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Lactams. VII.[1] Stereochemical Characterization and *Cis-Trans* Isomerization of 5-Ethyl-2-oxo-4-piperidineacetic Acid and Related Compounds[2]

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The stereochemistry of pairs of isomers found for 5-ethyl-2-oxo-4-piperidineacetic acid (I) and its derivatives [methyl ester (II), ethyl ester (III), and 1-benzyl derivative (IX)] has been established by interrelation of I with cincholoipon ethyl ester [(+)-VIIb], derived from the alkaloid cinchonine, through 3-ethyl-4-piperidineethanol (IV). *trans*-Acid IXa has been prepared by benzylation of *trans*-lactam ester IIIa and subsequent alkaline hydrolysis of the N-benzylated product (XIa); *cis*-acid IXb, by the alkaline hydrolysis of lactam ester Xb obtained from lactim ether VIIIb by the reaction with benzyl bromide. The lactim ether (VIIIb) has been synthesized from *cis*-lactam ester IIb by the methylation with dimethyl sulfate in boiling benzene.

It has been found that on thermal treatment at 180° either *cis*-acid IXb or *trans*-acid IXa is partially isomerized to give an equilibrated 67:33 mixture of IXa and IXb in 50 min. Under the same conditions the N-unsubstituted *trans*-acid (Ia) attains to an equilibrium faster than IXa, resulting in 33% conversion into Ib in 8 min. At 210° *cis*-acid Ib undergoes isomerization very rapidly to produce an equilibrated mixture of the same composition. In boiling 6 N hydrochloric acid either IXa or IXb gives an equilibrated 57:28:15 mixture of IXa, IXb, and the ring-opened product (XIII, R=$C_6H_5CH_2$) within 28 hr. In contrast, the methyl esters (IIa, b, Xa, b) of these acids have been found not to suffer such a *cis–trans* isomerization at 180° over a period of at least 1 hr. On the basis of these findings, mechanisms of the observed isomerizations are discussed.

In their earlier efforts toward a total synthesis of the alkaloid emetine,[4] Sugasawa and one (T.F.) of the present authors prepared a pair of crystalline stereoisomers (Ia,b)[4e] of 5-ethyl-2-oxo-4-piperidineacetic acid (I) as well as the corresponding ethyl esters (IIIa,b). They were also able to synthesize the crystalline N-benzyl (IXa)[4a,b,e] and N-(3,4-dimethoxyphenethyl) derivatives (XIIa)[4e] interrelated with one of the isomers of I, but refrained from assignments of stereochemistry to all these compounds for the reasons described previously.[4e] In view of the actual or potential utility of the *cis*- and *trans*-3-ethyl-4-piperidineacetic acid skeletons as possible key synthons[5] for syntheses of isoquinoline and indole alkaloids carrying such frameworks, we felt compelled to characterize the compounds in question with regard to stereochemistry. Sundberg and Holcombe[6] have recently reported the stereochemical characterization of IIIa,b on the basis of the interrelation with optically active *cis*-1-benzoyl-3-ethyl-4-piperidineacetonitrile (N-benzoylcincholoipononitrile) through gas–liquid chromatographic comparison of O-trimethylsilyl derivatives of 3-ethyl-1-methyl-4-piperidineethanol. Their work prompts us to describe our own efforts, which led to the establishment of the

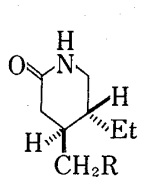
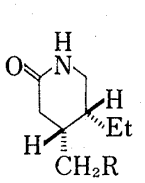
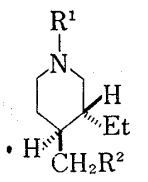
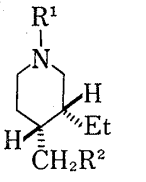
1) Paper VI in this series, T. Fujii, S. Yoshifuji, K. Yoshida, M. Ohba, S. Ikegami, and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 993 (1975).
2) Presented in part at the 36th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 16, 1973.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) *a*) S. Sugasawa and T. Fujii, *Proc. Japan Acad.*, **30**, 877 (1954); *b*) *Idem*, *Pharm. Bull.* (Tokyo), **3**, 47 (1955); *c*) S. Sugasawa and Y. Ban, *Proc. Japan Acad.*, **31**, 31 (1955); *d*) Y. Ban, *Pharm. Bull.* (Tokyo), **3**, 53 (1955); *e*) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).
5) For the term synthon, see E.J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).
6) R.J. Sundberg and F.O. Holcombe, Jr., *J. Org. Chem.*, **34**, 3273 (1969).

stereochemistry of the isomers under consideration together with a newly isolated crystalline isomer (IXb) and have culminated in a better understanding of a thermal or hydrolytic *cis–trans* isomerization reaction observed for Ia,b and IXa,b.

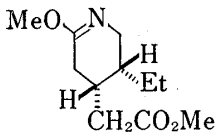
Various strategies are conceivable for establishing the stereochemical relationship between the ethyl and the acetic acid side chains of Ia,b. In the one we describe here, Ia and Ib are converted into piperidineethanols IVa and IVb, which are then interrelated with a substance of known stereochemistry. This strategy is essentially the same as that adopted by other groups[6–8] for previous assignments of stereochemistry to IIIa,b and XIIa. Treatment of Ia (mp 147—149°)[4e] with boiling ethanolic hydrogen chloride gave the ethyl ester (IIIa, mp 93—94°)[9] as reported previously.[4e] The crystalline ester was reduced with lithium aluminum hydride in tetrahydrofuran to afford piperidineethanol IVa as an oil. A similar esterification of Ib (mp 203—204°)[10] has been reported to furnish the oily isomeric ester (IIIb).[4e] In the present work, however, we found that the product from this esterification was contaminated with the crystalline isomer (IIIa). The occurrence of IIIa is probably due to a partial isomerization of Ib to Ia and/or that of IIIb to IIIa which might proceed under the esterification conditions employed.[11] For production of a stereochemically pure ester in the b-series, Ib was treated with diazomethane to give the methyl ester (IIb) as an oil, which was spectroscopically shown to be free from the contamination with the isomeric ester (IIa, mp 93—94°). The crystalline methyl ester (IIa) used for comparison was prepared from Ia as described above for IIb. That these esterifications with diazomethane occurred with retention of the relative configuration was evidenced by alkaline hydrolyses of IIa and IIb, which led to the starting acids, Ia and Ib, respectively. The lithium aluminum hydride reduction of IIb in boiling ether produced oily piperidineethanol IVb in 74% yield.

