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Lactams. XXIII.[1] Thermal *cis–trans* Isomerization of the 5-Ethyl-2-oxo-4-piperidineacetic Acid System: Effect of an *N*-Substituent[2]

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In order to investigate the effect of an *N*-substituent on thermal *cis–trans* isomerization of the 5-ethyl-2-oxo-4-piperidineacetic acid system, the *N*-alkyl analogs (±)-**1b**, **c** and (±)-**2b**, **c** and the *N*-(2-arylethyl) analogs (−)-**1f**, **g**, **i** and (+)-**2f**, **g**, **i** were separately heated neat at 180 °C, and the progress of their *cis–trans* isomerization reactions was followed by determining the isomer ratios in the reaction mixtures according to the previously reported C-13 nuclear magnetic resonance spectroscopic method. It has been found that in all cases the reaction comes to equilibrium within 28—130 min, when the *cis* and *trans* isomers exist in a ratio of 1 : 2. These results together with those obtained previously with the analogs (±)-**1a**, **d**, **e**, (−)-**1h**, (±)-**2a**, **d**, **e**, and (+)-**2h** indicate that a higher and/or bulkier *N*-substituent tends to decrease the rate of *cis–trans* isomerization of the 5-ethyl-2-oxo-4-piperidineacetic acid system, which is a useful synthon for the synthesis of benzo[*a*]quinolizidine-type *Alangium* alkaloids. Among the substrates used in the present equilibration study, (±)-**1b**, **c** and (±)-**2b**, **c** were prepared from the corresponding *N*-unsubstituted lactam esters (±)-**3** and (±)-**7** by the "lactim ether method."

Keywords——lactim ether synthesis; lactim ether alkylation; ester alkaline hydrolysis; lactam acid thermal *cis–trans* equilibration; lactam acid ^{13}C-NMR; ^{13}C-NMR stereoisomer determination

Thermal *cis–trans* isomerization of 1-(2-arylethyl)-5-ethyl-2-oxo-4-piperidineacetic acids (type **1**→**2**) has been an important process in our chiral syntheses of benzo[*a*]quinolizidine-type *Alangium* alkaloids[3] such as emetine, ankorine, alangicine, alangimarckine, desmethylpsychotrine, 10-demethylprotoemetinol, *etc.* by the "cincholoipon-incorporating method."[4]

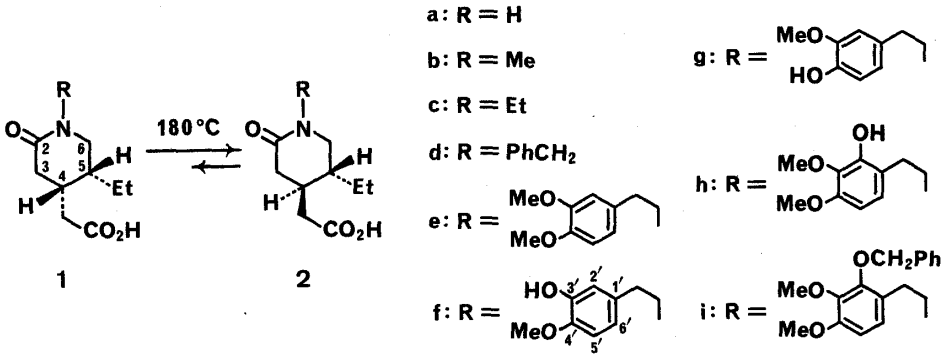


Chart 1

It has been found that the *N*-(2-arylethyl) analogs (±)-**1e** and (−)-**1h**, the *N*-benzyl analog (±)-**1d**, the *N*-unsubstituted analog (±)-**1a**, and their *trans* isomers (±)-**2a**, **d**, **e** and (+)-**2h** all give *cis–trans* equilibrated mixtures (**1** : **2** = 33 : 67) at 180 °C within 8—90 min, and that a higher substituent at the *N*-1-position tends to decrease the rate of isomerization.[4a,b,5]

