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208. Zen-ichi Horii, Takushi Kurihara, Shigeo Yamamoto, and Ichiya Ninomiya*1 : Studies on Ergot Alkaloids and Related Compounds. XIV.*2 Syntheses of N-Alkyl-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamides and Stereochemistry of Diethyl 4-Methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate.

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Preparations of diethyl-, *n*-butyl- and 2-hydroxyisopropylamide derivatives of 4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxylic acid (Ⅵ) were described. And the stereochemistries of diethyl 4-methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate (Ⅱ) and related compounds were also discussed.

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Our previous report[1] introduced the synthesis of a potent oxytocic ethyl 4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxylate (Ⅶ). Recently, Ohta and his coworkers also prepared Ⅶ by a convenient method starting from the Mannich product (Ⅱ). However, they did not deal with the stereochemistry of the compounds involved.

In the course of work searching for compounds with potent activity related to lysergic acid, we now wish to describe two routes of preparations of diethyl-, *n*-butyl- and 2-hydroxyisopropylamide derivatives of Ⅵ, which can be regarded as LSD_{25} analogs lacking only a pyrrole ring, and also discuss the stereochemistry of this series of compounds.

As Ohta reported,[2] Mannich condensation of ethyl 3,4-dihydro-1-naphthoylmalonate with methylamine and formalin afforded diethyl 4-methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate (Ⅱ) in good yield. Sodium borohydride reduction of Ⅱ gave a mixture of two epimeric alcohols (Ⅲa and Ⅲb), which was subsequently dehydrated by phosphorous oxychloride to give the unsaturated diester (Ⅴ). Hydrolytic decarboxylation of Ⅴ with 10% hydrochloric acid gave the amino acid (Ⅵ), upon purification through Duolite A-2 ion exchange resin. This amino acid (Ⅵ) was identical with the one prepared from the ester (Ⅶ)[1] upon acidic hydrolysis.

On treatment of the lithium salt of Ⅵ with sulfur trioxide-dimethylformamide complex[3] and then with amines, *i.e.*, diethylamine, *n*-butylamine, and isopropanolamine, were obtained the corresponding amides, N,N-diethyl-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide (Ⅷ), N-*n*-butyl-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]-quinoline-2-carboxamide (Ⅸ) and N-(2-hydroxyisopropyl)-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide (Ⅹ) in average 50 to 60% yields. Pharmacological activities of these amides are now under investigation.

Of these amide derivatives, the diethylamide (Ⅷ) was also prepared by an alternative route as follows. Ethyl N,N-diethylmalonamate[4] was acylated with 3,4-dihydro-1-naphthoyl chloride to give Ⅺ, which on Mannich condensation with methylamine and formalin was converted to ethyl 2-(N,N-diethylcarbamoyl)-4-methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylate (Ⅻ) in 61% yield. Reduction of Ⅻ with

*1 Toneyama, Toyonaka, Osaka-fu (堀井善一, 栗原拓史, 山本重雄, 二宮一弥).
*2 Part Ⅻ : This Bulletin, **14**, 1227 (1966).

1) Z. Horii, T. Watanabe, T. Kurihara, Y. Tamura : This Bulletin, **13**, 420 (1965).
2) M. Ohta, M. Otani, M. Kiyonari : Abstract of Papers at the 85th Annual Meeting of the Pharmaceutical Society of Japan (Tokushima, Oct., 1965).
3) W. L. Garbrecht : J. Org. Chem., **24**, 368 (1959).
4) R. Barré, P. L. Matte : Ann. ACFAS., **7**, 81 (1941); C. A., **40**, 1453^7 (1946).

