5-31-1988

Synthesis of strained bridgehead lactams

Quansing Tu
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 Bridgehead Lactams

Quansing Tu, Master of Science in Chemistry, 1988

Thesis Directed by : Dr. A. Greenberg, Professor in Department of Chemistry.

While 1-Azabicyclo(3,3,1)nonan-2-one was originally thought to be difficult to synthesize, two different methods (DCC and di-n-butyltin oxide) will produce it with high yield. DCC is a strong reagent for absorbing water; the di-n-butyltin oxide method uses a Dean-Stark to remove water and is very useful. Bredt's rule influences the synthesis and stability of the N-bridgehead bicyclic lactams, this is apparent in the lactam series in the behavior of the (2,2,2) compounds and the (3,2,1) compound which we tried unsuccessfully to synthesize.

SYNTHESIS OF STRAINED BRIDGEHEAD LACTAMS

By

Quansing Tu

Thesis submitted to the Faculty of The Graduate School of
the New Jersey Institute of Technology in partial fulfillment of
the requirements for the degree of
Master of Science in Chemistry
1988

APPROVAL SHEET

Title of Thesis : Synthesis of Strained Bridgehead Lactams

Name of Candidate : Quansing Tu

Master of Science in Chemistry

1988

Thesis and Abstract Approved by:

Dr. Arthur Greenberg / Date
Professor of Chemistry Department and
Co-Director of Air Pollution Research
Laboratory

Signatures of other members of the thesis committee :

Dr. Carol Venanzi Date
Professor of Chemistry Department

Dr. Barbara Kebbekus Date
Professor of Chemistry Department
Chairperson of the Department of
Chemical Engineering, Chemistry and
Environmental Science and Co-Director
of the Air Pollution Research Laboratory

VITA

Name : Quansing Tu

Permanent address:

Degree and date to be conferred : Master of Science
Chemistry,
1988.

Date of birth :

Place of birth :

Collegiate institutions attended :	Dates	Degree	Date of Degree
New Jersey Inst. of Tech.	1986-88	M.S.Chem	May 1988
Chinese Culture University	1976-80	B.S.Chem.	June 1980

Position held : Graduate Assistant,
Department of Chemistry,
New Jersey Institute of Technology.

TABLE OF CONTENTS

LIST OF FIGURES

ACKNOWLEDGMENTS

I would like to express my appreciation and gratitude to my advisor, Dr. Arthur Greenberg for his guidance and assistance in the accomplishment of this study. I would like to thank Lee Bernstein and Chin-Fang Juang for encouraging me in experiments and in spirit.

I would also like to express my love to my family, for their encouragement, understanding, and support, to make this possible.

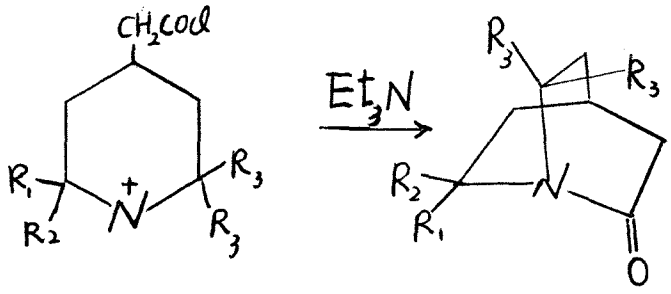
I. INTRODUCTION

Lactams are intramolecular (cyclic) amides: compounds formed by the (formal) elimination of water from an amino and a carboxyl group in the same molecule. Recently, there has been a renewed interest in bicyclic bridgehead lactams and some of these were thus synthesised[1,2]. The interest in bicyclic bridgehead lactams is due, in part, to their apparent violation of Bredt's Rule. In 1938, Lukes[3] noted that lack of resonance stabilization of the N-C=O moiety in the same manner as Bredt's Rule, forbids bridgehead lactams. Bredt's Rule expressed the idea that carbon - carbon double bonds at the bridgeheads of certain bicyclic systems should be incapable of existence. The reason for this prohibition is that in such olefins p orbitals, are held perpendicular to each other. An anti Bredt bicyclic lactam, if it could be synthesized, would posses an additional driving force for reaction in general and polymerization in particular compared to the bicyclic bridged lactams because the N-C=O resonance energy would be recovered in the polymer.