To interrelate the piperidineethanols (IVa,b) with a material of known stereochemistry, we degraded the alkaloid cinchonine to optically active ethyl *cis*-3-ethyl-4-piperidineacetate (cincholoipon ethyl ester) [(+)-VIIb] according to the procedure given in the literature.[12] This ester of known *cis* stereochemistry[12b,13] was then converted into optically active piperidineethanol (+)-IVb by the lithium aluminum hydride reduction. The infrared (IR) and nuclear magnetic resonance (NMR) spectra of (+)-IVb were superimposable on those of the racemic sample of IVb derived from Ib, but different from those of the racemic sample of IVa derived from Ia. Consequently, these results permitted the assignments of *trans* stereochemistry to compounds I—IV in the a-series, and *cis* configuration to those in the b-series. Proof of the correctness of the assigned stereostructures was further provided by the spectral comparison of N-tosyl (V) and N,O-ditosyl derivatives (VI) obtained by the reaction of the three isomeric piperidineethanols [IVa, IVb, (+)-IVb] with *p*-toluenesulfonyl chloride in 20% aqueous sodium hydroxide. The present assignments of stereochemistry to IIIa and IIIb are in agreement with those made by the American workers[6] and opposite to those reported by the Soviet workers.[7] It follows that a sample of 1-(3,4-dimethoxy-

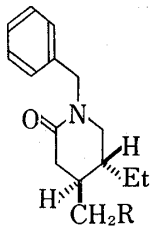
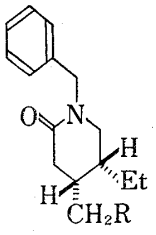
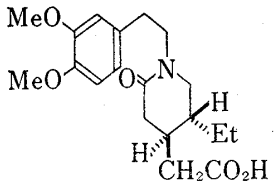
7) R.P. Evstigneeva and N.A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958).
8) A. Brossi, A. Cohen, J.M. Osbond, P. Plattner, O. Schnider, and J.C. Wickens, *J. Chem. Soc.*, **1959**, 3630.
9) Other research groups have reported that a sample of IIIa, obtained by the reductive cyclization of diethyl 3-(1-cyanopropyl)glutarate,[7] melted at 84—85°[7] or at 83—85°.[6] However, Fujii[4e] has already shown that the crystalline ester prepared by their method with his own hand melted at 93—94° and was identical with the one derived from Ia. In addition, he has also confirmed that the stereochemistry of IIIa is the same as that of Ia.[4e]
10) Reported previously[4e] as mp 205—207° (uncorr.).
11) To be fully discussed elsewhere in the near future.
12) *a*) A. Kaufmann, E. Rothlin, and P. Brunschweiler, *Ber.*, **49**, 2299 (1916); *b*) V. Prelog and E. Zalán, *Helv. Chim. Acta*, **27**, 535 (1944).
13) For a recent review, see W. Solomon, "Chemistry of the Alkaloids," ed. by S.W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, Chapter 11.

Ia: R=CO_2H Ib: R=CO_2H IVa: R^1=H, R^2=CH_2OH IVb: R^1=H, R^2=CH_2OH
IIa: R=CO_2Me IIb: R=CO_2Me Va: R^1=Ts, R^2=CH_2OH Vb: R^1=Ts, R^2=CH_2OH
IIIa: R=CO_2Et IIIb: R=CO_2Et VIa: R^1=Ts, R^2=CH_2OTs VIb: R^1=Ts, R^2=CH_2OTs
(+)-VIIb: R^1=H, R^2=CO_2Et



VIIIb

XIIa

IXa: R=CO_2H IXb: R=CO_2H
Xa: R=CO_2Me Xb: R=CO_2Me
XIa: R=CO_2Et

Et=ethyl; Me=methyl; Ts=*p*-toluenesulfonyl

Chart 1

phenethyl)-5-ethyl-2-oxo-4-piperidineacetic acid (XIIa, mp 151—153°) prepared by Fujii[4e] can be assigned the *trans* configuration on the basis of his interrelation of this substance with IIIa.

Fujii has also reported[4a,b,e] the preparation of crystalline (IXa, mp 105—106°) and oily stereoisomers (IXb) of 1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid. In the present work we followed his procedure and were able to not only raise the melting point of the former (IXa) to 110—111°, but make the latter (IXb) crystallize (mp 103—104°). Since it thus became evident that the previous interrelations[4e] of IXa,b with Ia,b were based on experiments using stereochemically somewhat impure samples of IXa,b, we tried the following alternative approach. Condensation of the potassium salt of IIIa, prepared by heating *trans*-ester IIIa with powdered potassium in xylene, with benzyl chloride in boiling xylene containing a little copper powder afforded the N-benzylated product (XIa). Alkaline hydrolysis of crude XIa produced acid IXa (mp 110—111°) in 71% overall yield. On the other hand, treatment of *cis*-ester IIb with dimethyl sulfate in refluxing benzene for 3 hr gave oily O-methyllactim VIIIb in 66% yield.[14] Reaction of VIIIb with benzyl bromide at 60° for 48 hr furnished the N-benzylated lactam (Xb), paralleling our recent experience[15] in the N-alkylation of O-methyllactims by use of reactive alkyl halides. Hydrolysis of the crude lactam ester (Xb) under alkaline conditions yielded acid IXb, identical with a sample of mp 103—104° isolated from a diastereoisomeric mixture[4a,b] of IX. The interrelations described above, therefore, made it possible to assign *trans* configuration to IXa and *cis* configuration to IXb.

Next our attention was focused on study of *cis–trans* isomerization of piperidineacetic acids I and IX. It has been reported[4e] that on treatment with boiling concentrated hydrochloric acid Ia and Ib separately gave a mixture of both isomers. This isomerization is also known to proceed thermally at 175—190° without any solvent.[4e] In the present study we found that each of IXa and IXb also undergoes a similar isomerization under acid hydrolytic conditions or on thermal treatment. To scrutinize these reactions, we first followed the progress of the isomerization of *cis*-acid IXb to *trans*-acid IXa at 180° by determining the

14) This portion of the work has been reported in a preliminary form.[20]
15) T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Ind.* (London), **1975**, 177.

isomer ratio in the reaction mixture that resulted. The quantitative analysis of the isomers was achieved by measuring relative heights of the methylene carbon signals of the ethyl groups appeared in the noise-decoupled carbon-13 NMR spectrum (see Table I). This method was found to be most satisfactory (accurate to ±1%) and convenient among those tested.