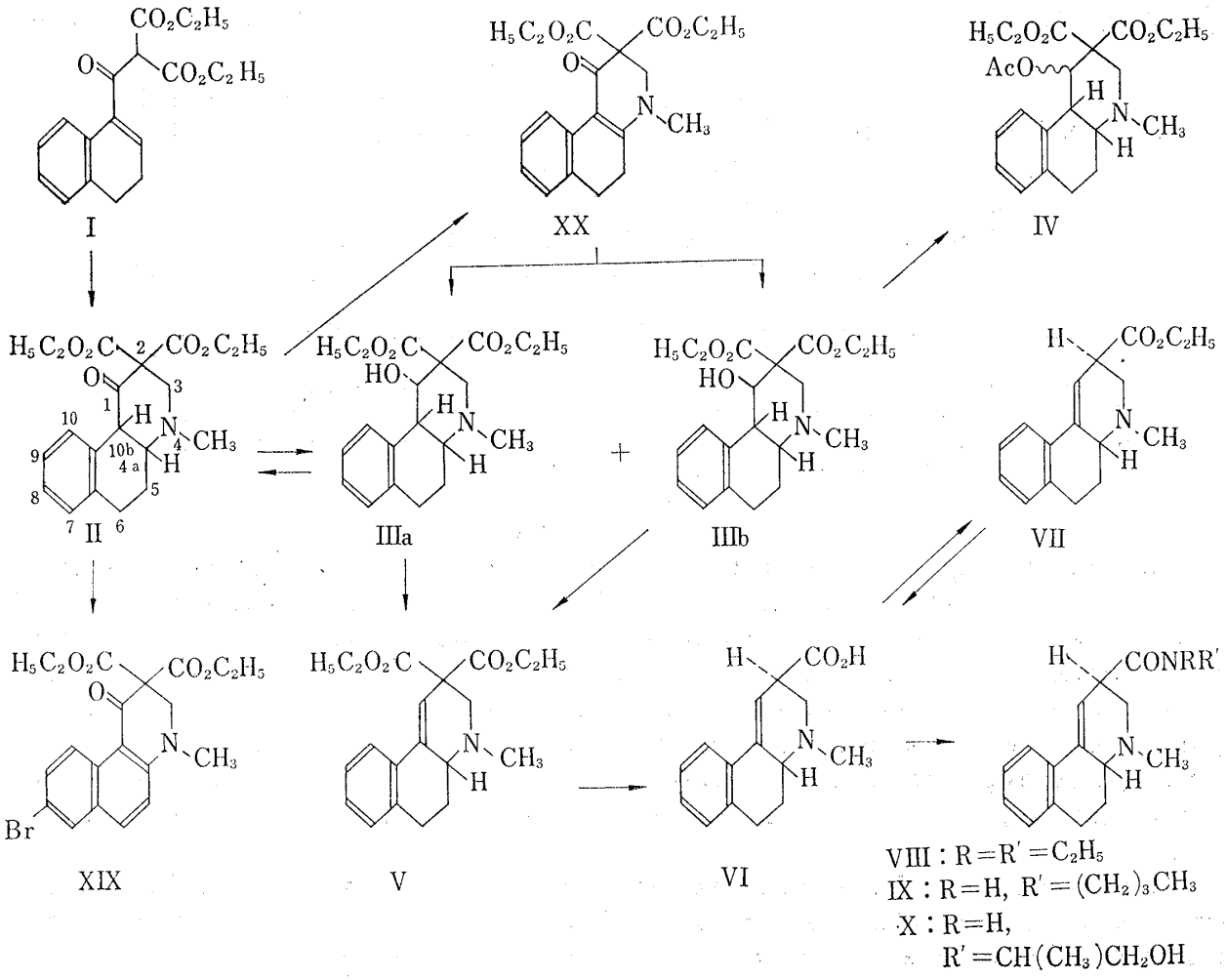


Chart 1.*3

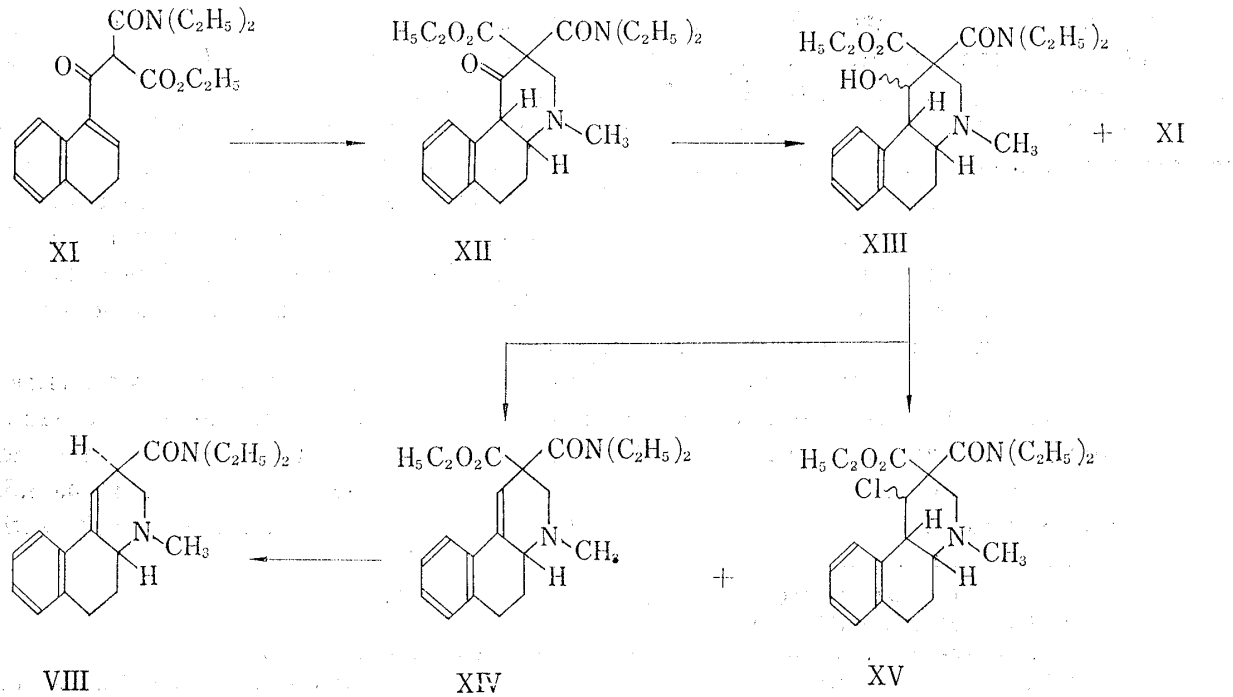


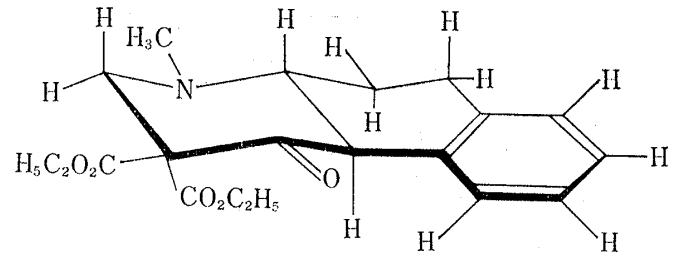
Chart 2.

*3 The projections used in this paper were depicted according to the reference 8).

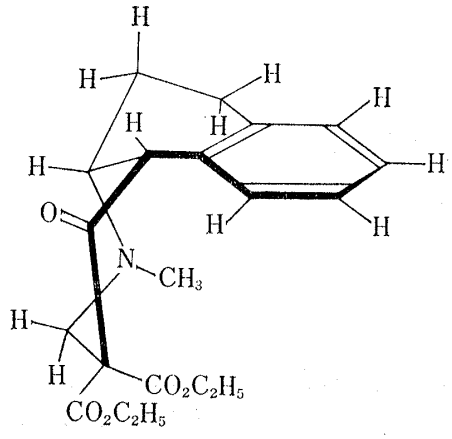
sodium borohydride in a mixture of tetrahydrofuran and ethanol afforded a mixture of two epimeric ethyl 2-(N,N-diethylcarbamoyl)-4-methyl-1-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylates (XIII) in 72% yield, accompanied by a small amount of the probably Retro-Mannich product (XI). Dehydration of XIII with phosphorous oxychloride and phosphoric acid in pyridine[5] afforded ethyl 2-(N,N-diethylcarbamoyl)-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxylate (XIV) in 71% yield, together with a very small amount of ethyl 2-(N,N-diethylcarbamoyl)-4-methyl-1-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylate (XV). Hydrolytic decarboxylation of XIV with ethanolic potassium hydroxide[6] afforded the diethylamide (VIII) in 81% yield, which is identical with the sample obtained by the method described above by comparison of their infrared spectra and vapor phase chromatography (VPC).

