa and XXⅡb), one which has the large aromatic group equatorial is preferred to that where it is axial.

*[6] Of this designation, see A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann and H. Gunthart: Helv. Chim. Acta, **37**, 2039 (1954).

10) Z. G. Hajos, K. J. Doebel, M. W. Goldburg: J. Org. Chem., **29**, 2527 (1964).

11) D. H. R. Barton, R. C. Cookson: Quart. Rev., **10**, 74 (1956).

Experimental*7

Reduction of Ethyl 4-Methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (II) with Sodium Borohydride——To a solution of II (6.2 g.) in EtOH (300 ml.) was added $NaBH_4$ (5.2 g.), and the mixture was stirred for 2.5 hr. at room temperature before decomposing the excess $NaBH_4$ by adding AcOH under ice-cooling. After evaporation of the solvent, the residue was basified with satd. $NaHCO_3$ and extracted with ether. The ether extract was washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a brown oil (3.4 g.), which was chromatographed over Al_2O_3. The former fraction eluted with benzene afforded ethyl *cis-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (IV) (820 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1724 (CO). Perchlorate, colorless needles, m.p. 189~190°, from EtOH-ether. *Anal.* Calcd. for $C_{17}H_{24}O_6NCl$: C, 54.61; H, 6.47. Found: C, 54.77; H, 6.43. The latter fraction eluted with benzene afforded the main product, ethyl *trans-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (III) (2.2 g.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1723 (CO). Perchlorate, colorless needles, m.p. 175~176°, from EtOH-ether. *Anal.* Calcd. for $C_{17}H_{24}O_6NCl$: C, 54.61; H, 6.47; N, 3.63. Found: C, 54.78; H, 6.60; N, 3.63.

Hydrogenation of II with Platinum Oxide Catalyst——The ester (II) (1.68 g.) was shaken in hydrogen atmosphere at room temperature in EtOH (20 ml.) in the presence of PtO_2 (60 mg.). Hydrogenation was completed in ca. 3 hr. with absorption of 1 mole of hydrogen. The catalyst was removed by filtration and the solvent was evaporated, leaving a brown oil. Distillation gave a viscous oil, $b.p_1$ 180~220° (bath temp.), showing the presence of two components in the ratio of 9:1 by v. p. c. Chromatographical separation (Al_2O_3–benzene) gave a pure sample of ethyl *cis-syn*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (V) (1.1 g.), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720 (CO), which was identified as a perchlorate, colorless needles, m.p. 198~199°, from EtOH-ether. *Anal.* Calcd. for $C_{17}H_{24}O_6NCl$: C, 54.61; H, 6.47. Found: C, 54.38; H, 6.41. The presence of IV as a minor product was detected by v. p. c. on the comparison with the authentic sample prepared from $NaBH_4$ reduction of II.

Reduction of II with Sodium Borohydride in the presence of Acetic Acid——To a solution of II (1.0 g.) and $NaBH_4$ (560 mg.) in anhyd. tetrahydrofuran (20 ml.) was added AcOH (10 ml.) in 30 min. with stirring. The solution was allowed to stand at room temperature for 90 min. The solution was made alkaline with 10% NaOH under ice-cooling and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an oily residue, which was distilled to give a pale yellow oil (0.8 g.), $b.p_2$ 190~220° (bath temp.). After purification through Al_2O_3 column employing benzene as eluent, was obtained IV (650 mg.) from the former fraction. From the latter fraction was obtained V (80 mg.). These compounds were identified as IV and V, respectively, on the comparison of the mixed melting point determination of their perchlorates and their IR spectra with authentic samples described above.

***trans-anti*-4-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylic Acid (VI)**——A solution of III (1.0 g.) dissolved in 10% HCl (20 ml.) was refluxed for 4 hr. The solution was condensed *in vacuo*, giving a crystalline hydrochloride. A solution of the hydrochloride in H_2O (20 ml.) was submitted to 60~100 mesh Duolite A-2 column employing H_2O as eluent, until the elution gave a negative $AgNO_3$ test. The combined eluate was evaporated to dryness under reduced pressure to give 550 mg. of free amino acid. This was recrystallized three times from H_2O and once from iso-PrOH to give an analytical sample as colorless crystals, m.p. 247~249° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.64; N, 5.72.