Considering the latent molecular symmetry in structures **1** and **2**, we have proposed[5] for such an isomerization process a mechanism of intramolecular acidolysis of the lactam bond with the exocyclic carboxyl group, as shown in Chart 2. The importance of activation of the lactam carbonyl group by inter- or intramolecular protonation with a proton dissociated from the

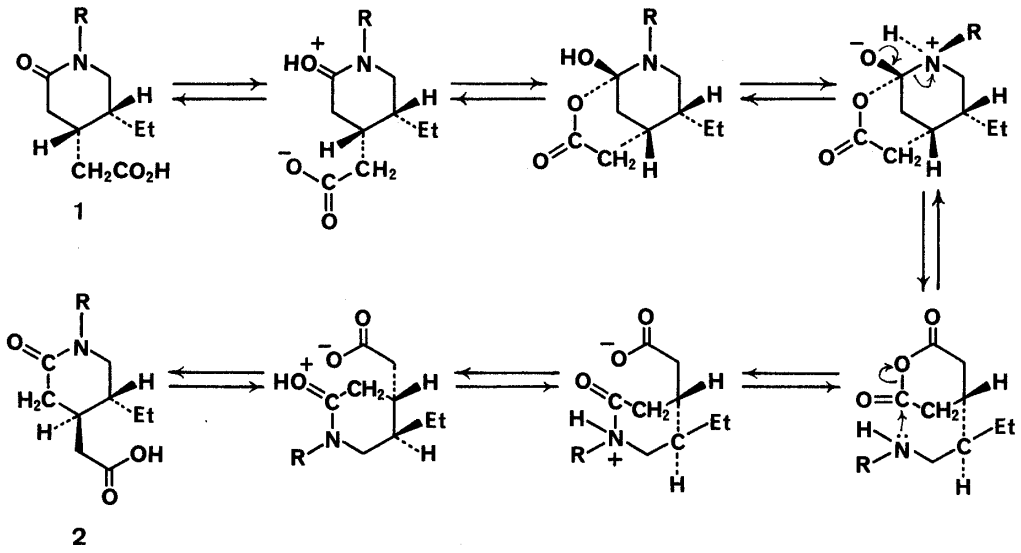


Chart 2

exocyclic carboxyl group in the first step may be supported by the unsusceptibility of the methyl esters of (±)-**1a**, **d** and (±)-**2a**, **d** to *cis–trans* isomerization under similar thermal conditions.[5] In the present work, the *N*-alkyl analogs (±)-**1b**, **c** and (±)-**2b**, **c** and the *N*-(2-arylethyl) analog (+)-**2i** were newly synthesized, and their thermal *cis–trans* isomerization reactions as well as those of the known[4b,e,g] *N*-(2-arylethyl) analogs (−)-**1f**, **g**, **i** and (+)-**2f**, **g** were investigated with a view to confirming the above *N*-substituent effect.

The syntheses of the new lactam acids (±)-**1b**, **c** and (±)-**2b**, **c** were achieved according to the previously reported "lactim ether method,"[6] as illustrated in Chart 3. Thus, the *cis*-lactim

