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Lactams. XV.[1] Chemistry of Unsaturated δ-Valerolactams[2]

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On the basis of chemical and spectroscopic evidence, the structure **5** has been assigned to an unsaturated lactam acid of mp 126—127° (slight effervescence) which was temporarily expressed by the structure **6** previously. The chemical evidence obtained here includes the results of the following reactions: esterifications of the lactam acid **5** to the ethyl ester **8** and to the methyl ester **9**; alkaline hydrolyses of the two esters **8** and **9** to the starting acid **5** at room temperature; conversion of **9** into the lactam amide **12**; $LiAlH_4$ reduction of **9** to the lactam alcohol **10**; chromic acid oxidation of **10** to the starting acid **5**; alkaline hydrolyses of the esters **8** and **9** to a mixture of **5** and the isomeric lactam acid **7** at a higher temperature; base-catalyzed isomerization of **5** to **7** or *vice versa*, reaching equilibrium; thermal decarboxylation of **5** to a mixture of **13** and **14**; base-catalyzed isomerization of **13** to **14**. The assigned structures of the lactam derivatives thus obtained were also supported by their ultraviolet, infrared, proton magnetic resonance, and C-13 nuclear magnetic resonance spectra.

Keywords——dihydropyridone; esterification; hydrolysis; $LiAlH_4$ reduction; chromic acid oxidation; thermal decarboxylation; base-catalyzed isomerization; UV; IR; NMR

The 3-ethyl-4-piperidineacetic acid skeleton has been one of the most useful common synthons in our recent syntheses of the Ipecac and *Alangium* alkaloids[4] and structurally parallel indoloquinolizidine alkaloids.[5] The appropriate racemic form of this important synthon is the *trans*- (**3a**) or *cis*-isomer (**3b**) of ethyl 5-ethyl-2-oxo-4-piperidineacetate,[4a,b,d,f,h] and its preparation[6] from the lactam ketone **1** through **4**, **5**, and **2a** or **2b** is among the synthetic routes currently available.[6,7] Although the intermediate unsaturated lactam acid of mp 126—127° (slight effervescence) derived from the hydrolysis of **4** has been temporarily assigned the exocyclic double bond structure **6** by Sugasawa and one (T. F.) of the present authors for convenience of expression in their papers,[6a,8] the location of the double bond still remains to be determined. We now present chemical and spectroscopic evidence that the position of unsaturation is endocyclic, as in structure **5**.

1) Paper XIV in this series: T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **26**, 2253 (1978).
2) Presented in part at the 43rd Meeting of the Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, November 20, 1976.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) *a*) T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731; *b*) T. Fujii, S. Yoshifuji, and K. Yamada, *ibid.*, **1975**, 1527; *c*) S. Yoshifuji and T. Fujii, *ibid.*, **1975**, 1965; *d*) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *ibid.*, **1976**, 2553; *e*) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977); *f*) T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Lett.*, **1977**, 3477; *g*) T. Fujii, H. Kogen, and M. Ohba, *ibid.*, **1978**, 3111; *h*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **27**, 1486 (1979).
5) T. Fujii, S. Yoshifuji, and H. Ito, *Heterocycles*, **7**, 149 (1977).
6) *a*) S. Sugasawa and T. Fujii, *Pharm. Bull.* (Japan), **3**, 47 (1955); *b*) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958); *c*) T. Fujii, S. Yoshifuji, and M. Tai, *ibid.*, **23**, 2094 (1975); *d*) T. Fujii, S. Yoshifuji, and M. Ohba, *ibid.*, **26**, 645 (1978).
7) *a*) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958), and references cited; *b*) E. E. van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **91**, 7342 (1969).
8) S. Sugasawa and T. Fujii, *Proc. Jpn. Acad.*, **30**, 877 (1954).

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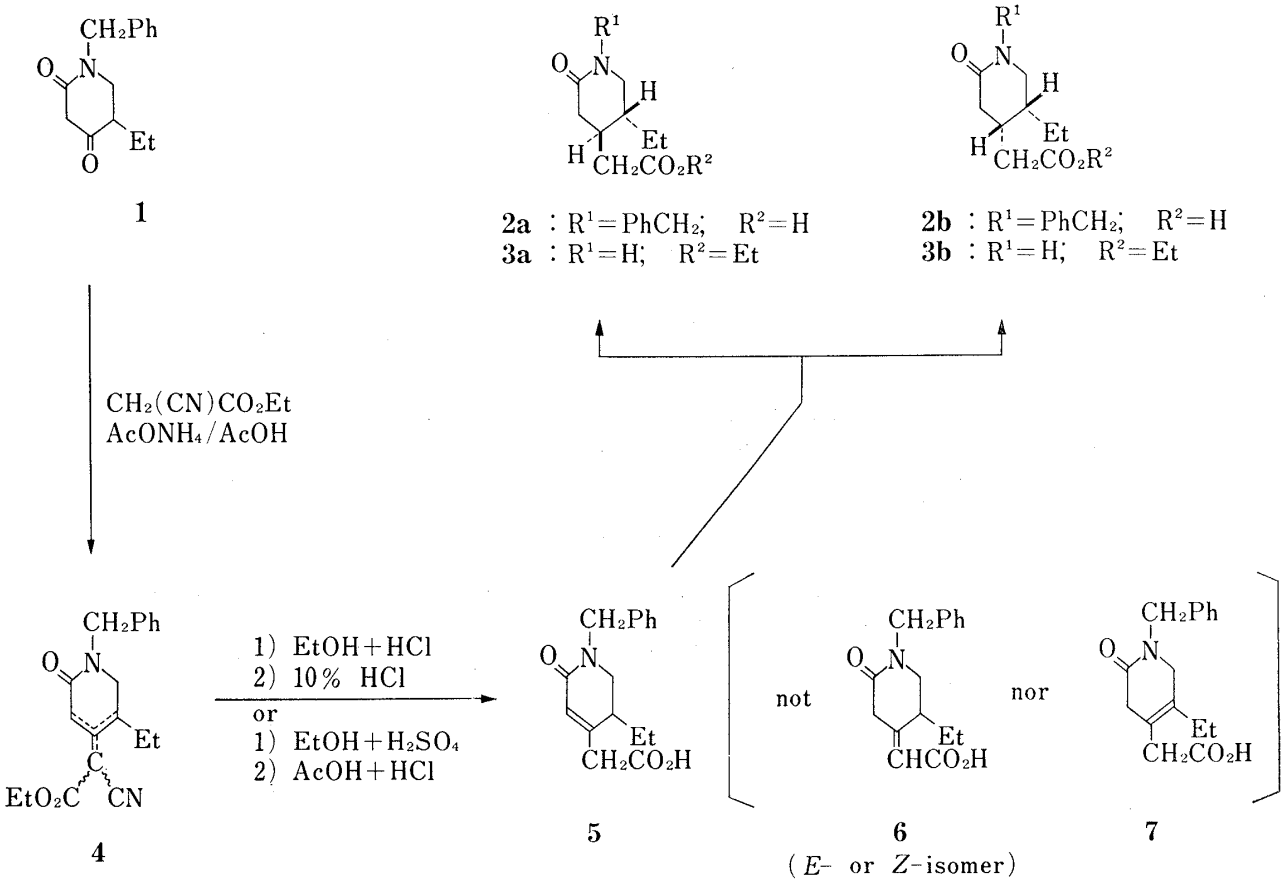