Stereochemistry

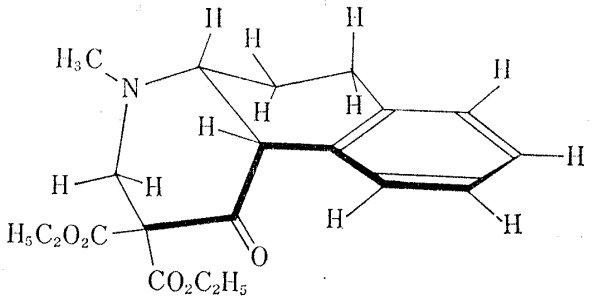
The structure of II as having a *cis* stable conformation was deduced from the following chemical transformations and also the nuclear magnetic resonance evidences. Three possible conformations (IIA, IIB and IIC) can be considered with respect to B/C ring juncture.



IIA



IIB



IIC

Fig. 1.

Hydrolytic decarboxylation of an epimeric alcohol (IIIa) with 20% hydrochloric acid on water bath for 90 min. followed by esterification afforded VII in 47% yield, accompanied by ethyl 4-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinoline-2-carboxylate (XVI) in 5% yield, which could not be obtained from VII under the same condition as above. On the contrary, when VII was refluxed with 20% hydrochloric acid for 90 min. followed by

5) J. Elks, G. H. Phillips, W.F. Wall : J. Chem. Soc., **1958**, 4001.
6) H. E. Zimmerman, H. J. Giallombardo : J. Am. Chem. Soc., **78**, 6259 (1956).

esterification was obtained ethyl 4-methyl-1,2,3,4,5,6-hexahydrobenzo[f]quinoline-2-carboxylate (XVII) in good yield. Catalytic hydrogenation of XVI over platinum oxide gave a dihydro derivative (XVIII) which was identical with the sample of the previously reported *cis-syn* ester,*[2,4] ethyl 4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylate, by comparison of their infrared spectra and retention times of VPC. In addition, oxidation of IIIa with dimethyl sulfoxide in acetic anhydride[7] gave the starting keto diester (II), indicating that the reduction had not changed the configuration at C_{4a} and C_{10b}. These chemical evidences clearly showed B/C ring juncture of II as of *cis* stable conformation.

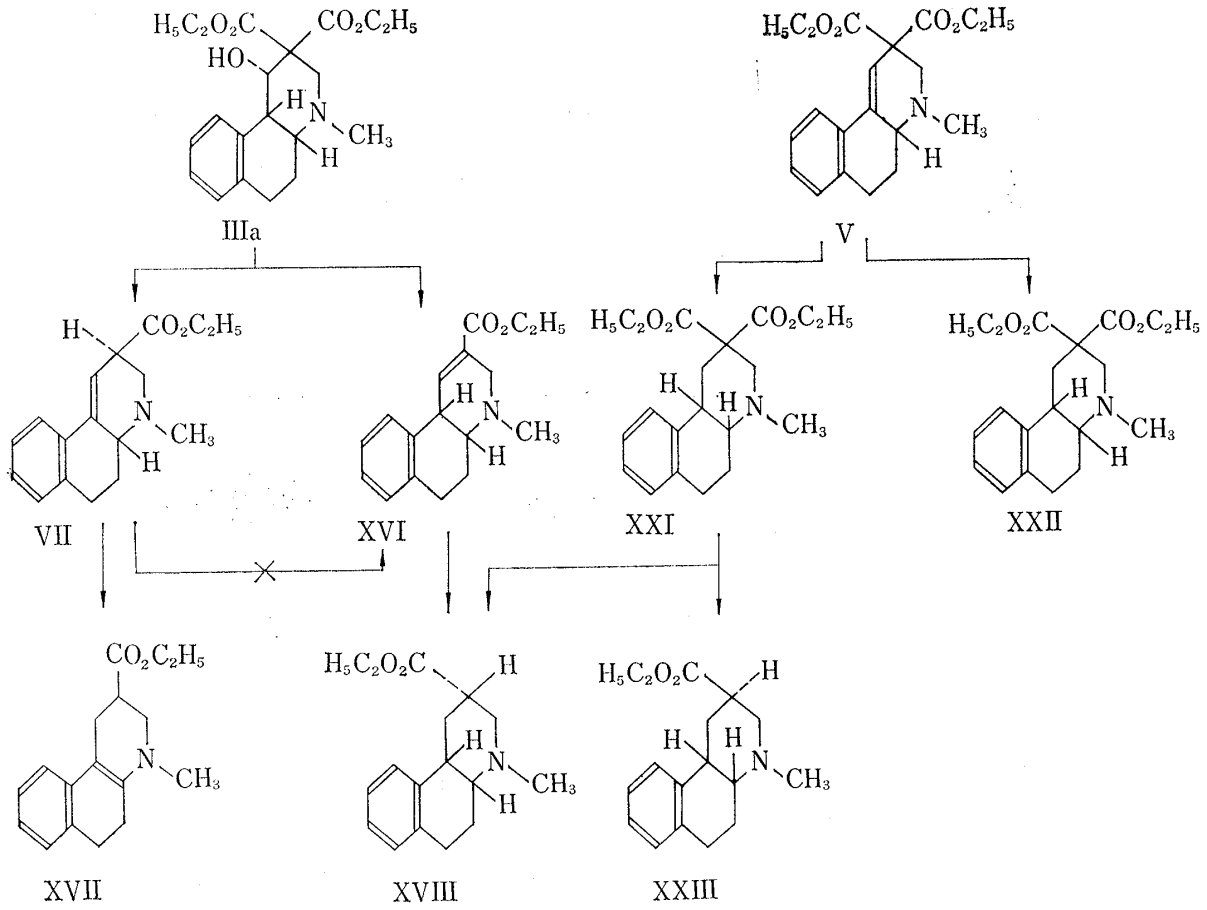


Chart 3.