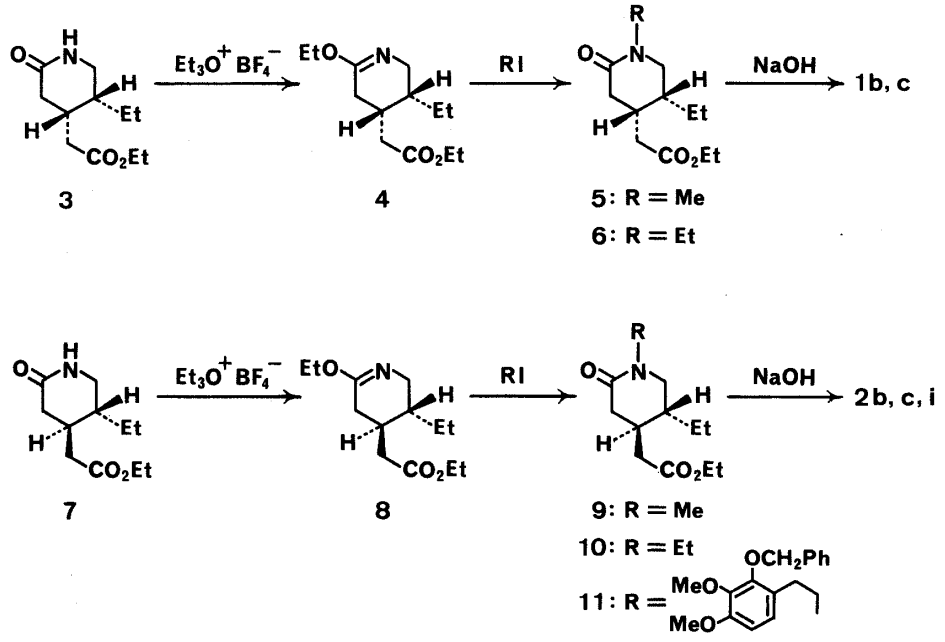


Chart 3

ether (±)-**4**, prepared from the *cis*-lactam ester (±)-**3**[7] by ethylation with triethyloxonium fluoroborate, was treated with an excess of MeI at refluxing temperature to give the *N*-methyl derivative (±)-**5**[8] in 80% yield together with a small amount of the *N*-ethylated product (±)-**6**. The formation of (±)-**6** is probably due to O→N ethyl migration during the methylation reaction, and we have already observed that such O→N alkyl migration takes place during the alkylation of *O*-alkylvalerolactims.[6] Similar ethylation of (±)-**4** with EtI afforded the *N*-ethyl derivative (±)-**6** in 76% yield. On hydrolysis with 1 N aqueous NaOH in EtOH at room temperature, the esters (±)-**5** and (±)-**6** produced the corresponding *cis*-lactam acids (±)-**1b** and (±)-**1c** in 92 and 93% yields, respectively.

In a parallel sequence of conversions, the *trans*-lactim ether (±)-**8** was prepared from the *trans*-lactam ester (±)-**7** according to the previously reported procedure,[9] and the methylation and ethylation of (±)-**8** with MeI and EtI gave the *N*-methyl derivative (±)-**9**[8] and the *N*-ethyl derivative (±)-**10** in 51 and 64% yields, respectively. In the methylation of (±)-**8**, the O→N ethyl migration product (±)-**10** was also obtained in 7.5% yield. Alkaline hydrolyses of (±)-**9** and (±)-**10** furnished the desired *trans*-lactam acids (±)-**2b** and (±)-**2c** in 83 and 87% yields, respectively. Similar hydrolysis of the known ester (+)-**11**[4b] afforded the *N*-(2-arylethyl) analog (+)-**2i** in 95% yield.

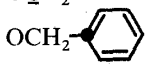
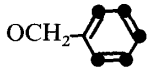
With the desired substrates prepared in the pure state, we proceeded to the thermal isomerization problem. The *cis*-lactam acids (±)-**1b**, **c** and (−)-**1f**, **g**, **i** were separately heated neat at 180 °C, and the progress of conversions to the *trans* isomers was followed by measuring the isomer ratios in the reaction mixtures. The quantitative analysis of the *cis* and *trans* isomers was carried out according to the previously reported carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopic method,[4a,b,5,7] which proved the most satisfactory (accurate to ±1%) and convenient among those tested. It consisted of the measurement of the relative heights of the methylene carbon signals of the $C_{(5)}$-ethyl groups (see Tables I and II) in the noise-decoupled ^{13}C-NMR spectra of the reaction mixtures. In all cases, a rapid decrease in the amount of the *cis* isomer (type **1**) was observed along with the appearance and rapid increase of the *trans* isomer (type **2**) at early stages of the reaction, and equilibrium (**1** : **2** = 1 : 2) was eventually attained in 28—130 min. The equilibration was also