Chart 1

The nuclear magnetic resonance (NMR) spectrum of the unsaturated lactam acid (**5**) in $CDCl_3$ showed a one-proton singlet at δ 6.00 assignable to a trisubstituted olefinic proton having no vicinal protons. This excluded the structure **7**, one of the four possible isomeric structures [**5**, (*E*)-**6**, (*Z*)-**6**, and **7**], but did not distinguish between structures **5** and **6** unequivocally because of the potential molecular symmetry (with respect to the two carbonyl functions) present in these unsaturated and conjugated systems. Thus, we tried to modify or convert the exocyclic carboxyl group in a way that would destroy the potential symmetry, hopefully without accompanying migration of the double bond.

Esterification of the lactam acid (**5**) under consideration with diazomethane (MeOH–ether, room temp.) furnished the methyl ester **9** in an excellent yield. Since treatment of **9** with KOH in EtOH at room temperature reproduced the starting lactam acid **5** in 96% yield, it was likely that the location of the double bond in **9** corresponded to that in **5**. Reduction of the lactam ester **9** with $LiAlH_4$ in ether at −65° for 10 hr gave the lactam alcohol **10** in 24% yield with recovery of 49% of **9**. The NMR spectrum of **10** in $CDCl_3$ revealed a two-proton triplet (J=6 Hz) at δ 3.78 ($CH_2\underline{CH_2}OH$) and a one-proton singlet at δ 5.78 (>C=CH–CON), establishing the endocyclic double bond structure. On oxidation with chromic acid in acetone at room temperature, the lactam alcohol **10** afforded the starting lactam acid **5** in 55% yield.

It is interesting to note that the alkaline hydrolysis of **9** at a higher temperature gave a result more complex than that at room temperature. When **9** was treated with KOH in boiling EtOH for 3 hr, a 35: 65 mixture of the isomeric lactam acid **7** (mp 153—154°) and the original lactam acid **5** was produced. The formation of **7** suggested that the isomerization of the lactam acid **5** itself to **7** might occur under similar conditions. We found that this was the case, and followed the progress of the isomerization of **5** in boiling 9% aq. KOH

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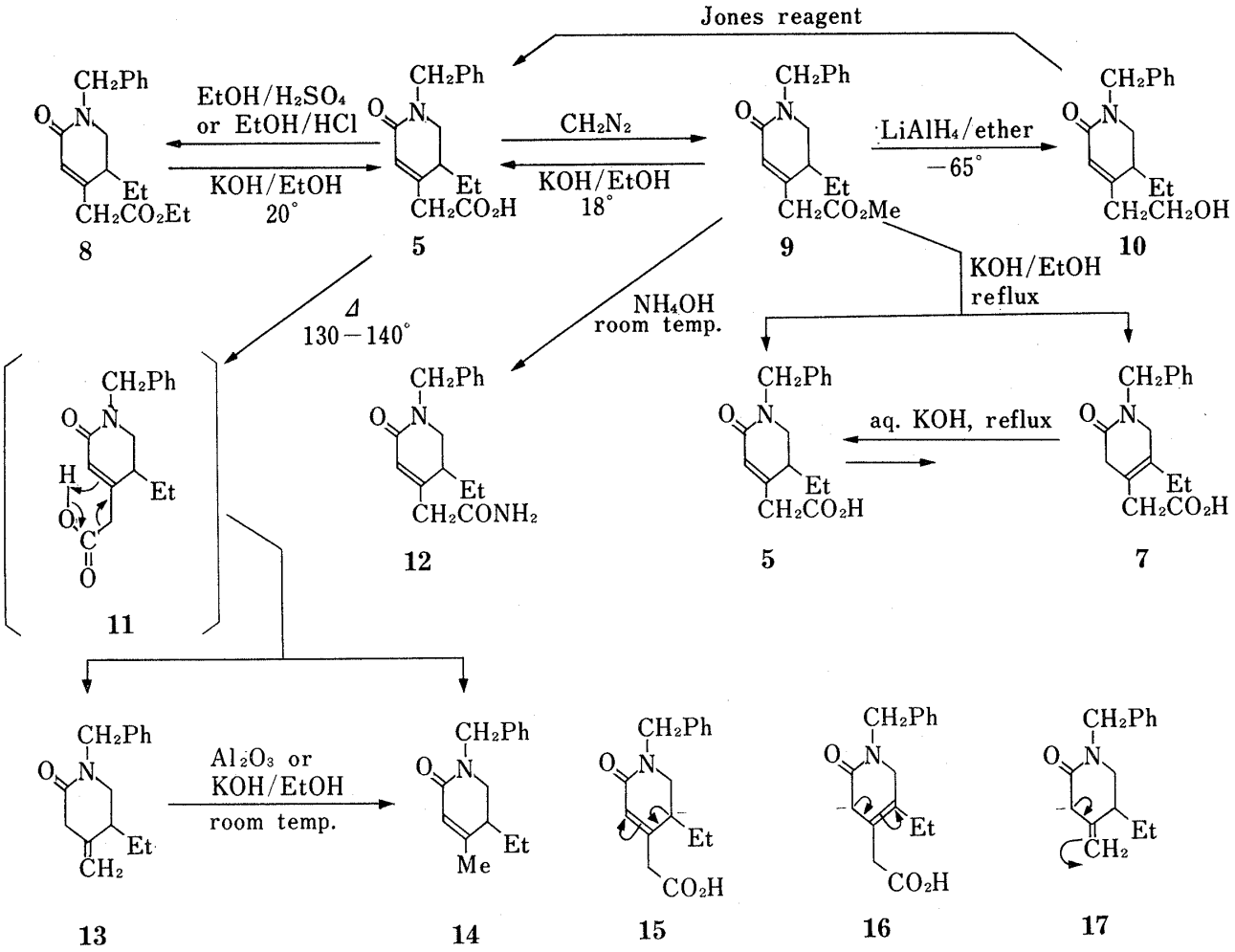