In 1979, Dr. H.K. Hall[4] first published the synthesis of 1-azabicyclo[3,3,1]nonan-2-one. However, the preparation is low yield (7%) in part due to ready polymerization under the conditions of generation.

The lactam class is considered an important research area since it also contains penicillins, cephalosporins and a variety of other bioactive compounds. Studies of enthalpies of reaction and formation as well as structural studies could provide data useful in assessing energetics and possibly kinetics of ring-opening polymerization. Such studies may be useful in understanding the structure and function of peptides, proteins and enzymes. It is also possible that some of these compounds could be useful pharmaceutical agents.

H. Pracejus[5,6] used ethyl chloroformate and triethylamine to react with amino acylchlorides to synthesize three derivatives of 2-quinuclidone (1-3).



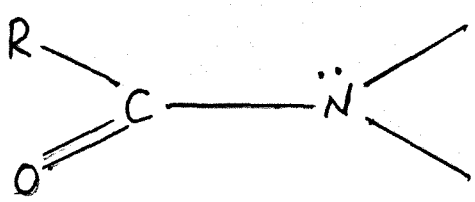
1, $R_1 = R_2 = R_3 = H$

2, $R_1 = R_2 = H$; $R_3 = CH_3$

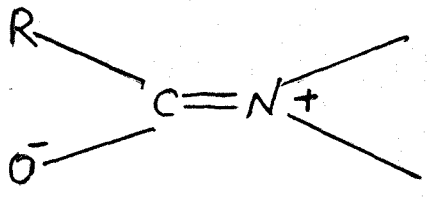
3, $R_1 = H$; $R_2 = R_3 = CH_3$

" It is interesting that these first lactam linkages remain the most highly strained known to date. Their aminoketone-like properties and high sensitivity to moisture have made them great examples in organic chemistry texts of results of loss of resonance "[7]. Although some of these lactams are very sensitive to moisture and easily

polymerized, these factors do not necessarily limit the study and synthesis of these compounds. From the structure of the lactam linkage



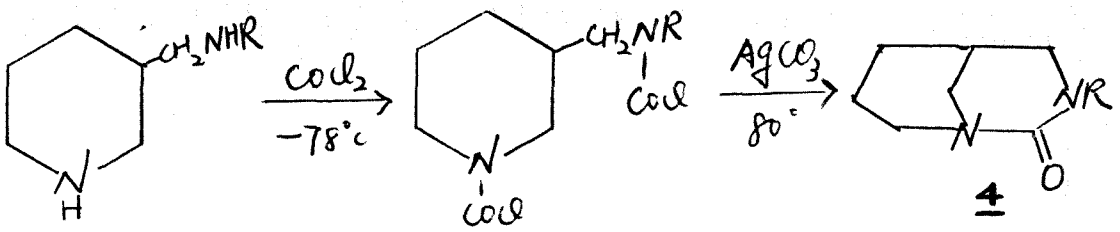
A



B

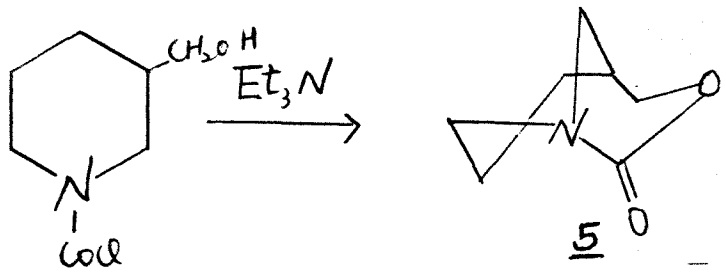
we can see that an amide or a medium-ring lactam should have a planar functional group due to resonance stabilization involving structure A and B. The 20 kcal/mol resonance usually assumed reflects the rotational barrier of simple amides[8]. A small bridgehead lactam such as 2-quinuclidone and its derivatives will lack part or all of the resonance stabilization. The amide or lactam group need not be confined to small bridgehead bicyclic systems in order to be twisted. Small monocyclic lactams are exclusively cis while the larger rings revert to the trans structure characteristic of simple amides. Medium-ring lactams can adopt the trans structure but this is accompained by twisting of the lactam linkage.