***cis-anti*-4-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylic Acid (VII)**——One gram of IV was refluxed with 10% HCl (30 ml.) for 4 hr. The reaction mixture was worked up as in the preparation of VI, giving 400 mg. of free amino acid. Three recrystallizations from H_2O and then from iso-PrOH afforded a pure sample as colorless crystals, m.p. 227~230° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.46; H, 7.76; N, 5.87.

***cis-syn*-4-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylic Acid (VIII)**——One gram of V was refluxed with 10% HCl (30 ml.) for 4 hr. The solution was treated as described above to give 480 mg. of free amino acid. Recrystallization as above afforded a pure sample as colorless crystals, m.p. 237~239° (decomp.). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.81; N, 5.72.

2-Hydroxymethyl-*trans-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IX)——To a stirred solution of $LiAlH_4$ (400 mg.) in anhyd. ether (40 ml.) was added a solution of III (1.0 g.) in anhyd. ether (20 ml.) at room temperature. The mixture was heated under reflux for 4 hr. before decomposing the excess $LiAlH_4$ by adding H_2O under ice-cooling. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Crude crystals (840 mg.) were obtained. Recrystallization from acetone gave a pure sample as colorless needles, m.p. 152~153°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3572 (OH). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.08; H, 9.29; N, 5.83.

*7 All melting points and boiling points are uncorrected. Vapor-phase chromatography was carried out with Shimadzu Gas Chromatograph GC-1B equipped with a hydrogen flame ionization detector, employing 3% SE-30 column (column temperature 185°).

2-Hydroxymethyl-*cis-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (X)——To a stirred solution of $LiAlH_4$ (300 mg.) in anhyd. ether (20 ml.) was added a solution of Ⅳ (800 mg.) in anhyd. ether (20 ml.) at room temperature. The mixture was treated as above for Ⅸ, giving 700 mg. of crude alcohol. Recrystallization from acetone gave a pure sample as colorless needles, m.p. 122.5～123°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3574 (OH). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.88; H, 9.03; N, 6.15.

2-Hydroxymethyl-*cis-syn*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XI)——To a stirred solution of $LiAlH_4$ (400 mg.) in anhyd. ether (20 ml.) was added a solution of Ⅴ (1.0 g.) in anhyd. ether (20 ml.) at room temperature. The mixture was treated as described above, giving 800 mg. of crude alcohol. Recrystallization from acetone gave a pure sample as colorless needles, m.p. 137～138°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571 (OH). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15. Found: C, 77.60; H, 9.15.

N,N-Diethyl-*trans-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxamide (XII)——*trans-anti*-Amino acid (Ⅵ) (300 mg.) and LiOH (30 mg.) were dissolved in MeOH (15 ml.). The solvent was removed on the steam bath under reduced pressure and dried. The residual Li-carboxylate was dissolved in anhyd. DMF (30 ml.), and condensed to about half a volume under reduced pressure. The resulting solution was cooled to 0° and treated rapidly with 1 ml. of DMF-SO_3 complex (containing 2 mole of SO_3), prepared by the method of Garbrecht[2] and stirred for 10 min. Then 450 mg. (5 moles) of $(C_2H_5)_2NH$ was added and stirred for another 10 min. before decomposing the complex by adding water (10 ml.). The solution was made alkaline, extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (180 mg.) was subjected to chromatography over Al_2O_3. A fraction eluted by benzene afforded Ⅻ (140 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640 (CO-N). This was characterized as a picrate as yellow needles, m.p. 208° (from EtOH). *Anal.* Calcd. for $C_{25}H_{31}O_8N_5$: C, 56.70; H, 5.90; N, 13.23. Found: C, 57.00; H, 5.90; N, 12.94. The starting material (Ⅵ) (85 mg.) was recovered from aqueous alkaline solution.

N,N-Diethyl-*cis-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxamide (XIII)——*cis-anti*-Amino acid (Ⅶ) (250 mg.) was treated as described above for the formation of Ⅻ to give the diethylamide (XIII) (94 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640 (CO-N), characterized as a picrate as yellow crystals, m.p. 183° (from EtOH). *Anal.* Calcd. for $C_{25}H_{31}O_8N_5$: C, 56.70; H, 5.90; N, 13.23. Found: C, 56.79; H, 5.67; N, 12.91. The starting amino acid (Ⅶ) (53 mg.) was recovered.