The nuclear magnetic resonance (NMR) spectra of these compounds also support this result. The NMR spectrum of dimethyl 4-methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate, prepared for comparison, exhibits C_{10b}-hydrogen as a doublet (J=7.2 c.p.s.) at 5.58τ, which is in agreement with the coupling constant of B/C *cis* ring juncture of the analogous octahydrophenanthrenes.[8] The signal of the aromatic protons appears as a sharp singlet at 2.96τ, which, as described in the preceding paper,*[2] can be explained as follows. In conformations IIA and IIB, the deshielding or shielding effect of C_1-carbonyl group exerting on the C_{10}-aromatic proton should break the equivalency of the aromatic protons. On the other hand, in conformation IIC, there

*[4] The designations such as "*cis-syn*" and "*cis-anti*" refer to the relationships of hydrogens at C_{4a}, C_{10b} and C_2, as described in the preceding paper.*[2]

7) J. D. Albright, L. Goldman: J. Am. Chem. Soc., **87**, 4214 (1965).

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

could be expected no such effect on C_{10}-proton, giving a singlet signal. The same result was also observed in the compound (XII). From these chemical and physical evidences, it is clearly concluded that the Mannich product (II) and therefore its hydrogenated alcohols (IIIa and IIIb) have B/C *cis* stable ring conformation, as depicted in IIC.

The stability of B/C *cis* ring system in II or III was examined from the behavior toward reduction of diethyl 4-methyl-1-oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinoline-2,2-dicarboxylate (XX), which was obtained by dehydrogenation of II. Treatment of II with one molar equivalent of bromine or N-bromosuccinimide gave a yellow crystalline substance (XIX) of positive Beilstein test in good yield, which showed the elemental composition of $C_{20}H_{20}O_5NBr$ and infrared bands at 1623 and 1600 cm^{-1} and ultraviolet absorption maximum at 265 mμ (ε=29600), suggesting the presence of a naphthalene ring. The NMR spectrum of XIX exhibits five aromatic protons, of which C_{10}-proton appears as a doublet at 0.62τ (J=9 c.p.s.),[9] indicating the coupling with C_9-proton. Thus, the structure of XIX was assigned as diethyl 4-methyl-1-oxo-8-bromo-1,2,3,4-tetrahydrobenzo[f]quinoline-2,2-dicarboxylate. Then, when the keto diester (II) was dehydrogenated with chloranil in *tert*-butyl alcohol,[10] the desired diethyl 4-methyl-1-oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinoline-2,2-dicarboxylate (XX) was obtained in 82% yield.

Reduction of the vinylogous lactam system,[11] either chemically or catalytically, has been known to give a mixture of B/C *cis* and *trans* alcohols among products. However, sodium borohydride reduction or catalytic hydrogenation over platinum oxide of XX afforded only a mixture of epimeric *cis* alcohols (IIIa and IIIb), suggesting that B/C *cis* configuration represents a much more stable structural arrangement than B/C *trans* in this series of compounds. The same result was also obtained in the reduction of V.

Hydrogenation of V over platinum oxide gave a single dihydro derivative (XXI), which was treated with 20% hydrochloric acid followed by esterification to give a mixture of *cis-anti* ester (XXIII) and *cis-syn* ester (XVIII) in the ratio of 9:1, each identical with the authentic samples described in the preceding paper.*2 The NMR spectrum of XXI exhibits the signal of aromatic protons as a multiplet at 1.80~2.90τ, suggesting B/C *cis* unstable conformation. However, only once in the hydrogenation of V with a large amount of platinum oxide was it possible to isolate diethyl 4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate (XXII), m.p. 117°, as crystals, recrystallized from *n*-hexane. *Anal.* Calcd. for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.67; H, 7.99; N, 3.97. The B/C *cis* stable conformation of XXII was suggested from the NMR spectrum which exhibits the signal of aromatic protons as a sharp singlet at 2.95τ. These results were in contrast with the fact that catalytic hydrogenation of lysergic acid gave a mixture of *cis* and *trans* dihydro derivatives.[12]

Finally, the configuration of C_1-hydroxyl group of IIIa and IIIb was assigned as follows. Products of sodium borohydride reduction of II were separated by chromatography through silica gel column employing chloroform as eluent to give two stereoisomers (IIIa and IIIb), both as perchlorates, m.p. 166~167° and 161~162.5°, respectively. Although dehydration of IIIa and IIIb were best effected by heating them with phosphorous oxychloride and phosphoric acid in pyridine to give V in about the same yields, IIIa, when treated with thionyl chloride in pyridine, gave V in 60% yield, whereas IIIb was

9) N. S. Bhacca, D. H. Williams: "Application of NMR Spectroscopy in Organic Chemistry," p. 97 (1964). Holden-Day, Inc., San, Francisco.
10) E. J. Agnello, G. D. Laubach: J. Am. Chem. Soc., **82**, 4293 (1960).
11) N. A. Nelson, J. E. Ladbury, R. S. P. Hsi: J. Am. Chem. Soc., **80**, 6633 (1958).
12) A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann, H. Gunthart: Helv. Chim. Acta, **37**, 2039 (1954).

recovered unchanged under the same condition.[13] In addition, differences in their retention times in vapor phase and column chromatographies[14] (IIIa eluted faster than IIIb) might indicate that the hydroxyl group is axial in IIIa, while equatorial in IIIb.

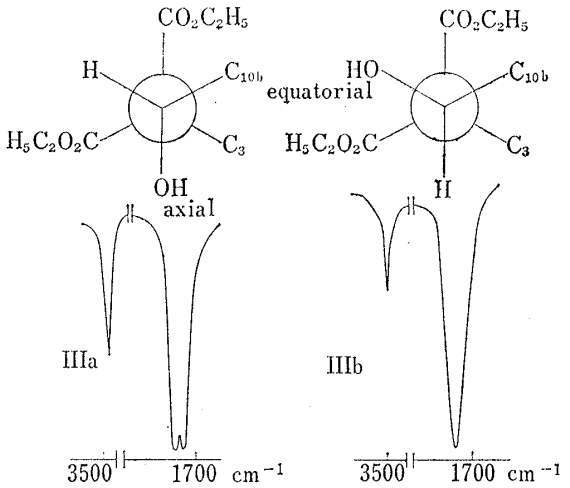


Fig. 2. Infrared Absorption Spectra of IIIa and IIIb in CCl_4

As shown by Newman projection in Fig. 2, the hydroxyl group in IIIa would be able to form hydrogen bonding with only an equatorial ethoxycarbonyl group giving two absorptions of esters, while the hydroxyl group in IIIb would be situated spatially in the midst of two ethoxycarbonyl groups, resulting a single absorption of ester in the infrared region. Furthermore, in the NMR spectrum of IIIa, the signal of C_3-methylene protons appears as AB type quartet at 6.95τ (J=15 c.p.s.) because the axial proton in the 1,3-diaxial position to the hydroxyl group is coupled with an equatorial proton, whereas the NMR spectrum of IIIb appears as a sharp singlet.

