methyl)benzamidoxime, needles from EtOH, mp 148—150°. IR ν_{max}^{KBr} cm^{-1}: 3421, 3285 (NH), 1749, 1220 (COO), 1648, 1535 (CONH), 1618 (C=N). NMR (in DMSO-d_6) δ: 2.11 (3H, s, CH_3), 4.56 (2H, t, J=6 Hz, CH_2), 6.42 (1H, t, J=6 Hz, NH), 7.23—7.76 (11H, m, aromatic protons and NH). *Anal.* Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.55; H, 5.50; N, 13.69. From the foregoing ethereal solution 0.14 g (6%) of N,N'-methylenebisbenzamide, mp 217—218°, was obtained.

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Lactams. XIV.[1] *cis-trans* Isomerization in the 5-Ethyl-2-oxo-4-piperidineacetic Acid System under Fischer-Speier Esterification Conditions[2]

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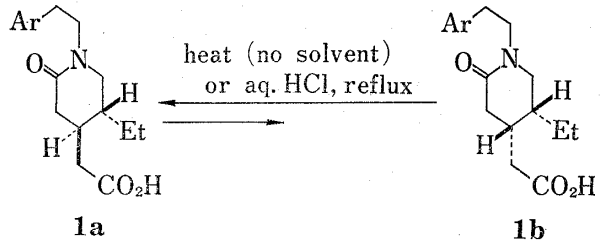
It has been found that the reaction of the *trans*- (**2a** or **3a**) or the *cis*-isomer (**2b** or **3b**) of 5-ethyl-2-oxo-4-piperidineacetic acid (**2**) or its ethyl ester (**3**) with 10% EtOH–HCl at reflux for 20—27 hr gave an equilibrated 70:30 mixture of the *trans*- (**3a**) and the *cis*-isomer (**3b**) of the ester (**3**) in a good yield. Such a *cis–trans* isomerization did not occur at all when the *trans*- (**2a**) or the *cis*-lactam acid (**2b**) was similarly esterified but at 15° for 16 hr, whereas at 32° it did occur to a slight extent. In contrast to the N-unsubstituted lactam acids (**2a, b**), *trans*- (**5a**) and *cis*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid (**5b**) could be converted into the corresponding ethyl esters (**7a, b**) by similar esterifications even at 32° with complete retention of their original stereochemistry. The *cis–trans* isomerization of the methyl esters (**6a, b**) of **2a, b** in 10% MeOH–HCl seemed somewhat easier than that of the ethyl esters (**3a, b**) in 10% EtOH–HCl. On the other hand, the N-benzylated methyl esters (**8a, b**) did not isomerize in 10% MeOH–HCl even after 5 hours' reflux.

Keywords——lactam acid; lactam ester; Fischer-Speier esterification; *cis–trans* isomerization; equilibrium; C-13 NMR spectroscopy; isomer ratio; quantitative analysis

Probably one of the most salient features in our recent synthetic incorporation of cincholoipon ethyl ester, derived from the cinchona alkaloid cinchonine, into some of the ipecac alkaloids[4] and the *Alangium* alkaloids ankorine[5] and alangicine[6] was the utilization of the potential molecular symmetry present in the title system (type **1**) for *cis*→*trans* isomerization (**1b**→**1a**). We found that such an isomerization was feasible through the *cis–trans* equilibration (**1b**⇄**1a**) under acid hydrolytic conditions[4,7] or, more efficiently, on thermal treatment (*e.g.*, 180°, without solvent).[4–7] The hydrolytic *cis*→*trans* isomerization was assumed[7] to proceed by a mechanism of ring opening followed by rotation and recyclization with another carboxyl group, apart from the mechanism[7] proposed for the thermal isomerization. In the

1) Paper XIII in this series, T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 2071 (1978).
2) Presented in part at the 2nd Symposium on Progress in Chemical Reaction and Synthesis organized by Pharmaceutical Society of Japan, Osaka, Japan, November 5—6, 1975.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731.
5) S. Yoshifuji and T. Fujii, *Tetrahedron Lett.*, **1975**, 1965.
6) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977).
7) T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.* (Tokyo), **23**, 2094 (1975).