N,N-Diethyl-*cis-syn*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxamide(XIV)——*cis-syn*-Amino acid (Ⅷ) (700 mg.) was treated as described above for the formation of Ⅻ to afford the diethylamide (XIV) (305 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640 (CO-N), characterized as a perchlorate as colorless crystals, m.p. 129～130° (from H_2O). *Anal.* Calcd. for $C_{19}H_{29}O_5N_2Cl \cdot H_2O$: C, 54.47; H, 7.22; N, 6.69. Found: C, 54.63; H, 7.38; N, 6.49. The starting amino acid (Ⅷ) (203 mg.) was recovered.

***trans-anti*-2,4-Dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XVI)**——To a solution of amino alcohol (Ⅸ) (4.8 g.) in pyridine (40 ml.) was added TsCl (4.8 g.) in small pieces with stirring under ice-cooling over 4 hr. The reaction mixture was made alkaline with satd. $NaHCO_3$, then extracted with a mixture of iso-PrOH-$CHCl_3$ (1:3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue showed the characteristic absorption band of a tosyl group (1361 and 1178 cm^{-1}) and was used to the following reaction without further purification. A solution of a crude tosylate (3.1 g.) in anhyd. ether (50 ml.) was added dropwise to the suspension of $LiAlH_4$ (2.0 g.) and anhyd. ether (30 ml.) under ice-cooling. The mixture was refluxed for 3 hr. before decomposing of excess $LiAlH_4$ by adding H_2O. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give a brown oil (2.1 g.), characterized as a methiodide, colorless needles, m.p. 232～233° (decomp.) after recrystallization from MeOH-ether. *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.76; N, 3.92. Found: C, 53.85; H, 6.70; N, 4.21.

***cis-anti*-2,4-Dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XVII)**——To a solution of amino alcohol (X) (1.0 g.) in pyridine (20 ml.) was added TsCl (800 mg.) in small pieces and stirred for 4 hr. The reaction was carried out in the same procedure as XVI to give the product (320 mg.), characterized as a methiodide, colorless needles, m.p. 219～220° (decomp.) after recrystallization from MeOH-ether. *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.76; N, 3.92. Found: C, 53.82; H, 6.63; N, 4.08.

***cis-syn*-2,4-Dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XVIII)**——To a solution of amino alcohol (Ⅺ) (1.5 g.) in pyridine (50 ml.) was added TsCl (1.2 g.) in small pieces with stirring under ice-cooling. The reaction was worked up as described above to yield the product (600 mg.), characterized as a methiodide, colorless needles, m.p. 268° (decomp.) after recrystallization from MeOH-ether. *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.76; N, 3.92. Found: C, 53.41; H, 6.76; N, 3.88.

Catalytic Hydrogenation of 2,4-Dimethyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (XV)——Six hundred milligram of XV*[8] was hydrogenated at room temperature under an atmospheric pressure of hydrogen in EtOH (7 ml.) in the presence of PtO_2 (60 mg.). After the uptake of 1 molar equivalent of hydrogen, the catalyst was filtered off and the solvent was evaporated. The residual oil was distilled *in vacuo* to give a brown oil (520 mg.), b.$p_{0.01}$ 80～90° (bath temp.). The column chromatography on Al_2O_3 using benzene as

*[8] Z. Horii, C. Iwata, I. Ninomiya, M. Ito and Y. Tamura: This Bulletin, **12**, 1405 (1964).

eluent gave 180 mg. of XVII, characterized as a methiodide. Recrystallization of methiodide from EtOH–ether gave colorless needles, m.p. 219~220°(decomp.). *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.76; N, 3.92. Found: C, 53.97; H, 6.65; N, 4.17.

Further elution by benzene afforded XVIII (310 mg.), which was identified as XVIII, by the comparison of IR spectra and v. p. c. with the authentic sample derived from XI.