Table I. Ethyl Carbon Shieldings of 5-Ethyl-2-oxo-4-piperidineacetic Acid Derivatives

Compound	$C_{(4)}/C_{(5)}$ stereochemistry	Solvent[b]	Chemical shifts for C_2H_5 carbons[a]	
			CH_3 carbon	CH_2 carbon
Ia	*trans*	A	10.2	22.5
Ib	*cis*	A	11.2	19.4
IIa	*trans*	B	11.0	23.5
IIb	*cis*	B	11.9	20.5
IXa	*trans*	B	10.6	23.2
IXb	*cis*	B	11.6	20.2
Xa	*trans*	B	10.9	23.6
Xb	*cis*	B	11.6	20.4

a) In ppm downfield from internal tetramethylsilane. See Experimental part for details of instrumentation and measurement.
b) The letter A refers to a 4: 1 mixture of $(CH_3)_2SO$ and $(CD_3)_2SO$; B, $CDCl_3$.

As shown in Fig. 1, a rapid decrease of the amount of IXb was observed along with the occurrence and a rapid increase of IXa at earlier stages of the isomerization, attaining to an equilibrium in 50 min. The equilibration was also conducted in the reverse direction to give the same mixture (IXa: IXb=67: 33) starting with IXa. Even at 110° *cis*-acid IXb underwent the isomerization, but only to an extent of 2% in 3 hr; 10% in 16 hr. The thermal isomerization of Ia,b was also investigated similarly. It was found that the reaction of Ia at 180° proceeded to an equilibrium more rapidly than that of IXa, resulting in 33% conversion into Ib in 8 min. The reverse experiment with Ib to check the attainment of equilibrium revealed that the rate of the isomerization to Ia was considerably slow (12% conversion in the first 15 min), probably owing to the inadequate reaction conditions under which Ib (mp 203—204°) remained unmelted. At 210°, however, Ib isomerized very rapidly to give an equilibrated mixture of Ia and Ib in a ratio of 67: 33 within 5 min.

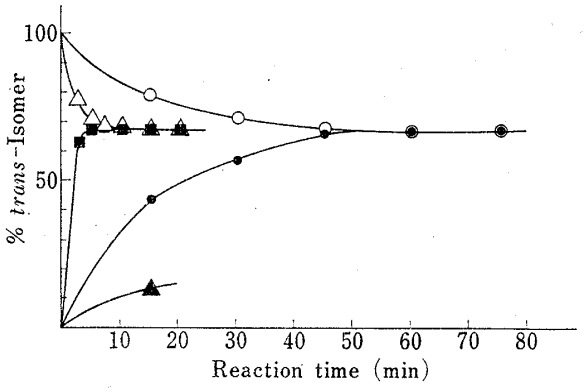
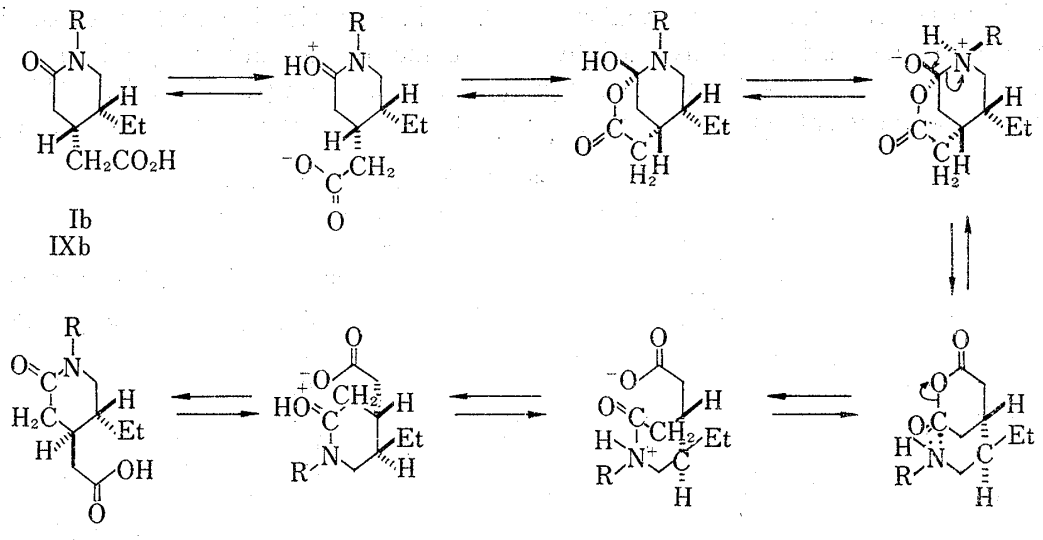


Fig. 1. Variation of the Isomer Composition with Time in the Thermal Isomerization of Lactam Acids Ia,b and IXa,b at 180°

—○—: *trans*-lactam acid IXa
—●—: *cis*-lactam acid IXb
—△—: *trans*-lactam acid Ia
—▲—: *cis*-lactam acid Ib
—■—: *cis*-lactam acid Ib at 210°

Considering the latent molecular symmetry in structures Ia,b and IXa,b, it is reasonable to assume that the equilibria described above are attained by a mechanism of intramolecular participation of the exocyclic carboxyl group, as shown in Chart 2, whereby the side chain at $C_{(4)}$ exchanges places with the endocyclic $C_{(3)}$—$C_{(2)}$ chain. Since all steps in this mechanism must be reversible, the observed ratio of the *trans* to the *cis* isomer in the equilibrated mixtures reflects the relative thermodynamic stabilities of both isomers, which are probably dependent on steric repulsion between the 4- and 5-substituents regardless of the presence or absence of a more remote N-substituent. The importance of the activation of the lactam carbonyl group by inter- or intramolecular protonation with a proton dissociated from the exocyclic carboxyl group



Ib
IXb

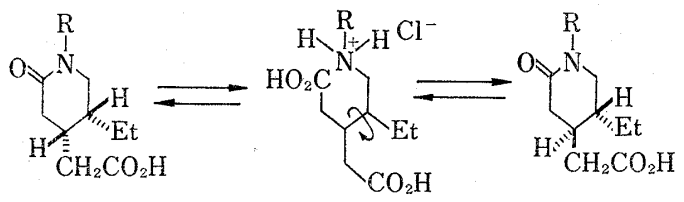
Ia
IXa

R=H or $C_6H_5CH_2$

Chart 2

in the first step may be suggested by the observation that the corresponding methyl esters (IIa,b, Xa,b) completely failed in undergoing such *cis–trans* isomerizations at 180° over a period of at least 1 hr. An alternative mechanism of nucleophilic attack of the lactam nitrogen on the exocyclic carbonyl carbon to form the intermediate bridged cyclic imide system is not favored taking into account this stability of the methyl esters and the partial double bond character of the central C—N bond of the lactam moiety which would cause the assumed bridged system to violate the Bredt rule.[16]