Experimental

M.ps and b.ps are uncorrected. Vapor phase chromatographies (VPC) were measured on Perkin-Elmer gas chromatograph model 800, employing SE-30 column (column temperature 190°). The NMR spectra were taken in $CDCl_3$ on Hitachi Perkin-Elmer H-60 type Spectrometer at 60 Mc., tetramethylsilane serving as internal reference.

Diethyl 4-Methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate (II)——To a suspension of the methylamine salt of I (5 g.) in EtOH (15 ml.) was added dropwise 37% HCHO (1.5 g.) at room temperature and the whole solution was vigorously stirred. After the solution became homogeneous, the mixture was allowed to keep at 5° overnight. The precipitated crystals were filtered (3.7 g.). The filtrate was concentrated *in vacuo* at room temperature to give a brown paste, which was dissolved in ether. The ether solution was washed with 10% HCl. The aqueous washing was neutralized with solid Na_2CO_3 and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an additional 1.1 g. of an oil which readily crystallized by adding a drop of EtOH. Recrystallization from EtOH gave white needles, m.p. 98~99°. IR ν_{max}^{KBr} cm^{-1}: 1751 (C=O), 1724 (CO_2Et). *Anal.* Calcd. for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.97; H, 6.61; N, 3.98. The perchlorate was recrystallized from EtOH-Et_2O, to give colorless needles, m.p. 178~179°. *Anal.* Calcd. for $C_{20}H_{26}O_9NCl$: C, 52.23; H, 5.69; N, 3.04. Found: C, 52.23; H, 5.64; N 3.04.

Diethyl 1-Hydroxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylates (IIIa and IIIb)——To an ice-cooled solution of II (10 g.) in EtOH (500 ml.) was added $NaBH_4$ (3.4 g.) in small portions and the mixture was stirred at room temperature for 2 hr. After the addition of AcOH (6 ml.), the mixture was poured into water (6 L.) and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give a pale-yellow oil (7.52 g.), which crystallized upon standing overnight. This was characterized as a perchlorate, m.p. 134~135°, colorless needles, recrystallized from EtOH-Et_2O. *Anal.* Calcd. for $C_{20}H_{28}O_9NCl$: C, 51.99; H, 6.10; N, 3.04. Found: C, 51.72; H, 6.41; N, 3.04. By the chromatographical separation over silica gel column using $CHCl_3$ as eluent was obtained IIIa (3.7 g.) from the first fraction. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3546 (OH); 1740 (CO_2Et), 1720 (CO_2Et). The perchlorate of IIIa was recrystallized from EtOH-Et_2O, to colorless needles, m.p. 166~167°. *Anal.* Calcd. for $C_{20}H_{28}O_9NCl$: C, 51.99; H, 6.10; N, 3.04. Found: C, 52.30; H, 6.05; N, 3.08. From the second fraction was obtained IIIb (4.2 g.), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630 (OH), 1734 (CO_2Et), which was contaminated with a very small amount of IIIa. The perchlorate of IIIb was recrystallized from EtOH-Et_2O, to colorless needles, m.p. 161~162.5°. *Anal.* Calcd. for $C_{20}H_{28}O_9NCl$: C, 51.99; H, 6.10; N, 3.04. Found: C, 51.48; H, 6.13; N, 3.17.

Acetylation of III (A mixture of IIIa and IIIb)——A solution of III (200 mg.), pyridine (2 ml.) and Ac_2O (1 ml.) was warmed on a water bath for 2 hr. The mixture was poured into ice-water, made alkaline

13) S. Bernstein, R. H. Lenhard, J. H. Williams: J. Org. Chem., **19**, 41 (1954).
14) D. H. R. Barton: J. Chem. Soc., **1953**, 1027.

and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue under reduced pressure gave Ⅳ (210 mg.) as a colorless oil, b.$p_{0.5}$ 180~220° (bath temp.) The perchlorate of Ⅳ was recrystallized from EtOH-Et_2O to colorless needles, m.p. 250~253°. IR ν_{max}^{Nujol} cm^{-1}: 1739 (CO_2Et), 1709 (OAc). *Anal.* Calcd. for $C_{22}H_{30}O_{10}NCl$: C, 52.43; H, 6.00; N, 2.77. Found: C, 52.21; H, 5.88; N, 2.66.

Dehydration of IIIa and IIIb to Diethyl 4-Methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2,2-dicarboxylate (V). a) Treatment of a mixture of IIIa and IIIb with $SOCl_2$ in Pyridine——A solution of Ⅲ (500 mg.) and $SOCl_2$ (1 ml.) in anhyd. pyridine (3 ml.) was kept at 25~30° for 30 min. The reaction mixture was poured into ice-water and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving a brown oil (390 mg.), which was chromatographed through Al_2O_3 using benzene as eluent to give Ⅴ (120 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1729 (CO_2Et). The perchlorate of Ⅴ was recrystallized from EtOH-Et_2O to give colorless needles, m.p. 124~125°. IR ν_{max}^{KBr} cm^{-1}: 1731 (CO_2Et), 1621 (C=C). *Anal.* Calcd. for $C_{20}H_{28}O_8NCl$: C, 54.11; H, 5.90; N, 3.13. Found: C, 54.14; H, 5.87; N, 2.91. Further eluate with $CHCl_3$ gave an equatorial alcohol (Ⅲb) (75 mg.), identical with the sample obtained above by comparison of their infrared spectra and the mixed melting point determination of their perchlorates.

b) Treatment of IIIa with $POCl_3$ and H_3PO_4 in Pyridine——A solution of Ⅲa (100 mg.), anhyd. pyridine (2 ml.), H_3PO_4 (0.02 ml.) and $POCl_3$ (0.4 ml.) was warmed on a water bath for 2 hr. The reaction mixture was poured into ice-water, acidified with 10% HCl and washed with ether to remove the soluble material. The aqueous layer was made alkaline with Na_2CO_3 and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was chromatographed through Al_2O_3 column using benzene as eluent to give an oil (Ⅴ) (51 mg.), identified with the sample prepared in b) by comparison of their infrared spectra and VPC.

c) Treatment of IIIb with $POCl_3$ and H_3PO_4 in Pyridine——A solution of Ⅲb (200 mg.), anhyd. pyridine (2 ml.), H_3PO_4 (0.04 ml.) and $POCl_3$ (0.5 ml.) was worked up in the same manner as described in b). giving a crude oil (140 mg.). Chromatography through Al_2O_3 using benzene as eluent gave Ⅴ (80 mg.), identified with sample prepared in a) by comparison of their infrared spectra and VPC.