In addition to the parent compound, other members of the 3.3.1 lactam series have been reported. There also have been some related molecules synthesised such as 3-isopropyl-1,3-diazabicyclo [3,3,1] nonan-2-one[9],



R=Isopropyl

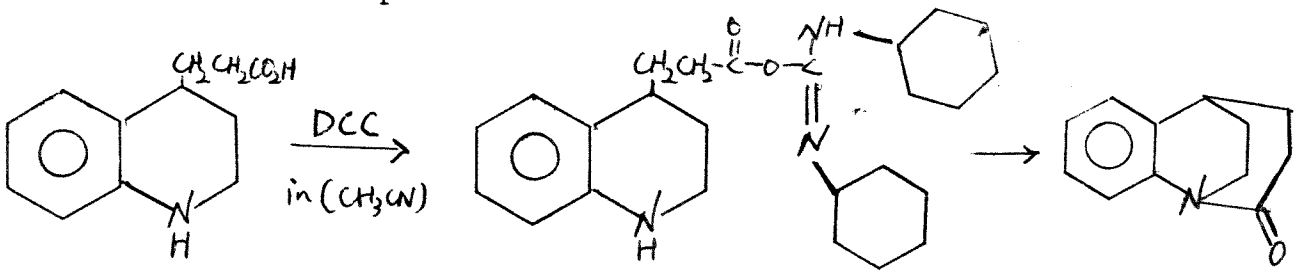
a bicyclic urea found to be stable toward boiling water, toluenesulfonic acid and phosphoric acid. The infrared carbonyl absorption at 1650 cm^{-1} further indicated the strainless conformation of this compound. Buchanan[10] reported synthesis of 5-phenyl-1-azabicyclo[3,3,1]nonan-2-one from the amino acid via the acid chloride-triethylamine route (10 % yield). From x-ray cystallography it has a trans lactam ring[11]. Another related lactam is 1-aza-3-oxabicyclo[3,3,1] nonan-2-one which is similiar to 1-azabicyclo[3,3,1]nonan-2-one. It was obtained via the acid chloride-triethylamine closure as shown below[10,11]



Hall, Shaw, and Deutschmann synthesized the related lactam, 1-azabicyclo[3,3,1]nonan-2-one by heating the amino acid between 180-285 ^{0}C at 0.05 torr and catching the lactam in a cold receiving flask[4]. The yield was about 7% as noted earlier. It is because the lactam polymerizes readily. When

we compare 1-azabicyclo[3,3,1]nonan-2-one with bicyclo [3,3,1]nonan-2-one, the IR adsorption showed that the lactam exhibits lower frequency than the corresponding ketone when one compares carbonyl groups (1680 cm^{-1} and 1720 cm^{-1})[12]. If one compare the carbonyl frequencies for 1-azabicyclo[2,2,2]octan-2-one and the corresponding ketone (1750 cm^{-1} and 1731 cm^{-1})[12], it is clear that one sees the opposite result. Thus,while the 2.2.2 system has very little resonance stabilization, the 3.3.1 system has significant stabilization. The related compound isopropyl-1,3-diazabicyclo[3,3,1]nonan-2-one has a lower absorption at the C=O group (1650 cm^{-1}) than the lactam and this is explained by an additional nitrogen atom adjacent to the carbonyl carbon which serves to stabilize the bridgehead C=O moiety by electron donation---an effect normally observed in ureas.

A new lactam system was obtained via dicyclohexylcarbodiimide (DCC) closure of the precursor amino acid at room temperature:[2]



6

The unsubstituted compound was previously made by

the mixed anhydride techniques which Somayaji and Einspahr[2] found less convenient than the DCC technique. Therefore, we used this method to synthesize 1-azabicyclo[3.3.1]nonan-2-one, and it was easily obtained (yield is 30.2%) which was proved by IR absorption compared with the standard spectrum. At the same time, it can be obtained by the di-n-butyltin oxide method[13] (yield is 68.5%). This encouraged us to attempt the synthesis of 1-azabicyclo[3,2,1] octan-7-one (less one carbon atom) via 4-piperidyl acetic acid hydrochloride. We also synthesized 1,3-Di-t-butylaziridinone via 3,3-dimethylbutyryl chloride reacted with bromine and formed 2-bromo-3,3-dimethyl-N-t-butylbutyramide, then reacted with potassium t-butoxide.[14]