In the study of isomerization under acid hydrolytic conditions, IXa or IXb was treated with boiling 6N hydrochloric acid and the progress of hydrolysis was followed by measuring the amount of the recovered lactam fraction. In either case the hydrolysis was found to come to an equilibrium and resulted in 15% conversion into the ω-amino acid hydrochloride (XIII, R=$C_6H_5CH_2$) in *ca.* 28 hr, being consistent with the previous results[17] obtained with a diastereoisomeric mixture of IX. Carbon-13 NMR spectroscopic quantitative analysis of the recovered lactam fractions carried out as described already and it revealed that either isomer was also equilibrated with another to afford the same mixture (IXa: IXb=67: 33) in this period. On the basis of our previous study on acid hydrolysis of piperidone derivatives,[17,18] it may be possible to formulate a mechanism of ring opening followed by rotation and recyclization with another carboxyl group, as delineated in Chart 3, for the hydrolytic *cis–trans* isomerization of I and IX. However, it is as yet



Ib
IXb

XIII
R=H or $C_6H_5CH_2$

Ia
IXa

Chart 3

16) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, 1962, pp. 298—302, 378.
17) T. Fujii and S. Yoshifuji, *Tetrahedron*, **26**, 5953 (1970).
18) *a*) T. Fujii, S. Yoshifuji, and A. Tamai, *Chem. Pharm. Bull.* (Tokyo), **19**, 369 (1971); *b*) T. Fujii and S. Yoshifuji, *ibid.*, **19**, 1051 (1971).

uncertain whether intramolecular catalysis of the lactam hydrolysis by the exocyclic carboxyl group[19] is involved in the ring opening of Ia,b and IXa,b, and further work is needed to define kinetically the role of the acetic acid chain at $C_{(4)}$.

The present results have confirmed that *trans* stereochemistry can be assigned to all compounds designated in this paper as a-series, and *cis* configuration to those in the b-series. Moreover, the facile *cis–trans* isomerization of the 5-ethyl-2-oxo-4-piperidineacetic acid systems described above will prove of great use in stereoselective synthesis of the related alkaloids. Our recent success in synthetic incorporation of cincholoipon ethyl ester [(+)-VIIb] into ipecac alkaloids[20] is only one representative of its general utility.

Experimental[21]

Methyl *trans*-5-Ethyl-2-oxo-4-piperidineacetate (IIa)——To a chilled (in an ice-water bath), stirred suspension of *trans*-acid Ia (mp 147—149°)[4e] (463 mg, 2.5 mmoles) in ethanol (20 ml) was added an ethereal solution (0.3 M, 20 ml) of diazomethane, and the mixture was further stirred at 0° for 1 hr to give a yellow, clear solution. After the excess of diazomethane had been destroyed by addition of glacial acetic acid (0.3 ml), the solution was evaporated to dryness *in vacuo* to leave a colorless solid (492 mg, 99%) of mp 90—92°. Recrystallization from isopropyl ether yielded an analytical sample of IIa as colorless needles, mp 93—94°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester CO), 1666 (lactam CO); NMR (in $CDCl_3$) τ: 9.25—6.35 (overlapped m), 6.30 (3H, s, CO_2CH_3), 2.38 (1H, b s, NH); ^{13}C NMR (see Table I). *Anal.* Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.37; H, 8.52; N, 6.76.

Methyl *cis*-5-Ethyl-2-oxo-4-piperidineacetate (IIb)——*cis*-Acid Ib[4e] (mp 203—204°)[10] was allowed to react with diazomethane in a manner similar to that described above for IIa. After having been treated with glacial acetic acid, the reaction mixture was concentrated under diminished pressure. The resulting oil was dissolved in ether, and the solution was washed successively with 10% aq. Na_2CO_3 and saturated aq. NaCl and dried over anhyd. Na_2SO_4. Evaporation of the solvent left IIb (90%) as a faintly yellow oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester CO), 1666 (lactam CO); NMR (in $CDCl_3$) τ: 9.20—6.40 (overlapped m), 6.32 (3H, s, CO_2CH_3), 2.35 (1H, b s, NH); ^{13}C NMR (see Table I); Mass Spectrum *m/e*: 199 (M^+). Although the IR and NMR spectra of IIb were distinct from those of IIa, thin-layer chromatography (TLC) could not distinguish between both samples under a variety of conditions examined. Purification of the oily sample of IIb by means of vacuum distillation was not attempted in order to avoid possible decomposition or partial isomerization.

Alkaline Hydrolysis of *trans*-Ester IIa——A solution of IIa (183 mg, 0.92 mmole) and 50% aq. KOH (200 mg) in ethanol (3 ml) was refluxed for 2 hr. The mixture was evaporated to dryness *in vacuo* and the residue was dissolved in H_2O (1 ml). To the aq. solution was added dropwise conc. aq. HCl until the solution was acid to Congo red paper. The precipitates that resulted were filtered off, washed with a small amount of ice-cold H_2O, and dried to give Ia (157 mg, 92%) as colorless needles, mp 147—149°, identical (by mixed melting-point test and IR spectrum) with an authentic sample.[4e]

Alkaline Hydrolysis of *cis*-Ester IIb——The oily methyl ester (IIb) was hydrolyzed as described above for IIa, giving Ib (90%) as colorless prisms, mp 202—204°, undepressed upon mixture with an authentic sample.[4e,10] The IR spectra of both samples were also identical.

***trans*-3-Ethyl-4-piperidineethanol (IVa)**——To a cooled (to *ca.* −5°), stirred suspension of $LiAlH_4$ (5.68 g, 150 mmoles) in tetrahydrofuran (200 ml) was added dropwise a solution of *trans*-ester IIIa[4e,9] (8.52 g, 40 mmoles) in tetrahydrofuran (270 ml) over a period of 1 hr. After having been stirred under cooling for 20 min, the mixture was refluxed for 20 hr. To the resulting slurry was added successively H_2O (5.7 ml), 15% aq. NaOH (5.7 ml), H_2O (17.3 ml),[22] and anhyd. Na_2SO_4 (250 g) with effective stirring and cooling. Insoluble

19) For an example of intramolecular catalysis of amide hydrolysis by the carboxyl group, see M.F. Aldersley, A.J. Kirby, P.W. Lancaster, R.S. McDonald, and C.R. Smith, *J. Chem. Soc., Perkin II*, **1974**, 1487.