Chart 2

by measuring the amounts of **5** and **7** by means of NMR spectroscopy (see Experimental). The isomerization was found to proceed to equilibrium, giving a 38: 62 mixture of **7** and **5** in approximately 12 hr. The attainment of equilibrium was checked by conducting the reverse experiment with **7**. In the isomerization of **5** to **7** or *vice versa*, the formation of the anion **15** or **16** is probably involved.

To prepare further derivatives, the lactam ester **9** was treated with conc. aq. NH_4OH at room temperature (26—29°) for 24 hr to provide the lactam amide **12** in 77 % yield. Esterification of **5** with EtOH–H_2SO_4 (reflux, 5 hr) or with EtOH–HCl (reflux, 6 hr) afforded the ethyl ester **8** in a good yield. Hydrolysis of **8** with KOH in EtOH at room temperature yielded the starting acid **5** exclusively, whereas that at reflux produced a mixture of **7** and **5**, as in the case of the methyl ester **9**.

Further interest in the chemical conversion of **5** originated from its melting point of 126—127° accompanied by slight effervescence,[6a] suggestive of the possibility of thermal decarboxylation at a higher temperature. When heated at 130—140° for 40 min, **5** evolved CO_2 to give a 52: 48 mixture of **13** and **14** in 96% yield, from which each component was isolated by silica gel chromatography. Prolonged heating of **5** resulted in an increase of the formation of **14** and a decrease of that of **13**, and eventually in the exclusive production of **14**. It was therefore clear that the primarily decarboxylated product was the exocyclic methylene derivative **13**, which isomerized successively to the more stable, conjugated system **14** under thermal conditions. On the basis of the generalization that β,γ-unsaturated acids

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undergo decarboxylation fairly readily *via* a cyclic six-center mechanism,[9] the six-membered transition state (**11**) is postulated for the easy decarboxylation of **5** to **13**. The isomerization of **13** to **14** was also found to occur readily on treatment of the former compound with alumina or KOH in EtOH at room temperature, and it might proceed through the formation of the anion **17**.

Indeed, the results described above favored the α,β-unsaturated lactam structure of **5**, but they could not rigorously exclude the alternative structure **6**, since all the reactions that were run were only assumed not to be accompanied by migration of the double bond unless otherwise noted. Therefore, we next tried to obtain additional evidence for the correctness of structures **5**, **8**, **9**, and **12** by comparing their spectra with those of compounds of established structure such as **7**, **10**, **13**, **14**, *etc.* It may be seen from Table I that the ultraviolet (UV) spectra of **10**, **14**, and 1-benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydropyridine (**18**),[6d] the α,β-unsaturated lactam (type A) models, showed a band in the 250 nm region

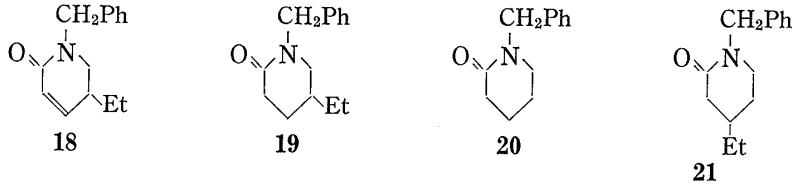

Chart 3

with ε of *ca.* 3000, in general agreement with the observation of Edwards and Singh.[10] On the other hand, **7** and **13**, the β,γ-unsaturated lactam (type B) models, and 1-benzyl-5-ethyl-2-piperidone (**19**),[11] the saturated lactam (type C) model, exhibited only benzenoid bands of much lower intensities in the same region. All the unsaturated lactams **5**, **8**, **9**, and **12** under

Table I. Ultraviolet and Infrared Spectra of δ-Valerolactams

Compound	Type[a]	UV spectrum[b]		IR spectrum [ν_{max} (cm^{-1})][c]			
		λ_{max} (nm)	ε	Side chain CO	C=C	Lactam CO	$\Delta\nu$[d]
18[6d]	A	253.5	3060	—	1662	1610	52
10	A	252	3290	—	1662	1610	52
14	A	253	3780	—	1666	1612	54
5	A	253	3990	1715	1662	1592	70
8	A	253	3320	1729	1666	1615	51
9	A	253	3440	1734	1666	1615	51
12	A	252.5	3430	1685	1665	1615	50
7	B	—[e]	—[e]	1712	1637	1612	25
13	B	—[e]	—[e]	—	1652[f]	1632	20
19[11]	C	—[e]	—[e]	—	—	1630	—
2a[6c]	C			1713	—	1607	—
2b[6c]	C			1713	—	1605	—
Methyl ester[6c] of **2a**	C			1730	—	1630	—
Methyl ester[6c] of **2b**	C			1730	—	1630	—

a) The letter A stands for an α,β-unsaturated lactam; B, β,γ-unsaturated lactam; C, saturated lactam.
b) Determined in abs. EtOH.
c) Measured in $CHCl_3$ at 0.2 M concentration.
d) $\Delta\nu=\nu_{C=C}-\nu_{lactam\ CO}$.
e) Only several benzenoid bands with ε values less than 200 were observed in the 250—270 nm region.
f) Shoulder.