II EXPERIMENTAL SECTION

A. Material and Apparatus

1.Solvents:

Acetonitrile (HPLC grade, Aldrich #27071-7), Triethylamine (Aldrich #23962-3), Ethyl Chloroformate (FLUKA #23131), Benzene (HPLC grade Aldrich #27070-9), Hydrochloric acid (ACS grade Fisher Scientific #3700-32), Sodium Hydroxide (ACS grade Fisher Scientific #3722-1), Methanol (HPLC grade, Aldrich #27047-4), Calcium Hydride(FLUKA #21170), N,N-dicyclohexylcarbodiimide (Aldrich # D8000-2), 95% Ethyl Alcohol (FLUKA #02890), Toluene (HPLC grade Aldrich #27037-7), Chloroform(HPLC grade Aldrich #27063-6), Ethyl acetate(Anhydrous 99% Aldrich #15485-7), Petroleum Ether (Spectrophotometric grade Aldrich #26173-4), Dichloromethane (HPLC grade Aldrich #27056-3). Diethyl Ether (AC grade Fluka), Potassium tert butoxide (AC grade Fluka), Tert-Butylamine (AC grade Fluka), Bromine (AC grade Fluka), Tert-Butylacetyl Chloride (AC grade Fluka).

2.Melting point Apparatus : Thomas Hoover capillary melting point apparatus.

3.Infrared spectrophometer : Perkin-Elmer 1310 spectrometer.

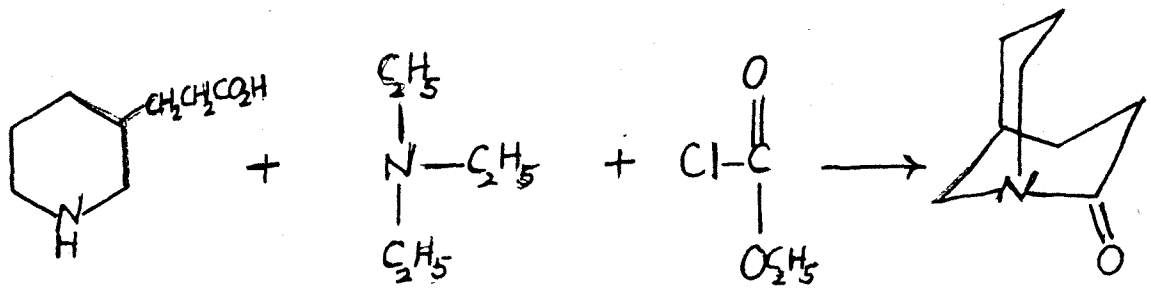
4.Ultra-Violet lamp: Model Uvsl-25 mineralight lamp.

5.Thin layer chromatography (TLC): Quality analysis by Merck Kieselgel 60 GF-254, silica gel pre-coated aluminium plate, depth is 0.25-mm. Purification and separation by E. Merck F254 20 * 20 cm.

6.Column Chromatography: Adsorption reagent by E. Merck Kieselgel 60, .04-.063 mm , 400-230 mesh silica gel 60.

B. Synthesis of 1-Azabicyclo(3,3,1)-2-one

1. Mixed Anhydride Reaction[10,11]



7

Weighed 405.6 milligram of β-(3-piperidyl) propionic acid (mp is 177 ^{o} C prepared by K. Zyla according to ref 15; The infrared spectrum is shown in Fig.1 , the homologue ∝-3-piperidyl acetic acid was similarly prepared, mp is 235^{o}C - 238^{o}C, it's IR is shown in Fig.2), then added 50 ml of dry acetonitrile (dried over molecular sieve 4A). To this solution, 0.38 ml of triethylamine was added drop by drop; 0.26 ml of ethyl chloroformate was also added dropwise. This mixture was then allowed to stir at room temperature for 24 hours.