1a **1b**

Chart 1

above alkaloid syntheses,[4–6] protection of the carboxyl group in **1a** was required for the operations in further steps and we decided to embody it by the Fischer–Speier esterification method.[8] However, the mechanistic similarity between the acidic hydrolysis and the acid-catalyzed alcoholysis of the lactam carbonyl–nitrogen bond could not exclude the possibility that the *trans*→*cis* isomerization might occur under these particular esterification conditions. We, therefore, scrutinized the reactions of some model compounds with ethanolic or methanolic hydrogen chloride in order to learn about reaction conditions under which the stereochemical purity of the lactam esters of type **1** could be secured.

Stereochemically pure samples of the *trans*- (**a**-series) and the *cis*-isomers (**b**-series) of 5-ethyl-2-oxo-4-piperidineacetic acid (**2**) and of its N-benzyl analog (**5**) were separately allowed to react with 10% (w/w) ethanolic hydrogen chloride (EtOH–HCl) under various conditions. All the esterifications proceeded smoothly to furnish the stereochemically pure or impure lactam esters (**3**, **7**) in good yields. The quantitative analysis of the *cis*- and the *trans*-isomers in the ester fractions was then carried out according to the previously reported carbon-13 nuclear magnetic resonance (NMR) spectroscopic method,[7] which was found to be most satisfactory (accurate to ±1%) and convenient among those tested. It consisted of the measurement of relative heights of the methylene carbon signals of the $C_{(5)}$-ethyl groups appeared in the noise-decoupled C-13 NMR spectra of the lactam ester fractions (see Table I). It may be seen from Table II that the esterifications of the N-unsubstituted lactam acids (**2a,b**) at 32° for 16 hr were accompanied by the *cis–trans* isomerization to a slight extent. The isomerization became faster at reflux, attaining to an equilibrium (**3a**: **3b**=70: 30) in *ca.* 27 hr. At 15°, however, no isomerization occurred for at least 16 hr. On the other hand, the esterifications of the *trans*- (**5a**) and the *cis*-isomer (**5b**) of the N-benzyl analog did not accompany any isomerized product even at 32° for 16 hr. As shown in Chart 2, the *cis–trans* isomerization may proceed through the proton-catalyzed ethanolysis of one lactam ester isomer to the ring-opened intermediate (type **4**), which may rotate and recyclize to the other isomer.

Table I. $C_{(5)}$-Ethyl Carbon Shieldings of Esters of 5-Ethyl-2-oxo-4-piperidineacetic Acid and Its N-Benzyl Analog

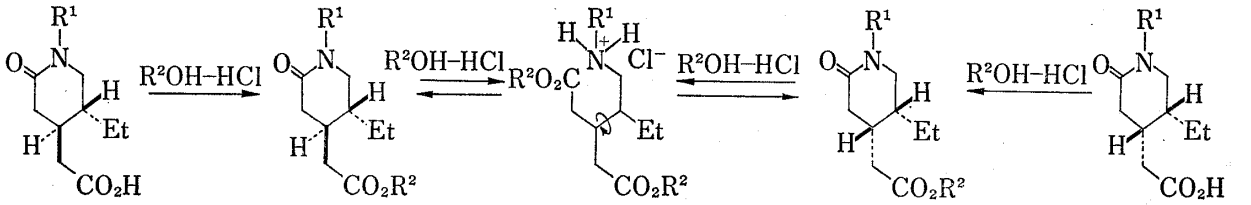
Compound	$C_{(4)}/C_{(5)}$ stereochemistry	Chemical shifts for $C_{(5)}$-C_2H_5 carbons in $CDCl_3$[a]	
		CH_3 carbon	CH_2 carbon
3a	*trans*	11.0	23.5
3b	*cis*	11.9	20.5
6a	*trans*	11.0[b]	23.5[b]
6b	*cis*	11.9[b]	20.5[b]
7a	*trans*	10.9	23.6
7b	*cis*	11.6	20.4
8a	*trans*	10.9[b]	23.6[b]
8b	*cis*	11.6[b]	20.4[b]

a) In ppm downfield from internal tetramethylsilane. See ref. 7 for details of instrumentation and measurement.
b) From ref. 7.

8) E. Fischer and A. Speier, *Ber. Dtsch. Chem. Ges.*, **28**, 3252 (1895).

