1-31-1990

Synthesis of strained lactams and study of their energetics and bonding

Jung-Chou Tsai
New Jersey Institute of Technology

Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research." If a, user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use" that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select "Pages from: first page # to: last page #" on the print dialog screen

ABSTRACT

Title of Thesis: Synthesis of Strained Lactams and Study of Their Energetics and Bonding

Jung-Chou Tsai, Master of Science in Chemistry, 1989

Thesis Directed by: Dr. Arthur Greenberg
Professor of Chemistry

In order to measure nitrogen and oxygen ionization energies of planar and nonplanar lactams, four compounds were synthesized successfully. The comparison of these ionization energies provides a qualitative insight into how the charge distribution of strained lactams varies with molecular geometry. Of special interest was the different ability of amides to exhibit resonance, monitored most sensitively by the core electron energy of nitrogen in the compounds. The nitrogen core (1s) ionization energies for the two nonplanar amides, 1,3-di-tert-butyl aziridinone (405.00 ev) and 1-azabicyclo[3.3.1]nonan-2-one (405.47) each having pyramidal nitrogens, indicated a nitrogen more negative than that in the comparable planar amide. This result is in accord with the classical view of amide bonding. An attempt to synthesize a bridgehead lactam 8,8,9,9-tetramethyl-1-azabicyclo[3.3.1]nonan-2-one was not successful and a postulated structure for the unanticipated product was proposed.

Synthesis of Strained Lactams and Study of Their Energetics and Bonding

by

Jung-Chou Tsai

A Thesis
Submitted to the Faculty of the Graduate Division of the
New Jersey Institute of Technology
in Partial Fulfillment of the Requirement for the
Degree of Master of Science in the Chemistry
Department of Chemical Engineering, Chemistry, and
Environmental Science
December 1989

APPROVAL PAGE

Title of Thesis: Synthesis of Strained Lactams and Study of Their Energetics and Bonding

Name of Candidate: Jung-Chou Tsai
Master of Science in Chemistry
1989

Thesis and Abstract Approved by:

Dr. Arthur Greenberg
Professor of Chemistry, NJIT
Date

Signatures of other Thesis Committee members:

Dr. Carol Venanzi
Professor of Chemistry, NJIT
Date

Dr. Guanli Wu
Visiting Professor of Chemistry, NJIT
Date

VITA

Name: Jung-Chou Tsai

Permanent address: 286 Tai Peng Road, Putai, Chiayi County
Taiwan, R.O.C.

Degree and date to be conferred: Master of Science
Chemistry, December 1989

Date of birth:

Place of birth:

Collegiate institutions attended	Degree
New Jersey Institute of Technology Newark, New Jersey	M.S. Chemistry Dec 1989
Tunghai University Taiwan, R.O.C.	B.S. Chemical Engineering June 1981

ACKNOWLEDGMENTS

This thesis is dedicated to my lovely wife, Iee-Chun, for her encouragement, understanding, and support in making this possible.

First, I would like to express my appreciation and gratitude to my advisors, Dr. Arthur Greenberg and Dr. Guanli Wu, for their guidance and assistance in the accomplishment of this study. I also thank Dr. Dekang Shen for sharing his experience of organic synthesis with me.

Thanks to Dr. T. Darrah Thomas of Oregon State University for running the ESCA; Dr. Jung-Tsang Chen of Rutgers-Newark for running the 400 MHZ NMR; Dr. Sam Sofer for allowing me to use the FTIR in his Biotechnology Laboratory at NJIT, and Ms. Jacqueline B. Kennedy for proofreading my thesis manuscript.

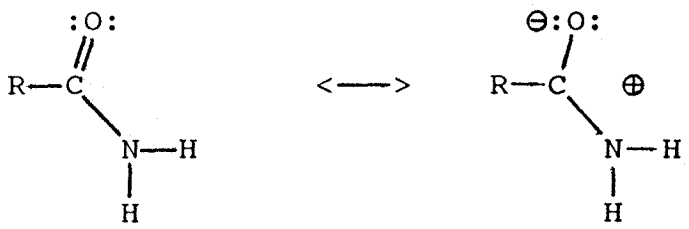
TABLE OF CONTENTS

List of Figures

CHAPTER I. Introduction

1.About Bonding and Energetics.

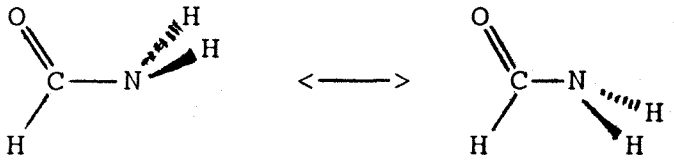
The principal resonance structures of amide, (A) and (B), were originally described by Pauling[1].



(A) (B)

The amides are very weak bases; since resonance stabilization is lost by addition of a proton to the nitrogen atom. It was expected that (A) contributes somewhat more than (B) to the structure of the group[1]. However, (B) represents nitrogen with a partial positive charge compared to the amine. The resonance stabilization in amides or lactams has been estimated at about 21 Kcal/mol.[1]

The simplest molecule having an amide group is formamide. The molecule is completely planar[1], as required for maximum resonance of the type depicted by (A) and (B). Because of contributions from the resonance structure (B) the nitrogen is expected to be positive relative to typical amines and the oxygen is expected to be negative relative to typical carbonyl oxygens. One picture of amide is very different from above coming from a discussion of rotational barriers. Wiberg and Laidig[2] used ab initio molecule orbital calculations and several basis sets to calculate a complete geometry optimization for the low-energy planar conformer of formamide(compare with (A),(B)) and for two saddle point conformers (C) and (D).



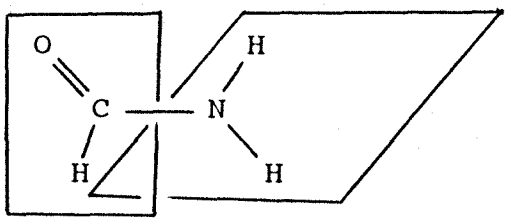
(C) (D)

These authors interpreted the nature of the interaction between an amino group and a carbonyl, in an amide, not to involve charge transfer from the nitrogen to the carbonyl oxygen, but rather results charge transfer from carbon to nitrogen. They used two results to support their viewpoint.

(1) In the classical view of amide resonance, (A) and (B), charge is transfered from nitrogen to oxygen, reducing the C=O bond order, and increasing the C-N bond order. The C-N bond length increases 0.08 Å on going from the planar conformation to the saddle conformation (C), suggesting that there is some C-N double bond character in the planar conformer. However, the C-O bond length decreases only 0.01 Å. This suggests that the carbonyl is relatively unaffected by the rotation.

(2) In examining the electron population at nitrogen, it can be seen to be larger in the planar conformer than in the saddle point species, (C). This is opposite of what would be expected on the basis of the simple resonance model. Wiberg and Laidig propose that the key factor may be the significant charge separation in the C-N bond in the planar structure due, in part, to a trigonal sp^2-hybridized nitrogen, which is more electronegative than the pyramidal sp^3 nitrogen in the saddle conformer. The sp^2-hybridized nitrogen in the planar conformer withdraws more electrons from carbon to nitrogen.

Keeping these points in mind, understanding of the 90-degree-twisted amide conformer having planar nitrogen (E) is interesting.



(E)

According to Pauling's resonance theory, one should expect the nitrogen to be more negative in the 90 degree-twisted-conformer (E) than in the planar conformer due to the absence of resonance in the structure with the amino group perpendicular to the carbonyl group For the same reason , the oxygen should be more negative in the planar conformer than in the 90-degree-twisted conformer (E). How the studies of Wiberg and Laidig apply to this conformer? Keep in mind, the conformer (E) still hold sp^2-hybridization at the nitrogen in spite of 90 degree twisting. It is general knowledge that an sp^2 center is more electronegative than an sp^3 hybridized atom. The more electronegative sp^2 nitrogen in 90-degree-twisted conformer (E) should withdraw more electron density from carbon to nitrogen. Thus, the conformer (E) should have a more negative nitrogen than the saddle conformers (C, D) and, in principle, be more stable.

Let us summarizes the order of negative charge in nitrogen.

<u>Pauling's resonance theory.</u>

<—— more negative on nitrogen

90 degree twisted structure > Saddle > Planar-point

(E) (C, D) (A, B)

Theory of Wiberg and Laidig

<—— more negative on nitrogen

90 degree twisted structure > Planar-point > Saddle

(E) (A, B) (C, D)

Which theory is right, Pauling or Wiberg and Laidig? The most direct way to decide this issue is via the charge distribution and the geometry of the molecule associated with it. Charge distribution and geometry are interconnected. Varying one means manipulating the other. Is there any tool to sense charge?

A physical method of growing importance in determining charges on atoms in molecules is X-ray photoelectron Spectroscopy (XPS), sometimes called ESCA[3] (Electron Spectroscopy for Chemical Analysis). Although the principles involved in this type of spectroscopy have been known for some time and there was some early experimental work, it has been only in the last few years that the method has been extensively applied. The method involves the ionization of the inner, core electron from an atom by X-radiation. The energy of the ionizing photons is known from their frequentcy ($E=h\nu$) and the kinetic energy of the photoionized electrons may be measured. The difference between these two quantities is the amount of energy (the binding energy) that must be provided to overcome the attraction of the nucleus

for the electron:

$$E_b = E_{h\nu} - E_k$$

It is normally assumed that the core electrons have little or no effect on the bonding properties of an atom and are, therefore, of no chemical interest. Although they may have no important effect on the bonding, the converse is not true. It appears that the chemical environment of an atom is reflected rather accurately by the binding energy[3]. For example, a more negative nitrogen in an amide group should increase the shield effect on the nucleus and therefore reduce binding energy. Thus, binding energy shifts and charge distribution and atomic charge analysis are employed. It is impossible to make a quantitative assignment of charge to each atom in a molecule. However, a first order approximation will relate the binding energy shifts to atomic charge shifts.

Professor T. Darrah Thomas, performing X-ray photoelectron spectroscopy research at Oregon State University, collaborated with our group on such a study. The following four compounds were synthesized in order to explore aspects of bonding in strained lactams.

(1) 6,6,7,7-tetramethyl-2-quinuclidone

(2) 1,3-di-tert-butyl-aziridinone

(3) 1-tert-butyl-2-pyrrolidone

(4) Di-tert-butyl-cyclopropanone

This group of molecules were (or are to be) submitted to Oregon State University for ESCA studies. In addition, a number of commercially-available lactams were purchased and sent for ESCA study. An attempt to synthesize 8,8,9,9-tetramethyl-1-azabicyclo[3.3.1]nonan-2-one was not successful and we will describe the nature of the compound formed in that attempt.

Another very interesting aspect of nonplanar strained lactams is energetics. Although the lactam linkage is of considerable structural importance in monomers, proteins, enzymes and β-lactam antibiotics, little is known about the energetics of distortion in this series. The resonance stabilization in amides and lactams has been estimated at about 21 kcal/mol. That will be somewhat less than 21 kcal/mol for nonplanar strained lactams. One would expect that the resonance energy of the highly strained , 1,3-di-tert-butyl aziridinone, should be significantly less than 21 kcal/mol.

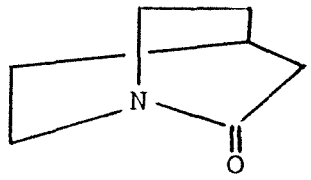
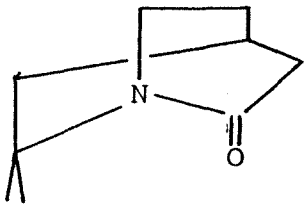
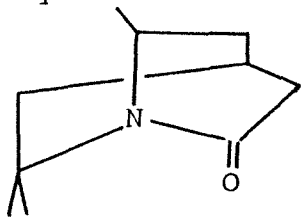
2. About Synthesis of Bridgehead Bicycle Lactams

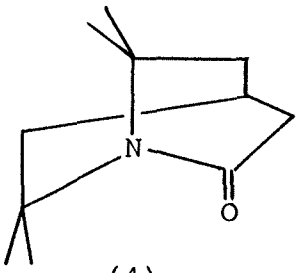
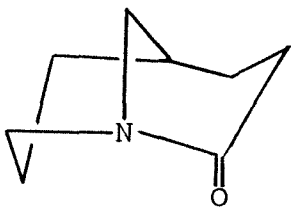
The bicyclic(l,m,n) bridgehead lactams where $l \neq 0, m \neq 0, n \neq 0$

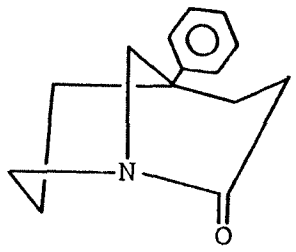
have attracted interest recently[4]. These twisted bridgehead lactams may help the understanding of the structure and the function of peptides, proteins, and enzymes and those antibiotic containing a zero bridge(m=0).

Historically it had been assumed that the twist bicyclic lactams containing bridgehead nitrogen should be very difficult if not impossible to synthesize. Bredts' rule[5] expresses the idea that carbon-carbon double bonds at the bridgeheads of certain bicyclic system would be incapable of existence, especially for small rings. Lukes[6] pointed out in 1938 that similar restrictions should apply to N-bridgehead compounds possessing adjacent carbonyl groups because resonance stabilization of the N-C=O moiety would create a bridgehead double bond. Although it was supposed that bicyclic lactams containing bridgehead nitrogen should very difficult to synthesize. This did not deter synthetic chemists from attempting to synthesize these compounds.

In the following Table, the methods of synthesis of some of these compound are summarized below:

Compound	Method	Reference
1-azabicyclo-[2.2.2] octan-2-one  (1)	Ammonia salt acid chloride	Yakhontov[7] and Rubsitov, 1957
2,2-dimethyl 2-quinuclidone  (2)	Ammonia salt acid chloride	Pracejus[8a], 1959
2,2,6-trimethyl 2-quinuclidone  (3)	Ammonia salt acid chloride	Pracejus[8b], 1965

6,6,7,7-tetramethyl 2-quinuclidone  (4)	Ammonia salt acid chloride	Levkoeva[9] Nikitskaya Yakhontov 1971
1-azabicyclo[3.3.1] nonan-2-one	Amino acid	Hall[10a,b] Shaw and Deutschmann 1980
	Di-n-butyltin oxide	Kosta Steliou[11] Marc-Andre and Poupart 1983
(5)	DCC method	Greenberg[12] 1988

5-phenyl-1-azabicyclo[3.3.1] nonan-2-one  (6)	Ammonia salt acid chloride	Buchanan[13a,b,c]

In 1957, L.N. Yakhontov and M.V. Rubsitov[7] reported the synthesis of 1-azabicyclo-[2.2.2]-octane-2-one (1). This is now only accepted with reservations, since characterization of the claimed lactam was incomplete. A significant step forward was the synthesis of 2,2-dimethyl (2) and 2,2,6-trimethyl-2-quinuclidones (3) by Pracejus(1959) from reaction of the corresponding acid chloride amine hydrochloride salt with triethylamine in ether. The parent compound (1) was characterized by infrared spectroscopy but could not be isolated in a pure state. However, the compounds, (2) and (3), were isolated, and showed abnormally high infrared carbonyl frequencies. The compound (4), 2,2,6,6-tetramethyl-2-quinuclidone, was synthesized sucessfully by Levkoeva in 1971[9a] and by our group.

The synthesis of 1-azabicyclo[3.3.1]nonan-2-one (5) was not published until 1980.[10b] While attempts at synthesis from the

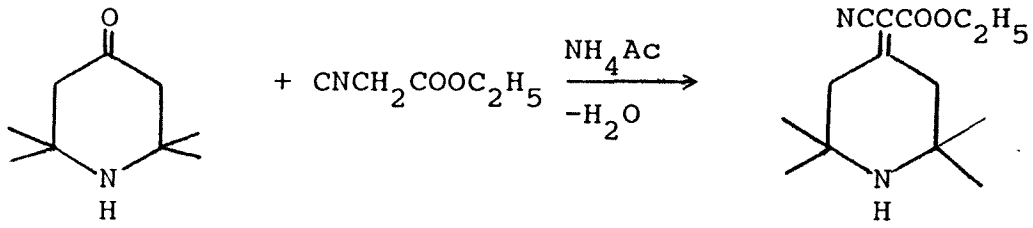
precursor amino acid through the acyl chloride-triethylamine route, sucessful for 2-quinuclidones, did not yield (5). The synthesis of this compound was accomplished by heating the amino acid between 180 ^{o} and 285 ^{o}C at 0.05 torr and catching the lactam in a cold receiving flask. The yield was about 7%. The conditions are fairly exact, since the lactam polymerizes readily.[10a] Subsequently, it was reported that di-n-butyltin oxide mediated ring closure the amino acid afforded 77% yield.[11] Our group found that synthesis of (4) from the amino acid via the mixed anhydride route (DCC method) provides a comparably high yield of this compound.[12] In contrast to the parent, Buchanan reported synthesis of 5-phenyl-1-azabicyclo[3.3.1]nonan-2-one (6) from amino acid via the acid chloride-trimethylamine route (10% overall yield).[13a,b] An attempt to prepare 8,8,9,9-tetramethyl-1-azabicyclo[3.3.1]nonan-2-one in our group, led to unanticipated compound, 8,8-dimethyl-1-azacyclooctane-2,6-dione because of cleavage elimination reaction in the case of Clemmensen reduction.

CHAPTER II. Experimental

All infrared spectra were recorded on a Perkin-Elimer 1310 spectrometer or a 1600 series FTIR. NMR spectra were taken on a Varian EM-360L spectrometer and Varian VXR400 at Rutgers University (Newark). Evaporations under vacuum were carried out with Buchi Rotoevaporator R110 apparatus. Melting points were recorded on a Thomas Hoover Capillary Melting point Apparatus and are uncorrected. Mass spectra were obtained from the center for Advanced Food Technology, cook collage, Rutgers University, New Brunswick, NJ.. Elemental analysis were determined by Dessert Analytics, Tucson, Arizona. E Merck TLC sheets (silica gel 60 F_{254} thickness 0.2 mm were used for detertion and silica gel (70-230 mesh) were used for column chromatography.

1. 2,2,6,6-Tetramethyl-2-quinuclidone

2,2,6,6- Tetramethyl-4-(carboxycyanomethylene) piperidine



(II) (III)

Scheme 1-1

A mixture of 2,2,6,6-tetramethyl-4-piperidone (II) (32.8 g; 210 mmole), ethyl cyanoacetate (23.7 g;210 mmole) and ammonium acetate (6.6 g; 85 mmole) was refluxed in 131 ml benzene for 1 hr with azeotropic removal of water (4 ml). The reaction mixture was cooled, treated with excess 50 % potassium carbonate, and extracted with benzene. After removal of solvent, 51.2 g(yield 97.5 %) syrup of technical grade (III) was obtained. It is readily soluble in the usual organic solvents. Infrared: 2200 cm^{-1} for CN, 3400 cm^{-1} for NH, 1740 cm^{-1} for CO, 1580-1600 cm^{-1} for C=C.(Fig. II-1)

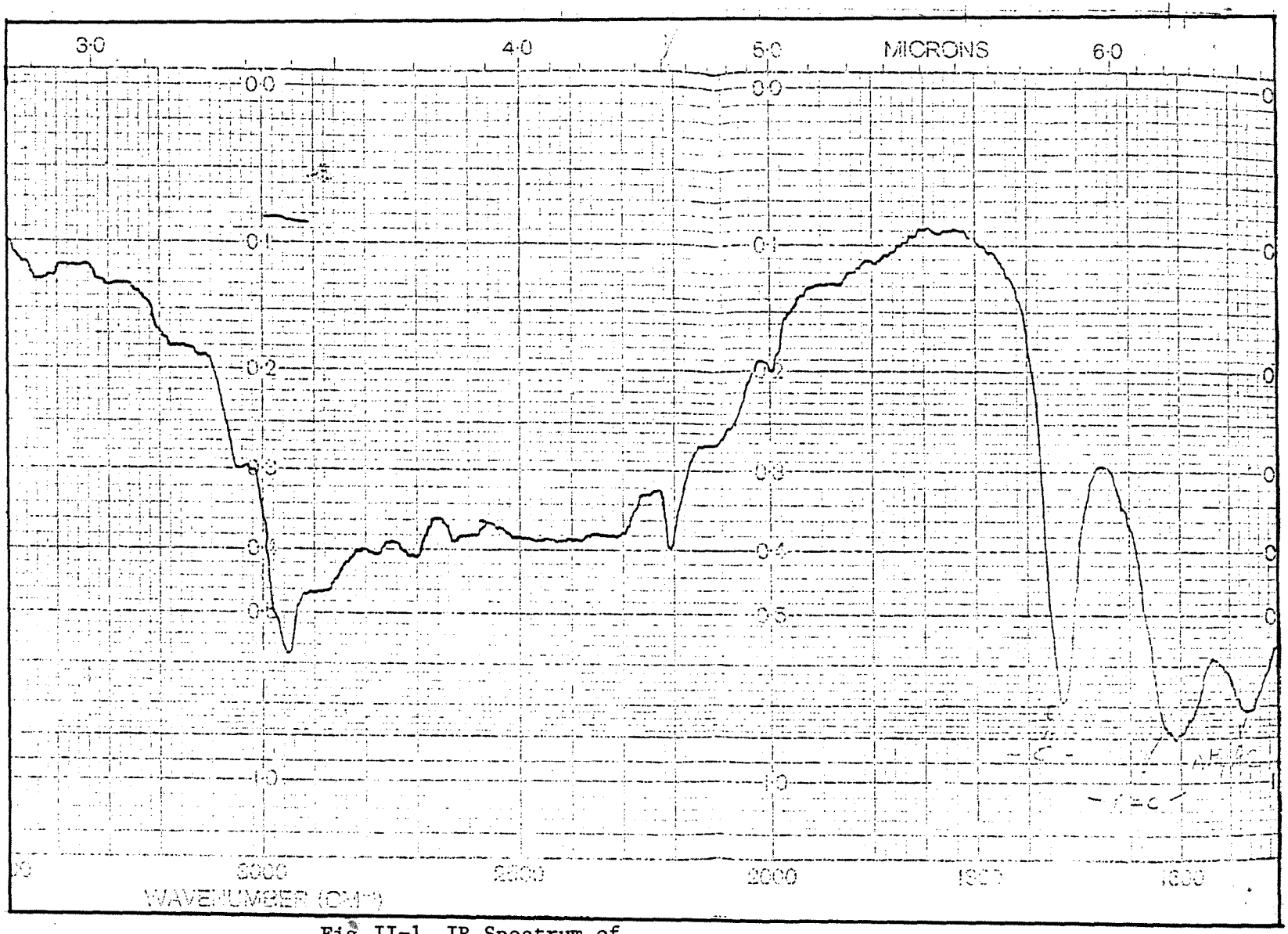
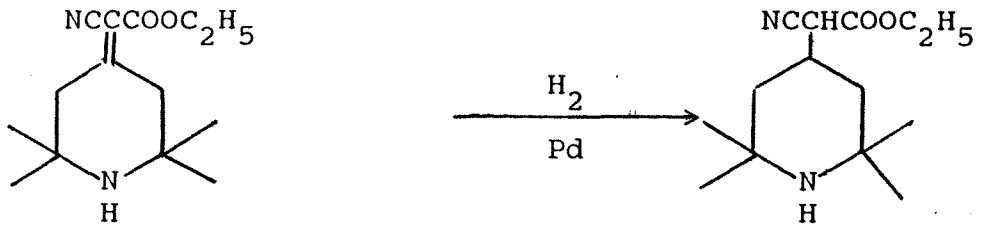


Fig. II-1 IR Spectrum of
2,2,6,6-tetramethyl-4-(Carboxycyanomethylene)
piperidine

2,2,6,6-Tetramethyl-4-(carboethoxycyanomethyl) piperidine



(III)

Scheme 1-2

Palladium(10%) on activated charcoal (total weight 0.5 g) was added to 4.5 g of Technical(III) in 60 ml of ethyl alcohol (anhydrous) and hydrogenated in a hydrogenation apparatus at room temperature (25 °C) and 24 psi. After the pressure of hydrogen was kept constant (about 15 hrs), the solution was filtered and ethyl alcohol was evaporated, 4.7 g(yield 100%) of Technical (IV) was obtained as a viscous yellow mass which crystallized on standing. Infrared: 2200 cm^{-1} for CN, 1740 cm^{-1} for CO, 1660 cm^{-1} for CONH, 1580 - 1600 cm^{-1} for C=C disappeared.(Fig. II-2)