The mixture was filtered, evaporated and redissolved in 50 ml of dry benzene. The solution was again filtered, evaporated to remove solvent (benzene). The yield is 28.4% (102.3 mg yellow liquid) The infrared of this product is shown in Figure 3, which shows two bands at 1730^{-1} cm and 1680 cm^{-1} .

*MM of β-(3-piperidyl) propionic acid is 158.0 gram.

*Density of triethylamine is 0.726.

*Density of ethyl chloroformate is 1.135.

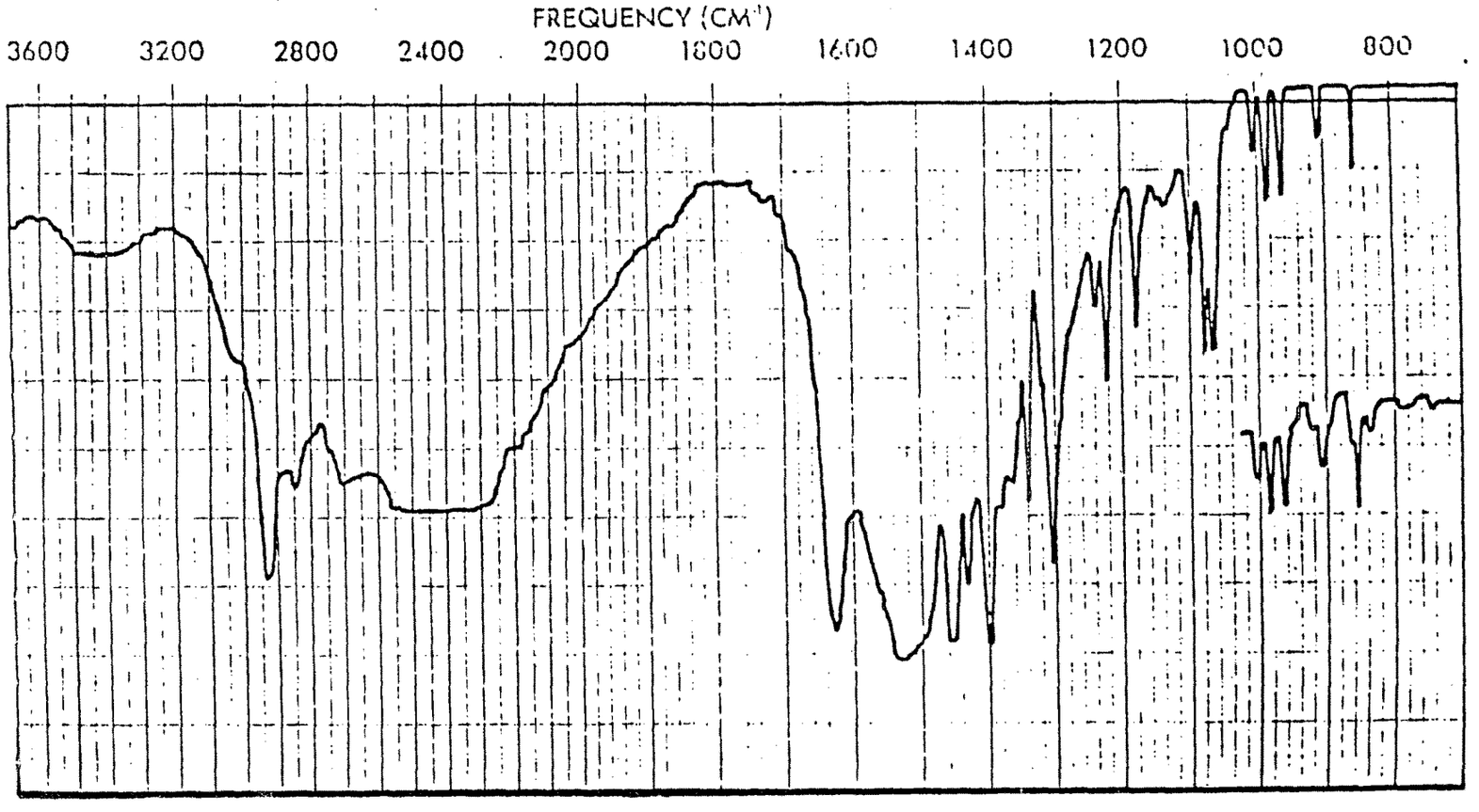


Figure 1. β-(3-piperidyl)propionic (KBr pellet)