Table I. ^{13}C-NMR Spectra of *N*-Alkyllactam Acids in $CDCl_3$

Carbon[b]	Chemical shift[a]			
	4,5-*cis* Isomer		4,5-*trans* Isomer	
	(±)-**1b**	(±)-**1c**	(±)-**2b**	(±)-**2c**
C(2)	170.3	169.8	170.8	170.4
C(3)	34.0	34.3	38.1	38.2
C(4)	31.9	31.8	33.8	33.8
C(5)	37.8	37.8	38.9	39.0
C(6)	52.0	49.3	53.5	50.6
$CCH_2\underline{C}H_3$	11.9	11.9	10.7	10.8
$C\underline{C}H_2CH_3$	20.8	20.5	23.2	23.4
$\underline{C}H_2CO_2H$	35.7	35.6	35.8	35.8
$CH_2\underline{C}O_2H$	175.0	175.0	174.4	174.4
NCH_3	34.9	—	34.8	—
$NCH_2\underline{C}H_3$	—	12.0	—	12.1
$N\underline{C}H_2CH_3$	—	42.2	—	42.2

a) In ppm downfield from internal Me_4Si. *b*) The underscored carbon in the partial structure is that to which the signal has been assigned. The ring carbons are numbered as indicated in Chart 1.

TABLE II. ^{13}C-NMR Data for *N*-(2-Arylethyl)lactam Acids in $CDCl_3$

Carbon[b]	Chemical shift[a]					
	4,5-*cis* Isomer			4,5-*trans* Isomer		
	(−)-**1f**	(−)-**1g**	(−)-**1i**	(+)-**2f**	(+)-**2g**	(+)-**2i**
C(2)	170.2	170.1	170.1	170.7	170.7	170.7
C(3)	33.9	34.0	34.0	38.2	38.2	38.3
C(4)	31.7	31.7	31.7	33.6	33.7	33.6
C(5)	37.9	37.9	37.9	39.0	39.0	39.0
C(6)	50.8	50.7	50.4	52.3	52.3	52.1
$CCH_2\underline{C}H_3$	11.8	11.8	11.8	10.6	10.6	10.6
$C\underline{C}H_2CH_3$	20.9	20.7	20.9	23.1	23.1	23.0
$\underline{C}H_2CO_2H$	35.8	35.8	35.6	35.8	35.8	35.7
$CH_2\underline{C}O_2H$	175.2	175.1	174.9	174.6	174.4	174.3
$ArCH_2\underline{C}H_2$	49.7	49.6	48.5	49.6	49.7	48.5
$Ar\underline{C}H_2CH_2$	32.6	32.9	27.9	32.7	33.0	27.9
C(1′)	131.8	130.4	124.9	131.9	130.5	124.8
C(2′)	115.2	114.5	150.9[c]	115.2	114.5	150.9[d]
C(3′)	145.6[e]	146.7	142.2	145.5[f]	146.7	142.3
C(4′)	145.7[e]	144.4	152.6[c]	145.8[f]	144.3	152.7[d]
C(5′)	111.1	111.6	107.5	111.0	111.6	107.5
C(6′)	120.2	121.3	124.8	120.2	121.4	124.8
3′-OMe	—	56.0	60.8	—	56.0	60.8
4′-OMe	56.0	—	56.0	56.0	—	56.0
$O\underline{C}H_2Ph$	—	—	75.4	—	—	75.3
OCH_2- 	—	—	137.8	—	—	137.7
OCH_2- 	—	—	128.0 128.3 128.5	—	—	128.0 128.3 128.5

a) In ppm downfield from internal Me_4Si. *b*) See Chart 1 for the numbering system. The carbon indicated by underscoring or by a black circle in the partial structure is that to which the signal has been assigned. *c*—*f*) Assignments indicated by a given superscript may be reversed.

confirmed by conducting the reactions of the *trans*-lactam acids (±)-**2b**, **c** and (+)-**2f**, **g**, **i** in the reverse direction to yield stereoisomeric mixtures in the same *cis*/*trans* ratio as above. Table III summarizes these results together with those reported[4a,b,5] previously for structurally parallel systems (±)-**1a**, **d**, **e**⇄(±)-**2a**, **d**, **e** and (−)-**1h**⇄(+)-**2h**.