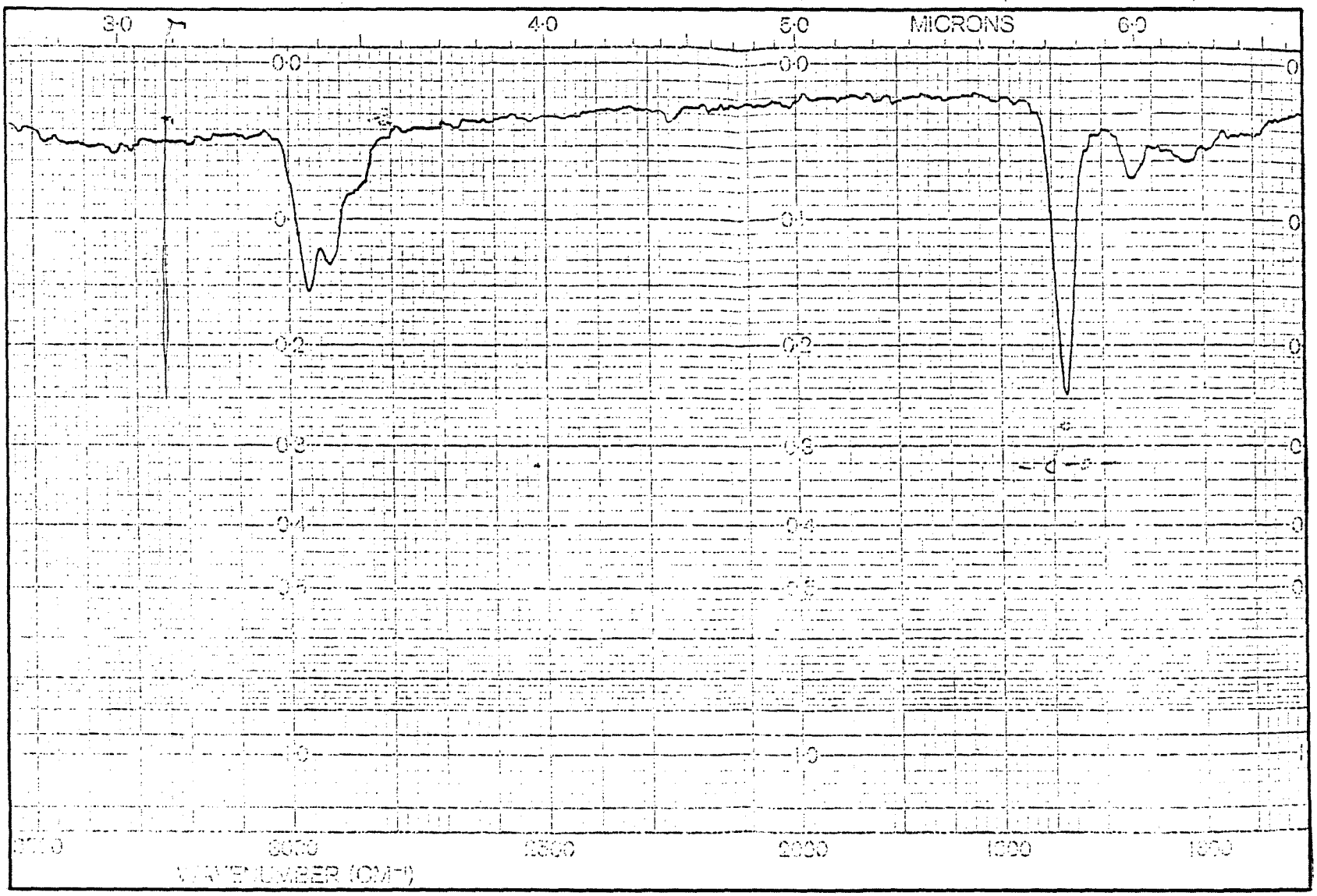
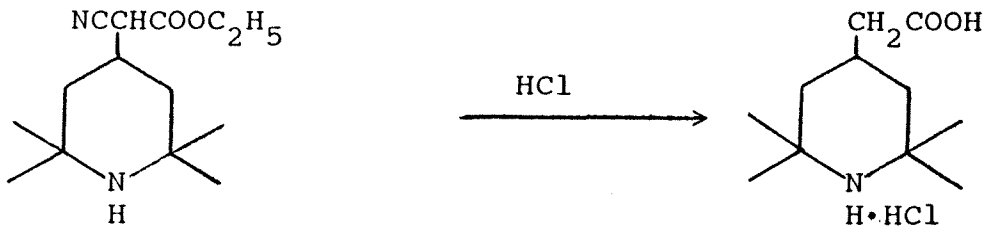


Fig.II-2 IR Spectrum of
2,2,6,6-tetramethyl-4-(Carboethoxycyanomethyl)
piperidine

2,2,6,6-Tetramethylpiperidyl-4-acetic acid

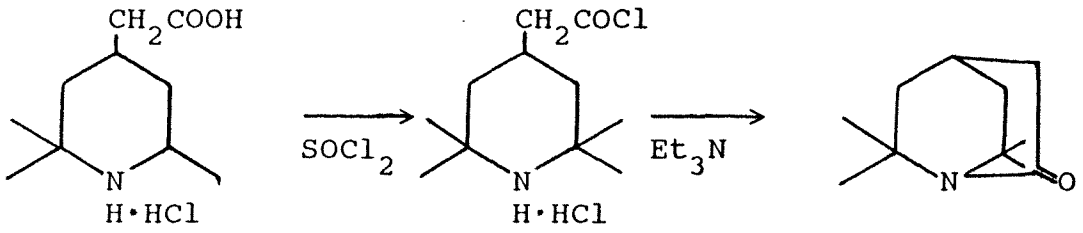


(IV) (V)

Scheme 1-3

Technical(IV) (17.0 g) was refluxed for 15 hrs with 127 ml of conc. hydrochloric acid. The reaction mixture was evaporated, the residual water was removed by azotropic distillation with benzene. A white solid (14.3 g, yield 93%) was formed. Infrared: 1719 cm^{-1} for COOH.(Fig. II-3)

6,6,7,7-Tetramethyl-2-quinuclidone



(V) (VI) (VII)

Scheme 1-4

Boiling thionyl chloride (15 ml) was added to 1.5 g (64 mmole) of the hydrochloride of (2,2,6,6,- tetramethyl-4-piperidyl) acetic acid heated to 60 °C, and the mixture was refluxed for 3 hrs. The reaction mass was evaporated under

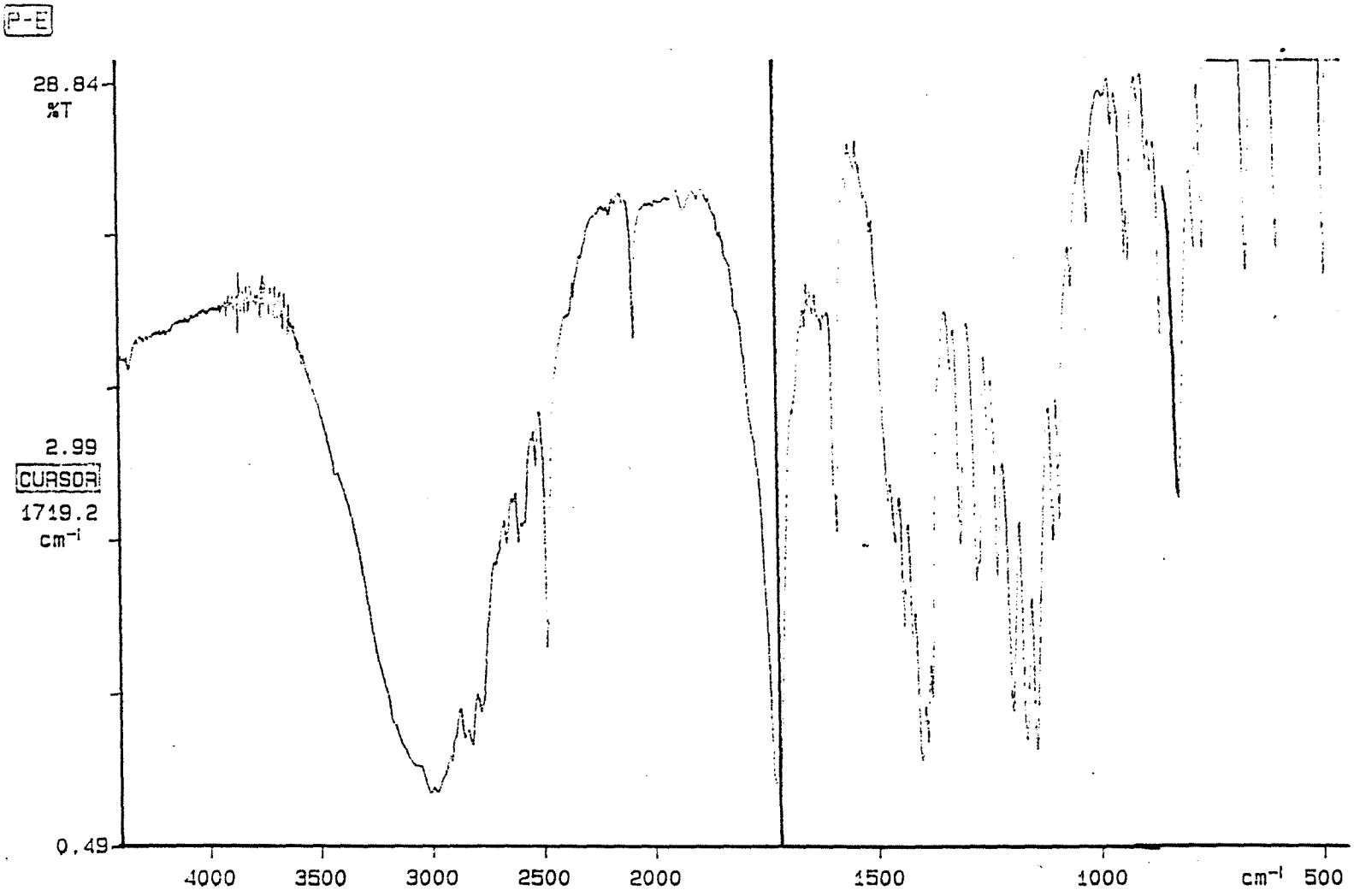


Fig.II-3 IR Spectrum of
2,2,6,6-tetramethylpiperidyl-4-acetic acid

vacuum. 3 ml of triethylamine and 30 ml ethyl ether was placed in the reaction vessel . The acetic chloride in 90 ml ether was added to the reaction vessel dropwise over 1.5 hrs with strong stirring and the mixture then refluxed for 6 hrs.. The precipitate was filtered. Ethyl ether was evaporated and the residue was sublimated in vacuum(5 mm), 0.3 g of (VII) (yield 26%) was provided. Infrared: 1749 cm^{-1} for CON (Fig. II-4) NMR:S, 1.09 ppm(6H);S, 1.44 ppm(6H) (Fig. II-5) Masss:m/e 84 base peak; m/e 181 (M)(16%); m/e 99 (42%); m/e 98 (27%) m/e 71 (32%); m/e 58 (79%). (Fig. II-6)

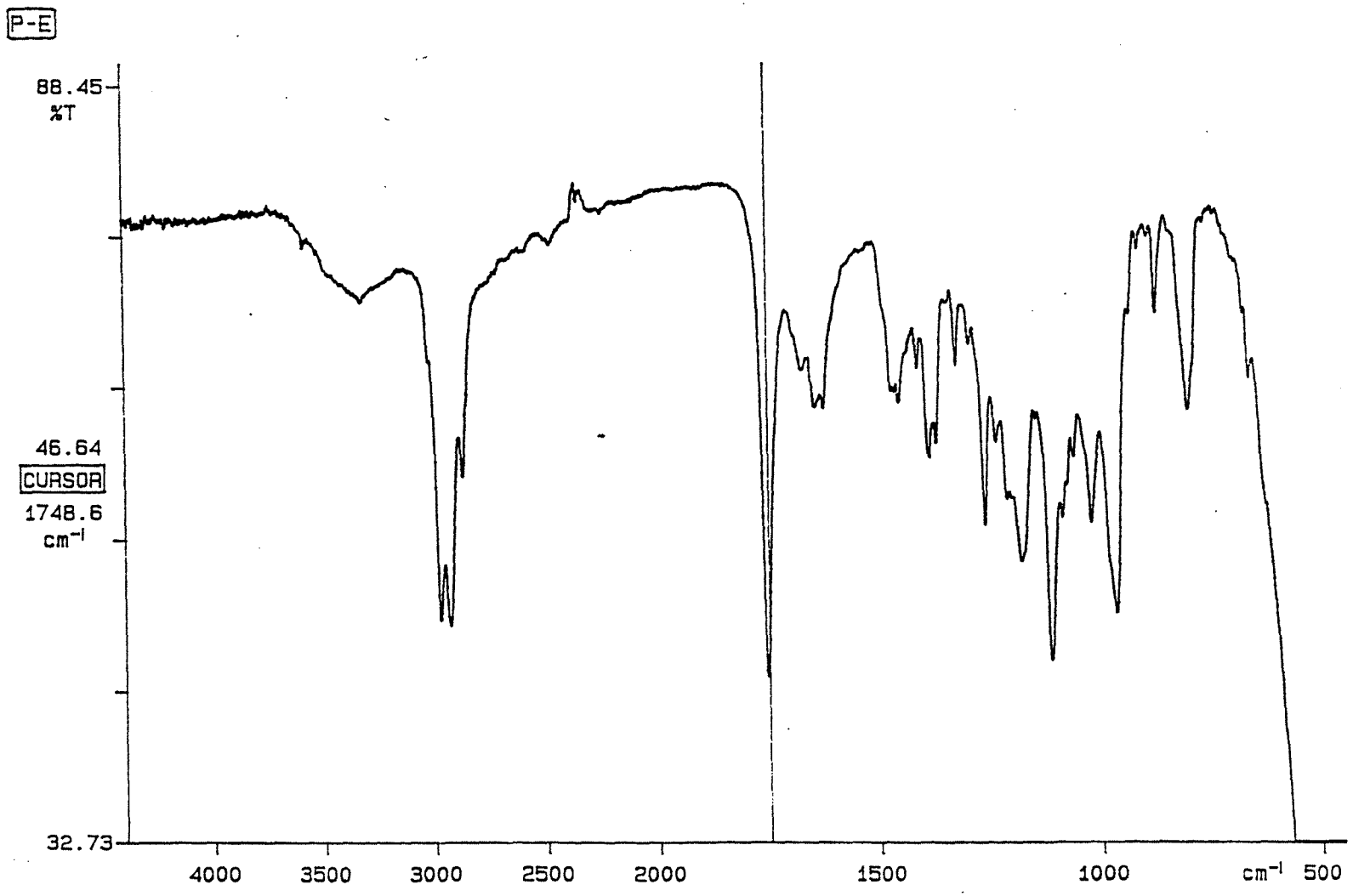


Fig.II-4 IR Spectrum of
2,2,6,6-tetramethyl-2-quinuclidone

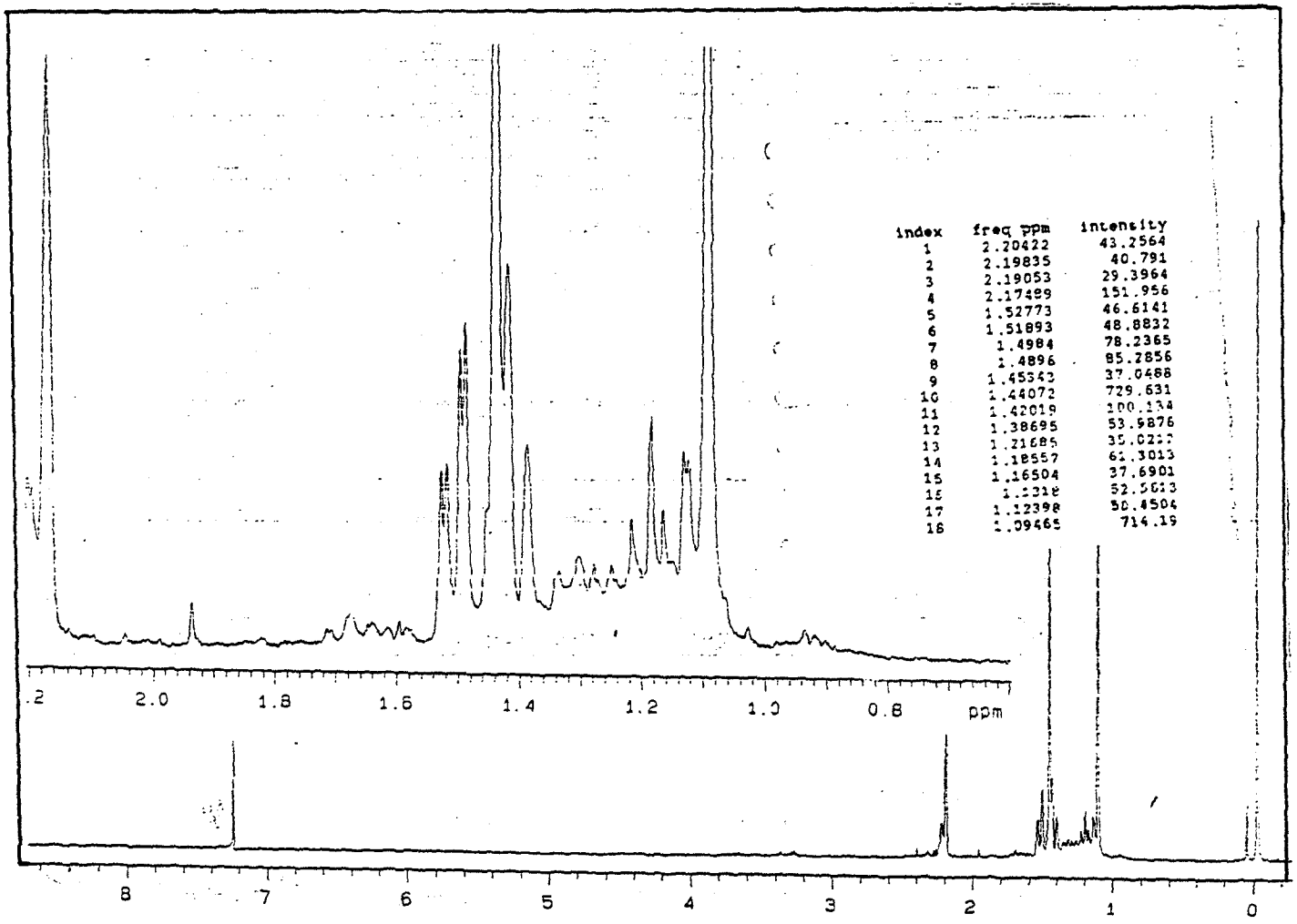


Fig.II-5 NMR Spectrum of
2,2,6,6-tetramethyl-2-quinuclidone

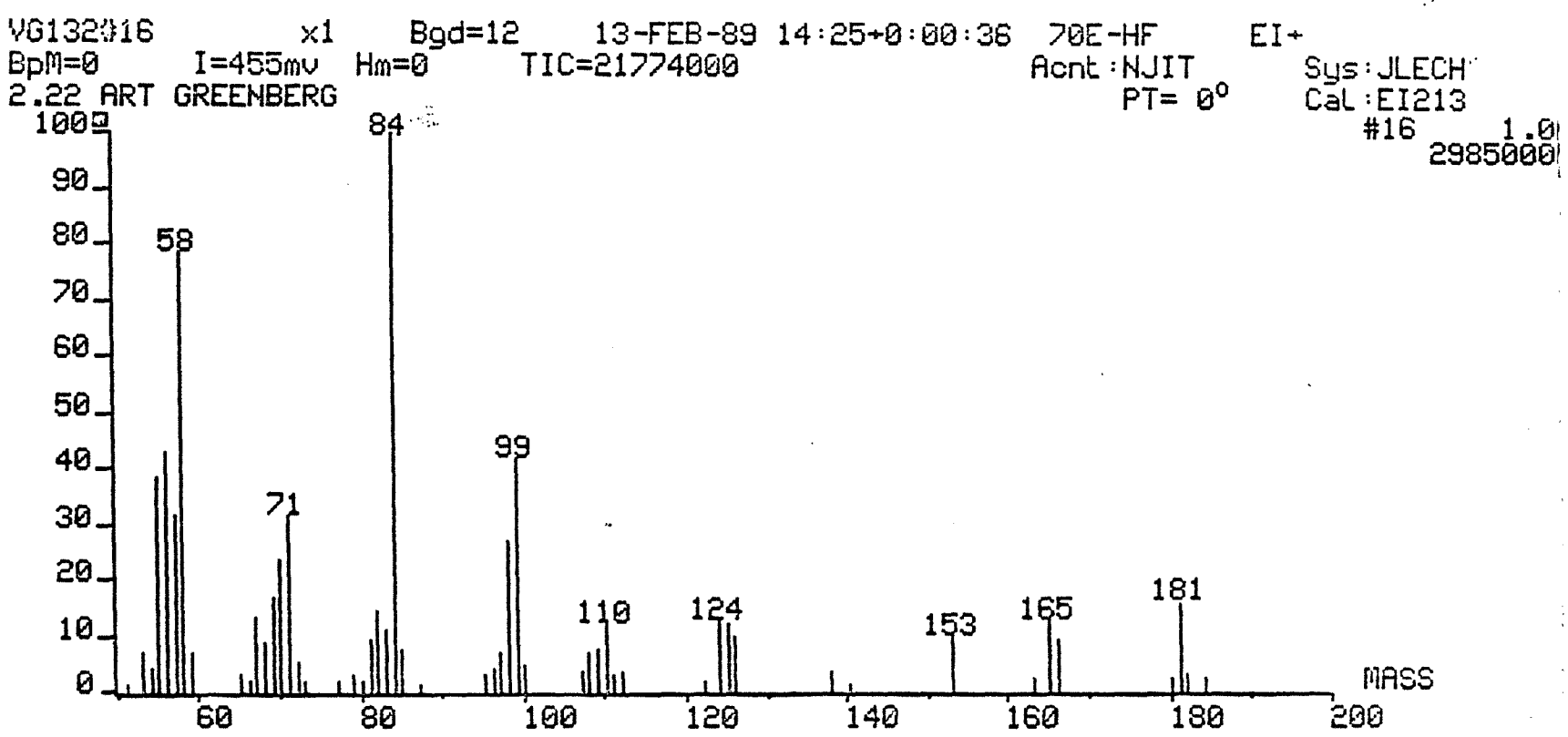
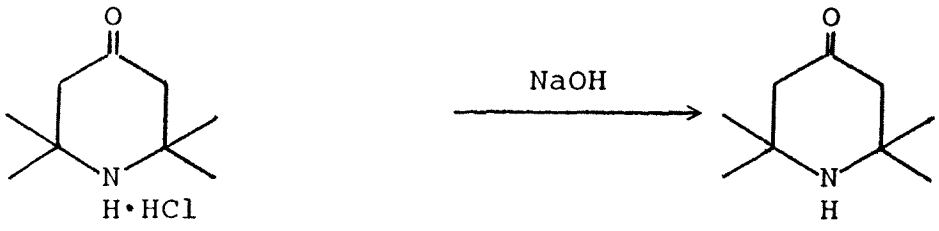


Fig.II-6 Mass Spectrum of
2,2,6,6-tetramethyl-2-quinuclidone

2. 8,8-Dimethyl-1-azacyclooctane-2,6-dione(tentative assignment)

<u>The neutralization of 2,2,6,6-tetramethyl-4-piperidone Hydrochloride</u>



(I) (II)

Scheme 2-1

Take 50 g (0.26 mole) of (I) dissolved in 60 ml distilled water (pH=2.5). Treat with cold 30% NaOH solution. The resulting sludge (pH=9) was extracted with total 300 ml benzene. After separation, benzene was evaporated. The white solid 2,2,6,6-tetramethyl-4-piperidone 32.8 g (yield 81%) was provided. Infrared:1700 cm^{-1} for CO (Fig. II-7) M.P.: 37 ^{o}C