TABLE II. Esterification of Lactam Acids by the Method of Fischer and Speier

Lactam acid		Reaction conditions			Lactam ester		
Compound	$C_{(4)}/C_{(5)}$ stereochemistry	Reagent	Temp. (°C)	Time (hr)	Yield (%)	% *trans*-Isomer	% *cis*-Isomer
2a	*trans*	EtOH–HCl	15	16	94	100 (**3a**)	0 (**3b**)
			32	16	95	98	2
			Reflux	0.83	92	95	5
			Reflux	5	96	82	18
2b	*cis*	EtOH–HCl	15	16	97	0 (**3a**)	100 (**3b**)
			32	16	92	3	97
			Reflux	0.83	87	8	92
			Reflux	2.5	93	20	80
			Reflux	5	90	41	59
			Reflux	27	92	70	30
5a	*trans*	EtOH–HCl	15	16	96	100 (**7a**)	0 (**7b**)
			32	16	98	100	0
5b	*cis*	EtOH–HCl	32	16	95	0 (**7a**)	100 (**7b**)



2a: R^1=H
5a: R^1=$PhCH_2$

3a: R^1=H; R^2=Et
6a: R^1=H; R^2=Me
7a: R^1=$PhCH_2$; R^2=Et
8a: R^1=$PhCH_2$; R^2=Me

4

3b: R^1=H; R^2=Et
6b: R^1=H; R^2=Me
7b: R^1=$PhCH_2$; R^2=Et
8b: R^1=$PhCH_2$; R^2=Me

2b: R^1=H
5b: R^1=$PhCH_2$

Chart 2

TABLE III. Reaction of Lactam Esters under Fischer-Speier Esterification Conditions

Lactam ester		Reaction conditions			Lactam ester recovered		
Compound	$C_{(4)}/C_{(5)}$ stereochemistry	Reagent	Temp. (°C)[a]	Time (hr)	Recovery (%)	% *trans*-Isomer	% *cis*-Isomer
3a	*trans*	EtOH–HCl	15	16	98	100 (**3a**)	0 (**3b**)
			Reflux	2.5	97	88	12
			Reflux	5	94	80	20
			Reflux	8.3	95	74	26
			Reflux	20	94	70	30
3b	*cis*	EtOH–HCl	15	16	96	0 (**3a**)	100 (**3b**)
			Reflux	2.5	95	22	78
			Reflux	5	94	41	59
			Reflux	8.3	90	54	46
			Reflux	27	91	70	30
6a	*trans*	MeOH–HCl	r.t.	16	92	100 (**6a**)	0 (**6b**)
			Reflux	5	92	80	20
6b	*cis*	MeOH–HCl	r.t.	16	94	14 (**6a**)	86 (**6b**)
			Reflux	5	90	50	50
8a	*trans*	MeOH–HCl	r.t.	16	99	100 (**8a**)	0 (**8b**)
			Reflux	5	98	100	0
8b	*cis*	MeOH–HCl	r.t.	16	96	0 (**8a**)	100 (**8b**)
			Reflux	5	99	0	100

a) The abbreviation r.t. stands for room temperature (14° ± 5°).

If such a mechanism is operative in the above isomerizations, lactam esters of that type should also undergo *cis–trans* isomerization under similar Fischer-Speier esterification conditions. Thus, the ethyl esters (**3a,b**) were separately treated with 10% (w/w) EtOH–HCl at 15° for 16 hr or at reflux; the methyl esters (**6a,b**, **8a,b**), with 10% (w/w) methanolic hydrogen chloride (MeOH–HCl) at room temperature for 16 hr or at reflux for 5 hr. The lactam ester fractions were recovered from these reaction mixtures and isomer ratios were determined C-13 NMR spectroscopically as described above (see Table I). Table III summarizes the results. It may be seen that in the reaction with EtOH–HCl **3a,b** did not isomerize at all at 15° for 16 hr, whereas at reflux each of them isomerized rapidly to give an equilibrated mixture (**3a**: **3b**=70: 30) within 20—27 hr, paralleling the results (Table II) of the esterifications of the corresponding lactam acids (**2a,b**). The *cis–trans* isomerization of the methyl esters (**6a,b**) in MeOH–HCl seemed somewhat easier than that of the ethyl esters (**3a,b**) in EtOH–HCl, and it suggested that the esterification of **2b** with MeOH–HCl is not safe stereochemically even at 9—19°. On the other hand, the methyl esters (**8a,b**) of the N-benzyl analog seemed much more stable: no isomerization was observed even after 5 hours' reflux.

In conclusion, the present results have provided a guide to stereochemically safe preparation of the ethyl and methyl esters of the 5-ethyl-2-oxo-4-piperidineacetic acid system by the Fischer-Speier esterification method. It is hoped that the guide will encourage further stereoselective syntheses using such a system as a key synthon.