9) *a*) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Co., New York, 1968, pp. 477—480; *b*) D. B. Bigley, *J. Chem. Soc.*, **1964**, 3897.
10) O. E. Edwards and T. Singh, *Can. J. Chem.*, **32**, 683 (1954).
11) T. Fujii and S. Yoshifuji, *Tetrahedron*, **26**, 5953 (1970).

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consideration were found to show UV spectra very similar to those of the type A models, indicating an α,β-unsaturated lactam structure. In addition, an equimolar mixture of the saturated lactam **19** and cyclohexylideneacetic acid[12] ($\lambda_{max}^{abs.\ EtOH}$ 219 nm) or ethyl cyclohexylideneacetate[13] ($\lambda_{max}^{abs.\ EtOH}$ 221 nm) displayed a UV spectrum (abs. EtOH) unlike that of **5** or **8**. This also led us to rule out the exocyclic double bond structure as in **6** for the unsaturated lactam acid or its ethyl ester in question.

In their infrared (IR) spectra in $CHCl_3$, all the α,β-unsaturated lactam models (the first three entries in Table I) revealed two strong absorption bands in the 1600—1700 cm^{-1} region. The saturated lactam models, **19** and the methyl esters of **2a** and **2b**, displayed their lactam ν_{CO} at 1630 cm^{-1}. It is generally agreed that in six-membered unsaturated lactams the carbonyl frequency is slightly raised by conjugation with a double bond as opposed to the more usual lowering.[10,14] However, we have already observed[15] that 2-piperidones possessing the carboxyl function show slightly lowered lactam ν_{CO}, as demonstrated in the cases of **2a** and **2b**, and the results of extended work[16] suggest a conjugation effect opposite to what has been suggested[14] for six-membered α,β-unsaturated lactams. Thus, we prefer to assign the lower frequency (1610—1612 cm^{-1}) band that occurred in the type-A models **10**, **14**, and **18** in the range 1600—1700 cm^{-1} to the lactam CO stretching vibration; and the higher frequency (1662—1666 cm^{-1}) band, to the conjugated C=C stretching vibration. The difference in frequency ($\Delta\nu$) between these two bands is 52—54 cm^{-1}, and is 20—25 cm^{-1} for the β,γ-unsaturated lactams **7** and **13**. The $\Delta\nu$ values observed for **5**, **8**, **9**, and **12** are in the range of 50—70 cm^{-1}, which supports their α,β-unsaturated structures.

Table II. Carbonyl Carbon Shieldings of 2-Piperidones

Compound	Type[b]	Chemical shifts[a] in $CDCl_3$		
		Side chain CO	Lactam CO	Δ(lactam CO)[c]
20[17]	C	—	169.6	0
19[11]	C	—	169.7	+0.1
21[11]	C	—	169.4	−0.2
2a	C	174.5	170.8	+1.2
2b	C	175.2	170.1	+0.5
Methyl ester[6c] of **2a**	C	172.5	169.1	−0.5
Methyl ester[6c] of **2b**	C	172.8	168.7	−0.9
7	B	173.7	168.8	−0.8
13	B	—	168.6	−1.0
18[6d]	A	—	164.2	−5.4
10	A	—	164.5	−5.1
14	A	—	164.6	−5.0
5	A	172.4	164.9	−4.7
8	A	169.7	163.8	−5.8
9	A	170.2	163.7	−5.9
12	A	171.5	164.1	−5.5

a) In ppm downfield from internal tetramethylsilane.
b) The letter A designates an α,β-unsaturated lactam; B, β,γ-unsaturated lactam; C, saturated lactam.
c) Deviation of the lactam CO shielding from that of 1-benzyl-2-piperidone (**20**).

12) J. D. Chanley, *J. Am. Chem. Soc.*, **70**, 244 (1948).
13) W. S. Wadsworth, Jr., and W. D. Emmons, "Organic Syntheses," Coll. Vol. 5, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 547.
14) *a*) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., Methuen and Co., London, 1958, pp. 213—215; *b*) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical—," Holden-Day, Inc., San Francisco, and Nankodo Co., Tokyo, 1962, p. 47.
15) T. Fujii, S. Yoshifuji, and A. Tamai, *Chem. Pharm. Bull.* (Tokyo), **19**, 369 (1971).
16) Y. Takai, Bach. Pharm. Sci. Thesis, Kanazawa University, March, 1978. In this work, differentiation in frequency between a lactam carbonyl and a conjugated double bond in the presence of a strong acid was studied. The results will be reported elsewhere at a later date.

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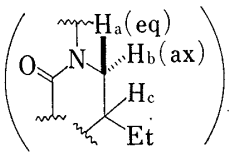
We next extended the spectroscopic approach to include carbon-13 NMR spectroscopy. The lactam CO shieldings of the first seven entries in Table II, selected as the saturated lactam models, were found not to deviate much (within ±1.2 ppm) from the CO shielding of 1-benzyl-2-piperidone (**20**).[17] The α,β double bond as in **18**, **10**, and **14** shifted the lactam CO absorption upfield by *ca.* 5 ppm, whereas the β,γ double bond as in **7** and **13** had little effect on the lactam CO shielding, paralleling what has been observed[18] for unsaturated carbonyl systems. Since an upfield shift of 4.7—5.9 ppm was evident for **5**, **8**, **9**, and **12**, the α,β-unsaturated lactam structures were assignable to them. Their side chain CO shielding data (Table II) were also consistent with the assigned structures.