4-Methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxylic Acid (VI)——a) From V: A solution of Ⅴ (5.0 g.) in 10% HCl (150 ml.) was warmed at 90° with stirring for 2 hr. Most of water was removed under reduced pressure and the residue was dissolved in H_2O (20 ml.). The solution was chromatographed through 60~100 mesh Duolite A-2 column using H_2O as eluent until the eluate showed negative ninhydrin test. The combined eluate was evaporated *in vacuo* on a water bath, leaving a crystalline solid (Ⅵ) (1.94 g). Recrystallization from water gave colorless needles, m.p. 172~174°. IR ν_{max}^{KBr} cm^{-1}: 1600 (CO_2^-), 1634 (C=C). *Anal.* Calcd. for $C_{15}H_{17}O_2N \cdot 1/2H_2O$: C, 71.40; H, 7.19; N, 5.55; Found: C, 71.30; H, 7.61; N, 5.43.

b) From VII: A solution of Ⅶ (500 mg.) in 10% HCl (5 ml.) was warmed at 90° with stirring for 2 hr. Upon worked up as usual was obtained a crystalline material (80 mg.) which was recrystallized from H_2O to colorless crystals, m.p. 172~173°, undepressed on admixture with the sample prepared in a).

Diethyl 4-Methyl-8-bromo-1,2,3,4-tetrahydrobenzo[f]quinoline-2,2-dicarboxylate (XIX)——To a stirred solution of Ⅱ (500 mg.) in $CHCl_3$ (20 ml.) was added a solution of Br_2 (220 mg.) in $CHCl_3$ (20 ml.) over a period of 2 hr. under water cooling. To the reaction mixture was added H_2O (20 ml.) and then saturated $NaHCO_3$ solution (20 ml.). The separated organic layer was washed with 10% $Na_2S_2O_3$ solution and with H_2O, dried over anhyd. Na_2SO_4 and evaporated. From the residue, upon adding a small amount of *n*-hexane, yellow crystals (420 mg.) were obtained, which were recrystallized from EtOH to give yellow needles, m.p. 155.5~157°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO_2Et), 1653 (C=O), 1623, 1600 (C=C). UV λ_{max}^{EtOH} mμ: 265 (ε=29600). NMR: 0.62 τ (doublet, 1H, J=9), 2.20~3.11τ (multiplet, 4H). *Anal.* Calcd. for $C_{20}H_{20}O_5NBr$: C, 55.31; H, 4.64; N, 3.23. Found: C, 55.28; N, 4.57; N, 3.35.

Diethyl 4-Methyl-1-oxo-1,2,3,4,5,6-hexahydrobenzo[f]quinoline-2,2-dicarboxylate (XX)——To a solution of Ⅱ (200 mg.) in *tert*-BuOH (20 ml.) was added chloranil (120 mg.) and the solution was refluxed for 3.5 hr. The solvent was removed *in vacuo*, $CHCl_3$ was added and the organic layer was washed with 10% NaOH and with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving a crystalline vinylogous lactam (XX) (165 mg.). Recrystallization from benzene and *n*-hexane gave pale green crystals, m.p. 148.5~149.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724 (CO_2Et), 1637, 1608, 1550 (vinylogous lactam). UV λ_{max}^{EtOH} mμ: 277 (ε=15700), 360 (ε=9180). NMR: 1.63τ (doublet in doublet, 1H, J=8, J=3), 2.69~2.90τ (multiplet, 3H). *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.67; H, 6.63; N, 3.92.

Sodium Borohydride Reduction of the Vinylogous Lactam (XX)——To a stirred solution of XX (200 mg.) in EtOH (10 ml.) was added $NaBH_4$ (400 mg.) in small portions at room temperature. After stirring for 3.5 hr., two drops of AcOH was added and the solution was poured into H_2O (100 ml.), extracted with ether, washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give an oil (117 mg.), which showed two peaks in the ratio of 9:1 on VPC. These two peaks were identical with those of the authentic alcohols (Ⅲb and Ⅲa), respectively. The oil was subject to chromatography through silica gel column using $CHCl_3$ as eluent to give an equatorial alcohol (Ⅲb) (90 mg.), identified with the authentic sample by comparison of their infrared spectra.

Hydrogenation of the Vinylogous Lactam (XX)——A solution of XX (100 mg.) in AcOH (10 ml.) was hydrogenated over PtO_2 catalyst (30 mg.) under the normal condition until two molar equivalent of H_2 was

absorbed. The catalyst was filtered and the filtrate was made alkaline by adding $NaHCO_3$ under ice-cooling, and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an oil (55 mg.) which showed two peaks in the ratio of 4:6 on VPC, each identical with those of the authentic samples (IIIa and IIIb), respectively.

Oxidation of IIIa with Dimethyl Sulfoxide in Acetic Anhydride——A mixture of IIIa (250 mg.) and dimethyl sulfoxide (3 ml.) in Ac_2O (2 ml.) was allowed to stand at room temperature for 24 hr. and then poured into ice-water. The resultion solution was made alkaline with $NaHCO_3$ and extracted with ether. The ether extract was washed with H_2O several times, dried over anhyd. Na_2SO_4 and evaporated. Chromatography of the residue through silica gel column using $CHCl_3$ as eluent afforded a keto diester (II) (55 mg.), which was completely identical with the authentic sample by comparison of their infrared spectra.