20) *a*) T. Fujii and S. Yoshifuji, *Tetrahedron Letters*, **1975**, 731; *b*) *Idem*, Abstracts of Papers, 7th Congress of Heterocyclic Chemistry, Chiba, Japan, October, 1974, pp. 200—204.

21) All melting points are corrected; boiling points, uncorrected. Spectra reported herein were measured on a JASCO-DS-402G or a JASCO-IRA-2 IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a JEOL-JNM-C-60H or a JEOL-JNM-PS-100 NMR spectrometer using tetramethylsilane as an internal standard. Optical rotations were determined with a JASCO-DIP-SL polarimeter. The following abbreviations are used: b=broad, d=doublet, DMSO=dimethyl sulfoxide, m=multiplet, q=quartet, s=singlet, t=triplet.

We are indebted to Mr. Y. Itatani and Misses M. Imai, S. Toyoshima, T. Tsuji, and H. Hyuga at Kanazawa University for microanalyses and NMR and mass spectral data.

22) This procedure for destruction of excess $LiAlH_4$ followed that given in the literature (L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, 1967, p. 584).

inorganic materials were removed by filtration and the filtrate was dried over a mixture of KOH pellets and anhyd. K_2CO_3. Evaporation of the solvent under vacuum left a faintly yellowish oil (5.3 g, 84%), which was distilled to furnish IVa (3.18 g, 51%) as a colorless, viscous oil, bp 128—129° (4 mmHg) [lit.[7] bp 131—132° (3 mmHg)]; IR ν_{max}^{film} cm^{-1}: 3260 (OH, NH), 1050 (C–O); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3300 (NH), 3140 (associated OH, NH), 1048 (C–O); Mass Spectrum *m/e*: 157 (M^+). The IR and NMR (in CCl_4) spectra of this sample differed from those of IVb or (+)-IVb.

The picrolonate of IVa was prepared in the following manner: To a solution of IVa (142 mg, 0.9 mmole) in ethanol (2 ml) was added a solution of picrolonic acid (238 mg, 0.9 mmole) in ethanol (12 ml). The mixture was then evaporated to dryness *in vacuo*. Recrystallization of the residual solid from benzene–ethanol (4: 1, v/v) produced yellow prisms, mp 225—226°. *Anal.* Calcd. for $C_{19}H_{27}O_6N_5$: C, 54.15; H, 6.46; N, 16.62. Found: C, 53.88; H, 6.49; N, 16.61. The NMR spectrum in pyridine-d_5 and the IR spectrum in the solid state of this specimen were different from those of the picrolonate of IVb or (+)-IVb.

***cis*-3-Ethyl-4-piperidineethanol (IVb)**——Prepared in 74% yield from *cis*-ester IIb by $LiAlH_4$ reduction in a manner similar to that described above for IVa except that the solvent was replaced with ether and the reflux time was shortened to 12 hr. Vacuum distillation of the product furnished IVb as a colorless, viscous oil, bp 137° (bath temp.) (3 mmHg) [lit.[7] bp 127—128° (2.5 mmHg)]; IR ν_{max}^{film} cm^{-1}: 3270 (OH, NH), 1056 (C–O); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3310 (NH), 3150 (associated OH, NH), 1056 (C–O); Mass Spectrum *m/e*: 157 (M^+). The IR and NMR (in CCl_4) spectra of this specimen matched those of (+)-IVb.

The picrolonate was prepared as described above for that of IVa and recrystallized from benzene–ethanol (4: 1, v/v) to light orange prisms, mp 194—195°. *Anal.* Calcd. for $C_{19}H_{27}O_6N_5$: C, 54.15; H, 6.46; N, 16.62. Found: C, 54.40; H, 6.57; N, 16.35. The NMR spectrum of this picrolonate in pyridine-d_5 was superimposable on that of the picrolonate of (+)-IVb. In the solid state, however, the IR spectra of both samples were not identical, suggesting that the racemic modification had crystallized as a racemic compound.[23]

(+)-*cis*-3-Ethyl-4-piperidineethanol [(+)-IVb]——Obtained in 76% yield from ethyl cincholoiponate [(+)-VIIb][12] (9.95 g, 50 mmoles) by reducing it with $LiAlH_4$ (4.29 g, 113 mmoles) in boiling tetrahydrofuran (430 ml) for 7 hr. The basic product was isolated as described above for IVa to give (+)-IVb as a colorless, viscous oil, bp 127—129° (4.5 mmHg) [lit.[12b] bp 103—108° (0.02 mmHg)]; $[\alpha]_D^{28}$ +12.5° ±0.1° (*c*=0.654, *l*=2, ethanol) [lit.[12b] $[\alpha]_D^{17}$ +13.1° ±0.4° (*c*=6.550, ethanol)]; IR ν_{max}^{film} cm^{-1}: 3270 (OH, NH), 1056 (C–O); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3310 (NH), 3150 (associated OH, NH), 1056 (C–O); Mass Spectrum *m/e*: 157 (M^+).

The picrolonate was obtained from the free base as described above for that of IVa and recrystallized from benzene–ethanol (9: 1, v/v) to yellow scales, mp 193—194°. *Anal.* Calcd. for $C_{19}H_{27}O_6N_5$: C, 54.15; H, 6.46; N, 16.62. Found: C, 54.24; H, 6.51; N, 16.69.

The starting ethyl ester [(+)-VIIb] was prepared from commercial cinchonine [Kishida Chemicals Co., mp 255—256°; $[\alpha]_D^{18}$ +225.4° ±0.8° (*c*=0.504, *l*=1, ethanol)] in 31% overall yield according to the literature procedure;[12] bp 100—102° (4 mmHg) [lit.[12b] bp 137—138° (11 mmHg)]; $[\alpha]_D^{28}$ +16.97° ±0.02° (neat, *l*=0.05) [lit.[12b] $[\alpha]_D^{17}$ +16.75— +16.85° ±0.05° (neat, *l*=1)]; IR ν_{max}^{film} cm^{-1}: 3320 (NH), 1730 (ester CO); NMR (in CCl_4) τ: 9.10 (3H, t, *J*=6 Hz, $CH_2C\underline{H}_3$), 8.78 (1H, s, NH), 8.75 (3H, t, *J*=7 Hz, $CO_2CH_2C\underline{H}_3$), 5.90 (2H, q, *J*=7 Hz, $CO_2C\underline{H}_2CH_3$); Mass Spectrum *m/e*: 199 (M^+).