Reduction of XV with Lithium in Liquid Ammonia——To a suspension of Li (100 mg.) in liq. NH_3 (200 ml.) was added XV (540 mg.) in dry ether (20 ml.) with stirring. After 3 hr., the blue color of the solution was discharged by adding NH_4Cl (3 g.), and NH_3 was allowed to evaporate. The residue, upon dissolving in H_2O, was extracted with ether, and the ether layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled *in vacuo* to give a brown oil, $b.p_1$ 130~135°, which was chromatographed over Al_2O_3. The first fraction eluted with benzene afforded XVII, identified with an authentic sample by the comparison of IR spectra, v. p. c. and by a mixed melting point determination of their methiodides. Further elution with benzene gave XVI (260 mg.), which was characterized as a methiodide, colorless needles, m.p. 232~233°(from EtOH–ether). *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.76; N, 3.92. Found: C, 53.79; H, 6.65; N, 4.17.

Reduction of XV with Diborane——A solution of XV (50 mg.) in dry tetrahydrofuran (7 ml.) was treated with B_2H_6 gas prepared from BF_3–etherate (6.4 g.) and $NaBH_4$ (1.2 g.) in diglyme (50 ml.) under a stream of N_2. After the evolution of gas ceased, the solution was refluxed with AcOH (19 ml.) for 1 hr. After cooling, the solution was neutralized with satd. $NaHCO_3$ and extracted with ether. The ether layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled under reduced pressure to give an oil (37 mg.), $b.p_3$ 140~150°(bath temp.). Chromatographical separation of the crude product on Al_2O_3–benzene afforded XVI (30 mg.) and XVII (trace). These were found to be identical with the authentic samples by the comparison of their IR spectra, v. p. c. and by the mixed melting point determination of their methiodides.

Reduction of XV with Sodium Borohydride——A solution of XV (110 mg.) in MeOH (17 ml.) was treated with $NaBH_4$ (360 mg.) in the same manner as mentioned for the reduction of the corresponding ester (II). The product was isolated by the usual manner and distilled *in vacuo* to give an oil (90 mg.), $b.p_3$ 140~150° (bath temp.) and then chromatographed on Al_2O_3. The fraction eluted by benzene afforded XVI (70 mg.) and XVII (trace), which were found to be identical with the authentic samples by their spectral comparisons.

Reduction of the Perchlorate of XV with Sodium Borohydride——A solution of the perchlorate of XV (ν_{max}^{Nujol} cm^{-1}: 1681 +(N=C)) (200 mg.) in MeOH (50 ml.) was treated with $NaBH_4$ (300 mg.) under ice-cooling in the same manner as mentioned for the reduction of II. The product was separated by working up as usual and chromatographed on Al_2O_3. The fraction eluted by benzene afforded XVI (100 mg.) and XVII (trace) which were found to be identical with the authentic samples by their spectral comparisons.

***trans*-4-Methyl-2-methylene-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XIX)**——A mixture of amino acid (VI) (205 mg.), dried over *in vacuo* at 100°, and freshly distilled Ac_2O (20 ml.) was placed in a sealed tube and heated in an oil bath at 170° for 20 min. The resulting brown solution was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and purified by Al_2O_3 column chromatography. Evaporation of the solvent gave 120 mg. of a crystalline lactam. Recrystallization from petr. benzine gave a pure sample, m.p. 120~121°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635 (CO–N), 1603, 890 (C=CH_2). *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.27; H, 7.33; N, 6.45.

***cis*-4-Methyl-2-methylene-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XX)**——A mixture of amino acid (VII) (410 mg.), dried over *in vacuo* at 100°, and freshly distilled Ac_2O (40 ml.) was placed in a sealed tube and heated in an oil bath at 170° for 20 min. The mixture was treated as described above for the preparation of XIX to give the *cis*-lactam (280 mg.). Recrystallization from petr. benzine afforded a pure sample, m.p. 85~86°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635 (CO–N), 1604, 890 (C=CH_2). *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.53; H, 7.55; N, 5.97.

Lactamization of isomeric *cis-syn*-amino acid (VIII) gave the same *cis*-lactam (XX). This was confirmed by the mixed melting point determination and by the comparison of IR spectra and v. p. c. *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.13; H, 7.24; N, 6.05.

Epimerization of IV under a Basic Condition——The *cis-anti*-ester (IV) (200 mg.) in 5 ml. of 20% ethanolic EtONa solution was refluxed under a stream of N_2 for 1.5 hr. The solution was poured into the ice-water and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Vapor phase chromatography of the residue showed 53% content of the epimerization product (V).