Hydrogenation of V to Diethyl 4-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2,2-dicarboxylate (XXI)——A solution of V (2.5 g.) in EtOH (40 ml.) was hydrogenated over PtO_2 (250 mg.) under the ordinary condition for about 25 hr. until about one molar equivalent of H_2 was absorbed. The catalyst was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed through Al_2O_3 column using benzene as eluent to give a colorless oil (XXI) (2.1 g.), having strong fluorescence. The perchlorate of XXI was recrystallized from EtOH–Et_2O, to colorless needles, m.p. 147~148°. IR ν_{max}^{KBr} cm^{-1}: 1730 (CO_2Et). *Anal.* Calcd. for $C_{20}H_{28}O_8NCl$: C, 53.87; H, 6.32; N, 3.14. Found: C, 53.79; H, 6.36; N, 3.09.

Ethyl 4-Methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxylate (VII)——**a)** A solution of V (1.5 g.) in 10% HCl (35 ml.) was warmed on a water bath for 2.5 hr. After evaporation of the solvent under reduced pressure, the residue was esterified by the Fischer method in EtOH. The solvent was removed and the residue was made alkaline with solid $NaHCO_3$, extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was chromatographed through Al_2O_3 column using benzene as eluent to give VII as an oil (720 mg.). The picrate of VII was recrystallized from EtOH to give yellow needles, m.p. 140~141°. IR ν_{max}^{KBr} cm^{-1}: 1731 (CO_2Et). *Anal.* Calcd. for $C_{23}H_{24}O_9N_4$: C, 55.20; H, 4.87; N, 11.20. Found: C, 54.97; H, 4.89; N, 11.31.

b) Esterification of VI: The carboxylic acid (VI) (7 mg.) was esterified by the Fischer method in EtOH and worked up as usual to give an oil, which was identical with the authentic sample[1] by comparison of their infrared spectra and VPC.

Ethyl 4-Methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinoline-2-carboxylate (XVI)——A solution of IIIa (2.09 g.) in 20% HCl (100 ml.) was warmed on a water bath for 2.5 hr. The mixture was condensed under reduced pressure. The residue was esterified by the Fischer method in EtOH. The solvent was removed and the residue was made alkaline with $NaHCO_3$. The separated oily material was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an oil (1.26 g.), which was chromatographed through silica gel column using $CHCl_3$ as eluent to give VII (750 mg. cited above) from the first fraction and XVI (75 mg.) from the latter fraction. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715 (CO_2Et), 1655 (C=C). The picrate of XVI was recrystallized from EtOH to yellow needles, m.p. 207~209° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1718 (CO_2Et). *Anal.* Calcd. for $C_{23}H_{24}O_9N_4 \cdot H_2O$: C, 53.28; H, 5.34; N, 10.81. Found: C, 53.42; H, 5.18; N, 10.80.

Ethyl 4-Methyl-1,2,3,4,5,6-hexahydrobenzo[f]quinoline-2-carboxylate (XVII)——A solution of VII (50 mg.) in 20% HCl (10 ml.) was refluxed for 90 min. The mixture was condensed under reduced pressure to give the residue, which was esterified by the Fischer method in EtOH. The solvent was removed and the residue was made alkaline with $NaHCO_3$. The separated oil was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give an oil (XVII) (37 mg.), identified with the authentic sample prepared previously[1] by comparison of their infrared spectra.

Hydrogenation of XVI to Ethyl 4-Methyl-1,2,3,4,4a,5,6,10b-octahydro-*cis-syn*(4a:10b)benzo[f]quinoline-2-carboxylate (XVIII)——A solution of XVI (50 mg.) in EtOH (10 ml.) was hydrogenated over PtO_2 (30 mg.) under the ordinary condition until one molar equivalent of H_2 was absorbed. The catalyst was filtered and the filtrate was evaporated under reduced pressure, giving an oil (XVIII) (45 mg.), identified with the authentic sample prepared previously*[1] by comparison of their infrared spectra and VPC.

Decarboxylation of XXI to Ethyl 4-Methyl-1,2,3,4,4a,5,6,10b-octahydro-*cis-anti*(4a:10b)benzo[f]quinoline-2-carboxylate (XXIII) and (XVIII)——A solution of XXI (20 mg.) in 20% HCl (5 ml.) was warmed for 2 hr. The mixture was condensed under reduced pressure to give the residue, which was esterified by the Fischer method in EtOH. The solvent was removed and the residue was made alkaline with $NaHCO_3$. The separated oil was extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an oil XXIII and XVIII in the ratio of 9:1 identified with the authentic samples, prepared previously*[2] by comparison of VPC.

The Methylamine Salt of Ethyl N,N-Diethyl-(3,4-dihydronaphthoyl)malonamate (XI)——A mixture of Mg (2.6 g.), abs. EtOH (3 ml.), ether (20 ml.) and CCl_4 (1 ml.) was warmed until the reaction started and to the reaction mixture was added a solution of ethyl N,N-diethylmalonamate (18.9 g.) in abs. EtOH (15ml.) and abs. ether (20 ml.) dropwise at such a rate that the vigorous reaction was maintained. After Mg has dissolved, a solution of 3,4-dihydro-1-naphthoyl chloride (18.5 g.) in abs. ether (20 ml.) was added and the mixture was refluxed for half an hour. After cooling, the reaction mixture was acidified with 10% H_2SO_4.

The separated organic layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residual oil was dissolved in ether (100 ml.) and to the ether solution was bubbled dried CH_3NH_2 gas under ice-cooling. The precipitated white crystals were collected, yielding the methylamine salt of XI (23.2 g.), m.p. 91~92°.

Ethyl 2-(N,N-Diethylcarbamoyl)-4-methyl-1-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylate (XII)——To a suspension of the above methylamine salt (5.6 g.) in EtOH (5 ml.) was added 37% HCHO (1.2 g.) at room temperature and the whole solution was vigorously stirred. After the solution became homogeneous, the mixture was allowed to keep at 5° overnight. The precipitated crystals were collected (XII) (3.0 g.). The filtrate was concentrated *in vacuo* at room temperature to give a brown paste, which was dissolved in ether. The ether extract was washed with 10% HCl. The aqueous washing was neutralized with solid $NaHCO_3$ and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an additional 0.5 g. of XII, which readily crystallized by adding one drop of EtOH. Recrystallization from EtOH gave colorless needles, m.p. 156~157°. IR ν_{max}^{KBr} cm^{-1}: 1739 (CO_2Et), 1727 (C=O), 1627 (CON–). *Anal.* Calcd. for $C_{22}H_{30}O_4N_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.37; H, 7.71; N, 7.26.