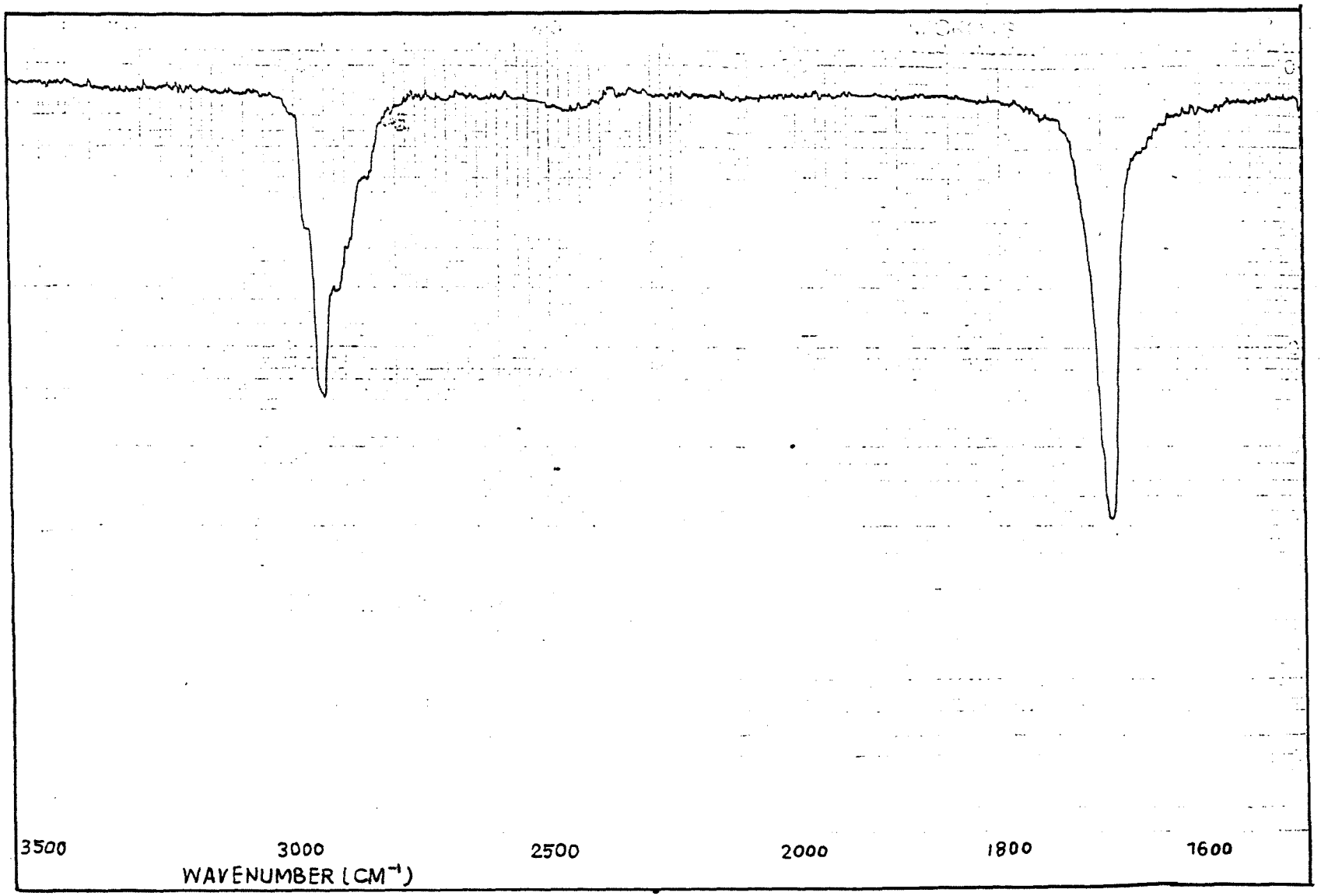
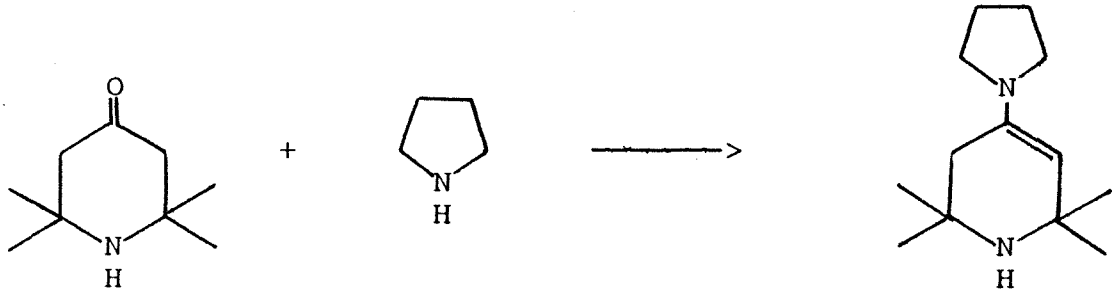


Fig.II-7 IR Spectrum of
2,2,6,6-tetramethyl-piperidone

2,2,6,6-Tetramethyl-4(N,N-tetramethyleneimine)-piperidine-3-ene

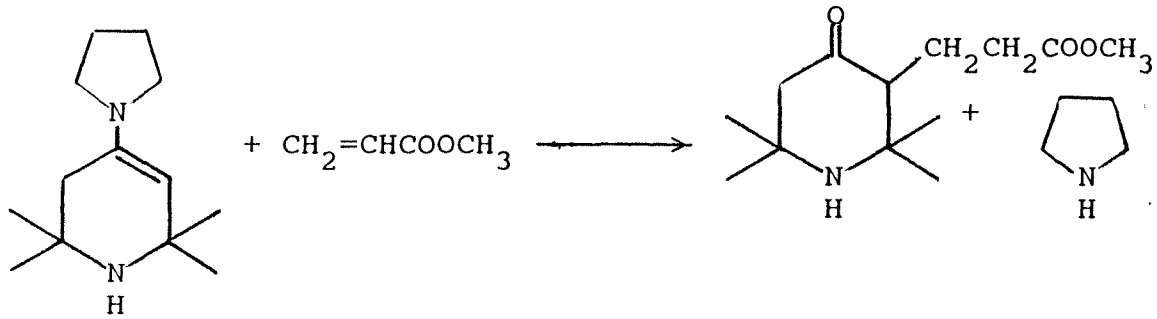


(II) (III)

Scheme 2-2

34 g (250 mmole) of 2,2,6,6-tetramethyl-4-piperidone and 22 g (300 mmole) pyrrolidine were added to 50 ml benzene. A Dean-Stark trap was used during reflux (7 hrs) until no further generation of water occurred. Benzene and excess pyrrolidine were removed under reduced pressure. The crude enamine was distilled under vacuum to yield a yellow liquid. (36.2 g, yield 74%, bp 105-110 °C/2 mm) Infrared :1640 cm^{-1} for -C=C-, 1700 cm^{-1}, trace.(Fig. II-8)

2,2,6,6-Tetramethyl-3(2'-methoxycarbonyl)-4-piperidone



Scheme 2-3

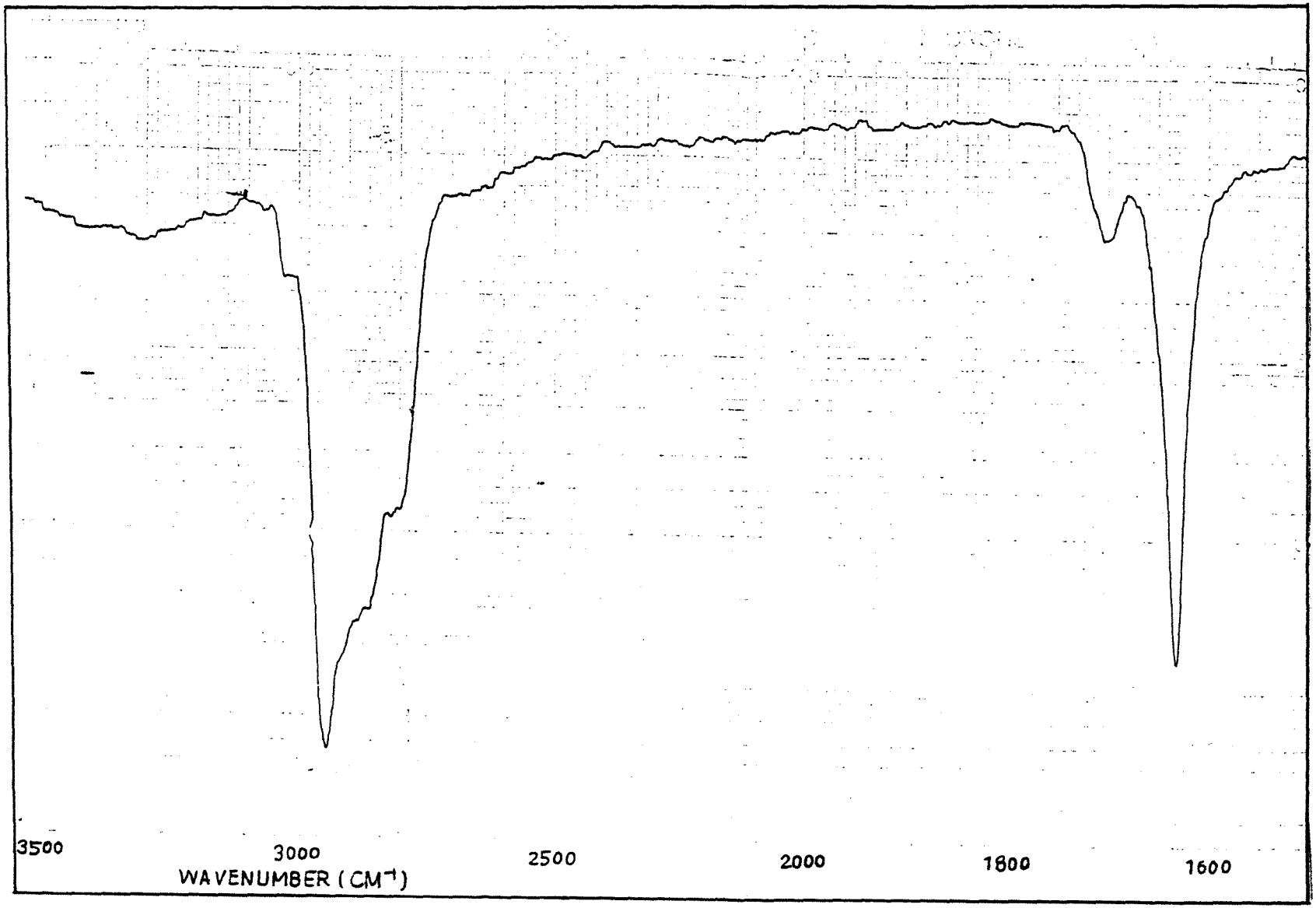
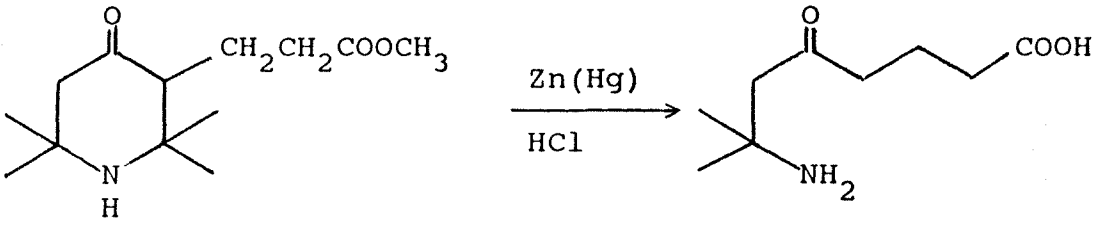


Fig.II-8 IR Spectrum of
2,2,6,6-tetramethyl-4-(N,N-tetramethyl)
piperidine-3-ene

A solution of 21.7 g (111 mmole) of the enamine(III) in 50 ml absolute ethanol was combined with 23.5 g (268 mmole) of methyl acrylate (Fluka), refluxed for 6 hrs and an additional hour following addition of 16 ml water. Solvent was removed by rotavaporation and the crude product was distilled under vacuum to obtain yellow liquid. (15.8 g, yield 60%, bp 114-121 °C/5 mm) Infrared :3325 cm^{-1} for NH, 1735 cm^{-1} for $-COOCH_3$,Note: the 1700 cm^{-1} for -CO-, and 1640 cm^{-1} for C=C bands dissappeared. (Fig. II-9)

Cleavage elimination reaction in the case of Clemmensen Reduction



(III) (IV)

Scheme 2-4

Amalgamated Zinc was prepared by stirring for 10 min a mixture of 75 g mossy Zinc, 5 g $HgCl_2$, 5 ml conc. hydrochloric acid and 100 ml water, then decanting. To Zn(Hg) was added 50 ml water, 75 ml conc. HCl and then, adding dropwise 15.2 g of (III). Following 7 hrs reflux, 25 ml conc. HCl was added and the reflux continued for another

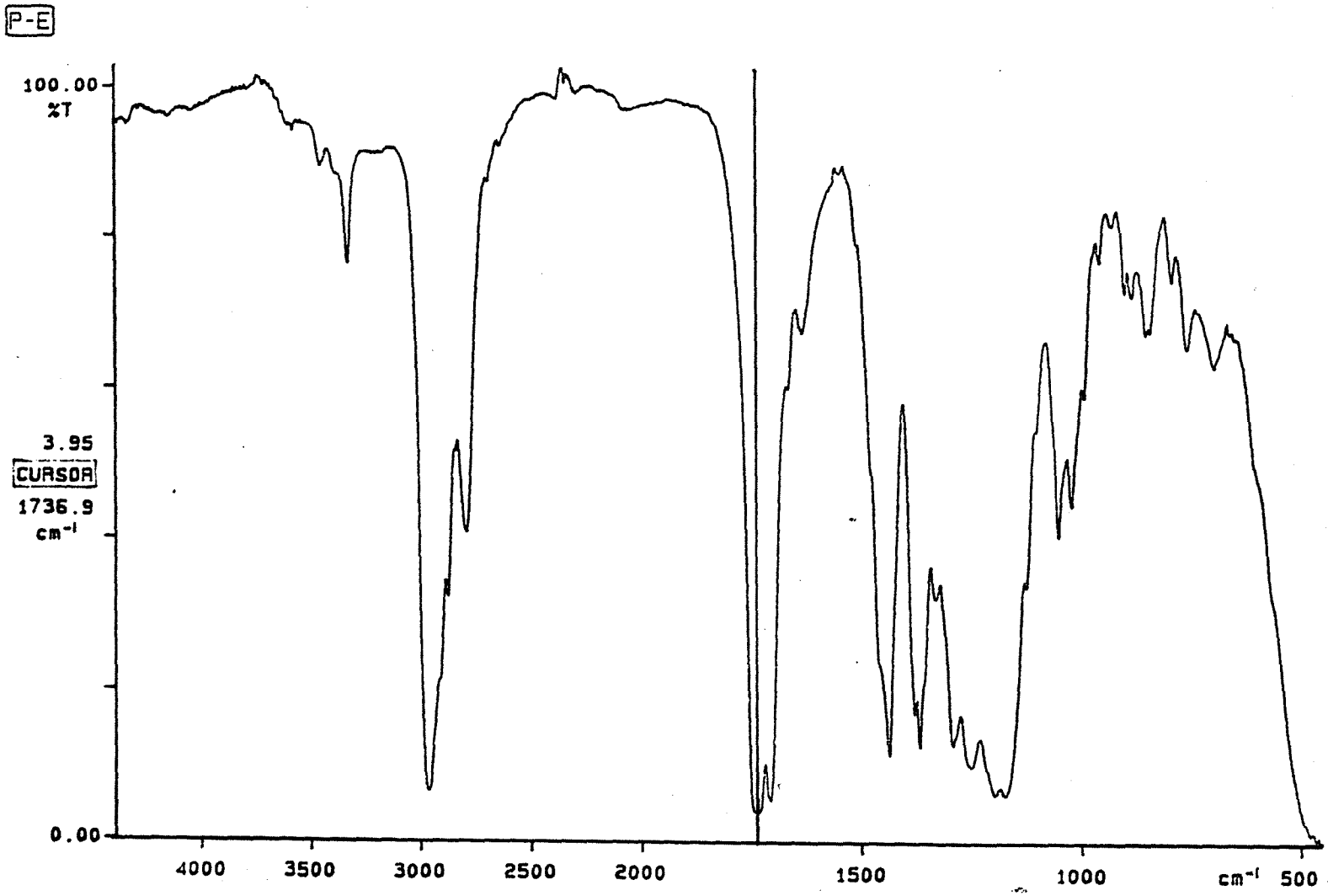
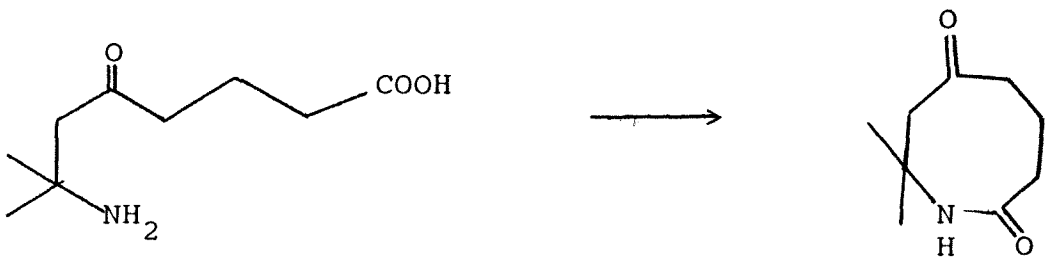


Fig.II-9 IR Spectrum of
2,2,6,6-tetramethyl-3-(2'-methoxycarbonyl)
4-piperidone

7 hrs during which time the yellow color of the reaction mixture disappeared. The zinc, was filtered off and ca 130 ml water and HCl were removed under vacuum. Then 130 ml water was added and the pH adjusted to ca 7.0-7.4 with 20% NaOH. The $Zn(OH)_2$ obtained was filtered and washed with water which was added to the filtrate. All of the water (ca 350 ml) was removed in vacuum and the residue extracted with 100 ml absolute ethanol under reflux; NaCl was filtered off and the ethanol removed in vacuum. 7.7 g of the crude, brown syrupy amino acid was obtained. The filtered NaCl was extracted with an additional 50 ml absolute ethanol to yield an additional 0.2 g of crude product (total yield 59%). Only a trace of ketone (IR 1700 cm^{-1}) removed while the IR band at 1570 cm^{-1} indicated the formation of amino acid (IV).(Fig. II-10)

8,8-Dimethyl-1-azacyclooctane-2,6-dione



Scheme 2-5

1200 mg (5.83 mmol) N,N-dicyclohexylcarbodiimide(DCC) in 75 ml acetonitrile was added to 1200 mg (5.63 mmol) of 5-keto-

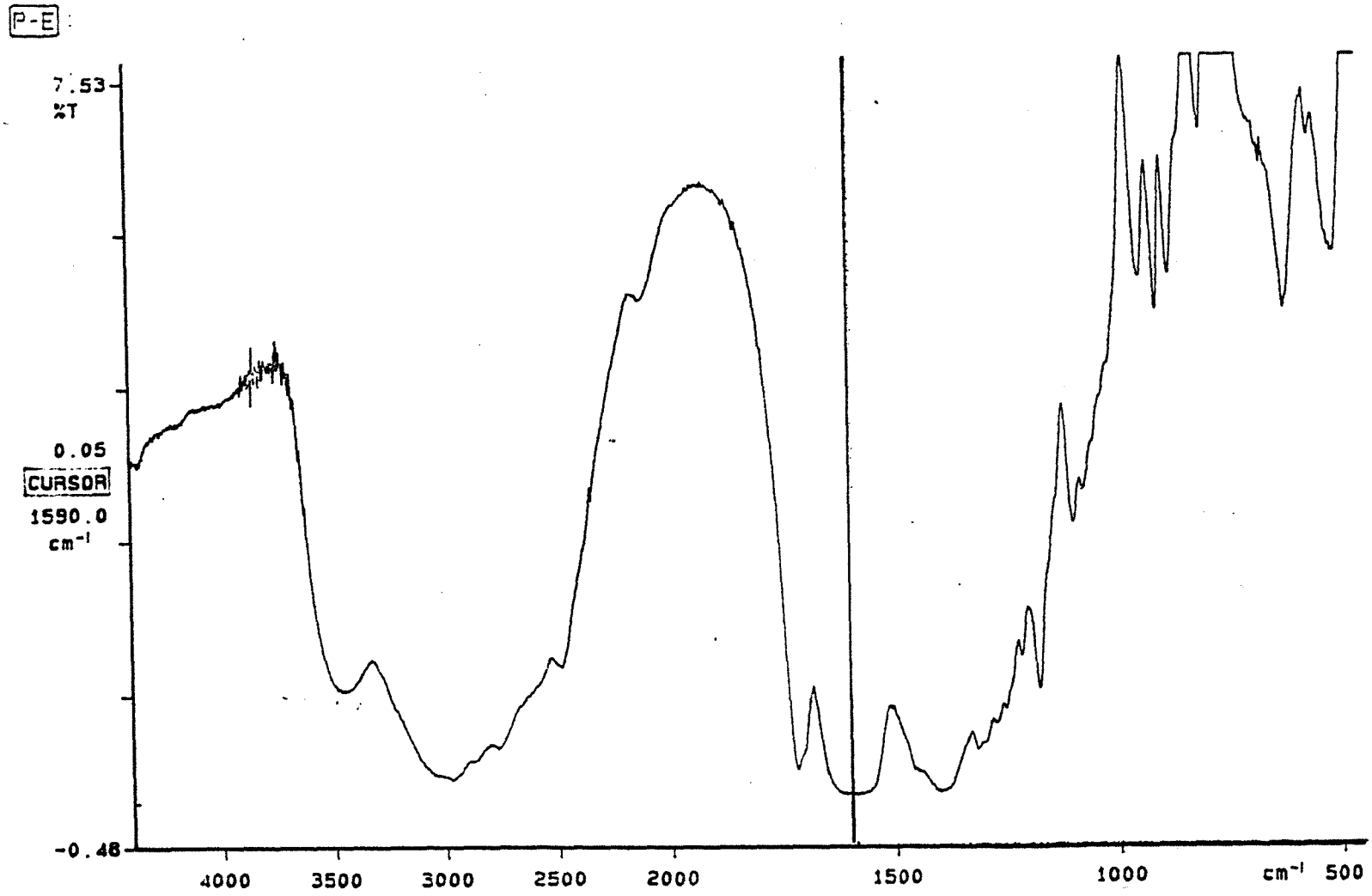


Fig.II-10 IR Spectrum of
(5-keto-7-methyl-7-amino)-octanoic acid

7-methyl-7-amino octanoic acid (IV) in 75 ml acetonitrile and the mixture refluxed for 3 hrs, then cooled to room temperature and subsequently cooled in an ice bath. N,N'-dicyclohexylurea was filtered off, the filtrate evaporated under reduced pressure and the residue extracted with 60 ml methylene chloride. Additional N,N'-dicyclohexylurea was filtered off, the filtrate retoevaporated and the residue washed with another 40 ml methylene chloride. Following solvent removal, the crude product was obtained as a brown syrup. The IR spectrum clearly shows the anticipated 1690 cm^{-1} carbonyl band (The same carbonyl band misled us to 8,8,9,9-tetramethyl-1-azabicyclo[3.3.1]nonan-2-one previously) but DCC(2100 cm^{-1}) is still present as is some of the urea. (Fig. II-11) 1.5 g of crude product is dissolved in 50 ml ethylacetate(remaining N,N'-dicyclohexylurea precipitates and is filtered. The filtrate is passed through a 60 mesh silica gel column. Elution with ethyl acetate is continued until no additional DCC is obtained (Via TLC). Then elution is done using 95% ethylacetate, 5% absolute ethanol and the product was obtained. A 90% isolated yield was obtained for this step. At all previous stages of purity, (V) was obtained as a wax. Initially, purified (V) (from aforementioned column chromatography) was also obtained as a wax by crystals formed upon standing for several days. Elemental analysis: calculated for $C_9H_{15}NO_2$ C, 64.00%; H,8.93%; N,8.28% found