Ethyl 4-Methyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (IIa)——In a three necked flask fitted with Dean-Stark water separator was placed 10% CH_3NH_2 in benzene (18 ml.). Ethyl 2-(bromomethyl)acrylate (3.7 g.) was added dropwise to the solution under stirring and ice-cooling, and stirred for 15 min. Then, 6-methoxy-2-tetralone (3 g.) in anhyd. benzene (50 ml.) was added at once and the mixture was heated under reflux for 3 hr. After cooling, the reaction mixture was extracted with 10% HCl, and the aqueous layer was washed with AcOEt, basified with Na_2CO_3 and the separated oil was extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue under reduced pressure gave 2.7 g. of a crude IIa as a red-brown oil, $b.p_1$ 190~210°(bath

temp.), IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1730 (CO), which crystallized by addition of EtOH but further purification failed. A perchlorate was recrystallized from EtOH to give a pure sample, m.p. 188~189°. *Anal.* Calcd. for $C_{18}H_{24}O_7NCl$: C, 53.80; H, 6.02; N, 3.49. Found : C, 53.64; H, 5.87; N, 3.49.

Reduction of IIa with Sodium Borohydride——To a stirred solution of IIa (2.6 g.) in EtOH (150 ml.) was added $NaBH_4$ (2.9 g.) at room temperature and stirred for 1.5 hr. After worked up as described for II, distillation gave a brown oil (1.8 g.), b.$p_{0.3}$ 180~220°(bath temp.), which showed the presence of three components in the ratio of 2.5:2.5:5 by v. p. c. After chromatographical separation on Al_2O_3-benzene, the first fraction gave ethyl *cis-anti*-4-methyl-8-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (IVa) after evaporation and distillation procedure, b.p_1 190~210° (bath temp.). IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1730 (CO). *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31. Found : C, 71.16; H, 8.23. (All attempts to obtain a crystalline salt failed.). From the second fraction, ethyl *cis-syn*-4-methyl-8-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (Va) was obtained. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1730 (CO). A picrate was recrystallized from EtOH to give yellow crystals, m.p. 112~113°(decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_{10}N_4 \cdot EtOH$: C, 54.19; H, 5.78; N, 9.61. Found : C, 54.06; H, 5.94; N, 9.70. Further elution by benzene, ethyl *trans-anti*-4-methyl-8-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (IIIa) was obtained as the main product, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (CO), characterized as a perchlorate, colorless needles from EtOH, m.p. 187~188°(decomp.). *Anal.* Calcd. for $C_{18}H_{26}O_7NCl$: C, 53.53; H, 6.49; N, 3.47. Found : C, 53.50; H, 6.40; N, 3.41.

Hydrogenation of IIa with Platinum Oxide Catalyst——The enamine(IIa) (2.6 g.) was shaken in hydrogen atmosphere at room temperature in EtOH (50 ml.) in the presence of PtO_2 (80 mg.). After the uptake of 1 molar equivalent of hydrogen, a treatment was carried out as described for II to give the product (2.3 g.), b.$p_{0.3}$ 180~220°(bath temp.), showing the presence of IVa and Va in the ratio of 1.5:8.5 by v. p. c. These were readily separated by chromatography on Al_2O_3 using benzene as eluent and identified as IVa and Va respectively by the comparison of IR spectra and v. p. c. with the samples obtained above.

Reduction of IIa with Sodium Borohydride in the presence of Acetic Acid——To a solution of IIa (2.7 g.) and $NaBH_4$ (1.8 g.) in anhyd. tetrahydrofuran(100 ml.) was added AcOH (30 ml.) in 30 min. with stirring. After standing for 1.5 hr. at room temperature, a treatment was carried out as described for II to give the crude product (2.2 g.), b.$p_{0.3}$ 180~220°(bath temp.), showing the presence of IIIa, IVa and Va in the ratio of 3:4.5:2.5 by v. p. c. These three components were obtained by eluting through Al_2O_3 column with benzene and identified respectively by the comparison of IR spectra and v. p. c. with the samples prepared from $NaBH_4$ reduction of IIa.

Summary

Ethyl *trans-anti-*, *cis-anti-*, and *cis-syn*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline-2-carboxylates (III, IV and V) were obtained by the reduction of ethyl 4-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (II), and their stereochemistries were discussed. Some derivatives of III, IV and V in which C_2-ethoxycarbonyl group was replaced by carboxyl, diethylcarbamoyl, hydroxymethyl and methyl groups were also prepared.

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