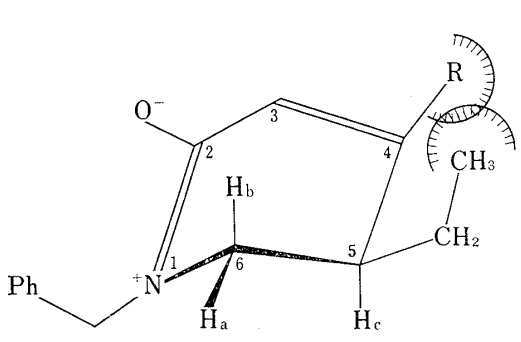
Yet another spectroscopic approach was a closer examination by means of proton magnetic resonance (PMR) spectroscopy. It may be seen from Table III that the methyl signals of the $C_{(5)}$–Et of the β,γ-disubstituted, α,β-unsaturated lactams **10** and **14** appeared upfield from those of the methyl ester of **2a**, which is a β,γ-disubstituted but saturated lactam,

Table III. Proton Magnetic Resonance Spectra of 2-Piperidones



Compound	Type[a]	Chemical shift (δ) in $CDCl_3$			Coupling constant (Hz)		
		$CCH_2\underline{Me}$[b]	H_a (eq)	H_b(ax)	J_{ab}	J_{ac}	J_{bc}
Methyl ester[6c] of **2a**	C	0.80[c]	3.24	2.92	12	5	8
13	B	0.82	3.30	2.92	12	5	7
7	B	0.93					
18[6d]	A	0.82[c]					
10	A	0.62	3.42	3.10	13	5	3
14	A	0.65	3.40	3.10	12	5	3
5	A	0.61	3.54	3.16	13	5	3
8	A	0.62	3.49	3.13	12	5	3
9	A	0.63	3.47	3.13	12	5	3
12	A	0.63[c]	3.46	3.14	12	5	3

a) The letter A stands for an α,β-unsaturated lactam; B, β,γ-unsaturated lactam; C, saturated lactam.
b) Unless otherwise stated, the signal was a three-proton triplet with $J=8$ Hz.
c) $J=7$ Hz.



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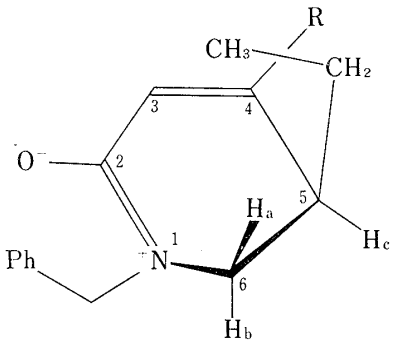

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Chart 4

17) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).
18) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, 1972, pp. 279—303.

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or of the β,γ-unsaturated lactam **13** by 0.15—0.20 ppm. However, this was not the case with **18**, which is also an α,β-unsaturated, γ-substituted lactam but unsubstituted at the β-position. The upfield shift observed for **10** and **14** may be interpreted in terms of a contribution of the conformer **23**, as shown in Chart 4. In the resonance structure **22** of the β,γ-disubstituted, α,β-unsaturated lactam, the lactam ring becomes flatter and the two side chains are brought so close together that their mutual steric repulsion should be significant. Such a repulsion would cause the molecule to rotate to the more stable conformer **23**, in which the methyl group of the axial-like ethyl group overhangs the unsaturated lactam ring and/or the phenyl ring of the N-benzyl group in such a manner that the methyl protons are shielded. In the case of **18**, however, the absence of one of the side chains should favor the existence of the conformer **22** (R=H), which would exhibit no upfield shift of the methyl proton signal. Whether the ethyl groups of **10** and **14** are really axial-like was then checked by examining the coupling pattern of the protons (H_a, H_b, H_c) at the 6- and 5-positions. This approach was based on the generalization that J_{bc} is larger than J_{ac} if the ethyl group is equatorial; and $J_{bc}=J_{ac}$, if it is axial, as illustrated in Figs. 1 and 2. From Table III it is evident that

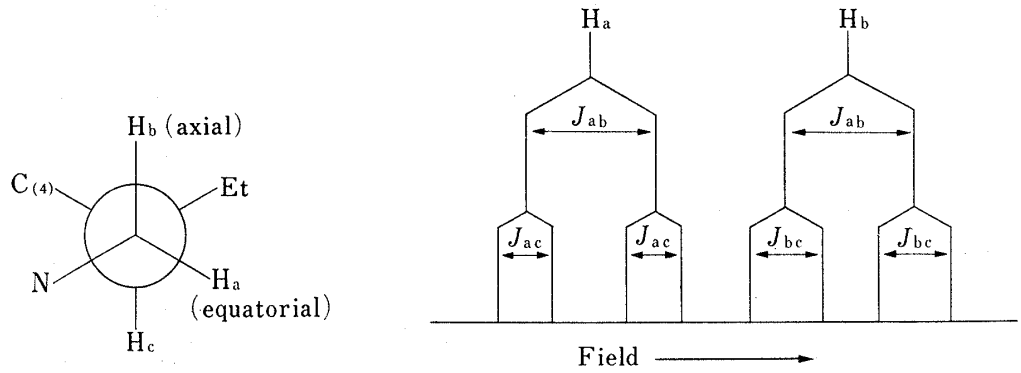

Fig. 1. Coupling Pattern for Equatorial $C_{(5)}$-Ethyl Compounds

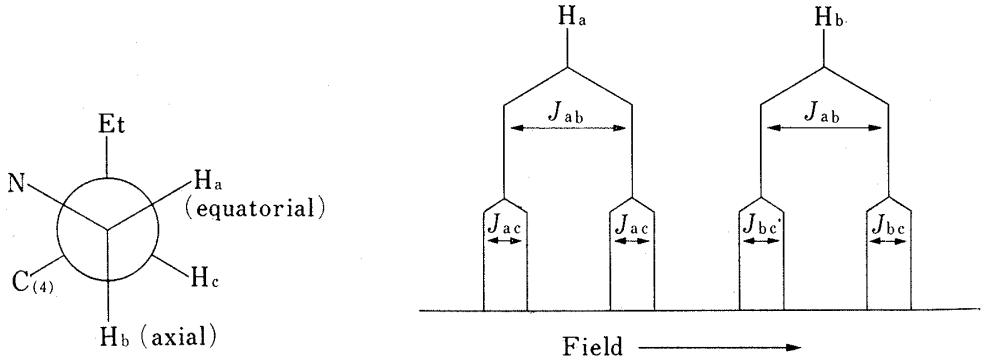

Fig. 2. Coupling Pattern for 2-Piperidones with an Axial $C_{(5)}$-Ethyl Group

H_a and H_b of the methyl ester of **2a** exhibited a coupling pattern of the Fig. 1-type, in agreement with the *trans*-4,5-diequatorial conformation acceptable for the methyl ester. On the other hand, the α,β-unsaturated lactam models **10** and **14** displayed a coupling pattern suggestive of a modified, axial-like $C_{(5)}$-ethyl structure. Since the unsaturated lactams **5**, **8**, **9**, and **12** showed similar trends, α,β-unsaturated lactam structures might be acceptable.