It may be seen from Table III that in all cases the thermal reaction comes to equilibrium within 8—130 min, when the *cis* and *trans* isomers exist in a ratio of 1 : 2. A higher and/or bulkier *N*-substituent obviously causes the rate of isomerization to decrease. In the proposed isomerization mechanism (shown in Chart 2), all steps must be reversible. Therefore, the observed 1 : 2 ratio of the *cis* to the *trans* isomer in the equilibrated mixtures should reflect the relative thermodynamic stabilities of the two isomers, which are probably dependent on steric repulsion between the 4- and 5-substituents regardless of the presence or absence of a remote *N*-substituent. However, a bulky *N*-substituent should cause the rates of the second and subsequent steps to decrease since these steps are most likely influenced by the steric nature of the lactam moiety. In addition, the slower isomerization of the *N*-benzyl analog (±)-**1d** or (±)-**2d** observed in tetralin solutions at 0.2 and 0.005 M concentrations (Table III) suggests the importance of intermolecular rather than intramolecular protonation of the lactam carbonyl group with a proton dissociated from the exocyclic carboxyl group in the first step of the *cis*–

TABLE III. Thermal *cis–trans* Equilibration of the Lactam Acids **1** and **2** at 180 °C

Lactam acid		Reaction conditions			Composition at equilibrium	
cis	*trans*	Solvent	Concn. (M)	Time (min)	*cis* (%)	*trans* (%)
(±)-**1a**		Nil[a]	—	5[b]	33	67
	(±)-**2a**	Nil	—	8[b]	33	67
(±)-**1b**	(±)-**2b**	Nil	—	28	34	66
(±)-**1c**	(±)-**2c**	Nil	—	40	33	67
(±)-**1d**	(±)-**2d**	Nil	—	50[b]	33	67
		Tetralin	0.2	70	33	67
		Tetralin	0.005	250	—[c]	—[c]
(±)-**1e**	(±)-**2e**	Nil	—	75[d]	33	67
(−)-**1f**	(+)-**2f**	Nil	—	90	32	68
(−)-**1g**	(+)-**2g**	Nil	—	90	33	67
(−)-**1h**	(+)-**2h**	Nil	—	90[e]	33	67
(−)-**1i**	(+)-**2i**	Nil	—	130	34	66

a) At 210 °C. *b*) From ref. 5. *c*) Although the *cis*/*trans* ratio was close to 1 : 2, the two isomers had not been equilibrated. *d*) From ref. 4*a*. *e*) From ref. 4*b*.

trans equilibration (Chart 2).

The present results have thus confirmed the effect of an *N*-substituent on the *cis–trans* equilibration of the 5-ethyl-2-oxo-4-piperidineacetic acid system. They also provide a sound basis for selection of suitable experimental conditions when *cis–trans* isomerization of structurally parallel systems is required for syntheses of target molecules.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected; boiling points are uncorrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. See ref. 1 for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet.

Materials——Among the substrates used in the *cis–trans* equilibration study, the following compounds were prepared according to the reported procedures: (±)-*cis*- [(±)-**1d**][5] and (±)-*trans*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid [(±)-**2d**];[5,10] (4*S*,5*R*)-(−)- [(−)-**1f**][4e] and (4*R*,5*R*)-(+)-5-ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic acid [(+)-**2f**];[4e] (4*S*,5*R*)-(−)- [(−)-**1g**][4g] and (4*R*,5*R*)-(+)-5-ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic acid [(+)-**2g**];[4g] (4*S*,5*R*)-(−)-1-(2-benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic acid [(−)-**1i**].[4b] Other substrates were obtained as described below.