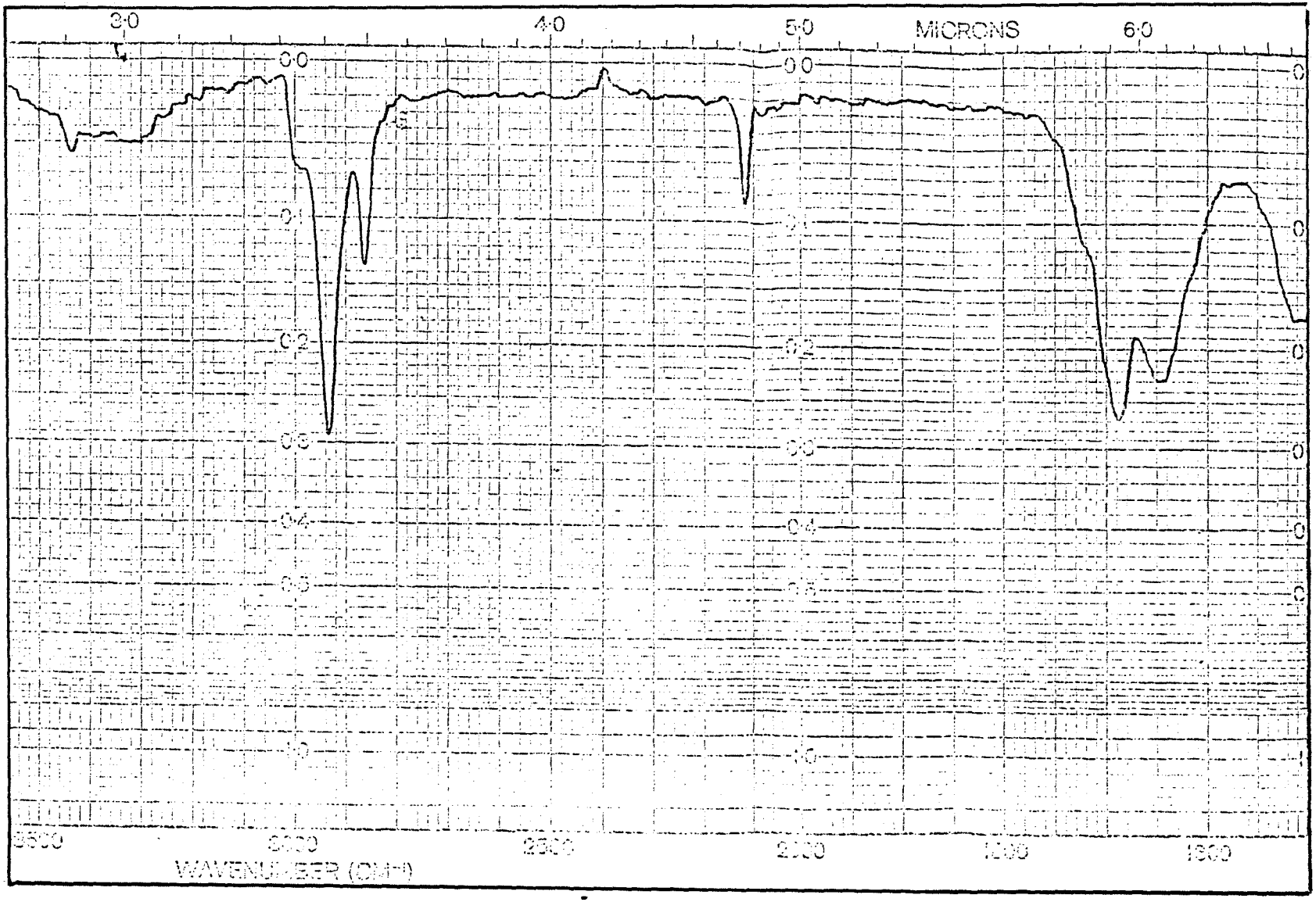


Fig.II-11 IR Spectrum of
8,8-Dimethyl-1-azacyclooctane-2,6-dione
(with DCC)

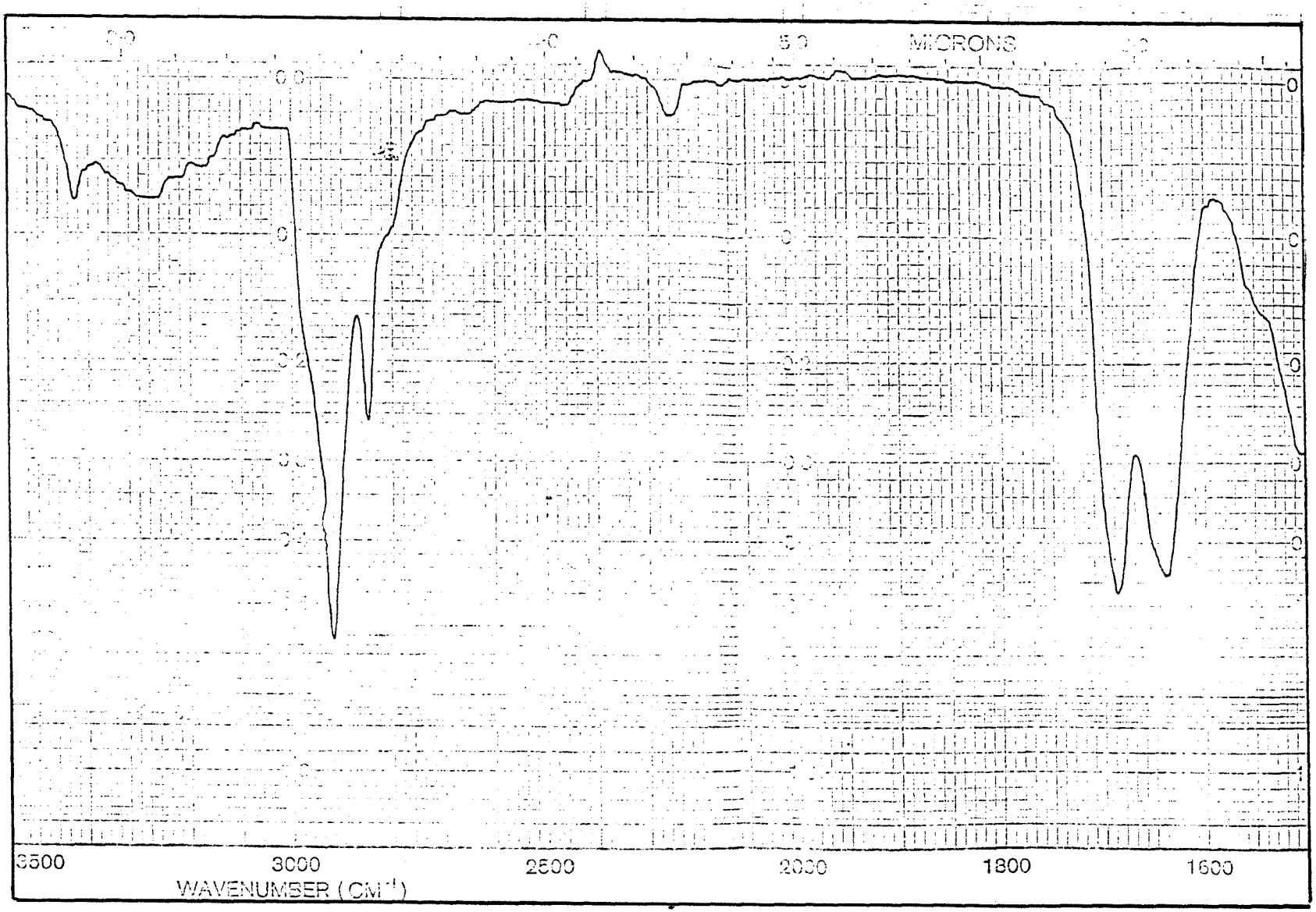


Fig.II-12 IR Spectrum of
8,8-Dimethyl-1-azacyclooctane-2,6-dione

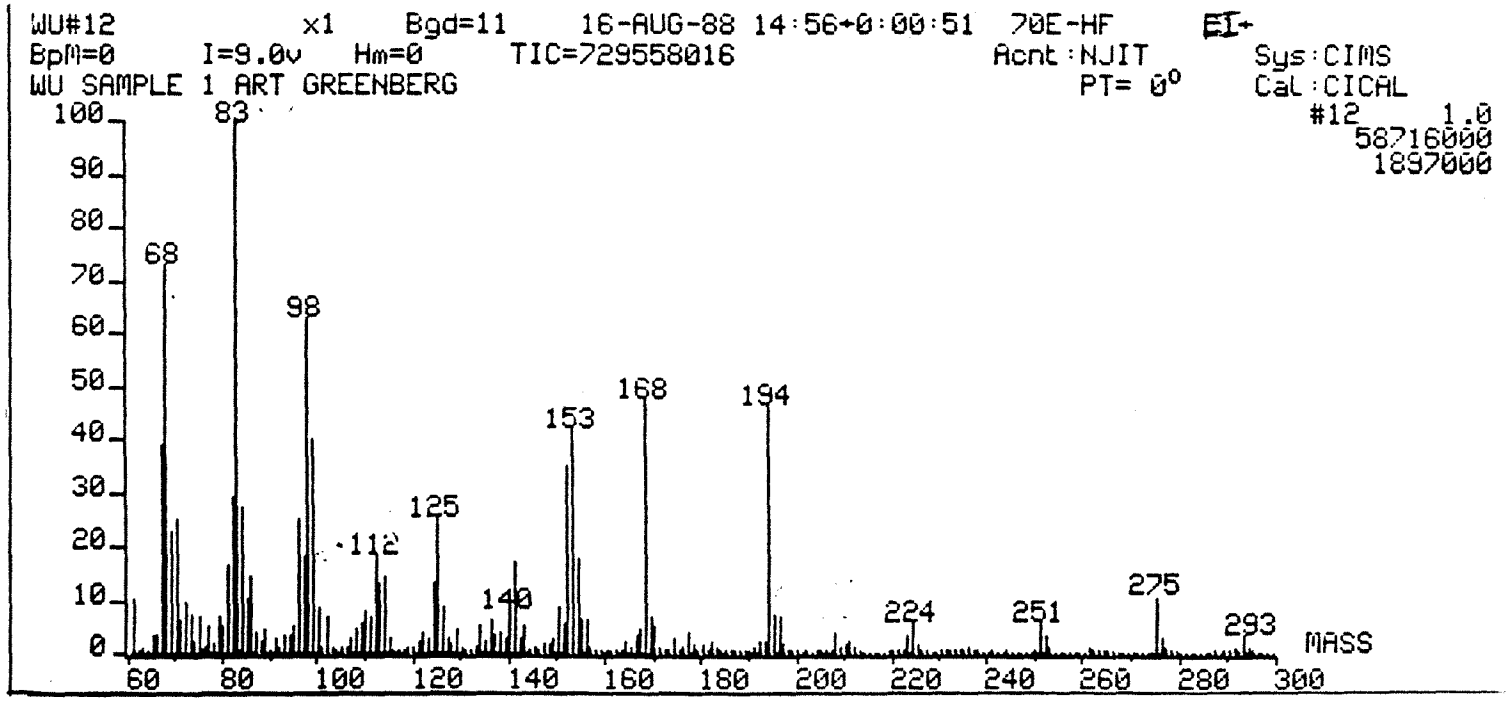
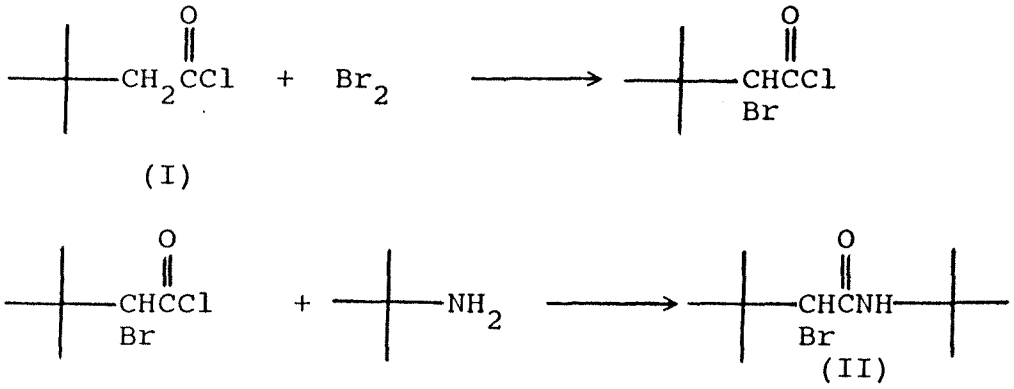


Fig.II-13 Mass Spectrum of
8,8-dimethyl-1-azacycloocatane-2,6-dione

C,64.98%;H,9.73%;N,8.95%. Infrared: 1690 cm^{-1} for C=O.(Fig. II-12) Mass:m/e 83 base peak; m/e 168 (M-1)(48%); m/e 153 (42%); m/e 98 (64%); m/e 68 (74%).(Fig.II-13)

3. 1,3-Di-tert-butylaziridinone

2-Bromo-3,3-dimethyl-N-t-butylbutyramide

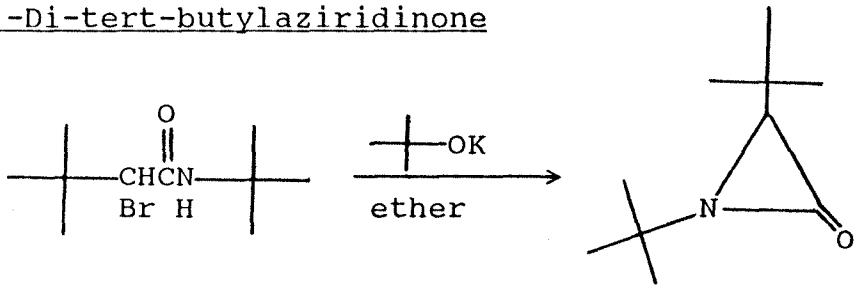


Scheme 3-1

Bromine (3.8 ml;69.6 mmole) was added dropwise to a solution of 3,3-dimethylbutyryl chloride (I) (8.4 g;62.4 mmole) in 20 ml of carbon tetrachloride, and the resulting solution was refluxed until the bromine color disappeared (about 6 hrs). The solution was then added to an ice-cold solution of t-butylamine (15.1 ml;144 mmole) in methylene chloride (100 ml) within 1 hr. After stirring for an additional 0.5 hr, water was added and the layers were separated. The water upper layer was collected. The organic layer was washed with 50 ml water again. The organic solution was washed with hydrochloric acid, aqueous sodium hydroxide, and distilled water until pH > 7. Methylene chloride was evaporated. The crude solid was put into an oven (temperature = 70 - 80 °C) for 2 hours, and 9.8 g (yield 63%) dried solid was formed.

M.P. 155 - 156 °C Infrared: 3410 cm^{-1} for NH,1660 cm^{-1} for CON.(Fig. II-14) NMR(60 MHZ,$CDCl_3$): S 4.35ppm(1H); S 1.48ppm(9H),S 1.2ppm(9H).(Fig. II-15)

1,3-Di-tert-butylaziridinone



Scheme 3-2

A solution of the α-bromo amide (II) (4.8 g;0.0192 mole) in 200 ml of ether was cooled to 0 °C in an ice bath. Potassium t-butoxide (3.1 g;0.0277 mole) was dried in an oven for 20 min at 70 °C, then added to the solution. After 20 min of stirring, an infrared spectrum of the solution indicated that the α-lactam formation was complete. The solution was filtered under nitrogen pressure and the solvent from the resulting cloudy solution was evaporated. The residue was taken up in petroleum ether, placed in a centrifuge tube, and cooled to -16 °C. Centrifugation gave a clear solution which on evaporation yield 2.2 g (67.8 %) of the crude α-lactam. On distillation (64 - 65 °C, 4mm),the pure product was obtained. Infrared: 2960 cm^{-1} for CH, 1838 cm^{-1} for the α-lactam.(Fig. II-16) NMR(60 MHZ, $CDCl_3$):S 0.9ppm(9H), S 1.25ppm(9H), S 2.68(1H).(Fig. II-17)

