Reaction of Sodium Tetramethoxyborohydride[9] and N,N′-Dicyclohexylformamidine (2a) in Methanol——113 mg (3 mmol) of $NaBH_4$ was dissolved in methanol (25 ml) and the solution was stirred for 2 hr at room temperature. To this solution[10] was added 625 mg (3 mmol) of **2a** and the reaction mixture was heated to 50 °C for 4 hr. Methanol was distilled off *in vacuo* and to the residue was added H_2O (10 ml). The aqueous layer was extracted with ether (15 ml × 3) which was dried over anhyd. Na_2SO_4. After evaporation of ether, the residue was dissolved in ethanol (2 ml), to which the ethanol solution saturated with 687 mg (3 mmol) of picric acid was added and the solution was allowed to stand overnight. The precipitate appeared was collected and dried to give N,N′-dicyclohexylformamidine picrate (mp 220—222° 110.9 mg, Y. 84.5%).

Solvent Effect for Stability of N,N′-Dicyclohexylformamidine (2a)——378 mg (1 mmol) of $NaBH_4$ was added to an alcohol solution (10 ml) (methanol, ethanol, and isopropanol) dissolving 208 mg (1 mmol) of N,N′-dicyclohexylformamidine (**2a**) and the reaction mixture was stirred for 2 hr at 50°. After evaporation of the solvent, the reaction mixture was processed as above and N,N′-dicyclohexylformamidine picrate was obtained in the yields of 32%, 39%, and 78% corresponding to methanol, ethanol, and isopropanol solvents, respectively.

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[9] H.I. Schlesinger, H.C. Brown, H.R. Hoekstra, and L.A. Rapp, *J. Am. Chem. Soc.*, **75**, 204 (1953).
[10] Evolution of hydrogen from the solution was not observed even when the reaction temperature rose to 50 °.

[Chem. Pharm. Bull. 26(7)2249—2253(1978)]

UDC 547.235.5.04 : 541.14.04

Thermal and Photochemical Behaviors of N-[(N-Nitrosobenzylamino)methyl]benzamide in Acidic Media

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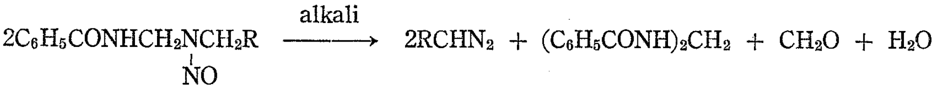
(Received January 10, 1978)

Thermal and photochemical behaviors of N-[(N-nitrosobenzylamino)methyl]benzamide in acidic media at room temperature have been demonstrated in characteristic fashions of its acid-catalyzed decompositions, *i.e.*, *in situ* formation of phenyldiazomethane, thermal denitrosation, photolytic denitrosation, and photorearrangement of nitroso group. These reactions are controlled by the acid and the solvent used.

Keywords——N-[(N-nitrosobenzylamino)methyl]benzamide; acid-catalyzed decomposition; phenyldiazomethane formation; denitrosation; photoelimination; photorearrangement

Synthetic value of N-[(N-nitrosoalkylamino)methyl]benzamides as excellent diazoalkane-generating agents has been already reported from this laboratory.[2] The base-catalyzed generation of diazoalkane is represented by the following general equation.



$$2C_6H_5CONHCH_2\underset{\substack{|\\ NO}}{N}CH_2R \xrightarrow{\text{alkali}} 2RCHN_2 + (C_6H_5CONH)_2CH_2 + CH_2O + H_2O$$

In contrast to this decomposition in alkaline media how the N-nitroso compounds behave in non-basic or acidic media drew our attention. Lately, there has been reported from this laboratory[3] an interesting information on this subject, in which N-[(N-nitrosobenzylamino)methyl]benzamide benzylated trifluoroacetic acid and, in the presence of ferric chloride,