The results described above have thus led to the conclusion that structure **5** is a complete expression for the unsaturated lactam acid to which the structure **6** was temporarily assigned before. It is of interest to note that the catalytic hydrogenation of **5** using Pd–C and H_2 in EtOH was found to give a mixture of **2a** and **2b** with a stereoselectivity (**2a** : **2b**=84 : 16) higher than that previously obtained (**2a** : **2b**=58 : 42)[6c] with Adams catalyst. Since catalytic

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hydrogenation is expected to proceed by the *cis* addition of hydrogen from the less hindered side of a double bond with or without the complication of accompanying double bond isomerization,[19] the observed variation in stereoselectivity suggests the occurrence of the structure **6** on the catalysts, especially on the Pd catalyst, by the competing isomerization of **5** prior to hydrogenation.

Experimental

All melting points are corrected; boiling points, uncorrected. Spectra reported herein were measured with a Hitachi 323 UV spectrophotometer, a JASCO IRA-2 IR spectrophotometer, a JEOL JMS-01SG mass spectrometer, a JEOL JNM-PS-100 NMR spectrometer, or a JEOL JNM-PFT-100 NMR spectrometer, equipped with a ^{13}C FT NMR system, using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet.

1-Benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydro-4-pyridineacetic Acid (5)——This compound was prepared according to the previously reported procedure,[6a,c,d] and recrystallized from 50% aq. EtOH as colorless needles, mp 126—126.5° (with slight effervescence); it was identical (by mixed melting-point test and IR spectrum) with a previous sample to which the structure **6** had been temporarily assigned; mass spectrum (MS) *m/e*: 273 (M^+); PMR ($CDCl_3$) δ: 1.02—1.62 (2H, m, $C\underline{H}_2Me$), 2.02—2.34 (1H, m, $H_{(5)}$), 3.22 (2H, s, $C\underline{H}_2CO_2H$), 4.31 and 4.93 (1H each, AB type d's, J=15 Hz, $C\underline{H}_2Ph$), 6.00 (1H, s, C=CHCON), 7.34 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II).

Ethyl 1-Benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydro-4-pyridineacetate (8)——i) By the EtOH/H_2SO_4 Method: A solution of **5** (5.30 g, 19.4 mmol) in abs. EtOH (25 ml) containing conc. H_2SO_4 (0.75 ml) was heated at reflux for 5 hr. The mixture was concentrated to a volume of *ca.* 15 ml and H_2O was added. The aqueous mixture was adjusted to pH 9—10 with Na_2CO_3 and extracted with benzene. The benzene solutions were combined, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*, leaving an oil. Vacuum distillation of the residue gave **8** (5.24 g, 90%) as a colorless oil, bp 163—164° (0.05 mmHg); MS *m/e*: 301 (M^+); PMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 1.04—1.56 (2H, m, $CC\underline{H}_2Me$), 2.00—2.26 (1H, m, $H_{(5)}$), 3.16 (2H, s, $C\underline{H}_2CO_2Et$), 4.14 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 4.30 and 4.87 (1H each, AB type d's, J=14 Hz, $C\underline{H}_2Ph$), 5.84 (1H, s, C=CHCON), 7.28 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II). *Anal.* Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.79; H, 7.89; N, 4.82.

ii) By the EtOH/HCl Method: A solution of **5** (2.00 g, 7.32 mmol) in 10% (w/w) ethanolic HCl (50 ml) was refluxed for 6 hr. The mixture was evaporated *in vacuo* and the residue was dissolved in benzene. The benzene solution was washed successively with H_2O, sat. aq. $NaHCO_3$, and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave **8** (2.12 g, 96%) as a colorless oil, identical (by IR spectrum) with a sample prepared by method(i).

Methyl 1-Benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydro-4-pyridineacetate (9)——To a solution of **5** (9.20 g, 33.7 mmol) in MeOH (100 ml) was added an ethereal solution (*ca.* 0.5 M) of diazomethane at room temp. until the mixture became yellow. After the excess of diazomethane had been destroyed by addition of glacial acetic acid, the solution was evaporated *in vacuo*. The residual oil was dissolved in benzene and the benzene solution was washed successively with H_2O, sat. aq. $NaHCO_3$, and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*. The residue (9.66 g, 100%) was purified by vacuum distillation to produce **9** (92% yield) as a colorless oil, bp 162° (0.06 mmHg); MS *m/e*: 287 (M^+); PMR ($CDCl_3$) δ: 1.02—1.62 (2H, m, $C\underline{H}_2Me$), 1.98—2.26 (1H, m, $H_{(5)}$), 3.17 (2H, s, $C\underline{H}_2CO_2Me$), 3.68 (3H, s, CO_2Me), 4.30 and 4.82 (1H each, AB type d's, J=15 Hz, $C\underline{H}_2Ph$), 5.82 (1H, s, C=CHCON), 7.26 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II). *Anal.* Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.01; H, 7.43; N, 4.87.

Hydrolysis of the Lactam Ethyl Ester 8 to the Lactam Acid 5——A solution of **8** (1.22 g, 4.05 mmol) in EtOH (6 ml) containing 50% aq. KOH (920 mg) was kept at 20° overnight. The solvent was removed by evaporation under vacuum and H_2O (10 ml) was added to the residue. The resulting aqueous solution was made acid to Congo red paper with 10% aq. HCl. The crystals that resulted were filtered off, washed with a little H_2O, and dried to provide **5** (1.10 g, 100%) as colorless needles, mp 122—123.5° (slight effervescence), identical (by mixed melting-point test and IR spectrum) with an authentic specimen.

Hydrolysis of the Lactam Methyl Ester 9 to the Lactam Acid 5——A mixture of **9** (1.00 g, 3.48 mmol), EtOH (6 ml), and 50% aq. KOH (930 mg) was kept at 18° overnight. The reaction mixture was worked up as described above for the hydrolysis of the ethyl ester **8**, giving **5** in 96% yield.