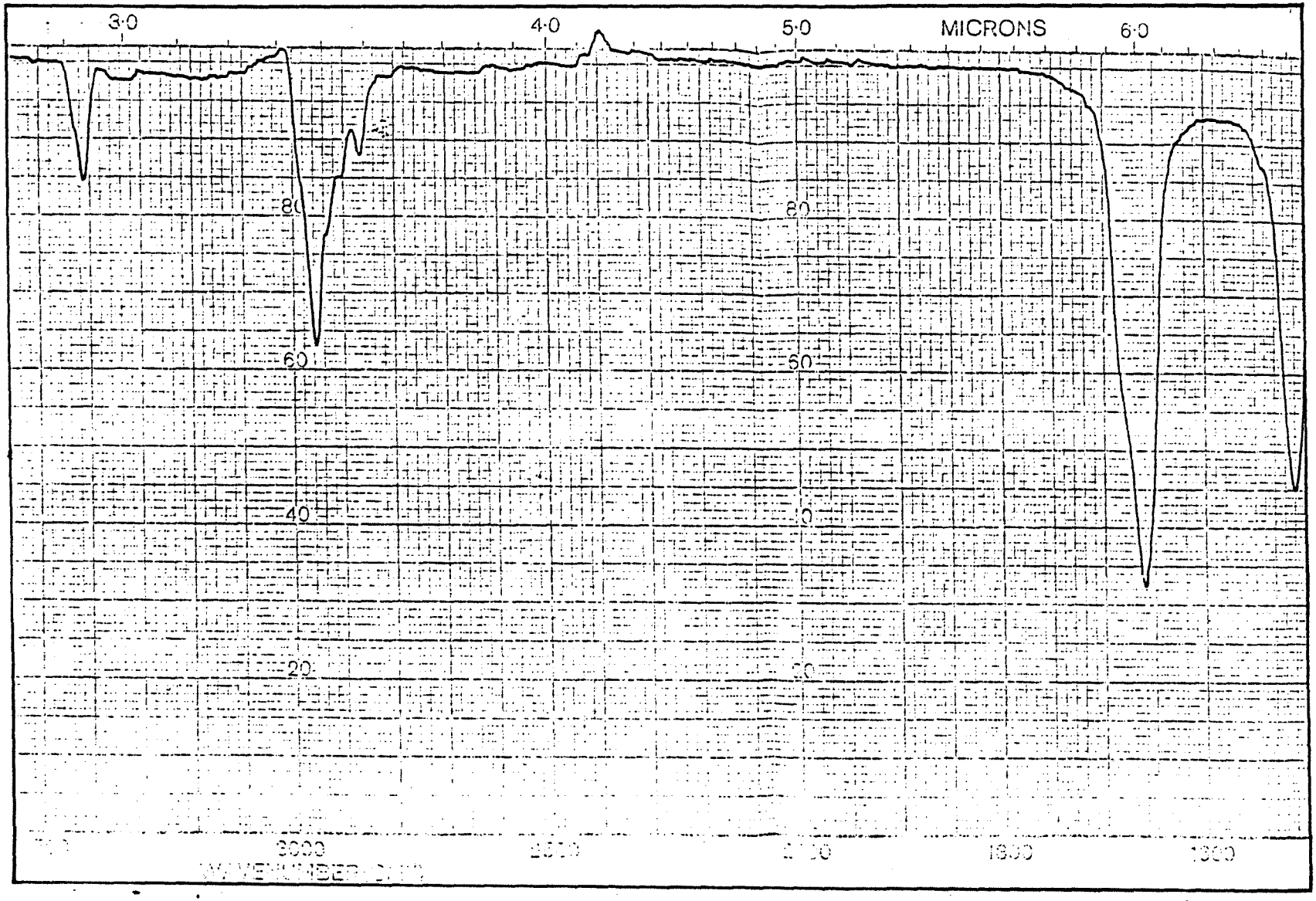


Fig.II-14 IR Spectrum of
2-bromo-3,3-dimethyl-N-t-butylramide

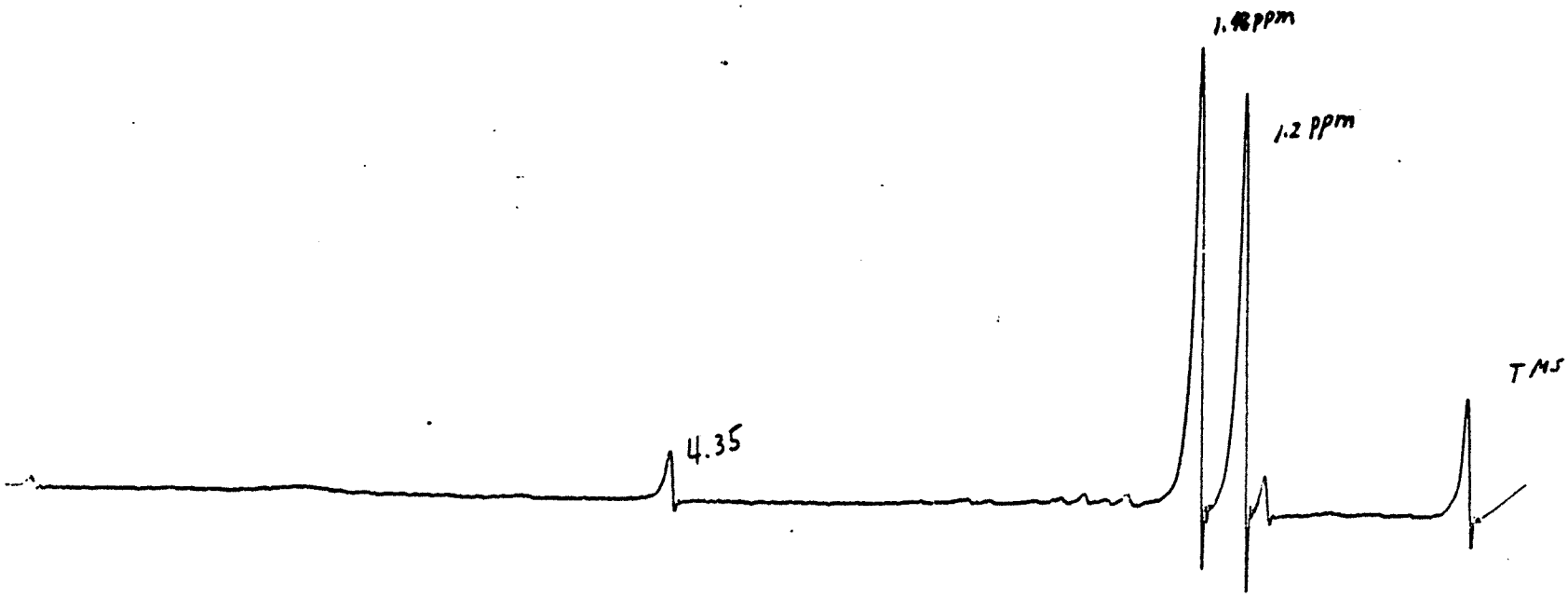


Fig.II-15 NMR Spectrum of
2-bromo-3,3-dimethyl-N-t-butylramide

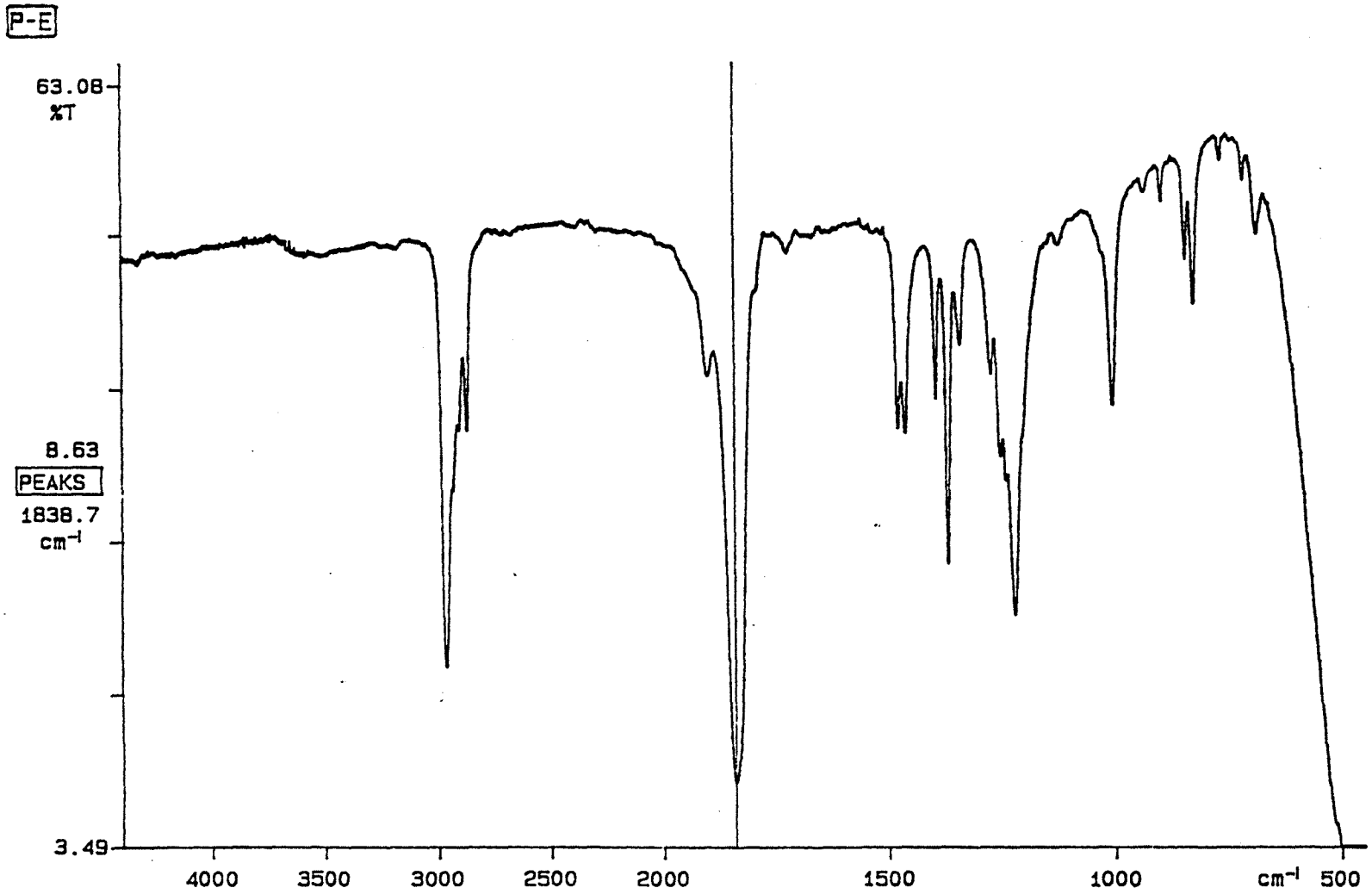


Fig.II-16 IR Spectrum
1,3-di-tert-butylaziridinone

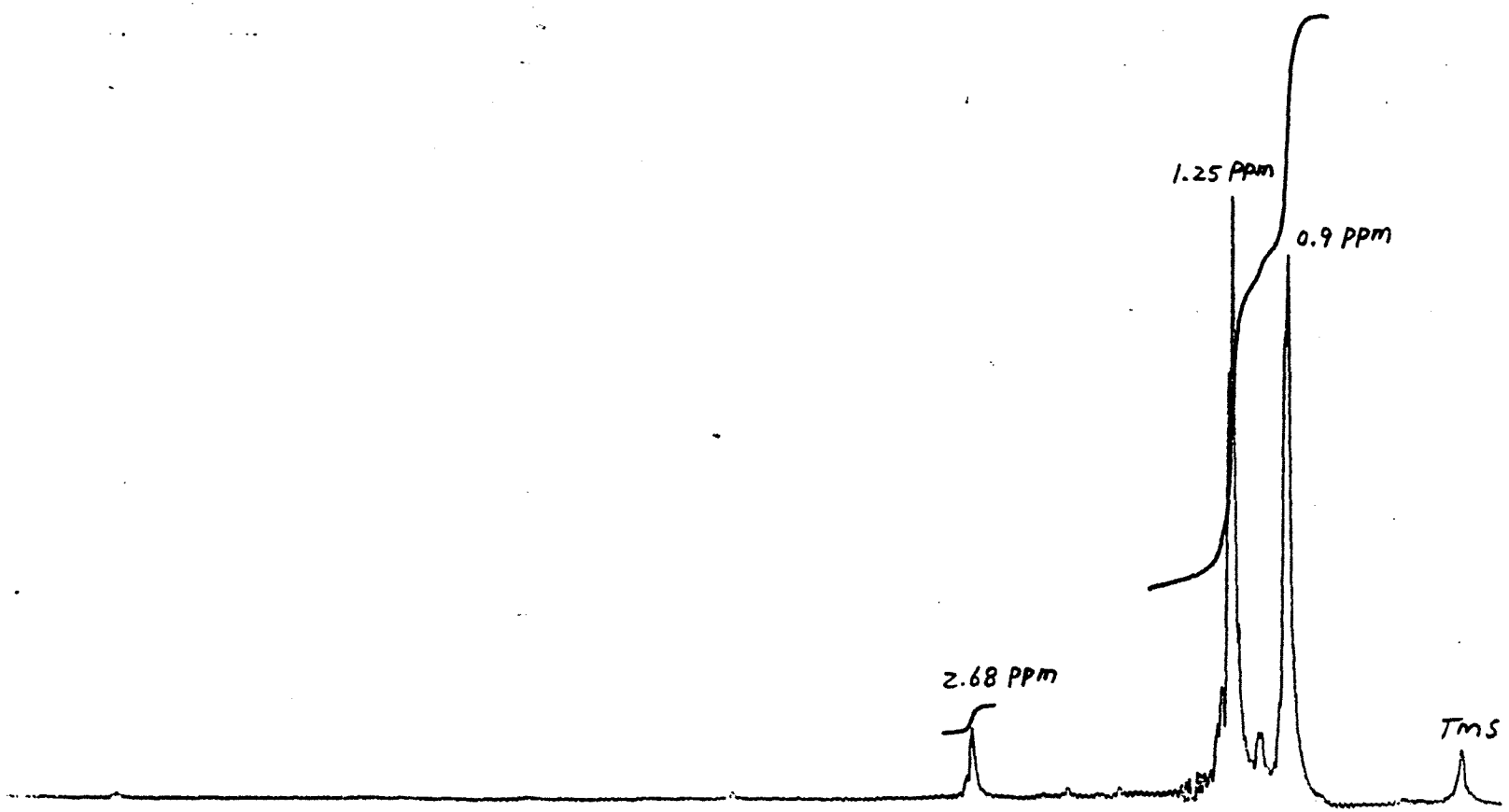
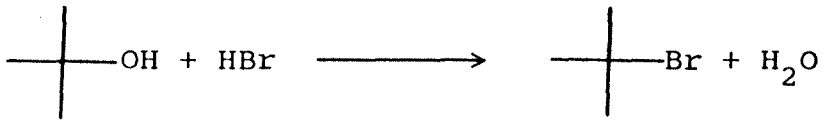


Fig.II-17 NMR Spectrum of
1,3-di-tert-butylaziridinone

4. 1-N-tert-butyl-2-pyrrolidinone

Tert-Butyl bromide

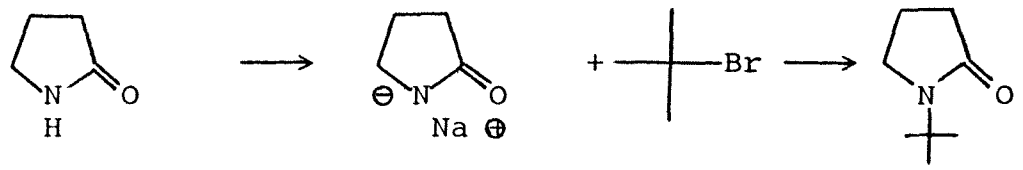


(I) (II)

Scheme 4-1

Concentrated sulphuric acid (65 ml) was added dropwise into hydrobromic acid (240 ml of 48% w/w solution; 2.1 mole)then stirred for 25 min, and the temperature rose to 38 °C. Some ice was added to the cooling water bath to keep the temperature of the solution around 20 °C. Tert-butyl alcohol (I) (76.7 g;1.04 mole) was added to the solution. After an additional 30 min, the organic layer (upper) was separated, washed twice with water and dried (anhydrous sodium sulfate). On distillation, the first fraction (17.8 g) contained dissolved isobutane and was rejected. The bulk (78 g, yield 55%) of the distillate had b.p. 76 °C/760 mm and there was no appreciable distillation residue.

Attempted synthesis of 1-tert-butyl-2-pyrrolidinone using tert-butyl bromide



(II) (III)

Scheme 4-2

A suspension of 5.44 g of 57% sodium hydride/mineral oil (actually 3.10 g NaOH 0.13 mole) in 200 ml of petroleum ether (200 ml) was allowed to settle and the residue washed with petroleum ether (200 ml/each) twice. After the excess petroleum ether was removed, 150 ml of dry toluene was added and the mixture stirred as 10 g (0.1174 mole) 2-pyrrolidinone in 25 ml of dry toluene was added dropwise over 1 hr. After the addition was complete, the mixture was refluxed for 1 hr then t-butyl bromide (17.8 g;0.13 mole) in dry toluene (25 ml) was added dropwise over 1 hr to the refluxing mixture. After the addition was complete, the mixture was refluxed for 15 hrs. The reaction mixture was filtered twice. Toluene was removed in vacuum (CA. 200 mm). Crude product was formed (<50 mg, yield < 1%) in the bottle. This was determined through observation of carbonyl frequency at 1691 cm^{-1} in the product which was different from carbonyl frequency of 2-pyrrolidinone (1666 cm^{-1}).(Fig. II-18,II-19)

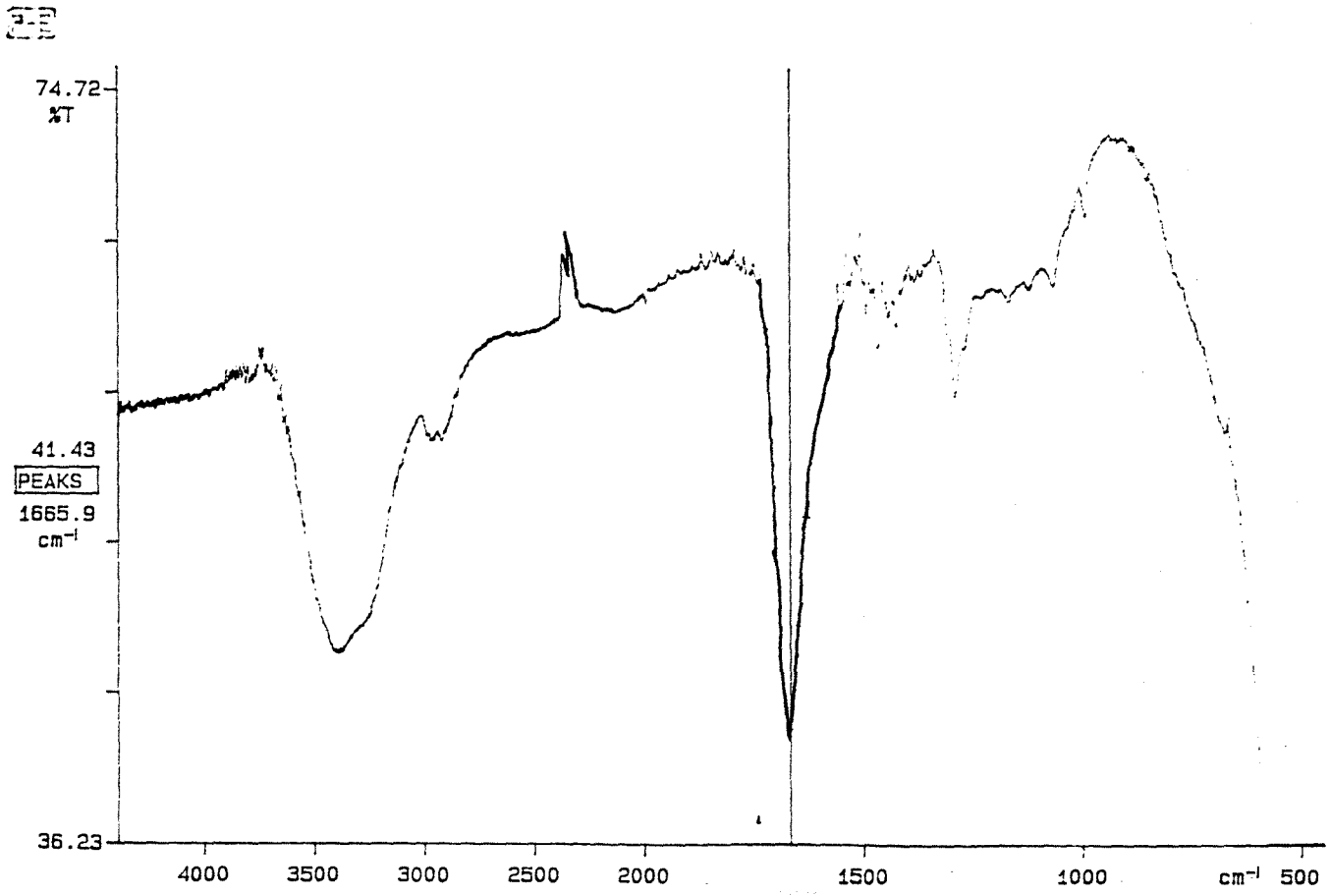


Fig.II-18 IR Spectrum of
2-pyrrolidinone

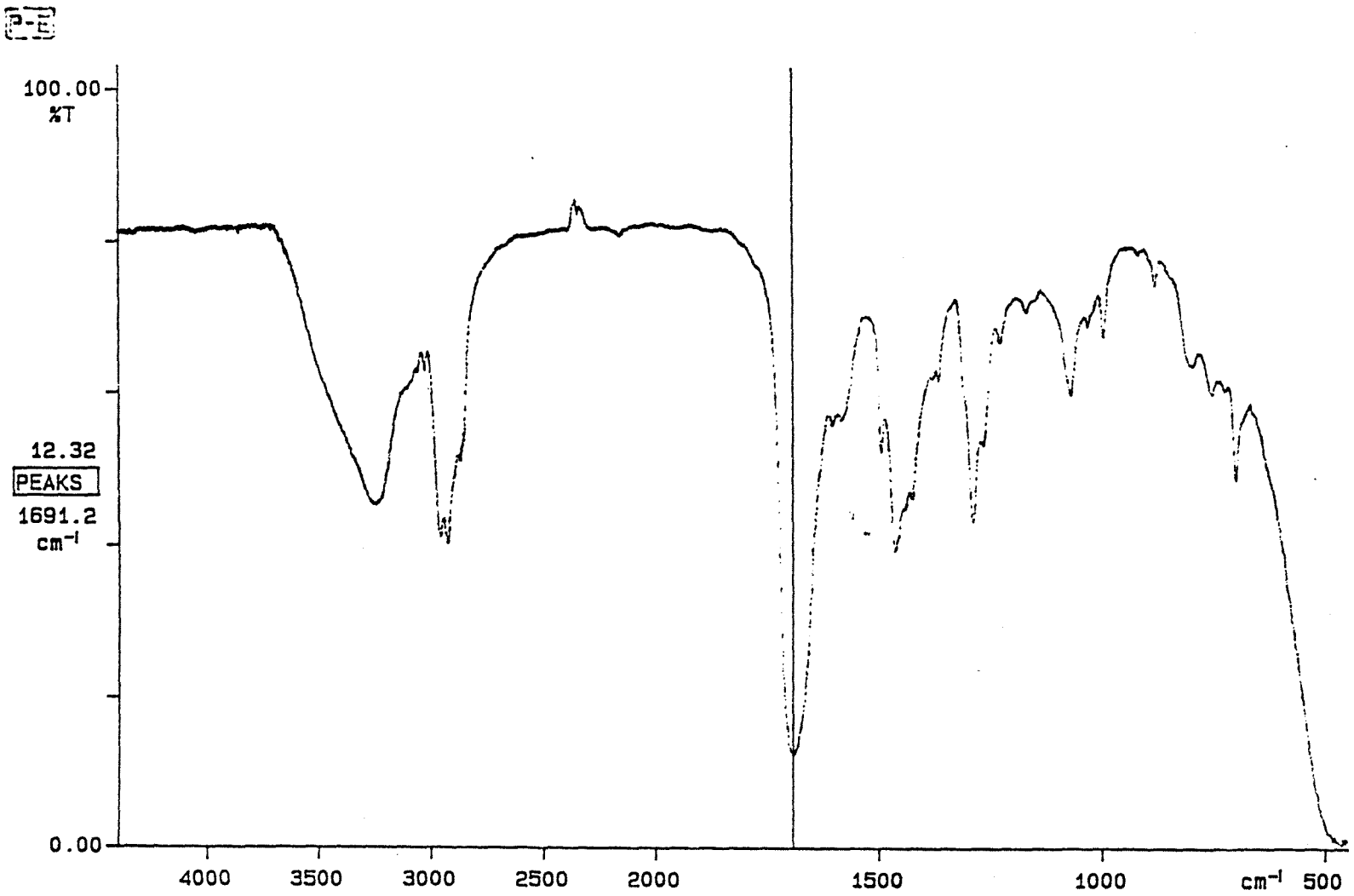


Fig.II-19 IR Spectrum of
1-tert-butyl-2-pyrrolidinone
(from tert-butyl bromide)

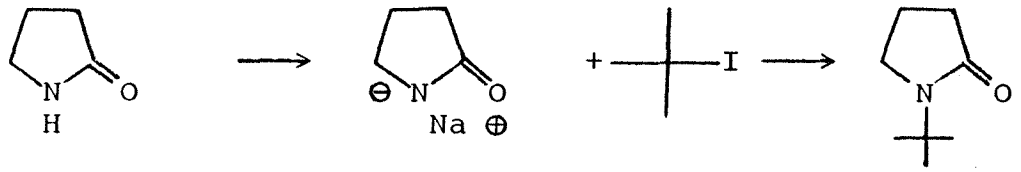
Tert-butyl iodide

(I) (II)

Scheme 4-3

Concentrated sulphuric acid (12 ml) was added dropwise into hydrogen iodide (50 ml of 57% w/w solution; 48.4 g ;0.378 mole) then stirred for 25 min. Some ice was added to the water bath to keep the temperature of the mixed solution around 20 °C. Tert-butyl alcohol (I) (14 g; 0.1898 mole) was added to the solution. After an additional 30 min, the organic layer (upper) was separated, washed with water three times and dried (anhydrous sodium sulfate). On distillation, the bulk fraction (18.5 g, yield 52%) of the distillate had b.p. 65-68 °C/CA. 200 mm n_D^{20} 1.5010.

Synthesis of 1-tert-butyl-2-pyrrolidinone using tert-butyl iodide



(II) (III)

Scheme 4-4

A suspension of 2.7 g of 57% sodium hydride/mineral oil (actually 1.54 g NaH 0.065 mole) in 20 ml of petroleum ether was allowed to settle and the residue washed twice with petroleum ether (80 ml/each) . After the excess petroleum ether was removed, 70 ml of dry toluene was added and the mixture stirred as 4.0 g (0.047 mole) 2-pyrrolidinone in 15 ml of dry toluene was added dropwise over 1 hr. After the addition was complete, the mixture was refluxed for 1 hr, then t-butyl iodide (9.5 g; 0.0516 mole) in 20 ml of dry toluene was added dropwise over 1 hr to the refluxing mixture. After the addition was complete, the mixture was refluxed for 14.5 hrs. The reaction mixture was filtered twice. Toluene was removed in vacuum (around 200 mmHg). Crude product (1 g) was obtained. The product was centrifuged then distilled again under vacuum. Crude product contaminated with 2-pyrrolidinone was formed(0.3 g; 0.0021 mole, yield 4.5%). Infrared: 1681 cm^{-1} for CO. (Fig. II-20)

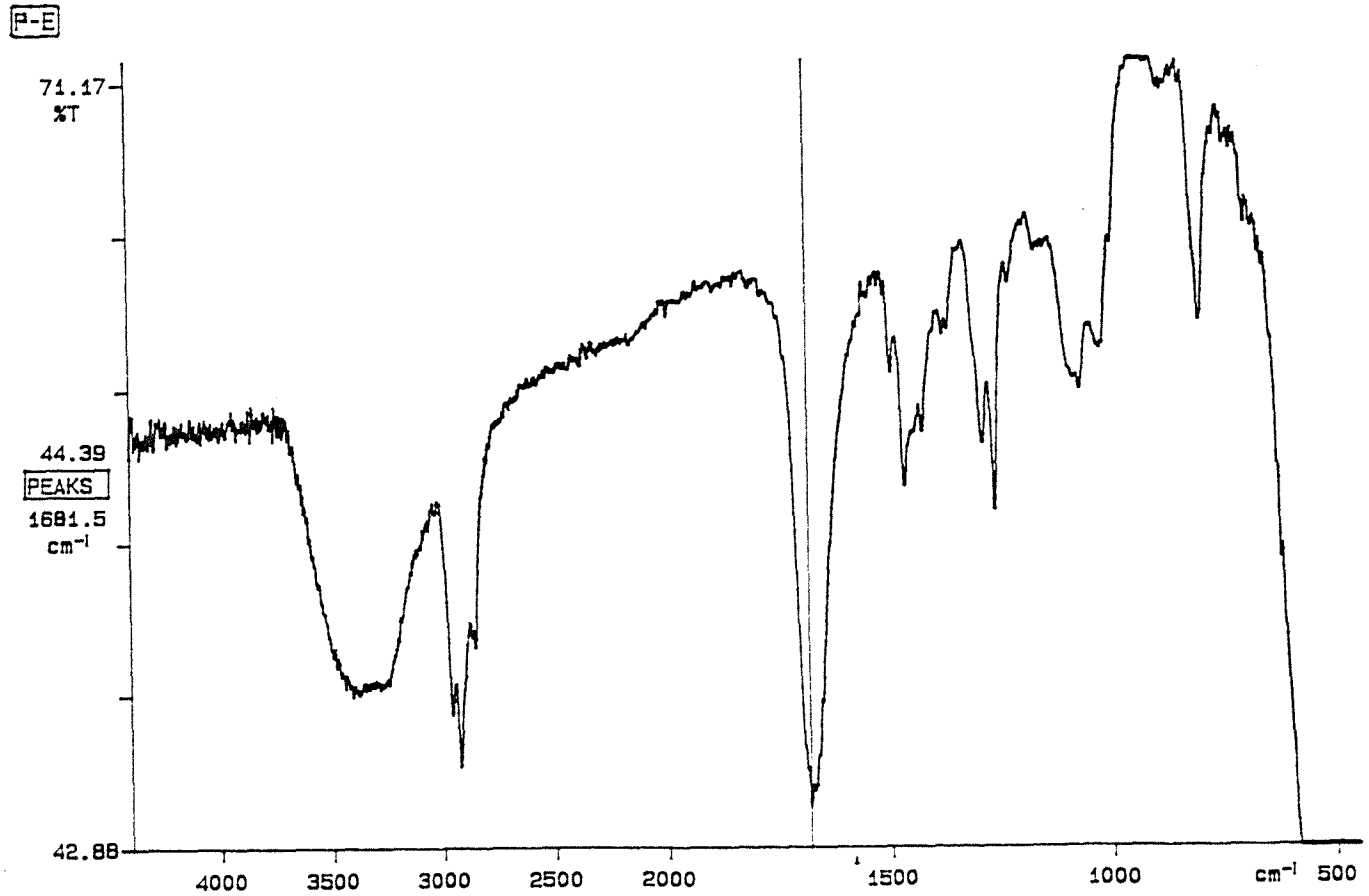
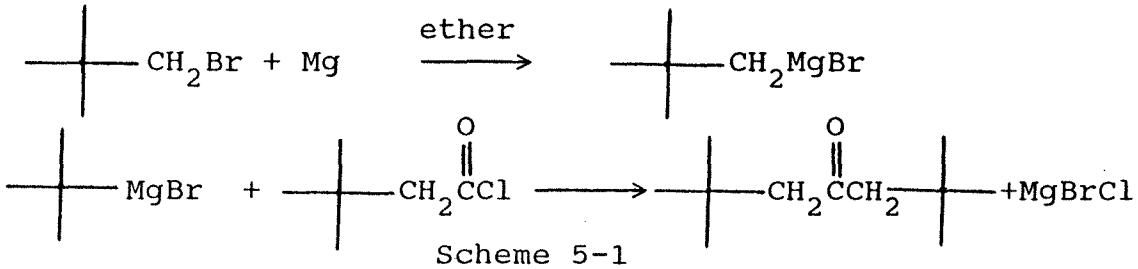


Fig.II-20 IR Spectrum of
1-tert-butyl-2-pyrrolidinone
(from tert-butyl iodide)

5. Trans-1,2-di-tert-butyl cyclopropanone

Di-neopentyl ketone

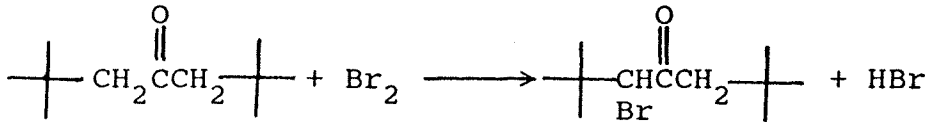


Scheme 5-1

2.7 g (0.11 gramatoms) of magnesium turnings was placed in a 500 ml flask. One small test tube contained ethereal magnesium and iodine as starter. First, some neopentylbromide (1/4 total weight) was added into the flask. While the reaction of the solution in the test tube started, the iodine solution was poured into the flask. Neopentylbromide (13.46 g; 0.1 mole) in 50 ml of anhydrous ethyl ether was added slowly (40 min). After addition, refluxed for 1 hr. The solution of neopentylmagnesium bromide was added dropwise over 30 min to a stirring solution of t-butylacetyl chloride (9.6 g; 0.071 mole)in 50 ml ether. The resulting suspension was stirred an additional 8 hrs at reflux and the crude reaction product worked up with concentrated aqueous hydrochloric acid in the usual fashion (10 ml HCl was added and washed with water five times). Vacuum distillation b.p. 70 °C (10 mm) afforded 8.2

g (yield 70%) dineopentyl ketone. Infrared: 1708 cm^{-1}.(Fig. II-21) NMR(400 MHZ, $CDCl_3$): S, 1.0ppm(18H);S, 2.2 ppm (4H) (Fig. II-22)