For another identification, a small sample of (+)-VIIb was converted into the hydrochloride by dissolving it in 10% ethanolic HCl and evaporating the resulting solution. Recrystallization of the residue from acetone provided (+)-VIIb·HCl as colorless needles, mp 160—161° (lit.[12b] mp 159—160°); $[\alpha]_D^{30}$ −11.4° ±0.2° (*c*=2.577, *l*=2, ethanol) [lit.[12b] $[\alpha]_D^{23}$ −9.3° ±1.0° (*c*=2.576, ethanol)].

Yet another way of identification was by hydrolyzing a small sample of (+)-VIIb in boiling 10% aq. HCl for 3 hr. Removal of the acid by evaporation and recrystallization of the residue from aq. acetone yielded cincholoipon hydrochloride as colorless prisms, mp 203—204° (lit.[12b] mp 202—203°); $[\alpha]_D^{30}$ −4.4° ±0.2° (*c*=2.418, *l*=2, H_2O) [lit.[12b] $[\alpha]_D^{18}$ −4.6° ±1° (*c*=2.418, H_2O)].

Tosylation of *trans*-Piperidineethanol IVa——A mixture of IVa (300 mg, 1.91 mmoles), 20% aq. KOH (20 ml), and *p*-toluenesulfonyl chloride (3.0 g, 15.7 mmoles) was stirred at room temperature for 3 days. The resulting mixture was extracted with three 20-ml portions of chloroform. The chloroform solution was washed successively with H_2O, 10% aq. HCl, and saturated aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*. The residual oil was then chromatographed on a 75-g alumina column using hexane–ethyl acetate (3: 1 to 1: 1, v/v) as eluent. A substance obtained from earlier fractions was the unchanged *p*-toluenesulfonyl chloride. From middle fractions was isolated 2-(*trans*-1-tosyl-3-ethyl-4-piperidyl)ethyl tosylate (VIa) (230 mg, 26%) as a colorless, thick oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1367, 1342, 1178, 1167 ($ArSO_2N$, $ArSO_2$-OR); NMR (in $CDCl_3$) τ: 7.54 (6H, s, two $C_6H_4C\underline{H}_3$'s), 5.75—6.15 (2H, unresolved m, CH_2OTs), 2.15—2.85 (8H, aromatic protons); Mass Spectrum *m/e*: 465 (M^+). The IR and NMR spectra did not match those of the N,O-ditosyl derivative of (+)-IVb described below.

Later fractions of the chromatography gave *trans*-1-tosyl-3-ethyl-4-piperidineethanol (Va) (295 mg, 50%) as a solid, mp 58—64°, which was recrystallized from isopropyl ether to colorless needles, mp 69—70°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3530 (b, associated OH), 1340, 1162 ($ArSO_2N$); NMR (in $CDCl_3$) τ: 8.22 (1H, s, OH),

23) *Cf.* ref. 16, pp. 43—47.

7.55 (3H, s, $C_6H_4C\underline{H}_3$), 2.60 (2H, d, J=8 Hz, H(3′) and H(5′)), 2.40 (2H, d, J=8 Hz, H(2′) and H(6′)); Mass Spectrum m/e: 311 (M^+). *Anal.* Calcd. for $C_{16}H_{25}O_3NS$: C, 61.70; H, 8.09; N, 4.50. Found: C, 61.42; H, 7.96; N, 4.57. The IR and NMR spectra differed from those of the N-tosyl derivative of (+)-IVb described below.

Tosylation of *cis*-Piperidineethanol IVb——The procedure used here was virtually identical with that described above for the tosylation of IVa. 2-(*cis*-1-Tosyl-3-ethyl-4-piperidyl)ethyl tosylate (VIb) was isolated in 30% yield from earlier fractions of the column chromatography as a colorless, thick oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1354, 1336, 1178, 1167 ($ArSO_2N$, $ArSO_2OR$); NMR (in $CDCl_3$) τ: 7.54 (6H, s, two $C_6H_4C\underline{H}_3$'s), 5.70—6.15 (2H, b t, $CH_2C\underline{H}_2OTs$), 2.10—2.80 (8H, aromatic protons); Mass Spectrum m/e: 465 (M^+). The IR and NMR spectra were identical with those of the N,O-ditosyl derivative from (+)-IVb described below. *cis*-1-Tosyl-3-ethyl-4-piperidineethanol (Vb) (62% yield) was obtained from later chromatographic fractions as a colorless, thick oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3530 (associated OH), 1335, 1162 ($ArSO_2N$); NMR (in $CDCl_3$) τ: 8.28 (1H, s, OH), 7.57 (3H, s, $C_6H_4C\underline{H}_3$), 6.42 (2H, t, J=6 Hz, $CH_2C\underline{H}_2OH$), 2.60 (2H, d, J=8 Hz, H(3′) and H(5′)), 2.40 (2H, d, J=8 Hz, H(2′) and H(6′)); Mass Spectrum m/e: 311 (M^+). The IR and NMR spectra matched those of the N-tosyl derivative from (+)-IVb described below.

Tosylation of (+)-IVb——This reaction and the work-up were carried out in the same way as described above for the tosylation of IVa, affording the N-tosyl (71% yield) and the N,O-ditosyl (19% yield) derivatives. The N-tosyl derivative was a colorless, viscous, oily substance, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3530 (associated OH), 1335, 1162 ($ArSO_2N$); NMR (in $CDCl_3$) τ: 8.28 (1H, s, OH), 7,57 (3H, s, $C_6H_4C\underline{H}_3$), 6.42 (2H, t, J=6 Hz, $CH_2C\underline{H}_2OH$), 2.60 (2H, d, J=8 Hz, H(3′) and H(5′)), 2.40 (2H, d, J=8 Hz, H(2′)and H(6′)); Mass Spectrum m/e: 311 (M^+). The N,O-ditosyl derivative was also obtained as a colorless, thick oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1354, 1336, 1178, 1167 ($ArSO_2N$, $ArSO_2OR$); NMR (in $CDCl_3$) τ: 7.54 (6H, s, two $C_6H_4C\underline{H}_3$'s), 5.70—6.15 (2H, b t, $CH_2C\underline{H}_2OTs$), 2.10—2.80 (8H, aromatic protons); Mass Spectrum m/e: 465 (M^+).