(±)-*cis*-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetic Acid Ethyl Ester [(±)-4]——A solution of triethyloxonium fluoroborate[11] (26.5 g, 139 mmol) in CH_2Cl_2 (96 ml) was added dropwise to a stirred, ice-cooled solution of (±)-**3**[7] (13.5 g, 63.3 mmol) in CH_2Cl_2 (90 ml) over a period of 1 h. After having been stirred at room temperature for 18 h, the reaction mixture was poured into 5% aqueous K_2CO_3 (200 ml), the pH of the resulting aqueous mixture was adjusted to 9, and a colorless solid that resulted was removed by filtration. The aqueous layer of the filtrate was separated from the CH_2Cl_2 layer and extracted with CH_2Cl_2. The CH_2Cl_2 solution and extracts were united, dried, and concentrated to leave a faintly yellowish oil. The oil was then purified by column chromatography [alumina, hexane–AcOEt (5 : 1, v/v)] and subsequent vacuum distillation, giving (±)-**4** (7.42 g, 49%) as a colorless oil, bp 107—108 °C (2 mmHg); mass spectra (MS) *m/e*: 241 (M^+); infrared spectra (IR) ν_{max}^{film} cm^{-1}: 1733 (ester CO), 1678 (C=N); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1678 (C=N); proton nuclear magnetic resonance (^{1}H-NMR) ($CDCl_3$) δ: 0.94 (3H, t, J=6.2 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $CO_2CH_2\underline{Me}$), 4.03 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 4.14 (2H, q, J=7.1 Hz, $CO_2C\underline{H}_2Me$).

(±)-*cis*-5-Ethyl-1-methyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-5]——A mixture of (±)-**4** (2.00 g,

8.29 mmol) and MeI (23.5 g, 166 mmol) was heated under reflux for 26 h. Evaporation of the excess MeI from the reaction mixture left a yellow oil, which was dissolved in H_2O (10 ml). The aqueous solution was saturated with K_2CO_3 and extracted with benzene. The benzene extracts were dried over anhydrous K_2CO_3 and concentrated to leave a yellow oil (1.93 g). Purification of the oil by column chromatography [alumina, hexane–AcOEt (1 : 1, v/v)] furnished (±)-**5** (1.50 g, 80%) as a faintly yellowish oil, MS *m/e*: 227 (M^+); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1641 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1632 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.2 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 1.86 (1H, br, $H_{(5)}$), 2.93 (3H, s, NMe), 4.14 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$). Earlier fractions of the above chromatography gave a yellowish oil (110 mg), which was shown to be a mixture of (±)-**5** and a small amount of the *N*-ethylated product (±)-**6** on thin-layer chromatographic (TLC) analysis.

(±)-*cis*-1,5-Diethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-6]——A mixture of (±)-**4** (2.12 g, 8.78 mmol) and EtI (12.93 g, 82.9 mmol) was sealed in a glass tube and heated in an oil bath kept at 60 °C for 120 h. Heating was continued for an additional 72 h after addition of EtI (6.50 g, 41.7 mmol). The reaction mixture was then worked up as described above for (±)-**5**, yielding (±)-**6** (1.62 g, 76%) as a yellow oil. Vacuum distillation of the oil gave a colorless sample, bp 137 °C (1.5 mmHg); MS *m/e*: 241 (M^+); IR ν_{max}^{film} cm^{-1}: 1734 (ester CO), 1640 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1628 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.2 Hz, $CCH_2\underline{Me}$), 1.12 (3H, t, J=7.2 Hz, $NCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 1.83 (1H, br, $H_{(5)}$), 3.42 (2H, q, J=7.2 Hz, $NC\underline{H}_2Me$), 4.14 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$).

(±)-*trans*-5-Ethyl-1-methyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-9]——A mixture of (±)-**8**[9] (2.00 g, 8.29 mmol) and MeI (35.3 g, 249 mmol) was heated under reflux for 20 h. The reaction mixture was then worked up and chromatographed as described above for (±)-**5**, and (±)-**9** (960 mg, 51%) was obtained as a pale yellowish oil, MS *m/e*: 227 (M^+); IR ν_{max}^{film} cm^{-1}: 1733 (ester CO), 1640 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1631 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.1 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.2 Hz, $OCH_2\underline{Me}$), 2.95 (3H, s, NMe), 4.14 (2H, q, J=7.2 Hz, $OC\underline{H}_2Me$). The *N*-ethylated product (±)-**10** (150 mg, 7.5%) was isolated from earlier fractions of the above chromatography as a pale yellow oil, which was identical (by comparison of IR spectra and TLC behavior) with authentic (±)-**10**.