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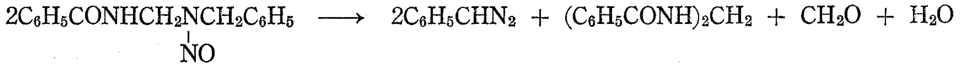
[1] Location: *2-2-1 Oshika, Shizuoka, 422, Japan.*
[2] M. Sekiya, Y. Ohashi, Y. Terao, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **24**, 369 (1976).
[3] Y. Ohashi, Y. Terao, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **26**, 653 (1978).

several other protic materials such as ethanol, acetic acid, phenol and thiols. However, the chemical behaviors in acidic media have still remained unclarified. The present paper describes further studies on thermal and photochemical behaviors of N-[(N-nitrosobenzylamino)methyl]-benzamide (I) in acidic media. Demonstrations using a number of acids, such as hydrogen chloride, acetic acid, trifluoroacetic acid, or Lewis acids, have revealed four characteristic fashions of the decompositions of I occurred at room temperature depending upon the acid and the solvent used.

The formation of phenyldiazomethane, which is recognizable as its *in situ* formation, is one of the decomposing fashions of I (see Eq. 1). As reported previously,[3] this type of the decomposition is influenced in trifluoroacetic acid giving benzyl trifluoroacetate and in the presence of ferric chloride in tetrahydrofuran bringing about benzylation of several protic materials.

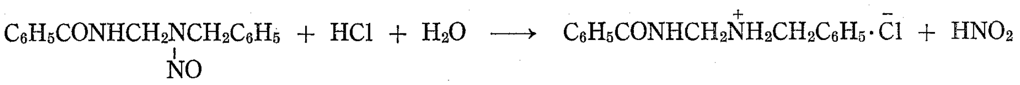


$$2C_6H_5CONHCH_2\underset{\overset{|}{NO}}{N}CH_2C_6H_5 \longrightarrow 2C_6H_5CHN_2 + (C_6H_5CONH)_2CH_2 + CH_2O + H_2O \qquad (1)$$

I

Although solubility of I in benzene is much lower than in tetrahydrofuran, boron trifluoride in benzene induced a considerable evolution of nitrogen at room temperature, but ferric chloride and aluminum chloride were inert. Boron trifluoride brought about surprisingly the formation of *p*-dibenzylbenzene together with N,N′-methylenebisbenzamide.

The second fashion of the decomposition is denitrosation of I which was indicated almost quantitatively on dissolving I in benzene containing hydrogen chloride at room temperature. Process of this denitrosation was indicated by precipitation of N-(benzylaminomethyl)benzamide hydrochloride (see Eq. 2).

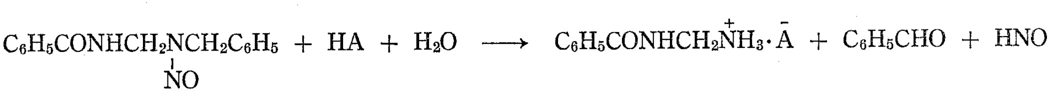


$$C_6H_5CONHCH_2\underset{\overset{|}{NO}}{N}CH_2C_6H_5 + HCl + H_2O \longrightarrow C_6H_5CONHCH_2\overset{+}{N}H_2CH_2C_6H_5\cdot\overset{-}{Cl} + HNO_2 \qquad (2)$$

I

The denitrosation of I influenced by hydrogen chloride was shown to depend on the solvent used, since in chloroform or acetone the quantitative reaction was observed as represented by Eq. 2, similarly to that in benzene, whereas hydrogen chloride was almost ineffective in water at room temperature or even in methanol at reflux.