Experimental[9]

Materials——Among the stereochemically pure samples used in the present work were those of *trans*-5-ethyl-2-oxo-4-piperidineacetic acid (**2a**),[7,10,11] *cis*-5-ethyl-2-oxo-4-piperidineacetic acid (**2b**),[7,10] ethyl *trans*-5-ethyl-2-oxo-4-piperidineacetate (**3a**),[7,10,11] *trans*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid (**5a**),[7,10,11] *cis*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid (**5b**),[7,10] methyl *trans*-5-ethyl-2-oxo-4-piperidineacetate (**6a**),[7] methyl *cis*-5-ethyl-2-oxo-4-piperidineacetate (**6b**),[7] methyl *trans*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetate (**8a**),[7] and methyl *cis*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetate (**8b**).[7] They were prepared according to the procedure reported in the literature as indicated, whereas the other samples were obtained in the manner described below.

Ethyl *cis*-5-Ethyl-2-oxo-4-piperidineacetate (3b)——A solution of **2b**[7,10] (1.11 g, 6 mmol) in 10% (w/w) ethanolic hydrogen chloride (EtOH–HCl) (25 ml) was kept in a refrigerator (1—2°) for 24 hr. The solution was then evaporated *in vacuo*, and sat. aq. NaCl (20 ml) was added to the crystalline residue. The resulting mixture was made basic with anhyd. K_2CO_3 under cooling and extractad with $CHCl_3$ (1×40 ml, 2×20 ml). The $CHCl_3$ extracts were washed with sat. aq. NaCl (2×15 ml), dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave **3b** (1.24 g, 97%) as a colorless oil, bp 146° (10^{-3} mmHg); MS *m/e*: 213 (M^+); IR ν_{max}^{film} cm^{-1}: 3220 (b, NH), 1728 (ester CO), 1667 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3405, 3200 (NH), 1729 (ester CO), 1659 (lactam CO); NMR ($CDCl_3$) δ: 0.95 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.0 Hz, $OCH_2\underline{Me}$), 1.10—1.90 (4H, m, $H_{(4)}$, $H_{(5)}$, and $CC\underline{H}_2Me$), 2.13—2.62 (4H, m, $H_{(3)}$'s and $C\underline{H}_2CO_2Et$), 2.91—3.44 (2H, m, $H_{(6)}$'s), 4.14 (2H, q, J=7.0 Hz, $OC\underline{H}_2Me$), 7.22—7.50 (1H, b, NH). The C-13 nuclear magnetic resonance (NMR) spectroscopic quantitative analysis as described below and infrared (IR) spectroscopy failed in detecting the presence of the *trans*-isomer (**3a**) in the crude or the distilled sample of **3b**.[12]

Ethyl *trans*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetate (7a)——A solution of **5a**[7,10,11] (826 mg, 3 mmol) in 10% (w/w) EtOH–HCl (30 ml) was allowed to stand in a refrigerator (1—2°) for 20 hr. The solution was evaporated *in vacuo*, and H_2O (10 ml) was added to the residue. The resulting mixture was made basic

9) All melting points are corrected; boiling points, uncorrected. IR spectra were measured in Nujol mulls, in liquid films, or in $CHCl_3$ solutions at 0.2 M concentration. See also ref. 1 for details of instrumentation and measurement. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet.

10) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).

11) T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.* (Tokyo), **26**, 645 (1978).

12) The esterifications of **2a** and **2b** were previously effected with 12.5% EtOH–HCl at reflux for 3.5 hr, giving **3a** (83.2% yield; mp 93—94°) and **3b** [82.6% yield; bp 165—166° (0.02 mmHg)], respectively.[10] Although the highest stereochemical purity of the crystalline sample of **3a** prepared by that method was secured by recrystallization,[7,10] it is most likely in the light of the results in Table II that the previous oily sample of **3b** was contaminated with **3a**. This was also supported by a separate experiment.[7]

with 10% aq. Na_2CO_3 under cooling and extracted with benzene (1×20 ml, 2×10 ml). The benzene extracts were washed with H_2O (10 ml), dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave **7a** (890 mg, 98%) as a colorless oil, MS *m/e*: 303 (M^+); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1644 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1633 (lactam CO); NMR ($CDCl_3$) δ: 0.80 (3H, t, $J=7.0$ Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, $J=7.0$ Hz, $OCH_2\underline{Me}$), 1.0—3.40 (10H, m, $H_{(3)}$'s, $H_{(4)}$, $H_{(5)}$, $H_{(6)}$'s, $CC\underline{H}_2Me$, and $C\underline{H}_2CO_2Et$), 4.12 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2Me$), 4.52 and 4.62 (1H each, AB type d's, $J=14$ Hz, $C\underline{H}_2Ph$), 7.26 (5H, s, Ph). This sample was C-13 NMR (see below) and IR spectroscopically shown to be free from the contamination with the *cis*-isomer (**7b**).