(±)-*trans*-1,5-Diethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-10]——A stirred mixture of (±)-**8**[9] (3.00 g, 12.4 mmol) and EtI (3.88 g, 24.9 mmol) was heated in an oil bath kept at 60 °C for 24 h. After addition of EtI (9.67 g, 62 mmol), the mixture was further stirred at the same temperature for 142 h, during which time two 3.88-g portions of EtI were added. The reaction mixture was then worked up as described above for (±)-**5**, affording (±)-**10** (1.92 g, 64%) as a faintly yellowish oil, MS *m/e*: 241 (M^+); IR ν_{max}^{film} cm^{-1}: 1734 (ester CO), 1636 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1630 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.1 Hz, $CCH_2\underline{Me}$), 1.12 (3H, t, J=7.2 Hz, $NCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 3.39 (2H, q, J=7.2 Hz, $NC\underline{H}_2Me$), 4.14 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$).

(±)-*cis*-5-Ethyl-1-methyl-2-oxo-4-piperidineacetic Acid [(±)-1b]——A solution of (±)-**5** (1.48 g, 6.51 mmol) and 1 N aqueous NaOH (9.8 ml) in EtOH (20 ml) was kept at room temperature for 24 h. Removal of the solvent from the reaction mixture by vacuum distillation left a pale yellow oil, which was partitioned between H_2O (8 ml) and benzene (20 ml). The aqueous extracts were made acid to Congo red with concentrated aqueous HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated to leave (±)-**1b** (1.20 g, 92%) as a faintly yellow solid. Recrystallization from EtOH–AcOEt (3 : 1, v/v) gave an analytical sample as colorless prisms, mp 129—130 °C; MS *m/e*: 199 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1721 (CO_2H), 1608 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.1 Hz, $CCH_2\underline{Me}$), 1.15—1.55 (2H, m, $CC\underline{H}_2Me$), 1.7—2.1 (1H, m, $H_{(5)}$), 2.96 (3H, s, NMe), 11.01 (1H, s, CO_2H); ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.21; H, 8.51; N, 6.93.

(±)-*cis*-1,5-Diethyl-2-oxo-4-piperidineacetic Acid [(±)-1c]——A solution of (±)-**6** (1.10 g, 4.56 mmol) and 1 N aqueous NaOH (7 ml) in EtOH (15 ml) was kept at room temperature for 24 h. The reaction mixture was worked up as described above for (±)-**1b**, yielding (±)-**1c** (900 mg, 93%) as a colorless solid. For analysis, it was recrystallized from EtOH–AcOEt (1 : 15, v/v) to give colorless prisms, mp 115—117 °C; MS *m/e*: 213 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1715 (CO_2H), 1595 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz, $CCH_2\underline{Me}$), 1.13 (3H, t, J=7.1 Hz, $NCH_2\underline{Me}$), 1.75—2.05 (1H, br, $H_{(5)}$), 3.42 (2H, q, J=7.1 Hz, $NC\underline{H}_2Me$), 11.25 (1H, s, CO_2H); ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.87; H, 9.08; N, 6.79.

(±)-*trans*-5-Ethyl-1-methyl-2-oxo-4-piperidineacetic Acid [(±)-2b]——The *trans*-lactam ester (±)-**9** was hydrolyzed as described above for (±)-**1b**, and crude (±)-**2b** was obtained in 83% yield as a colorless solid. For analysis, the solid was recrystallized from EtOH–AcOEt (1 : 3, v/v) to form colorless prisms, mp 154—156 °C; MS *m/e*: 199 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1716 (CO_2H), 1610 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz, $CCH_2\underline{Me}$), 1.35—1.8 (2H, br, $CC\underline{H}_2Me$), 2.97 (3H, s, NMe), 11.29 (1H, s, CO_2H); ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.33; H, 8.80; N, 7.18.