α-Bromodineopentyl Ketone



Scheme 5-2

To 11.3 g (0.066mole) of dineopentyl ketone in 50 ml of carbon tetrachloride was added bromine (10.3 g; 0.065 mol) in 60 ml carbon tetrachloride over a period of 120 min while flushing with nitrogen to eliminate HBr gas. After addition was completed, more N_2 was flushed through for 2 hrs and the solution was stirred overnight. The carbon tetrachloride was evaporated and the product was distilled. 11.8 g (63-77 °C/5mm) of α-bromodineopentyl ketone was formed. (yield 66%) Infrared: 1708 cm^{-1} for CO.(Fig. II-23) NMR(400 MHZ, $CDCl_3$): S, 1.05 ppm(18H);S, 2.25 ppm(2H);S, 4.05 ppm(1H) (Fig. II-24)

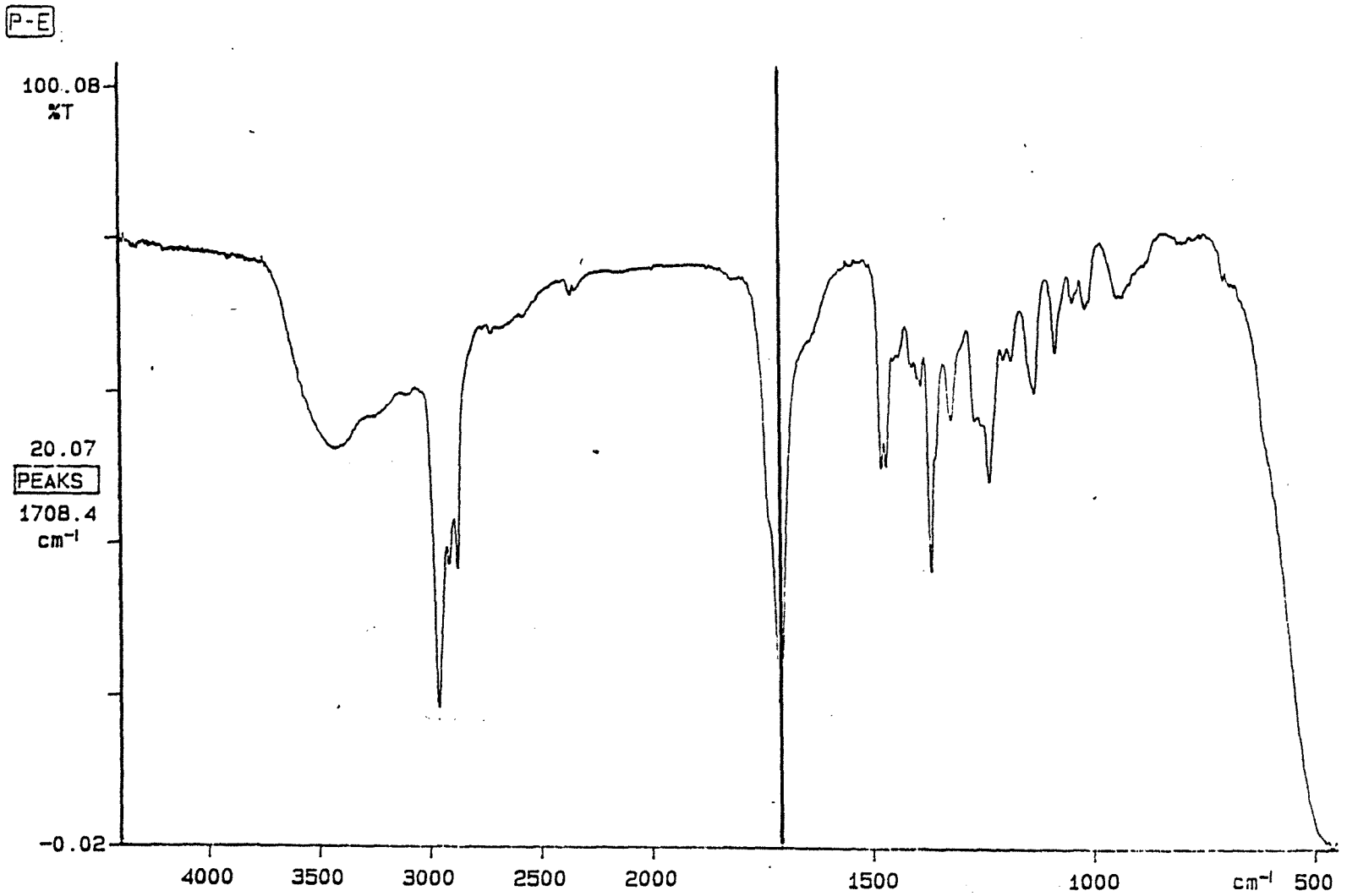


Fig.II-21 IR Spectrum of
dineopentyl ketone

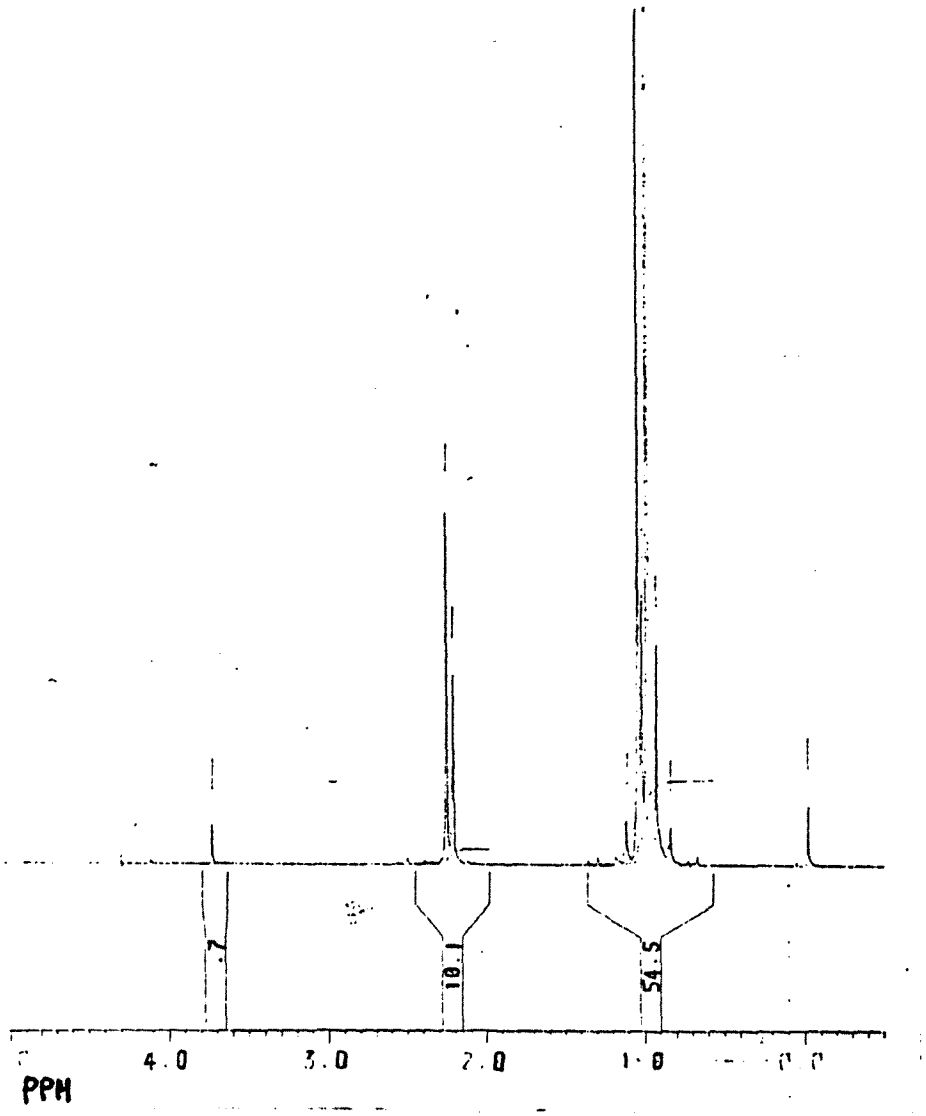


Fig.II-22 NMR Spectrum of
Dineopentyl ketone

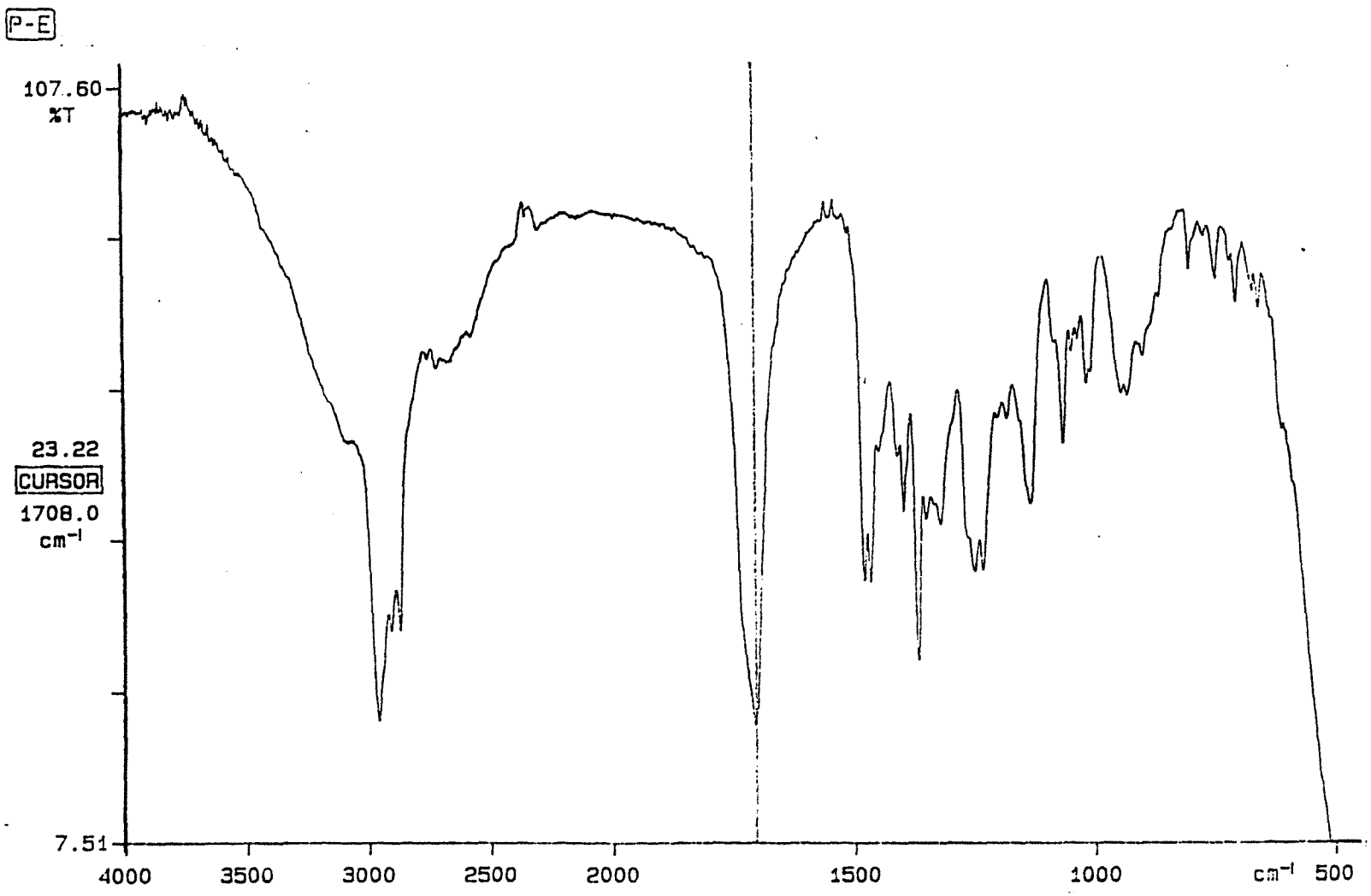


Fig.II-23 IR Spectrum of
α-bromodineopentyl ketone

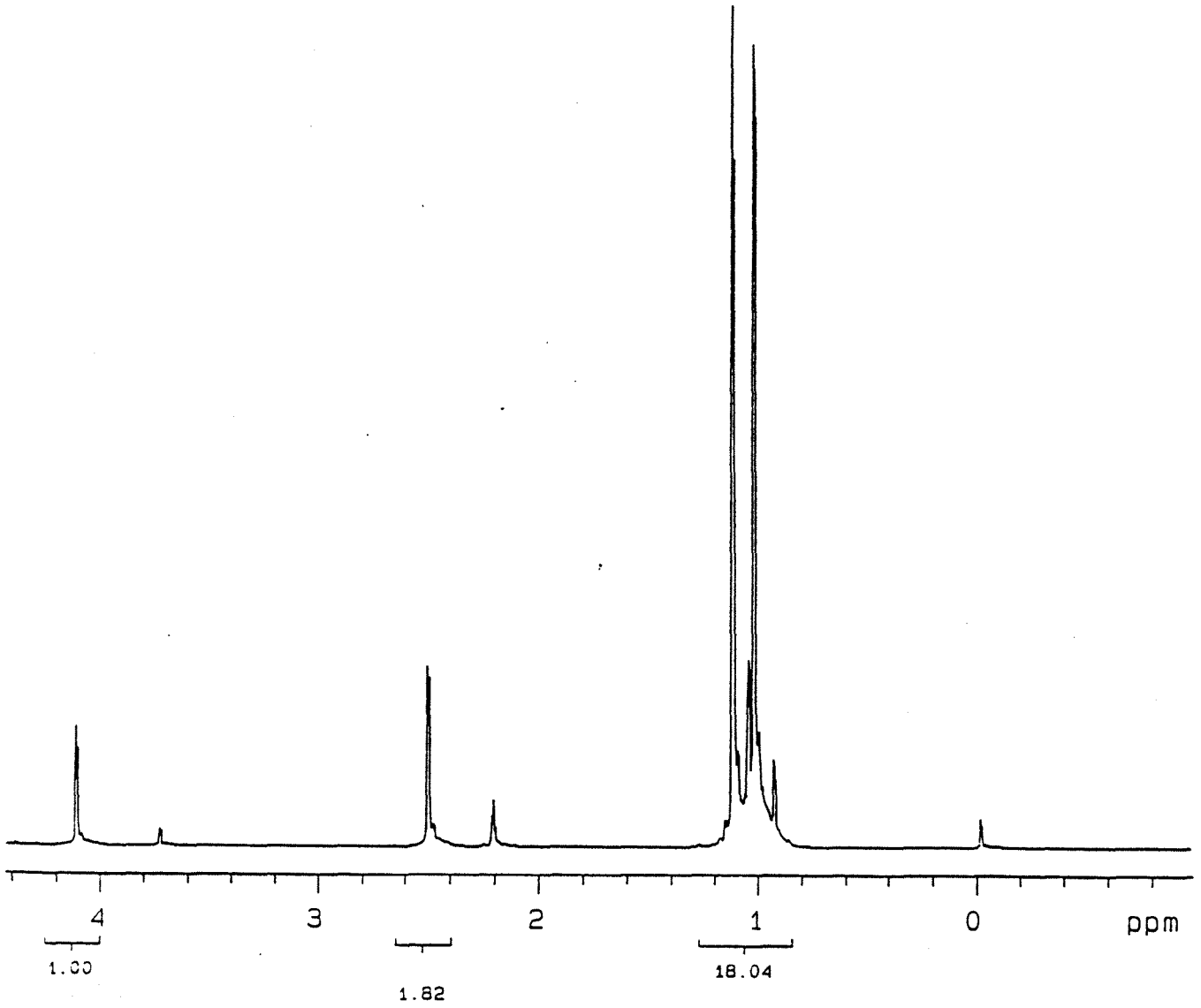
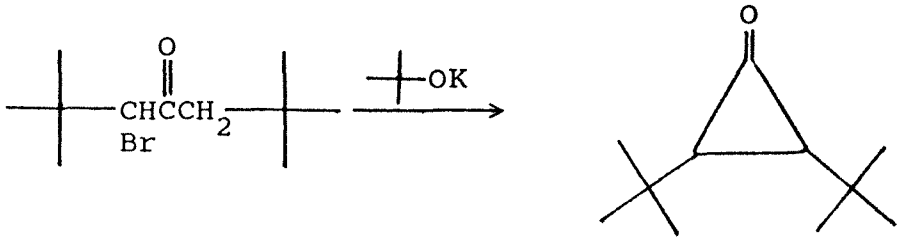


Fig.II-24 NMR Spectrum of
α-bromodineopentyl ketone

Trans-di-tert-butylecyclopropanone



Scheme 5-3

To α-bromodineopentyl ketone(6.0 g; 24 mmol) in 25 ml tert-butyl alcohol in a dried flask equipped with magnetic stirrer in an ice-water bath. Potassium tert-butoxide (2.55 g; 22.8 mmol) in 50 ml ethyl ether was added slowly(30 min). The mixture was concentrated (CA. 60 °C, 25mm) and trap-to-trap distillated (25-100 °C/0.1mm). 2.99 g of crude product was obtained and the infrared band indicated the carbonyl of the cyclopropanone. However, this is present in much smaller quantity relative to the Favorskii product ester (1770 cm^{-1}).Based upon the relative intensities of the two carbonyl bands in the crude product we would estimate that only 12-20% is the cyclopropane. Infrared: 1822 cm^{-1} for CO.(Fig. II-25)

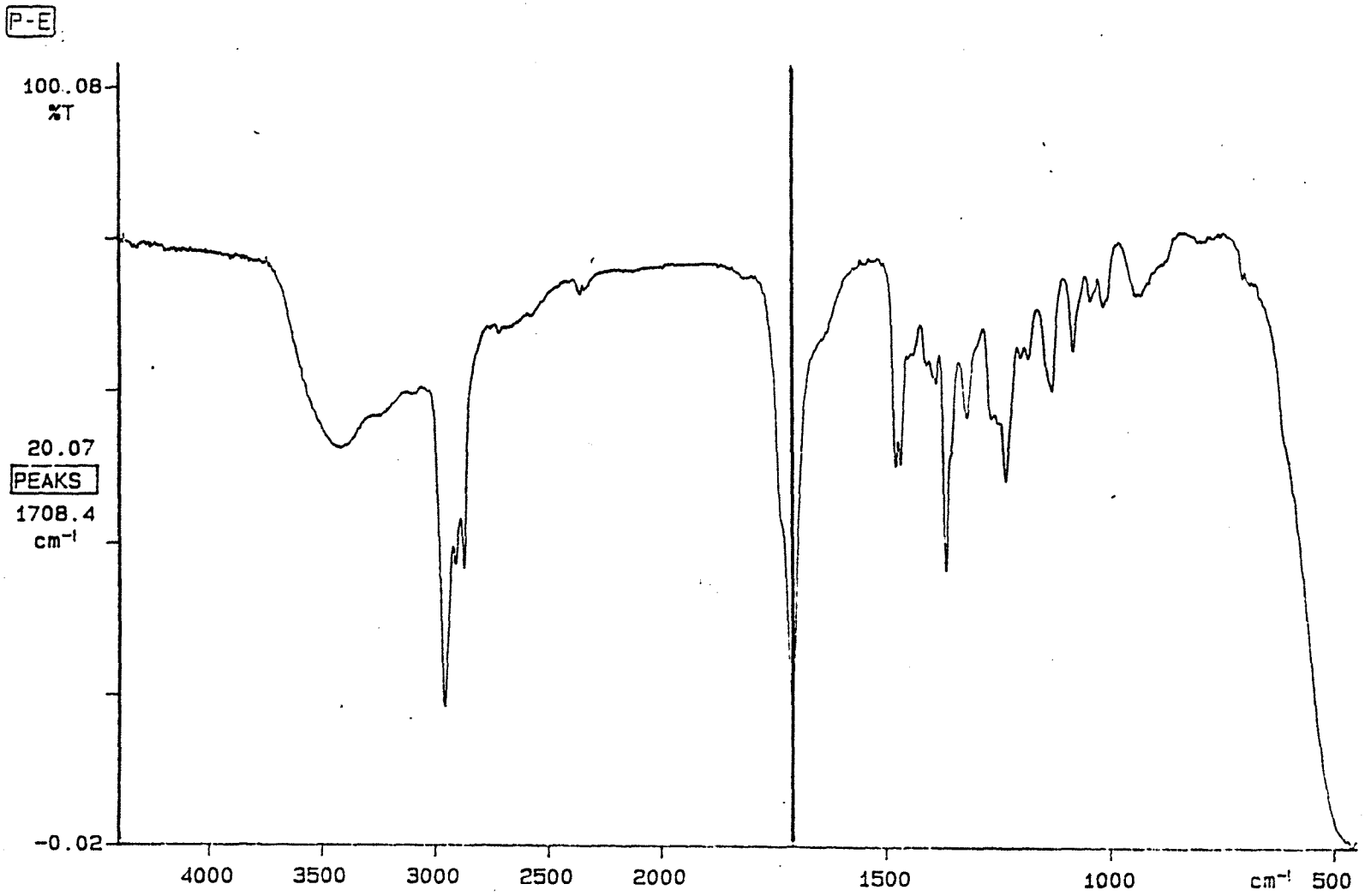


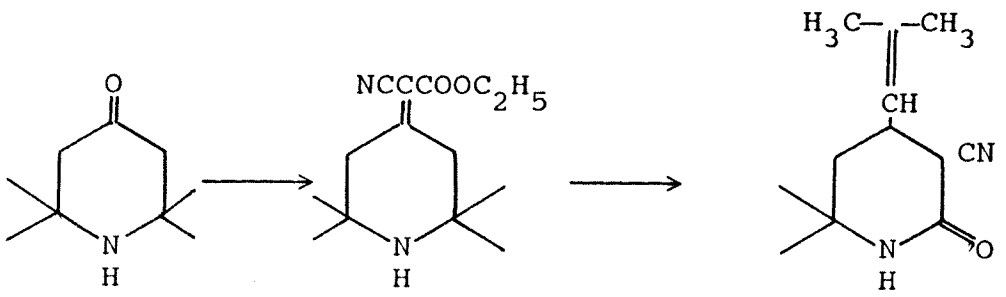
Fig.II-25 IR Spectrum of
Trans-di-tert-butylcyclopropanone
and Favorskii ester product (See text)

CHAPTER III. Result & discussion

1. Synthesis

a) 6,6,7,7-tetramethyl-2-quinuclidone

The first step(Scheme 1-1) provided 2,2,6,6-tetramethyl-4-(carboxycyanomethylene) piperidine. This reaction proceeded most completely under the action of ammonia acetate in refluxing benzene with azeotropic distillation of the water formed during 1 hr. Nikitskaya's procedure[9b] provided high yield.



Prolonged heating of the reaction mixture leads to

further N-acetylation of the ester and rearrangement of the N-acetyl derivative formed into 3-cyano-4-(β,β-dimethylvinyl)-6,6-dimethyl-Δ^{3}-dehydro-2-piperidone (IR: 1670 cm^{-1},Fig. III-1), which, naturally, decreased the yield of the ester.

Compared to Pracejus' procedure[8a,b] for 2,2-dimethyl and 2,2,6-trimethyl-2-quinuclidone, acetate acid was used to draw off water. The NH group has to be protected first. Nikitskaya's procedure made a good improvement in this step.