Methyl *cis*-3-Ethyl-6-methoxy-2,3,4,5-tetrahydro-4-pyridineacetate (VIIIb)——A solution of IIb (996 mg, 5 mmoles) and dimethyl sulfate (631 mg, 5 mmoles) in dry benzene (5 ml) was heated at reflux for 3 hr. The solution was cooled, 50% aq. K_2CO_3 (4 ml) was added, and the resulting mixture was extracted with three 20-ml portions of ether. The combined ethereal solutions were dried over anhyd. Na_2SO_4 and evaporated under vacuum to leave a colorless oil (1.02 g), shown by TLC to contain a slight amount of the unchanged IIb. Purification by vacuum distillation gave VIIIb (700 mg, 66%) as a colorless oil, bp 96—97° (2 mmHg); IR ν_{max}^{film} cm^{-1}: 1736 (ester CO), 1680 (C=N); NMR (in $CDCl_3$) τ: 9.00 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 6.36 (3H, s, OCH_3), 6.30 (3H, s, CO_2CH_3).

***trans*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetic Acid (IXa)**——i) Repetition of the Previous Method:[4a,b] A solution of (1-benzyl-5-ethyl-4-piperidylidene)acetic acid[4a,b] (whose partial structure in respect to the double bond is as yet uncertain)[4a,b] (8.40 g, 30.7 mmoles) in ethanol (90 ml) was hydrogenated over Adams catalyst (250 mg) at 20° and atmospheric pressure for 7 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness *in vacuo* to leave a colorless solid (quantitative yield), mp 68—85°, which was shown to be a 42: 58 mixture of the *cis*-acid (IXb) and the *trans*-acid (IXa) by ^{13}C NMR spectroscopic quantitative analysis as described later.

For separation of both isomers, a portion (2.675 g) of the crude product was recrystallized four times from ethyl acetate (10 ml) to yield an analytical sample of IXa (1.045 g) as colorless plates, mp 110—111° (lit.[4a,b] mp 105—106°); IR $\nu_{max}^{CHCl_3}$ (0.2 M solution) cm^{-1}: 1713 (CO_2H), 1607 (lactam CO); NMR (in $CDCl_3$) τ: 5.40 (2H, s, $C_6H_5C\underline{H}_2N$), 2.73 (5H, s, phenyl protons), −1.80 (1H, s, CO_2H); ^{13}C NMR (see Table I). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.59; H, 7.69; N, 5.05. This sample was found to be identical (by mixed melting-point test and IR and NMR spectra) with that obtained by method-(ii).

On the other hand, the previous sample (100 mg) of IXa that had been prepared by Sugasawa and Fujii[4a,b] was recrystallized in the same way as above, giving colorless plates (88 mg), mp 110—111°, identical with the present sample.

The procedure for isolation of the *cis*-isomer (IXb) from the reaction product will be described later.

ii) From *trans*-Lactam Ester IIIa: Powdered potassium (240 mg, 0.006 g.-atom) was slurried in dry xylene (12 ml) and a solution of IIIa (1.28 g, 6 mmoles) in dry xylene (20 ml) was added dropwise with stirring at room temperature. The mixture was then kept stirring for 30 min. To the resulting solution was added dropwise a solution of benzyl chloride (840 mg, 66 mmoles) in dry xylene (15 ml). After addition of copper powder (100 mg), the mixture was heated under reflux for 33 hr. After cooling, the dark brown reaction mixture was filtered for removal of insoluble materials. The filtrate was washed with two 10-ml portions of H_2O, dried over anhyd. Na_2SO_4, and concentrated to dryness *in vacuo*, leaving the N-benzylated ester (XIa) as a brown oil (1.96 g).

The total amount of the oil (XIa) was treated with 50% aq. KOH (1.12 g) in ethanol (25 ml) at room temperature for 20 hr. The mixture was then concentrated to dryness *in vacuo*. To the residue was added H_2O (15 ml) and the resulting insoluble oil was removed by extraction with two 15-ml portions of ether. The aq. solution was adjusted to pH 1 with 10% aq. HCl and an oily substance that separated was extracted with four 20-ml portions of chloroform. The combined chloroform solutions were washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the solvent under vacuum left a light brown solid (1.17 g, 71% from IIIa),

mp 100—103°, whose IR spectrum was superimposable on that of a sample of IXa prepared by method-(i). Recrystallization of the solid from hexane–ethyl acetate (1: 1, v/v) yielded an analytical sample of IXa, mp 110—111°. *Anal.* Found: C, 70.02; H, 7.67; N, 4.81. This specimen was identical in all respects (*i.e.*, melting point, IR and NMR spectra) with that obtained by method-(i).

iii) Isomerization of *cis*-Acid IXb at 180°: *cis*-Acid IXb (500 mg) was heated in a sealed glass tube at 180° for 5 hr, turning a light brown oil without any loss in weight. A portion (440 mg) of the product crystallized from a 1: 1 mixture (5 ml) of hexane and ethyl acetate in colorless prisms (320 mg), mp 96—98°. Two more recrystallizations from the same solvent system produced *trans*-acid IXa (242 mg, 55%) as colorless plates, mp 109—110°, undepressed upon mixture with authentic IXa. The IR spectra of both samples were also identical.

On the other hand, the mother liquor from the first recrystallization of the crude product was evaporated to dryness *in vacuo*. The residue was repeatedly recrystallized from hexane–ethyl acetate (1: 1, v/v) to afford the unaltered *cis*-acid (IXb) (63 mg, 14%) as colorless prisms, mp 103—104°, identified with an authentic sample.

iv) From *cis*-Acid IXb by Isomerization in Boiling Hydrochloric Acid: A mixture of IXb (1.16 g) and 6.04 N aq. HCl (8 ml) was heated at reflux for 32 hr. The resulting mixture was worked up as reported previously[17] and a colorless solid (990 mg, 85%), mp 83—88°, was obtained from the acid fraction. A portion (940 mg) of the solid was subjected to fractional recrystallization as described under method-(iii), giving *trans*-acid IXa (393 mg, 42%), mp 110—111°, and the unchanged *cis*-acid (IXb) (130 mg, 14%), mp 102—103°. Both acids were identified with authentic samples, respectively.