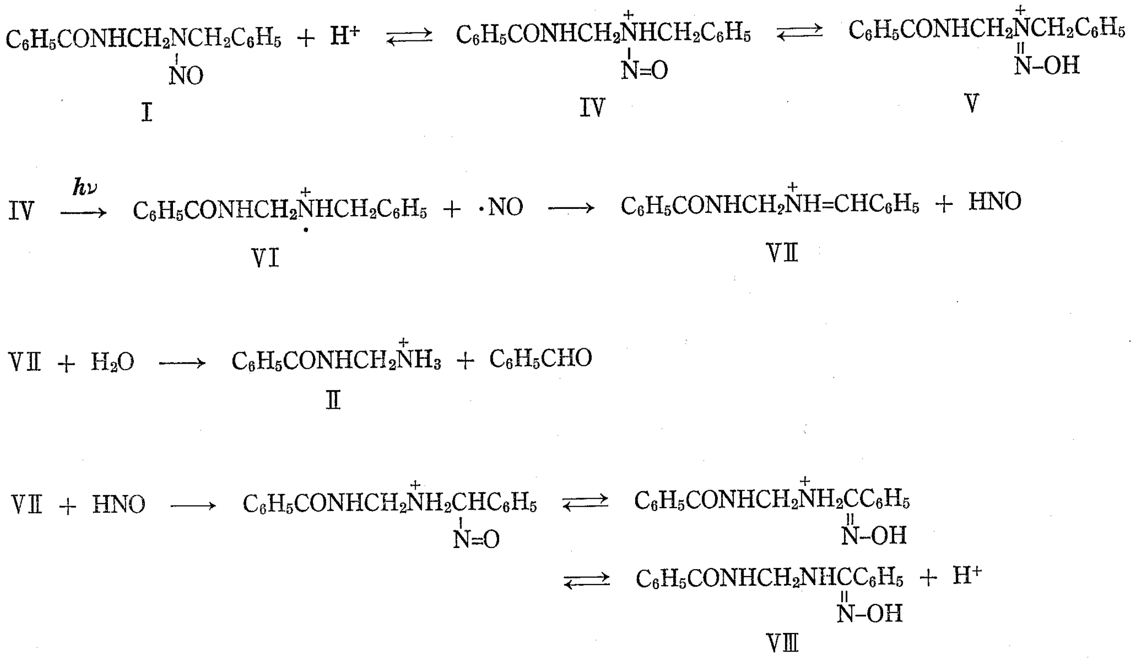
Another two fashions of the decomposition of I are noted photochemically. Photochemical function of Lewis acid such as aluminum chloride, ferric chloride and titanium tetrachloride toward I was first examined under ultraviolet (UV) irradiation at room temperature using 400 W high-pressure mercury lamp with Pyrex filter. The irradiation of I in benzene solution containing aluminum chloride underwent a gradual decomposition, giving N-(benzamidomethyl)ammonium chloride (IIa) in 78% yield together with benzaldehyde. Easy conversion of IIa into N,N-bis(benzamidomethyl)ammonium chloride (III) was noted on refluxing in ethanol. The structures of IIa and III were assigned by their microanalytical, nuclear magnetic resonance (NMR) and infrared (IR) spectral data. Ferric chloride and titanium tetrachloride were inert even under the irradiation. A photochemical decomposition similar to the case of aluminum chloride was shown in methanol containing hydrogen chloride and in benzene containing trifluoroacetic acid. In the former IIa was obtained in best yield (90%) and in the latter N-(benzamidomethyl)ammonium trifluoroacetate (IIb) in low yield (27%).



$$C_6H_5CONHCH_2\underset{\overset{|}{NO}}{N}CH_2C_6H_5 + HA + H_2O \longrightarrow C_6H_5CONHCH_2\overset{+}{N}H_3\cdot\overset{-}{A} + C_6H_5CHO + HNO \qquad (3)$$