(±)-*trans*-1,5-Diethyl-2-oxo-4-piperidineacetic Acid [(±)-2c]——The *trans*-lactam ester (±)-**10** was hydrolyzed as described above for (±)-**1b**, producing crude (±)-**2c** in 87% yield as a colorless solid. Recrystallization of the solid from EtOH–AcOEt (1 : 5, v/v) gave an analytical sample as colorless prisms, mp 136—137.5 °C; MS *m/e*: 213 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1701 (CO_2H), 1598 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.1 Hz, $CCH_2\underline{Me}$), 1.14

(3H, t, J=7.2 Hz, $NCH_2\underline{Me}$), 1.35—1.8 (2H, br, $CC\underline{H}_2Me$), 3.44 (2H, q, J=7.2 Hz, $NC\underline{H}_2Me$), 11.24 (1H, s, CO_2H); ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.66; H, 9.12; N, 6.68.

(4*R*,5*R*)-(+)-1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid [(+)-2i]——A solution of (+)-**11**[4b] (1.16 g, 2.40 mmol) and 1 N aqueous NaOH (7.5 ml) in EtOH (15 ml) was kept at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in H_2O (20 ml). The aqueous solution was made acid to Congo red with 10% aqueous HCl and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and evaporated to leave (+)-**2i** (1.04 g, 95%) as a colorless solid, mp 108—110 °C. Recrystallization of the solid from hexane–AcOEt (1 : 1, v/v) gave an analytical sample as colorless, minute plates, mp 109—110 °C; $[\alpha]_D^{20}$ +49.2° (c=0.50, EtOH); MS m/e: 455 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1715 (CO_2H), 1595 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, t, J=7.0 Hz, $CH_2\underline{Me}$), 3.85 and 3.89 (3H each, s, two OMe's), 5.09 (2H, s, $OC\underline{H}_2Ph$), 6.62 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.87 (1H, d, J=8.5 Hz, $H_{(6')}$), 7.2—7.55 (5H, m, Ph), 11.41 (1H, s, CO_2H); ^{13}C-NMR (Table II). *Anal.* Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.78; H, 7.28; N, 3.17.

Equilibration of the *cis*-Lactam Acids 1 and the *trans*-Lactam Acids 2——i) Without Solvent: Aliquots (*ca.* 50 mg) of (±)-**1b**, **c**, (−)-**1f**, **g**, **i**, (±)-**2b**, **c**, and (+)-**2f**, **g**, **i** were separately sealed in ampules and placed in an oil bath kept at 180±1 °C. At intervals the ampules were removed, cooled immediately, and broken, and the relative amounts of the *cis* and *trans* isomers in the reaction mixtures were determined by carbon-13 Fourier transform nuclear magnetic resonance (^{13}C-FT-NMR) spectroscopy as reported previously.[5] In the noise-decoupled ^{13}C-NMR spectra in $CDCl_3$, the *cis* isomers showed the methyl and methylene carbon signals of the $C_{(5)}$-Et group at 11.8—11.9 and 20.5—20.9 ppm, whereas in the *trans* isomers these signals appeared at 10.6—10.8 and 23.0—23.4 ppm, respectively (see Tables I and II). For the ^{13}C-FT-NMR spectroscopic determination, the relative heights of the methylene carbon signals of the isomeric $C_{(5)}$-Et groups were utilized. In all cases, the determinations were found to be accurate to ±1%. The results of the equilibration study are summarized in Table III.

ii) In Solution: The *cis*-lactam acid (±)-**1d** and the *trans*-lactam acid (±)-**2d** were separately dissolved in tetralin at 0.2 M and 0.005 M concentrations. Aliquots (2 ml for the 0.2 M solutions; 30 ml for the 0.005 M solutions) of these solutions were placed in flasks and heated in an oil bath kept at 180±1 °C. At intervals the flasks were removed and cooled immediately, and the reaction mixtures were partitioned by extraction with a mixture of benzene and 10% aqueous Na_2CO_3. The aqueous extracts were made acid to Congo red with concentrated aqueous HCl and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to dryness to leave mixtures of the *cis* and *trans* isomers in 89—94% yields as colorless solids. The isomeric ratios of these mixtures were then determined in the same manner as described above under item (i). The results are included in Table III.

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