1-Benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydro-4-pyridineethanol (10)——To a stirred, chilled (−65°) suspension of $LiAlH_4$ (132 mg, 3.48 mmol) in dry ether (20 ml) was added dropwise a solution of **9** (1.00 g, 3.48 mmol) in dry ether (20 ml) over a period of 30 min. After having been stirred at −65° for 10 hr, the reaction mixture

19) H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, Inc., Menlo Park, 1972, Chapter 1.

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was treated with 10% aq. H_2SO_4 (20 ml) and the ethereal layer was separated from the aqueous layer. The aqueous layer was salted out with NaCl and extracted with benzene. The combined ethereal and benzene solutions were washed with sat. aq. $NaHCO_3$ and dried over anhyd. Na_2SO_4. Evaporation of the solvents from the dried extracts left a yellowish oil, which was purified by column chromatography [silica gel (150 g), AcOEt–benzene (3: 1, v/v), AcOEt] to furnish the starting ester **9** (489 mg, 49%) and **10** (221 mg, 24%) as a pale yellow oil, MS *m/e*: 259 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 3400 (b, OH), other bands (Table I); PMR ($CDCl_3$) δ: 1.02—1.60 (2H, m, C<u>H</u>$_2$Me), 1.84—2.10 (1H, b, $H_{(5)}$), 2.40 (2H, t, J=6 Hz, C<u>H</u>$_2$CH$_2$OH), *ca.* 2.9 (1H, b, OH), 3.78 (2H, t, J=6 Hz, CH$_2$C<u>H</u>$_2$OH), 4.26 and 4.81 (1H each, AB type d's, J=14 Hz, C<u>H</u>$_2$Ph), 5.78 (1H, s, C=CHCON), 7.28 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II).

The α-Naphthylurethan of **10**: A mixture of **10** (128 mg, 0.49 mmol) and α-naphthylisocyanate (100 mg, 0.59 mmol) was kept at room temp. overnight. The resulting, solidified mixture was extracted with hot benzene. Concentration of the benzene extracts left a yellow glass (172 mg, 81%), which crystallized on trituration with isopropyl ether–EtOH. Recrystallization from MeCN yielded colorless needles, mp 123—124°. *Anal.* Calcd. for $C_{27}H_{28}N_2O_3$: C, 75.67; H, 6.56; N, 6.54. Found: C, 75.74; H, 6.53; N, 6.40.

Oxidation of the Lactam Alcohol 10 to the Lactam Acid 5——To a solution of **10** (100 mg, 0.386 mmol) in acetone (2 ml) was added 10 drops of the supernatant of a mixture of $K_2Cr_2O_7$ (1 g), H_2O (2 ml), and conc. H_2SO_4 (2 g). After having been kept at room temp. overnight, the reaction mixture was evaporated *in vacuo* and H_2O (10 ml) was added to the residue. The aqueous mixture was extracted with benzene and the combined benzene solutions were extracted with sat. aq. $NaHCO_3$. The alkaline aqueous solution was then adjusted to pH 1 with conc. aq. HCl and extracted with benzene. When worked up in the usual manner, the benzene extracts afforded **5** (58 mg, 55%), mp 125.5—126.5° (slight effervescence), identical (by mixed melting-point test and IR spectrum) with an authentic sample.

1-Benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydro-4-pyridineacetamide (12)——A mixture of **9** (1.00 g, 3.48 mmol) and conc. aq. NH_4OH (20 ml) was stirred at 26—29° for 24 hr. The crystals that resulted were filtered off, washed with a little H_2O, and dried to furnish **12** (729 mg, 77%), mp 142—143.5°. Recrystallization from hexane–AcOEt (1: 2, v/v) produced an analytical sample as colorless scales, mp 143.5—144.5°; MS *m/e*: 272 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 3500, 3430, 3320, 3200 ($CONH_2$), other bands (Table I); PMR ($CDCl_3$) δ: 1.04—1.64 (2H, m, C<u>H</u>$_2$Me), 2.04—2.32 (1H, m, $H_{(5)}$), 3.08 (2H, s, C<u>H</u>$_2$CONH$_2$), 4.27 and 4.81 (1H each, AB type d's, J=14 Hz, C<u>H</u>$_2$Ph), 5.81 (1H, s, C=CHCON), 5.90 and 6.35 (1H each, b, $CONH_2$), 7.22 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II). *Anal.* Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.55; H, 7.17; N, 10.55.

1-Benzyl-5-ethyl-2-oxo-1,2,3,6-tetrahydro-4-pyridineacetic Acid (7)——A mixture of the ethyl ester **8** (8.4 g, 28 mmol), 50% aq. KOH (7.7 g), and EtOH (40 ml) was heated at reflux for 3 hr. The mixture was concentrated *in vacuo* and H_2O (60 ml) was added to the residue. After having been washed with benzene, the aqueous solution was made acid to Congo red paper with 10% aq. HCl and kept in a refrigerator for 2 days. The crystals that resulted were filtered off and dried to give 6.7 g of a mixture of **5** and **7**, mp 110—113°. A portion (4.82 g) of the mixture was recrystallized from H_2O–EtOH (9: 1, v/v) to yield the first crop of colorless crystals, mp 113—118°. Immediately after removal of these crystals by filtration, the mother liquor started to precipitate colorless pillars, mp 145.5—148°. The crystals of the higher melting point were collected by filtration (311 mg) and recrystallized from H_2O–EtOH (9: 1, v/v) to furnish an analytical sample of **7** as colorless pillars, mp 153—154°; MS *m/e*: 273 (M^+); PMR ($CDCl_3$) δ: 0.93 (3H, t, J=8 Hz, CH$_2$<u>Me</u>), 2.03 (2H, q, J=8 Hz, C<u>H</u>$_2$Me), 3.08—3.24 (4H, b, C<u>H</u>$_2$CO$_2$H, $H_{(3)}$'s), 3.74 (2H, b, $H_{(6)}$'s), 4.64 (2H, s, C<u>H</u>$_2$Ph), 7.24 (5H, s, Ph), 10.40 (1H, s, CO_2H); other spectra (Tables I and II). *Anal.* Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.19; H, 7.03; N, 4.88.