The last step of intramolecular cyclization reaction, according to the Levkoveva's[9a] procedure gives polymer (IR 1643 cm^{-1},Fig III-23) almost exclusively. Dr. Guanli Wu's modified procedure provided a 26% yield of the desired compound. Another improvement in the synthetic procedures involves further dilution of triethylamine in ether and slow dropwise addition of the suspension of 2,2,6,6-tetramethyl-4-piperidinyl acetyl chloride hydrochloride in ethyl ether to triethylamine solution, thereby allowing the favorited procedure of the intramolecular cyclization to obtain the desired compound. Long heating of the sample as well as excess any triethylamine tended to promote polymerization.(Fig III-3)

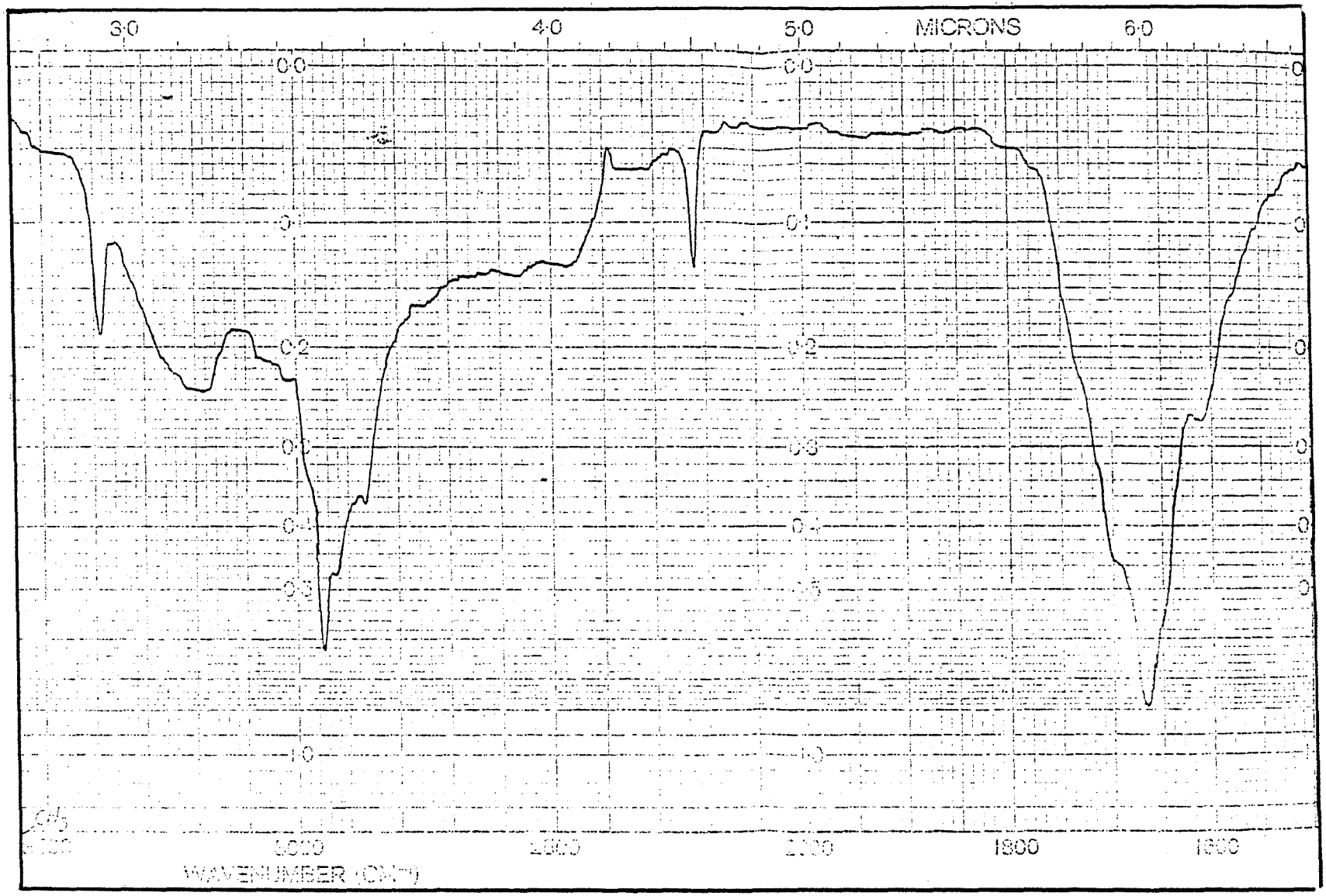


Fig.III-1 IR Spectrum of
3-Cyano-4-(β,β-dimethylvinyl)-6,6-dimethyl
Δ^3-dehydro-2-piperidone

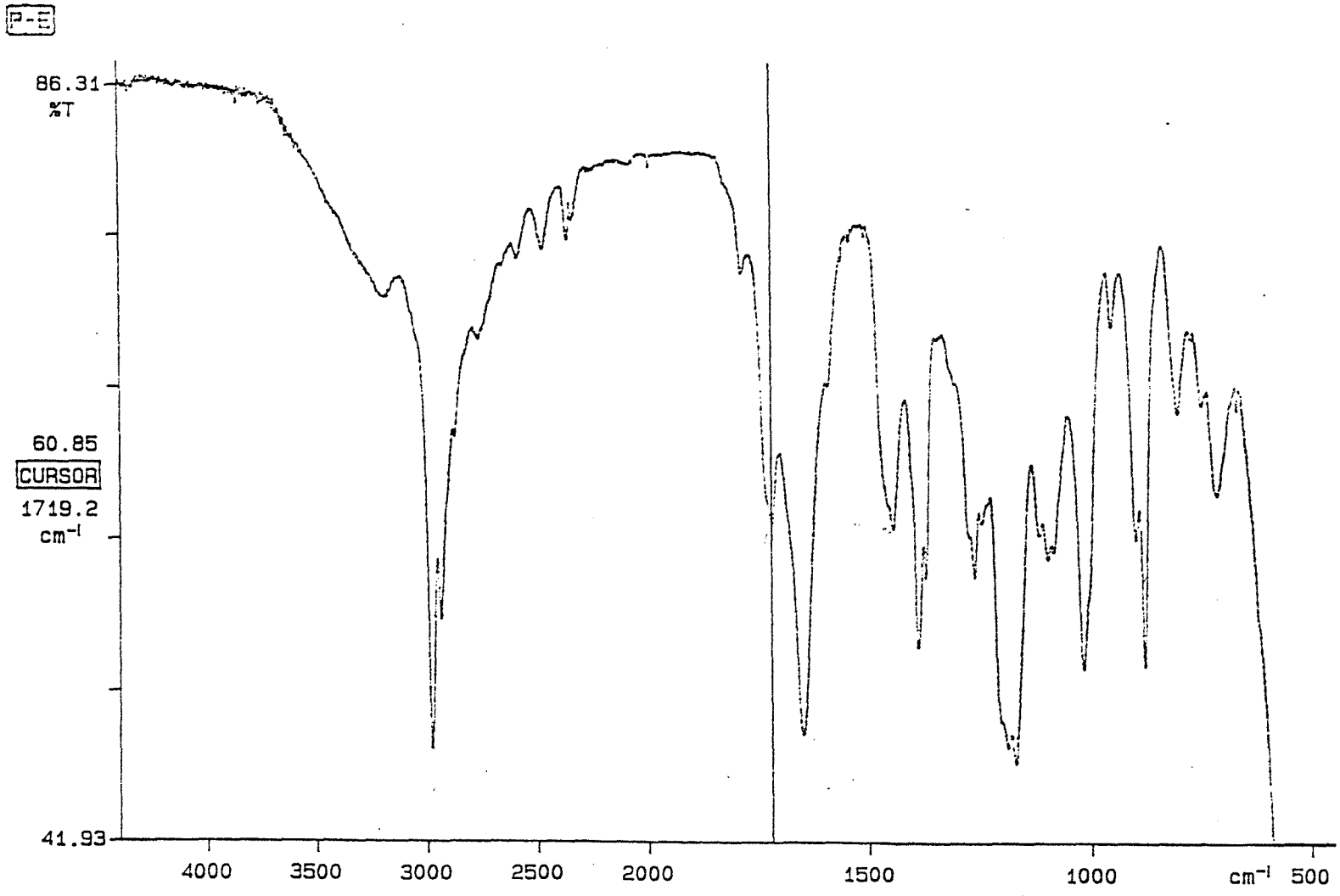


Fig.III-2 IR Spectrum of
Polymerization of
2,2,6,6-Tetramethyl-2-quinuclidone

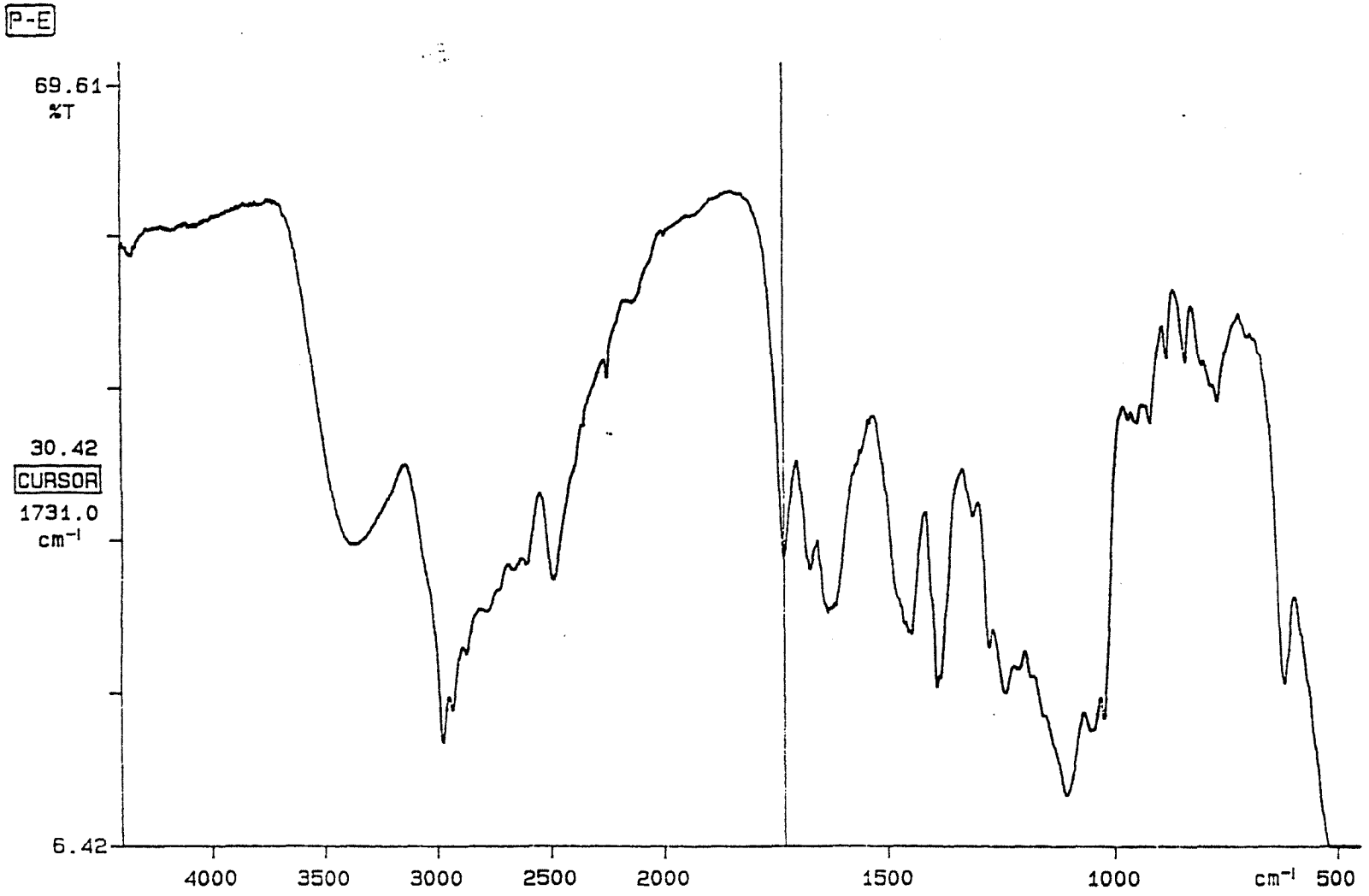


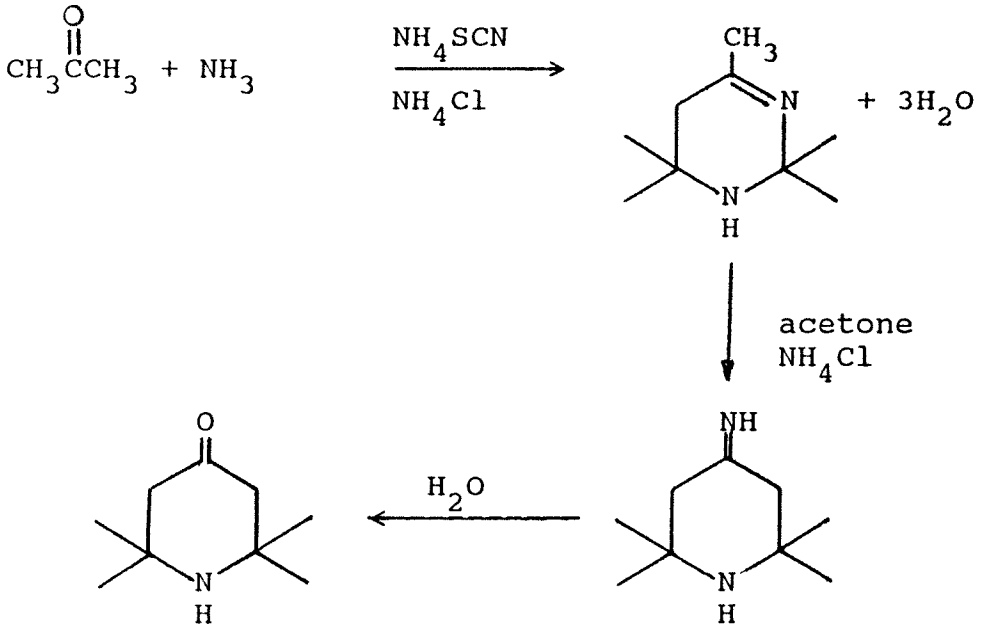
Fig.III-3 IR Spectrum upon
Standing of
2,2,6,6-tetramethyl-2-quinuclidone

b) Unanticipated keto lactam

8,8-dimethyl-1-azacyclooctane-2,6-dione

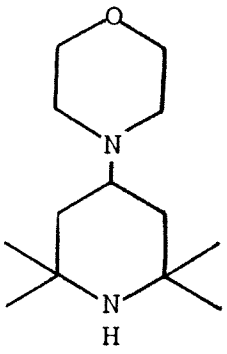
An attempt to synthesize 8,8,9,9-tetramethyl-1-azabicyclo[3.3.1]nonan-2-one was not successful and an unanticipated keto lactam suspected to be 8,8-dimethyl-1-azacyclooctane-2,6-dione, was formed.

Although our starting material, 2,2,6,6-tetramethyl-4-piperidone is commercially available, it can be readily synthesized according to the Scheme below:[14]

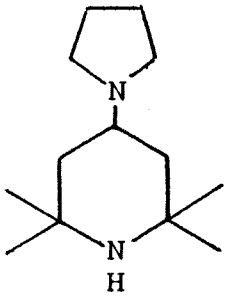


The synthesis of the keto-lactam starts with the synthesis of the pyrrolidino enamine. The morpholino enamine was also explored, but the yields were relatively low, consistent with the observation of Stork et al..[15] A considerable amount of unreacted starting material remained after water

evolution ceased. The final yield, following the purification of the pyrrolidino enamine, was 74%.



morpholino enamine

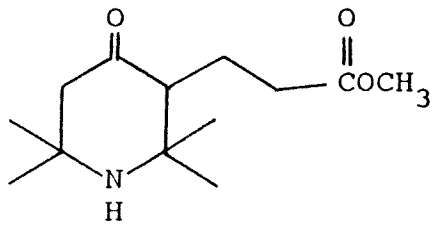


pyrrolidino enamine

The enamine could suffer attack, in principle, at the carbon or at the sterically hindered endocyclic nitrogen. In fact, steric hindrance causes C-alkylation and this, therefore, increases the utility of the enamine for synthesis of the bridgehead lactam family (See Conclusion Part 3). Reaction of the enamine with methyl acrylate, in refluxing absolute ethanol and subsequent hydrolysis, gave the keto ester (scheme 2-3) in 60% yield. Originally, we expected the carbonyl group of the keto ester was expected to be reduced to hydrocarbon. We also expected the piperidine ring to increase the solubility of the substrate in the acidic medium thus improving yield. Hence, we chose to use the Clemmenson reaction[16a,b] to accomplish this.

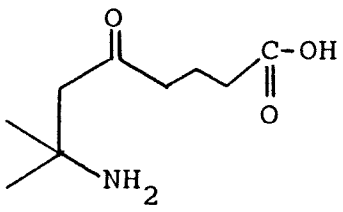
Unforturately a cleavage elimination reaction occurred under acid condition (The Clemmenson method cannot, of course, be

used for the reduction of acid-sensitive compounds) Following the Clemmenson reaction, the unanticipated compound (2) appeared.



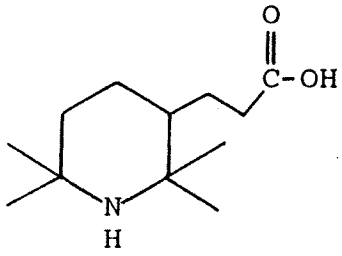
(1)

in fact



(2)

expected



(3)

Since compound (1) is sensitive to acid condition, we tried the modified Woeff-Kishner reduction procedure(Huang-Minlon procedure[17a,b])-the complementary reduction to Clemmenson reduction- to provide the desired compound (3). No matter what solvent we used, triethyleneglycol or diethylglycol, the final product was contaminated. Nevertheless, the IR spectra had showed up the keto group (1700 cm^{-1}) had disappeared.

Finally, the amino acid compound (2) was cyclized by the mixed anhydride method. Although dicyclohexylcarbodiimide

(DCC) can, in principle, be removed by its reaction in water and the product lactam was stable for 6 hours of reflux in water, even these conditions did not destroy all the DCC. Nevertheless, partial purification was achieved by refluxing the crude lactam in 95% aqueous ethanol and filtering off dicyclohexyl urea. The contaminated product was chromatographed on a silica gel column. Pure ethyl acetate eluted DCC and subsequent elution by 95% ethyl acetate/5% ethanol provided lactam free of DCC.

Unless the product is highly purified it is a highly viscous wax. Highly purified material crystallized upon standing several days. The mass spectrum (Fig. II-13) shows molecular ion corresponding to 8,8-dimethyl-1-azacyclooctane-2,6-dione. X-ray studies are under way to confirm this structure.

c) <u>1,3-Di-tert-butylaziridinone(an alpha-lactam)</u>

We synthesized 1,3-di-tert-butylaziridinone successfully several times by following the method of Sheehan[18]. Its precursor 2-bromo-3,3-dimethyl-N-tert-butylbutyramide (Scheme 3-1) was prepared from the reaction of acid chloride and tert-butylamine. next we used hydrochloric acid, aqueous sodium hydroxide, and distilled water to take out excess

tert-butyl-amine hydrochloride salt and to keep pH >7 to make sure the free amine was present. Sometimes, the undesired ester during the last cyclization (IR 1732 cm^{-1}, Fig. III-4) step was produced from water contaminated in ether as well as by the rapid drop of etheral potassium tert-butoxide.

d) <u>1-tert-butyl-2-pyrrolidinone</u>

We made an attempt to react tert-butyle bromide with sodium 2-pyrrolidinone salt (Scheme 4-2). A very low yield (<1%) was provided due to steric hindrance from attachment of the tert-butyl group. Tert-butyl iodide was tried as a substitute because this alkyl iodides are usually more reactive alkyl bromides. This procedure (Scheme 4-4) provided a 4% yield. Purification is difficult to obtain due to the low yield and the fact that the starting material (2-pyrrolidinone) has the same boiling point range as the desired compound. Further purification was accomplished by column chromatography, with 100% ethyl acetate as the mobile phase. The desired compound was in the first fraction.

Another synthetic method was tried by Hatada and Ono[19] using γ-butyrolactone as starting material. Several 1-substituted 2-pyrrolidinones were synthesized, including 1-N-tert-butyl

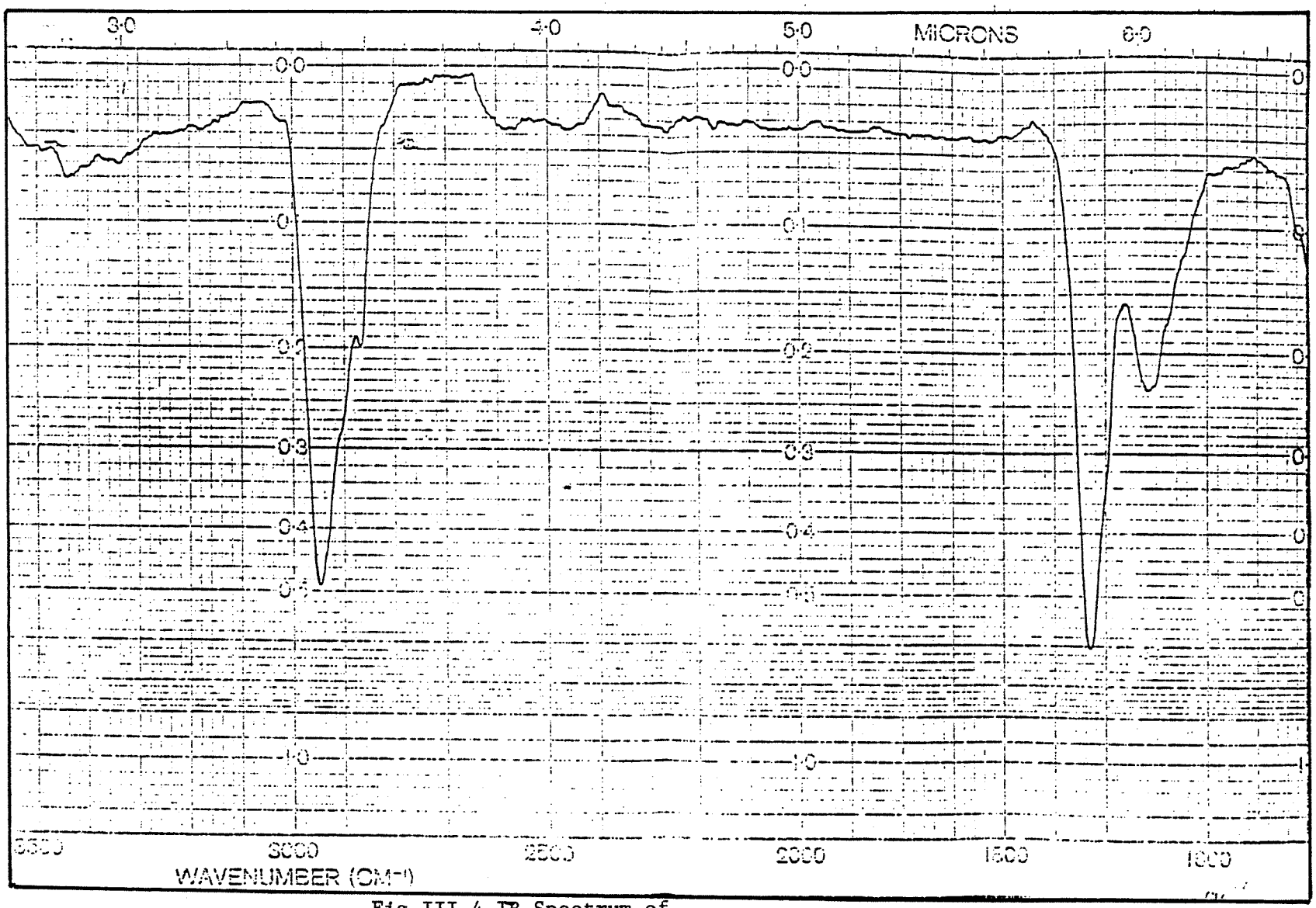


Fig.III-4 IR Spectrum of
Ester during cyclization of
1,3-Di-tert-butyl-aziridinone

2-pyrrolidinone. Compared to 1-isobutyl and 1-s-butyl 2-pyrrolidinone, which had 85% and 64% yield with IR,NMR and B.P. data, only 4% yield of 1-tert-butyl-2-pyrrolidinone with IR data was achieved. IR 1672 cm^{-1} was claimed by Hatada and Ono, while IR 1682 cm^{-1} was indicated by the desired compound we tested.

e) <u>Trans-2,3-di-tert-butylcyclopropanone</u>

Trans-2,3-di-tert-butylecyclopropanone possesses an elusive functionality because of the possible breadth of reactions associated with the carbonyl group in a three-membered ring and the synthetic relevance to the Favorskii* reaction[20]. The desired compound was produced by the reaction of potassium tert-butoxide with alpha-bromodineopentyl ketone. This reaction was carried out heterogeneously in ether and homogeneously in tert-butyl alcohol. The latter case corresponds to conditions of the Favorskii reaction. Potassium tert-butoxide and tert-butyl alcohol was chosen because of the unfavorable Favorskii reaction. However, a lot of the ester was provided ; use of even a small excess of base results in complete conversion to the undesired ester. Slow dropping and strong stirring may help prevent ester formation.