I II

IIa: A=Cl
IIb: A=CF$_3$COO



$$\underset{\text{I}}{C_6H_5CONHCH_2\underset{NO}{\underset{|}{N}}CH_2C_6H_5} + H^+ \rightleftarrows \underset{\text{IV}}{C_6H_5CONHCH_2\underset{N=O}{\underset{|}{\overset{+}{N}}}HCH_2C_6H_5} \rightleftarrows \underset{\text{V}}{C_6H_5CONHCH_2\underset{N\text{-}OH}{\underset{\|}{\overset{+}{N}}}CH_2C_6H_5}$$

$$\text{IV} \xrightarrow{h\nu} \underset{\text{VI}}{C_6H_5CONHCH_2\underset{\bullet}{\overset{+}{N}}HCH_2C_6H_5} + \cdot NO \longrightarrow \underset{\text{VII}}{C_6H_5CONHCH_2\overset{+}{N}H{=}CHC_6H_5} + HNO$$

$$\text{VII} + H_2O \longrightarrow \underset{\text{II}}{C_6H_5CONHCH_2\overset{+}{N}H_3} + C_6H_5CHO$$

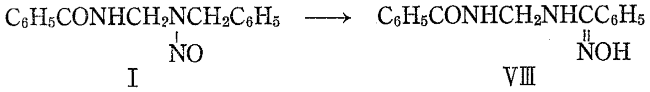
$$\text{VII} + HNO \longrightarrow C_6H_5CONHCH_2\overset{+}{N}H_2\underset{N=O}{\underset{|}{C}}HC_6H_5 \rightleftarrows C_6H_5CONHCH_2\overset{+}{N}H_2\underset{N\text{-}OH}{\underset{\|}{C}}C_6H_5$$

$$\rightleftarrows \underset{\text{VIII}}{C_6H_5CONHCH_2NH\underset{N\text{-}OH}{\underset{\|}{C}}C_6H_5} + H^+$$

Chart 1

The acid-catalyzed reaction may be represented by Eq. 3 and mechanistically may involve photoelimination of HNO followed by hydrolysis as shown in Chart 1. On referring to previous papers,[4] the photolytic denitrosation of I may proceed through radical cleavage of the N-protonated I (IV). Successively, the radical fragment ·NO abstracts a benzylic hydrogen leading to the more resonanced iminium ion (VII) and HNO. High susceptibility of VII toward solvolysis (alcoholysis or hydrolysis) may result in the formation of N-(benzamidomethyl)ammonium ion (II) and benzaldehyde.

An acetic acid solution of I was shown to undergo, when irradiated, another fashion of the photodecomposition, a photorearrangement, giving N-(benzamidomethyl)benzamidoxime (VIII) in 50% yield. Its NMR and IR spectra were well interpreted to fit the structure VIII. Also, VIII showed negative in Lieberman nitroso test, exhibited no UV absorption band over 300 nm, and easily afforded O-acetyl derivative with acetic anhydride.



$$\underset{\text{I}}{C_6H_5CONHCH_2\underset{NO}{\underset{|}{N}}CH_2C_6H_5} \longrightarrow \underset{\text{VIII}}{C_6H_5CONHCH_2NH\underset{NOH}{\underset{\|}{C}}C_6H_5}$$

Mechanistically, this photorearrangement of I may involve the iminium ion intermediate VII, shown in Chart 1, which successively accepts HNO yielding the oximino product VIII.

Experimental

All melting points are uncorrected. IR spectra were determined with a Hitachi EPI-G2 spectrometer. NMR spectra were measured with a Hitachi R-24 spectrometer (60 MHz) using tetramethylsilane as an internal standard. Mass spectra (MS) (60 eV) were recorded with a Hitachi RMS-4 spectrometer. UV irradiation was carried out in a Pyrex glass vessel at room temperature under nitrogen atmosphere, using a Riko 400 W high-pressure mercury lamp.

N-[(N-Nitrosobenzylamino)methyl]benzamide (I), mp 105°, as the substrate was prepared according to the previously reported method.[2]

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[4] T. Axenrod and G.W.A. Milne, *Tetrahedron*, **24**, 5775 (1968); Y.L. Chow, M.P. Lau, R.A. Perry, and J.N.S. Tam, *Can. J. Chem.*, **50**, 1044 (1972); Y.L. Chow, *Accounts Chem. Res.*, **6**, 354 (1973).