The Methyl Ester of **7**: The acid **7** was esterified with diazomethane in a manner similar to that described above for the methylation of **5**, affording the methyl ester (99% yield) as an almost colorless oil, MS *m/e*: 287 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1736 (ester CO), 1639 (b, lactam CO); PMR ($CDCl_3$) δ: 0.93 (3H, t, J=8 Hz, CH$_2$<u>Me</u>), 2.03 (2H, q, J=8 Hz, C<u>H</u>$_2$Me), 3.00—3.16 (4H, C<u>H</u>$_2$CO$_2$Me, $H_{(3)}$'s), 3.68 (3H, s, CO_2Me), 3.56—3.84 (2H, m, $H_{(6)}$'s), 4.63 (2H, s, C<u>H</u>$_2$Ph), 7.29 (5H, s, Ph).

Hydrolysis of the Lactam Methyl Ester 9 to a Mixture of the Lactam Acids 5 and 7——A solution of **9** (1.00 g, 3.48 mmol) in EtOH (6 ml) containing 50% aq. KOH (900 mg) was refluxed for 3 hr. The reaction mixture was then worked up as described above for the hydrolysis of the ethyl ester **8** at room temp., giving 882 mg of a mixture (mp 109—113°) of **5** and **7**. Quantitative analysis of the mixture by means of PMR spectroscopy (see below) revealed that it was a 65: 35 mixture of **5** and **7**.

Determination of the Lactam Acids 5 and 7 in an Isomeric Mixture——Sample solutions were prepared by dissolving mixtures of **5** and **7** in $CDCl_3$ at 5% (w/v) concentration. The PMR spectra of these solutions were taken at 23° with a JEOL JNM-PS-100 NMR spectrometer, and the relative areas of the methyl proton signals due to the isomeric $C_{(5)}$–C_2H_5 groups (see Table III) were obtained. The isomer compositions of the sample solutions were then estimated from a calibration curve which had been constructed using analytical samples of **5** and **7**. This determination was found to be accurate to ±1%.

Isomerization Study of the Lactam Acids 5 and 7——The lactam acid **5** (1.00 g) was dissolved in 9% aq. KOH (50 ml). Aliquots (*ca.* 5 ml) of the solution were placed in flasks fitted with reflux condensers and heated at reflux in an oil bath. At intervals the flasks were removed and cooled, and the reaction mixtures

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were adjusted to pH 1 with 10% aq. HCl and extracted with benzene. The benzene extracts were separately dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*, leaving solid residues. The relative amounts of **5** and **7** in the residues were then determined by the PMR spectroscopic method described above. The isomeric acid **7** was treated in a similar manner, and the results are given in the text.

Decarboxylation of the Lactam Acid 5 to 1-Benzyl-5-ethyl-4-methylene-2-piperidone (13) and 1-Benzyl-2,3-dihydro-3-ethyl-4-methyl-6(1*H*)-pyridone (14)——The lactam acid **5** (1.00 g, 3.66 mmol) was heated neat in an oil bath kept at 130—140° for 40 min, evolving CO_2. After cooling, the pale yellow, oily product (850 mg) was chromatographed on a 130-g silica gel column using benzene–AcOEt (3: 1, v/v) as eluent. Earlier fractions from the column gave **13** (417 mg, 50%) as a pale yellow oil, MS *m/e*: 229 (M^+); PMR ($CDCl_3$) δ: 1.08—1.78 (2H, m, $C\underline{H}_2Me$), 2.10—2.45 (1H, m, $H_{(5)}$), 3.18 (2H, m, $H_{(3)}$'s), 4.47 and 4.65 (1H each, AB type d's, J=14 Hz, $C\underline{H}_2Ph$), 4.80 (2H, m, $C{=}CH_2$), 7.26 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II).

Later fractions afforded **14** (388 mg, 46%) as a colorless solid, mp 44—45°; bp 148° (2 mmHg); MS *m/e*: 229 (M^+); PMR ($CDCl_3$) δ: 1.06—1.62 (2H, m, $C\underline{H}_2Me$), 1.78—2.06 (1H, m, $H_{(3)}$), 1.88 (3H, d, J=1.5 Hz, $C_{(4)}$–Me), 4.33 and 4.81 (1H each, AB type d's, J=14 Hz, $C\underline{H}_2Ph$), 5.72 (1H, q, J=1.5 Hz, $H_{(5)}$), 7.26 (5H, s, Ph), other protons (Table III); other spectra (Tables I and II). *Anal.* Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.33; H, 8.60; N, 6.06.

In a separate experiment, replacement of silica gel by alumina (Merck aluminum oxide 90) in the above chromatography furnished **14** in 91% yield, suggesting the isomerization of **13** to **14** on the alumina.

Isomerization of 13 to 14——i) With Alumina: Compound **13** (100 mg) was slowly passed through a 10-g alumina (Merck aluminum oxide 90) column using hexane–AcOEt (10: 1, v/v) as eluent. Concentration of the eluate provided 74 mg (74%) of **14**, identical [by thin-layer chromatography (TLC) and IR spectrum] with an authentic specimen.

ii) With KOH: A solution of **13** (100 mg) in EtOH (5 ml) containing 10% aq. KOH (0.2 ml) was kept at room temperature overnight. The reaction mixture was concentrated *in vacuo* and H_2O (5 ml) was added. The aqueous mixture was adjusted to pH 1 with conc. aq. HCl and extracted with benzene. The benzene extracts were washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to leave **14** (96 mg, 96%) as a colorless solid, mp 42—44°, which was identified with an authentic sample by comparison of their TLC behavior and IR spectra.

Catalytic Hydrogenation of the Lactam Acid 5 to a Mixture of 2a and 2b——A solution of **5** (500 mg, 1.83 mmol) in EtOH (15 ml) was hydrogenated over 10% Pd–C (400 mg) at 20° and atmospheric pressure for 1 hr. Removal of the catalyst by filtration and concentration of the filtrate under vacuum left a colorless solid, mp 86—108°, in an almost quantitative yield. The solid was shown to be an 84: 16 mixture of the *trans*-acid (**2a**) and the *cis*-acid (**2b**) by ^{13}C NMR spectroscopic quantitative analysis as described previously.[6c]

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