***cis*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetic Acid (IXb)**——i) Repetition of the Previous Method:[4a,b] The mother liquor from the first recrystallization of the hydrogenation product described above for IXa under method-(i) was evaporated to dryness *in vacuo*. The residue crystallized from hexane–ethyl acetate (1: 1, v/v) (7 ml) in colorless prisms (680 mg), mp 89—92°. Three more recrystallizations furnished an analytical sample of IXb (316 mg) as colorless prisms, mp 103—104° (depressed to 89—90° on admixture with *trans*-isomer IXa of mp 110—111°); IR $\nu_{max}^{CHCl_3}$ (0.2 M solution) cm^{-1}: 1713 (CO_2H), 1605 (lactam CO); NMR (in $CDCl_3$) τ: 9.18 (3H, t, $J=6$ Hz, $CH_2C\underline{H}_3$), 5.52 and 5.28 (1H each, a pair of AB type d's, $C_6H_5C\underline{H}_2N$), 2.71 (5H, s, phenyl protons), −1.41 (1H, s, CO_2H); ^{13}C NMR (see Table I). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.98; H, 7.56; N, 5.21. The IR and NMR spectra were different from those of IXa, but matched those of a sample of IXb prepared by method-(ii) described below.

ii) From *cis*-Lactim Ether VIIIb: A mixture of VIIIb (213 mg, 1 mmole) and benzyl bromide (171 mg, 1 mmole) was placed in a tightly stoppered glass tube and heated in an oil bath kept at 60—62° for 48 hr. The resulting yellow oil was extracted with a mixture of 5% aq. Na_2CO_3 (5 ml) and benzene (20 ml). The benzene layer was separated from the aq. layer, washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness under diminished pressure, leaving the N-benzylated lactam ester (Xb) as a yellow oil. Hydrolysis of the oil was effected with 50% aq. KOH (600 mg) in ethanol (1 ml) at room temperature for 24 hr. Concentration of the reaction mixture under vacuum left a light brown oil, which was dissolved in H_2O (6 ml). The aq. solution was washed with two 10-ml portions of ether and adjusted to pH 1 with 20% aq. HCl. The oily substance that separated was extracted with benzene. The benzene solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, giving a faintly yellow solid (160 mg, 58% from VIIIb), mp 83—90°, whose IR spectrum was superimposable on that of authentic IXb. Recrystallization from hexane–ethyl acetate (1: 1, v/v) provided an analytical sample of IXb as colorless prisms, mp 103—104°. *Anal.* Found: C, 69.84; H, 7.75; N, 4.95. This sample was identical (by mixed melting-point test and IR and NMR spectra) with that obtained by method-(i).

Methyl *trans*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetate (Xa)——Prepared in an almost quantitative yield from *trans*-acid IXa and diazomethane in a manner similar to that described above for IIb. The ester (Xa) was a colorless, viscous, oily substance, IR ν_{max}^{film} cm^{-1}: 1734 (ester CO), 1642 (lactam CO); NMR (in $CDCl_3$) τ: 9.19 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 6.32 (3H, s, CO_2CH_3), 5.46 and 5.36 (1H each, a pair of AB type d's, $C_6H_5C\underline{H}_2N$), 2.72 (5H, s, phenyl protons); ^{13}C NMR (see Table I); Mass Spectrum *m/e*: 289 (M^+).

Methyl *cis*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetate (Xb)——*cis*-Acid IXb was allowed to react with diazomethane as described above for IIb, producing Xb (98% yield) as a colorless, viscous oil, IR ν_{max}^{film} cm^{-1}: 1737 (ester CO), 1642 (lactam CO); NMR (in $CDCl_3$) τ: 9.20 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 6.32 (3H, s, CO_2CH_3), 5.54 and 5.30 (1H each, a pair of AB type d's, $C_6H_5C\underline{H}_2N$), 2.72 (5H, s, phenyl protons); ^{13}C NMR (see Table I); Mass Spectrum *m/e*: 289 (M^+). The IR and NMR spectra were distinct from those of the *trans*-isomer (Xa).

Quantitative Analysis of Lactam Acids Ia,b, and IXa,b in an Isomeric Mixture——Sample solutions were prepared by dissolving mixtures of Ia and Ib in a 4: 1 mixture of DMSO and DMSO-d_6 at 5% (w/v) concentration or by dissolving mixtures of IXa and IXb in $CDCl_3$ at 5% (w/v) concentration. The proton-noise-decoupled, natural abundance pulsed Fourier transform (FT) carbon-13 NMR spectra of these sample solutions were taken at 23° with a JEOL-JNM-PFT-100 NMR spectrometer equipped with a ^{13}C FT NMR System. The measurement conditions were as follows: spectral width, 5000 Hz; pulse width, 9 μsec; repetition time, 3 sec; number of pulses accumulated, 2000—3000; number of data points, 8192. Chemical shifts were recorded in ppm downfield from tetramethylsilane as an internal standard. For determination of the 1-unsubsti-

tuted derivatives (Ia, b), relative heights of the methyl carbon signals due to the isomeric C_2H_5 groups (see Table I) were obtained; for the 1-benzyl derivatives (IXa, b), those of the methylene carbon signals of the isomeric C_2H_5 groups (see Table I). The isomer compositions of the sample solutions were then estimated from a calibration curve which had been constructed on analytical samples of Ia,b or IXa,b. These determinations were found to be accurate to $\pm 1\%$.

Determination of Lactam Esters IIa,b and Xa,b in an Isomeric Mixture——Sample solutions were prepared by dissolving mixtures of IIa and IIb or mixtures of Xa and Xb in $CDCl_3$ at 5% (w/v) concentration. The relative amounts of both isomers in the mixtures were then determined ^{13}C FT NMR spectroscopically in a manner similar to that described above for the corresponding acid derivatives (see Table I). The determinations were also found to be accurate to $\pm 1\%$.

Isomerization Study of Lactam Acids Ia,b and IXa,b——i) Thermal Isomerization: Aliquots (60—80 mg) of Ia,b and IXa,b were separately sealed in small ampoules and placed in an oil bath kept at 110°, 180°, or 210°. At intervals the ampoules were removed, cooled, and broken and the relative amounts of a pair of isomers in the reaction product were obtained by ^{13}C FT NMR spectroscopy as described above. The results are shown in Fig. 1 and in the text.

ii) Treatment of IXa or IXb with Hydrochloric Acid: Following the progress of hydrolysis of each of IXa and IXb in boiling 6.04 N aq. HCl at 0.528 M concentration was accomplished in the same manner as described previously.[17] The isomer composition of the lactam acid fraction was determined as in the case of the thermal isomerization runs above. The results are summarized in Theoretical part.

Thermal Stability of Lactam Esters IIa,b and Xa,b——Small samples (60—80 mg) of IIa,b or Xa,b were separately heated in sealed ampoules at $180° \pm 2°$ (bath temp.) for 1 hr. In each case, there was no loss in weight during the reaction. The ^{13}C FT NMR spectroscopic quantitative analysis as described above and IR spectroscopy failed in detecting another isomer in the reaction mixture; the spectra were identical with those of the starting ester.

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