---

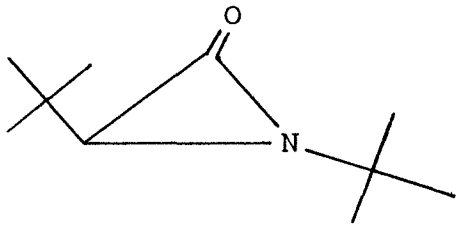
* Favorskii's skeletal rearrangement of alpha-halo-genated ketones in the presence of certain nuclephilic bases (such as hydroxides, alkoxides, or amines)gives carboxylic acid salts, esters, or amides respectively. From the viewpoint of the Loftfield mechanism, cyclopropanone is a transient intermediate. Concerted or subsequent ejection of halide ion leads to a cyclopropanone which is rapidly cleaved by alkoxide to give the rearrangement product (the ester).[21]

2.Study of Bonding and Energetics of 1,3-di-tert-butylaziridinone and 1-azabicyclo[3.3.1]nonan-2-one

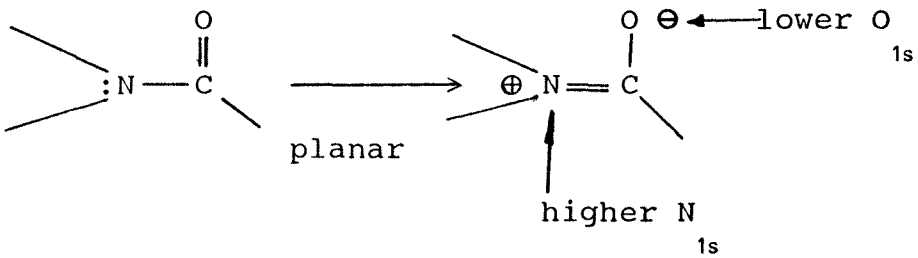
a) 1,3-di-tert-butyleaziridinone

The experimental geometry data for 1,3-di-tert-butylaziridinone are not available yet. However, the X-ray diffraction geometry data for the closeing related 1,3-diadamantyl aziridinone[22] are available. Structurally, the N atom of 1,3-di-tert-butylaziridinone is undoubtly pyramidal by analogy to the known structure of the diadamantyl analogue because of the high barrier to reach planarity at the N atom in aziridinone. The carbonyl carbon-nitrogen bond

length with 1.328 Å is shorter than the two other inner ring bond lengths of 1.446 Å (carbon-carbon) and 1.509 Å (carbon-nitrogen), indicating a certain double bond character. Nitrogen is found to be lying 0.534 Å out of the plane defined by its three substitutes. That corresponds roughly to an adamantyl group tilted by 20^{o} away from the ring plane. In the major isomer the two carbon adamantyl groups are trans to the plane of the ring.

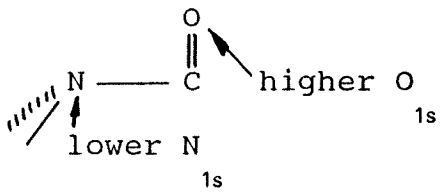


Having an idea about the geometry of the molecule, we know that the N atom in 1,3-di-tert-butylaziridinone is pyramidal. For N and O in normal amides, Pauling's resonance principle leads me to expect that the N is more positive with higher N_{1s} ionization energy (determined by ESCA); the O, should be more negative with a low O_{1s} ionization energy.



But for the non-planar (pyramidal) molecule like 1,3-di-tert-butylaziridinone, the N is more negative and the O is more positive compared to the planar normal amide. This

means that the N_{1s} ionization should be lower and the O_{1s} higher than in planar normal amide molecules.



The results of ESCA support the point view above.(ESCA were obtained by Dr. Darrah T. Thomas' Research group at Oregon State University)

	N_{1s}	O_{1s}
1-methyl-2-pyrrolidinone (MP)	405.45 ev	536.69 ev
1,3-di-tert-butylaziridinone (AZ)	405.00 ev	537.36 ev
1-azabicyclo[3.3.1]nonan-2-one (BC)	405.07 ev	536.67 ev

A crucial step going from 1-methyl-2-pyrrolidinone to 1,3-di-tert-butylaziridinone is to make the nitrogen pyramidal. The nitrogen ionization shift due to that can only be calculated theoretically. Eyermann and Jolly indicated in their calculation a 0.3 ev higher ionization energy for pyramidal ammonia compared to a theoretically planar ammonia.[23] The Oregon State University photoelectron group has done a similar calculation with the nitrogen embedded in a pyramidal and a planar aziridinone. The results show good agreement with Eyermann's value. Therefore, one might "remove" the pyramidalization effect from 1,3-di-tert-

butylaziridinone by subtracting 0.3 ev to yield a value of 407.7 ev. The result would come closer to assessing the "pure" resonance effect and comparison with 1-methyl-2-pyrrolidinone would now indicate 0.7 to 0.8 stabilization. The OSU photoelectron group has estimated the resonance hindering effect more accurately by considering partial ionization shift of the substitutent and ring effect. The -0.6 ev is responsible for the resonance hindering effect fo N_{1s} ionization energy shift from 1-methyl-2-pyrrolidinone to 1,3-di-tert-butylaziridinone.

Having considered the nitrogen atom and its ionization energy in 1,3-di-tert-butylaziridinone we now switch to the oxygen atom in the same molecule. The oxygen ionization energy of 537.36 ev in 1,3-di-tert-butylaziridinone is by far more positive than the one in 1-azabicyclo[3.3.1]nonan-2-one although the nitrogen ionization energy of these two nitrogen ionization energy of them are nearly the same. anticipating that the nitrogen hybridization and its ability to take part in resonance is about equal for both lactams, there must be another effect influencing the increased oxygen ionization energy of the alpha-lactam compared to the bridgehead one. Since the two lactams differ the most in the number of ring atoms, one immediately would suspect the ring strain effect to be the reason for the fact of the high oxygen ionization energy of the three-membered ring.

This suspicion can be reinforced by the following comparison:

	O_{1s}	IR(Carbonyl)
1,3-di-tert-butylaziridinone (AZ)	537.36 ev	1835 cm^{-1}
(three-membered ring)		
2-azetidinone (AT)	537.32 ev	1760 cm^{-1}
(four-membered ring)		
1-azabicyclo[3.3.1]nonan-2-one (BC)	536.67 ev	1680 cm^{-1}

For planar amide molecules like formamide, N-N-dimethylformamide, N-N-dimethylacetamide, 2-pyrrolidinone, A rough correlation between nitrogen and oxygen ionization energies would state that the oxygen ionization energies are lowered with decreasing nitrogen ionization energies.

	N_{1s}	O_{1s}
formamide (FA)	406.26 ev	537.72 ev
N-N-dimethylformamide (DF)	405.95 ev	537.06 ev
2-pyrrolidinone (PY)	405.62 ev	537.01 ev
N-N-dimethylacetamide (DA)	405.55 ev	536.61 ev
1-methyl-2-pyrrolidone (MP)	405.45 ev	536.69 ev

Assuming this is the overall tendency (Fig. III-5), one notices two remarkable peaks interrupting the downward line

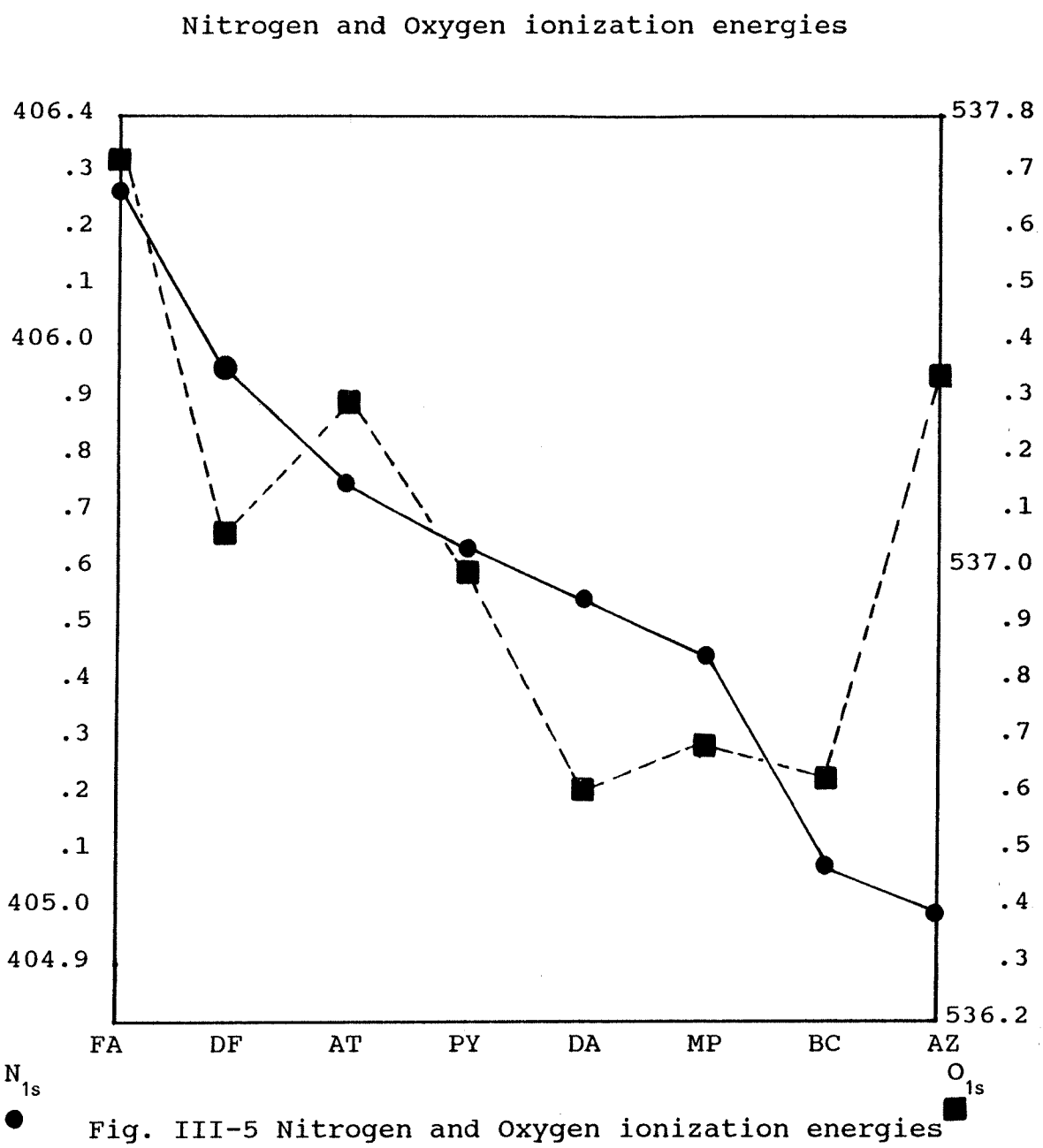
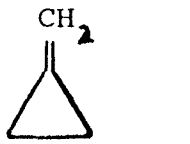
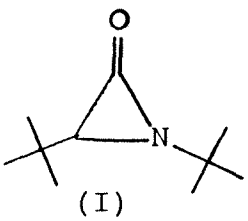


Fig. III-5 Nitrogen and Oxygen ionization energies

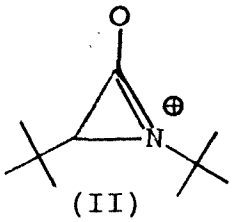
that connects the amides : 2-azetidinone, the four-membered ring and 1,3-di-tert-butylaziridinone, the three-membered ring. Note that the peak of the four-membered ring is about a third in height compared to the three-membered ring. Which means oxygen ionization shift of the four-membered ring is only one third of the three-membered (more strained) to a higher than the four-membered ring.

Except the atom ionization energy, calorimetric data is vital to estimate hindering resonance effect. Doing the similar comparison, cyclopropene is about 12 kcal/mole more strained than methylcyclopropane.





(I)



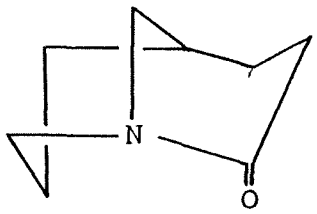
(II)

Since the N atom is undoubtly pyramidal, this should somewhat decrease the 18-20 Kcal/mole resonance energy normally found in amides and lactams. We expect greatly

reduced contribution by type(II) and reduced resonance. This may be the cause of IR spectroscopic behavior of 1,3-di-tert-butylaziridinone wherein they show carbonyl frequency about 60 cm^{-1} higher than corresponding ketones rather than about 60 cm^{-1} lower as normal amides and lactams show. Further interest in this regard is the degree of C=N double bond resonance of the type(II) normally invoked for amides or lactams. So, heat combustion of the alpha-lacatam will be valuable to prove above point of view.

b) 1-azabicyclo[3.3.1]nonan-2-one

Unfortunately there is no experimental geometry data for this molecule available. However, a bridge will compel the nitrogen atom in this molecule to be pyramidal. The steric conformation of 1-azabicyclo[3.3.1]nonan-2-one is shown in the figure below.



A nitrogen ionization energy shift from 1-methyl-2-pyrrolidinone to 1-azabicyclo[3.3.1]-nonan-2-one is -0.38 ev. The effects contributing to the shift are namely the same as for the three-membered ring but differ in magnitude.

No matter what the geometry of 1-azabicyclo[3.3.1]nonan-2-one, the nitrogen atom is pyramidal. It is not too far off if we account +0.3 ev for a pyramidal atom like 1,3-di-tert-butylaziridinone. Therefore, one might "remove" the pyramidalization effect from 1-azabicyclo[3.3.1]nonan-2-one by subtracting 0.3 ev to yield a value of 404.77 ev. But, a ring-strain effect will play no role in the bridgehead lactam where all carbons other than the carbonyl carbon are able to reach their favored sp^3 hybridization. The substituent effect was estimated about -0.2 ev by Oregon State University photoelectron group. After considering the substituent and ring effect effect, the contribution due to resonance hindering to the total shift can readily be calculated to be about -0.5 ev.

When we take a look at the oxygen ionization energy of 1-aza-bicyclo[3.3.1]nonan-2-one and compare the absolute number with the one of 1-methyl-2-pyrrolidinone. We hardly realize a difference at all, though their nitrogen ionization energies differ quite a bit. The IR carbonyl absorption agree with that too. The bridgehead lactam shows up 1690 cm^{-1} for the carbonyl which is in the normal range of lactam. This bridgehead is well below the carbonyl absorption of the three-memebered ring. More strained molecule, more oxygen ionization energy shift.

CHAPTER IV. Conclusion

Contradictory Views of the Amide Bonding

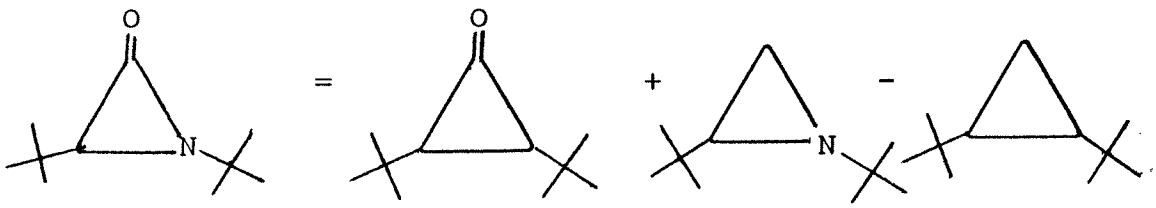
The experimental ionization energy, has shown the atomic charge on nitrogen in two nonplanar lactams to be more negative than in comparable planar compounds. According to the Classical Resonance Theory of Pauling, the pyramidal sp^3-hybridized nitrogen is responsible for the relatively increased electron population of nitrogen on nonplanar lactams because of the resonance hindrance. The nitrogen ionization energy shift due to the hindrance of resonance (actual molecule minus hypothetical molecule with planar nitrogen) is found to be -0.6 ev for 1,3-di-tert-butyl-aziridinone and -0.5 ev for 1-azabicyclo(3.3.1)nonan-2-one.

The experimental results contradict the calculation of Wiberg and Laidig. Wiberg's calculated results for foramide-showing a more positive nitrogen in the saddle conformer(nevertheless, it is nonplanar) than in the planar

conformer-can not be transferred to larger nonplanar lactam investigated here.

Further comparison for the alpha-lactam

Until now, very few three-membered ring compounds are found to be stable. 1,3-di-tert-butyl-aziridinone is one of them. This alpha-lactam can be synthesized quantitatively. Working with the alpha-lactam, it is not difficult to get 1,2-di-tert-butyl-aziridinine in spite of a 20% overall yield using the method of Sheehan.[23] Considering the best analogue for the alpha-lactam focused on the carbonyl part, perhaps the 2,3-di-tert-butylcyclopropanone, which was made twenty years ago by F. Greene,[20] is the best choice.

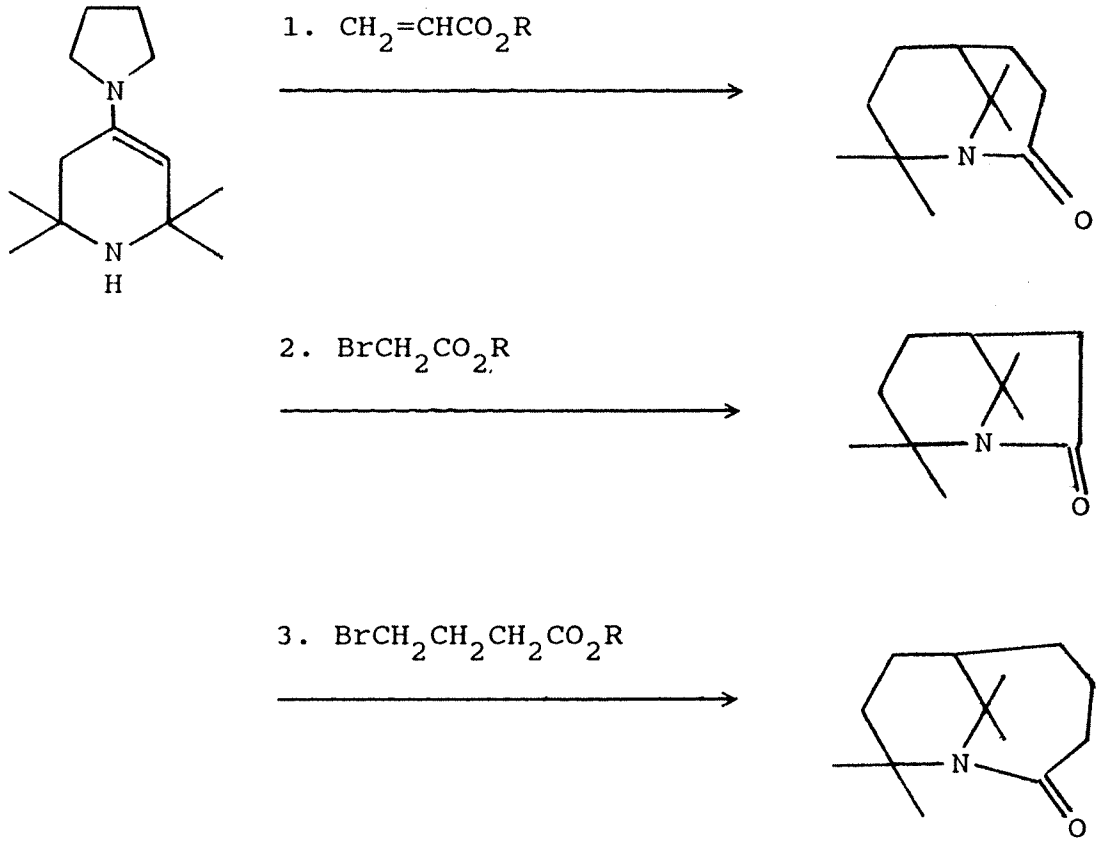


The comparison between them might give us more information about three-membered ring strained lactam.

A excellent starting point for bridgehead lactam

It is surprising to us that the bridgehead lactam has received so little attention. No one has explored this group in a systematic manner; indeed, the literature citations for

this class are few. In fact, few bridgehead lactams were synthesized. The pyrrolidino enamine may be an excellent starting point for this series of compound. We could create different ring size compounds, depending on different material as shown in the following scheme.



References

(1) Pauling, L. "The nature of chemical bond", 3rd. Cornell University press: Ithaca, NY, 1960, pp. 281-282.

(2) Wiberg, K. B. ; and Laidig, K. E., J. Am. Chem. Soc. 1987, 109, 5935.

(3) Huheey, J. E. "Inorganic Chemistry", 3rd. Harper & Row, Publishers, NY, 1983, pp. 169-175.

(4) Hall, H. K.,Jr. ; El-Shekeil, A. Chem. Rev. 1983, 93, 81.

(5) Bredt, J. ; Thouet, H. ; and Schmitz, J., Ann. 1924, 437, 1

(6) Lukes, R., Collect. Chem. Commun. 1938, 10, 848

(7) Yakhontov, L. N. ; and Rubsitov, M. V., J. Gen. Chem. USSR, 1957, 27, 83.

(8) a) Pracejus, H., Chem. Ber. 1959, 92, 988.
b) Pracejus, H., Chem. Ber. 1965, 98, 2897.

(9) a) Levkoeva, E. I. ; Nikitskaya, E. S. ; Yakhontov, L. N. Khim. Geterot. Soed. 1971(3), 378.
b) Nikits-kaya, E. S. ; Sharapov, I. M. ; Levkoeva, E. I. ; Usovskaya, V. S. ; Vlasov, A. S. ; Kukushkina, T. E. ; Yakhontov, L. N. ; and Rubsitov, M. V., Khim-Farmats. Zh., 1970, No. 10, 58.

(10) a) Hall, H. K., J. Am. Chem. Soc. 1960, 82, 1209.
b) Hall, H. K., Jr. ; Shaw, R. G., Jr. ; Deutschmann, A., J. Org. Chem. 1980, 45, 3722.

(11) Steliou, K. ; and Poupart, M., J. Am. Chem. Soc. 1983, 105, 7130.

(12) Greenberg, A., Tu,Quansing's masters thesis, NJIT, 1988.

(13) a) Buchanan, G. L., J. Chem. Soc, Chem Commun. 1981, 814.
b) Buchanan, G. L., J. Chem. Soc. Perkin Trans I, 1984, 2669.
c) Buchanan, G. L.; Kitson, D. H.; Mallinson, P. R.; Sim, G. A.; White D.; Cox, P. J., J. Chem. Soc. Perkin Trans. II , 1983, 1709.

(14) Reference of Shen, D. K., Biotechnoly lab. NJIT.

(15) Stork, G.; Brizzolara, A; Landesman, H.; Szmuszkovicz ; Terrell, R., J. Am. Chem. Soc. 1963, 85, 207.

(16) a) King, F. E., J. Chem. Soc., 1935, 982.
b) Bradlow, H. L.; Vanderwerf, C. A., J. Am. Chem. Soc, 1947, 69, 1254.

(17) a)Huang, M., J. Am. Chem. Soc., 1946, 68, 2487.
b)Leonard, N. J. ; Nommensen, E. W., J. Am. Chem. Soc., 1949, 71, 2808.

(18) Sheenhan, J. C.; Beeson, J. H.; J. Am. Chem. Soc. 1967, 89, 304.

(19) Hatada, K.; Ono, Y., Bull. Chem. Soc. Jan. 1977, 50, 2517.

(20) Pazos, J.; Pacifici, J.; Pierson, G.; Sclove, D.; Greene, F., J. Org. Chem. 1974, 39, 1990.

(21) Kende, A. S., "Organic Reaction", 1960, vol.11, pp 261

(22) Wang, A. H. -J; Paul, I. C.; Talaty, E. R.; Dupuy, A. E., J. Chem. Soc., Chem. Commun. 1972, 43.

(23) Eyermann, C. J.; Jolly, W. L., J. Phys. Chem. 1983, 87, 3080.

(24) Sheehan, J. C.; Tulis, R. W., J. Org. Chem. 1974, 39, 2264.