Thermal Decomposition of I Induced by Boron Trifluoride——To a stirred solution of 3.23 g (0.012 mol) of I dissolved in 400 ml of dry benzene 1.7 g (0.012 mol) of boron trifluoride etherate was added. Vigorous evolution of nitrogen was immediately observed at room temperature and ceased after 5.5 hr's stirring. The reaction solution was concentrated under reduced pressure, and the residue was treated with dry ether. Filtration of the ether-insoluble material gave N,N′-methylenebisbenzamide, mp 217—218°, undepressed on admixture with an authentic specimen. Yield, 0.92 g (60%). The ethereal solution was concentrated and the residual oil was chromatographed over silica-gel using benzene as an eluent. By concentration of the eluate 0.18 g (12%) of *p*-dibenzylbenzene was obtained, mp 84—87° (lit.[5] mp 84—85°). NMR (in $CDCl_3$) δ: 3.92 (4H, s, CH_2), 7.07—7.18 (14H, m, aromatic protons). MS *m/e*: 258 (M^+). *Anal.* Calcd. for $C_{20}H_{18}$: C, 92.99; H, 7.01. Found: C, 93.04; H, 7.01.

Thermal Denitrosation of I Induced by Hydrogen Chloride——Into 400 ml of dry benzene containing 0.44 g (0.012 mol) of dry HCl 3.23 g (0.012 mol) of I was dissolved. Shortly afterwards white precipitates appeared in the solution at room temperature, which was filtered and identified as N-(benzylaminomethyl)-benzamide hydrochloride, mp 169—172° (lit.[6] mp 169°), by comparison of its IR spectrum with that of an authentic specimen. Yield, 3.25 g (98%). Almost quantitative amount of N-(benzylaminomethyl)benzamide hydrochloride was deposited likewise when acetone or ethyl acetate was used as the solvent instead of benzene and also when excess amount of HCl was introduced into the solution of I.

Photochemical Decomposition of I in Acidic Media——a) In Benzene Solution Containing Aluminum Chloride: A solution of 3.23 g (0.012 mol) of I and 1.6 g (0.012 mol) of $AlCl_3$ dissolved in 400 ml of benzene was irradiated under N_2 atmosphere at room temperature for 6.5 hr. The deposited precipitates in the reaction solution were collected by filtration and extracted with water. Evaporation of the water extracts under reduced pressure left the crude crystals of N-(benzamidomethyl)ammonium chloride (IIa). Careful recrystallization from EtOH gave leaflets, mp 195° (dec.) (lit.[7] mp 189—190°). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3301 (NH), *ca.* 2870 (NH_3^+), 1659, 1546 (CONH). NMR (in DMSO-d_6): δ: 4.44 (2H, d, $J=6$ Hz, CH_2), 7.40—8.06 (5H, m, aromatic protons), 8.49 (3H, broad s, NH_3), 9.65 (1H, t, $J=6$ Hz, NH). *Anal.* Calcd. for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.67; H, 5.92; N, 14.86. Yield, 1.74 g (78%). Prolonged refluxing the solution of IIa in EtOH gave the precipitates, which were identified as N,N-bis(benzamidomethyl)ammonium chloride (III), leaflets from EtOH, mp 197—199° (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3298 (NH), *ca.* 2700 (NH_2^+), 1658, 1547 (CONH). NMR (in DMSO-d_6) δ: 3.70 (2H, s, HCl and NH), 4.62 (4H, d, $J=6$ Hz, CH_2), 7.50—8.10 (10H, m, aromatic protons), 9.86 (2H, t, $J=6$ Hz, CONH). *Anal.* Calcd. for $C_{16}H_{18}ClN_3O_2$: C, 60.09; H, 5.67; N, 13.14. Found: C, 60.36; H, 5.65; N, 13.12.