Ethyl *cis*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetate (7b)——The *cis*-lactam acid (**5b**)[7,10] was esterified as described above for the esterification of **5a**, affording **7b** (95% yield) as a colorless oil, MS *m/e*: 303 (M^+); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1644 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1633 (lactam CO); NMR ($CDCl_3$) δ: 0.79 (3H, t, $J=7.0$ Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, $J=7.0$ Hz, $OCH_2\underline{Me}$), 1.07—3.22 (10H, m, $H_{(3)}$'s, $H_{(4)}$, $H_{(5)}$, $H_{(6)}$'s, $CC\underline{H}_2Me$, and $C\underline{H}_2CO_2Et$), 4.12 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2Me$), 4.45 and 4.69 (1H each, AB type d's, $J=15$ Hz, $C\underline{H}_2Ph$), 7.27 (5H, s, Ph). No contamination of this sample with the *trans*-ester (**7a**) was indicated by means of C-13 NMR (see below) and IR spectroscopy.

Quantitative Analysis of the *cis*- and *trans*-Lactam Esters (3a,b, 6a,b, 7a,b, or 8a,b) in an Isomeric Mixture——Performed C-13 NMR spectroscopically in a manner similar to that described previously[7] for analysis of **2a,b**, **5a,b**, **6a,b**, or **8a,b** (see Table I).

Isomerization Study of the Lactam Acids (2a,b, 5a,b) under Fischer-Speier Esterification Conditions—— The lactam acids (**2a**, **2b**, **5a**, and **5b**) (0.6 mmol) were separately dissolved in 10% (w/w) EtOH–HCl (6 ml). The resulting solutions were refluxed for the time specified in Table II or sealed in small ampoules and placed in a thermoregulated constant temperature bath kept at $15°\pm0.1°$ or at $32°\pm0.1°$ for 16 hr. The reaction mixtures were evaporated *in vacuo* and sat. solutions (5 ml each) of $NaHCO_3$ in H_2O were added to the residues. The resulting mixtures were separately extracted with $CHCl_3$ (3×10 ml). The $CHCl_3$ solutions were washed with sat. aq. NaCl (10 ml), dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving crude lactam esters. After having been weighed, the ester fractions were submitted to the C-13 NMR spectroscopic analysis (see above) for determination of isomer ratios. The results are summarized in Table II.[12,13]

Stereochemical Stability of the Lactam Esters (3a,b, 6a,b, 8a,b) under Fischer-Speier Esterification Conditions——The stereochemical stability of the ethyl esters (**3a, b**) (0.6 mmol) in 10% (w/w) EtOH–HCl (6 ml) was examined in a similar manner to that described above for the lactam acids (**2a,b, 5a,b**). In the cases of the methyl esters (**6a,b, 8a,b**), they were dissolved in 10% (w/w) methanolic hydrogen chloride (MeOH–HCl) (3 ml) at 0.14 M concentration and the resulting solutions were kept at room temp. ($14°\pm5°$) for 16 hr or refluxed for 5 hr. For isolation and isomer analysis of ester fractions, the reaction mixtures were worked up as described above for the esterification of the lactam acids (**2a,b, 5a,b**). Table III summarizes the results thus obtained. Small portions of the ester fractions from the reactions of **6a** (room temp., 16 hr, or refluxing, 5 hr) and of **6b** (refluxing, 5 hr) with MeOH–HCl were recrystallized from isopropyl ether to give colorless needles, mp 92—93°, identical (by IR spectrum and mixed melting-point test) with authentic **6a**.[7] The crude ester fractions obtained from the reactions of **8a** and of **8b** with MeOH–HCl, respectively, showed IR spectra superimposable on those of authentic **8a**[7] and **8b**.[7]

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13) For stereochemically safe esterification procedure for preparation of **3a** and **3b**, see ref. 11 (**3a**) and the present paper (Experimental section, under the name of **3b**).