Ethyl 2-(N,N-Diethylcarbamoyl)-1-hydroxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylate (XIII)——To an ice-cooled and stirred solution of XII (3.3 g.) in THF (100 ml.) and EtOH (30 ml.) was added $NaBH_4$ (1.4 g.) in small portions and the mixture was stirred for 2 hr. After adding AcOH (3 ml.), the mixture was poured into H_2O (1 L.) and the resulting solution was saturated with NaCl and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (2.7 g.) was subject to chromatography through silica gel column using $CHCl_3$ as eluent. From the first fraction was obtained a Retro-Mannich product (150 mg.), identified with an authentic sample (XI) by comparison of their infrared spectra. From the second fraction was obtained a mixture of epimeric alcohols (XIII) (2.4 g.), which showed two peaks in VPC. The picrate of XIII was recrystallized from EtOH to yellow needles, m.p. 212~213°. IR ν_{max}^{KBr} cm^{-1}: 1737 (CO_2Et), 1631 (CON–). *Anal.* Calcd. for $C_{28}H_{34}O_{11}N_5$: C, 54.53; H, 5.56; N, 11.38. Found: C, 54.32; H, 5.68; N, 11.66.

Ethyl 2-(N,N-Diethylcarbamoyl)-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxylate (XIV)——A solution of XIII (870 mg.), anhyd. pyridine (3 ml.), H_3PO_4 (0.2 ml.) and $POCl_3$ (2.5 ml.) was warmed on a water bath for 3 hr. The reaction mixture was poured into the ice-water, made alkaline with $NaHCO_3$ and extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated, giving an oil (680 mg.), which was chromatographed through Al_2O_3 column using benzene as eluent to give, from the first fraction, crystals, identified as ethyl 2-(N,N-diethylcarbamoyl)-4-methyl-1-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-2-carboxylate (XV) (90 mg.), which showed positive Beilstein test. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1734 (CO_2Et), 1641 (CON–). The perchlorate of XV was recrystallized from EtOH to colorless needles, m.p. 214°. IR ν_{max}^{KBr} cm^{-1}: 1739 (CO_2Et), 1629 (CON–). *Anal.* Calcd. for $C_{22}H_{32}O_7N_2Cl_2$: C, 52.07; H, 6.35; N, 5.52. Found: C, 52.19; H, 6.44; N, 5.44. From the second fraction was obtained colorless needles (XIV) (590 mg.), which was recrystallized from petr. benzine, m.p. 108~108.5°. IR ν_{max}^{KBr} cm^{-1}: 1728 (CO_2Et), 1634 (CON–). *Anal.* Calcd. for $C_{22}H_{29}O_3N_2$: C, 71.51; H, 7.91; N, 7.85. Found: C, 71.33; H, 8.14; N, 7.45.

N,N-Diethyl-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide (VIII)——**a) From the Half Amide (XIV):** To a solution of KOH (30 mg.) in 95% EtOH (10 ml.) was added XIV (180 mg.). After refluxing for 40 min., the solvent was removed under reduced pressure. To the residue was added H_2O (10 ml.) and the solution was warmed at 90° for 15 min. After cooling, the solution was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was chromatographed through silica gel using $CHCl_3$ and EtOH as eluents to give an oil (VIII) (110 mg.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1644 (CON–). The picrate of VIII was recrystallized from acetone to yellow needles, m.p. 212~213°. IR ν_{max}^{KBr} cm^{-1}: 1627 (CON–). *Anal.* Calcd. for $C_{25}H_{29}O_8N_5$: C, 56.91; H, 5.54; N, 13.27. Found: C, 56.81; H, 5.76; N, 13.32.

b) From the Amino Acid (VI): The amino acid (VI) (100 mg.) and LiOH (11 mg.) were dissolved in MeOH (10 ml.). The solvent was removed on a steam bath under reduced pressure and dried. The residual lithium carboxylate was dissolved in anhyd. DMF (20 ml.) and condensed to about half a volume under reduced pressure. The resulting solution was cooled to 0° and treated rapidly with DMF–SO_3 complex (0.8 ml.) prepared by the method of Garbrecht (containing 2 molar equivalent of SO_3), and stirred for 15 min. Then, Et_2NH (200 mg.) was added to the solution above and stirred for another 15 min., before decomposing the complex by adding H_2O (10 ml.). The solution was made alkaline, extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (65 mg.) was subject to chromatography through silica gel column. A fraction eluted by $CHCl_3$ afforded VIII (50 mg.), identical with the authentic sample prepared by the method a) by comparison of their infrared spectra.

N-*n*-Butyl-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide (IX)——As treated as above, from the amino acid (VI) (100 mg.) and *n*-butylamine (200 mg.) was obtained the *n*-butylamide (IX) (46 mg.) as an oil. The perchlorate of IX was recrystallized from iso-PrOH to colorless needles, m.p. 198~200°. IR ν_{max}^{KBr} cm^{-1}: 3311 (NH), 1653 (CON–). *Anal.* Calcd. for $C_{19}H_{27}O_5N_2Cl$: C, 57.21; H, 6.82; N, 7.02. Found: C, 56.94; H, 6.82; N, 6.95.

N-(2-Hydroxyisopropyl)-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide (X)——As treated as above, an oily 2-hydroxyisopropylamide (X)(108 mg.) was obtained from the amino acid (Ⅵ) (300 mg.) and isopropanolamine (300 mg.). The perchlorate of X was recrystallized from iso-PrOH to colorless needles, m.p. 150~151°. IR ν_{max}^{Nujol} cm^{-1}: 1650 (CON-), 1625 (C=C). *Anal.* Calcd. for $C_{17}H_{25}O_6N_2Cl$: C, 53.92; H, 6.28; N, 6.98. Found: C, 53.74; H, 6.61; N, 6.65.