The filtrate of the reaction solution was concentrated under reduced pressure, and the residue was treated with dry ether. N-(Benzylaminomethyl)benzamide hydrochloride, mp 168—169°, weighing 0.33 g (10%), was obtained as the ether-insoluble material, and benzaldehyde was detected from the ethereal solution by gas chromatography.

b) In Methanol Solution Containing Hydrogen Chloride: A solution of 5.39 g (0.02 mol) of I dissolved in 400 ml of MeOH containing 0.73 g (0.02 mol) of HCl was irradiated for 1 hr. The reaction solution was concentrated under reduced pressure, and the residue was treated with dry ether. Benzaldehyde was gas chromatographically detected from the ethereal solution. The ether-insoluble material was extracted with water, and 3.36 g (90%) of IIa was obtained from the extracts. Water-insoluble material, weighing 0.38 g (7%), was identified as N-(benzamidomethyl)benzamidoxime described afterwards.

c) In Benzene Solution Containing Trifluoroacetic Acid: A solution of 3.23 g (0.012 mol) of I dissolved in 400 ml of benzene containing 1.37 g (0.012 mol) of trifluoroacetic acid was irradiated for 1 hr. The deposited precipitates in the reaction mixture were collected and identified as N-(benzamidomethyl)ammonium trifluoroacetate (IIb), leaflets from AcOEt, mp 103—107°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3352 (NH), *ca.* 2960 (NH_3^+), 1662, 1516 (CONH). NMR (in DMSO-d_6) δ: 4.43 (2H, d, $J=6$ Hz, CH_2), 7.42—7.92 (5H, m, aromatic protons), 8.18 (3H, broad s, NH_3), 9.45 (1H, t, $J=6$ Hz, CONH). *Anal.* Calcd. for $C_{10}H_{11}F_3N_2O_3$: C, 45.46; H, 4.20; N, 10.60. Found: C, 45.74; H, 4.27; N, 10.71. Yield, 0.84 g (27%). The filtrate of the reaction mixture was concentrated under reduced pressure, and the residue was triturated with a small amount of dry ether to give 0.25 g (18%) of N,N′-methylenebisbenzamide, mp 217°.

Photorearrangement of I in Acetic Acid——A solution of 5.39 g (0.02 mol) of I in 400 ml of AcOH was irradiated for 1 hr. The reaction solution was concentrated under reduced pressure, and the residue was treated with dry ether to give 2.67 g (50%) of ether-insoluble material which was identified as N-(benzamidomethyl)benzamidoxime (VIII), fine prisms from AcOEt, mp 173—175°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3368, 3270 (NH, OH), 1642, 1554 (CONH), 1626 (C=N). NMR (in DMSO-d_6) δ: 4.50 (2H, t, $J=6$ Hz, CH_2), 6.24 (1H, t, $J=6$ Hz, NH), 7.29—7.88 (10H, m, aromatic protons), 8.85 (1H, t, $J=6$ Hz, NH), 9.92 (1H, s, OH). MS *m/e*: 269 (M^+). *Anal.* Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.47; H, 5.65; N, 15.44. The solution of VIII in Ac_2O soon gave the precipitates, which were identified as O-acetyl-N-(benzamido-

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[5] A.B. Galun, A. Kaluszyner, and E.D. Bergmann, *J. Org. Chem.*, **27**, 2373 (1962).
[6] Y. Watase, Y. Terao, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **21**, 2775 (1973).
[7] S.J. Kanewskaja, *Chem. Ber.*, **69**, 266 (1936).

methyl)benzamidoxime, needles from EtOH, mp 148—150°. IR $\nu_{\max}^{\mathrm{KBr}}$ 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.

Acknowledgement The authors are indebted to Mr. K. Narita and other members of the Analysis Center of this college for microanalysis and mass spectral measurement.

Chem. Pharm. Bull.
26(7)2253—2257(1978)

UDC 547.466.1.04: 541.63.04

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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(Received January 10, 1978)

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

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[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.
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[4] T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731.
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[7] T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.* (Tokyo), **23**, 2094 (1975).