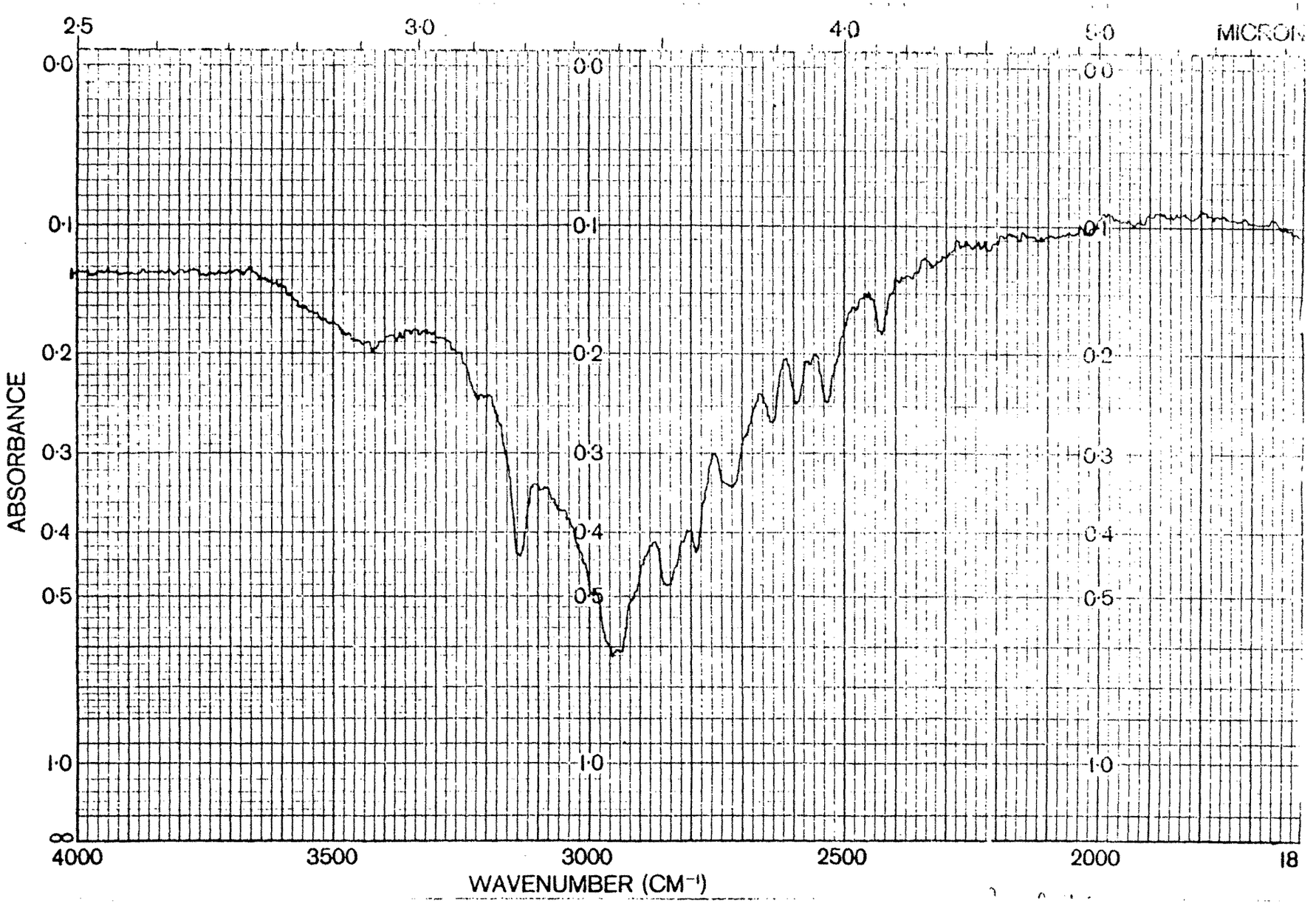
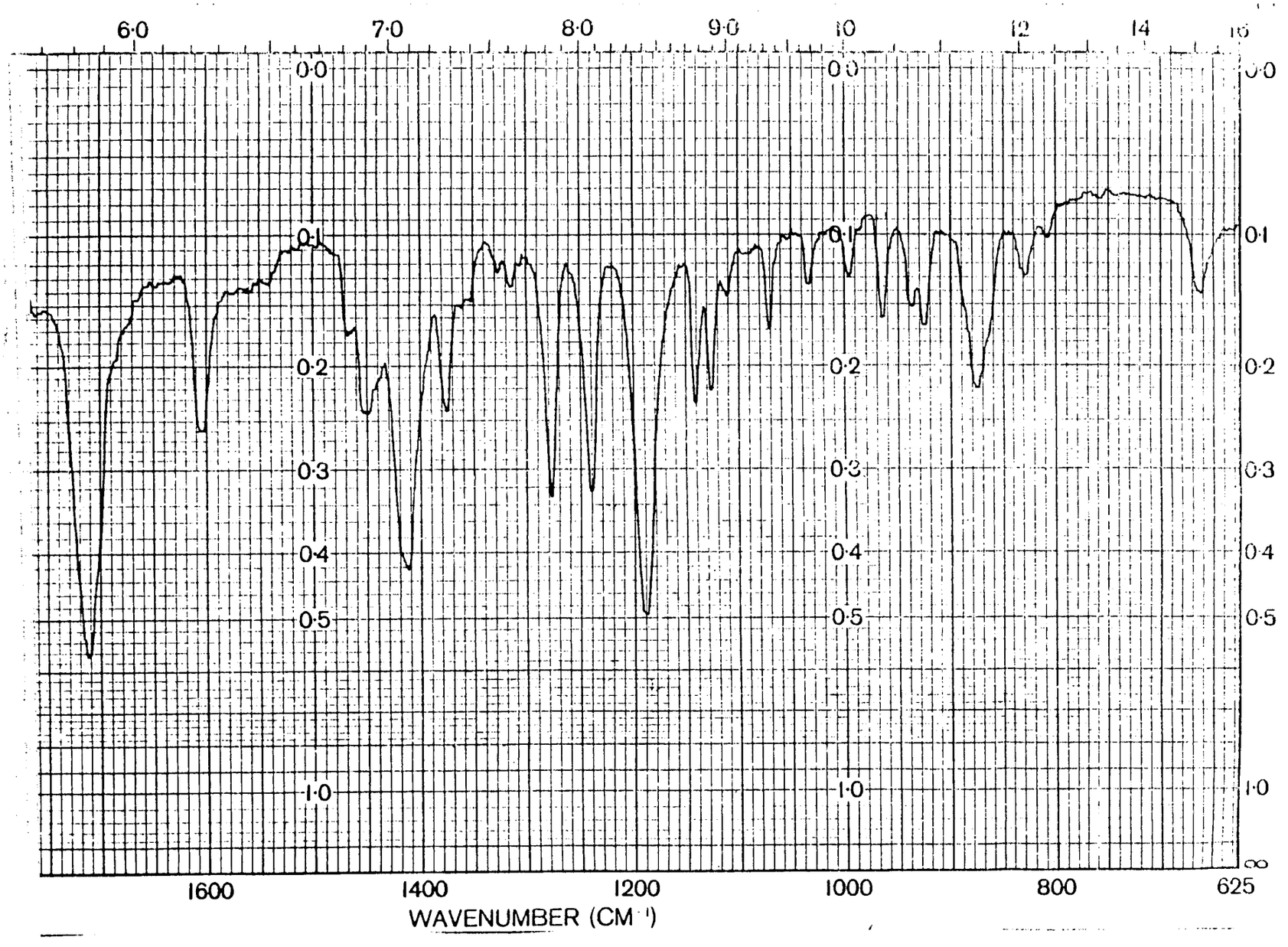


Figure 2 α-3-piperidyl acetic acid (KBr pellet)


6·0
7·0
8·0
9·0
10
12
14
16
0·0
0·1
0·2
0·3
0·4
0·5
1·0
1600
1400
1200
1000
800
625
WAVENUMBER (CM⁻¹)

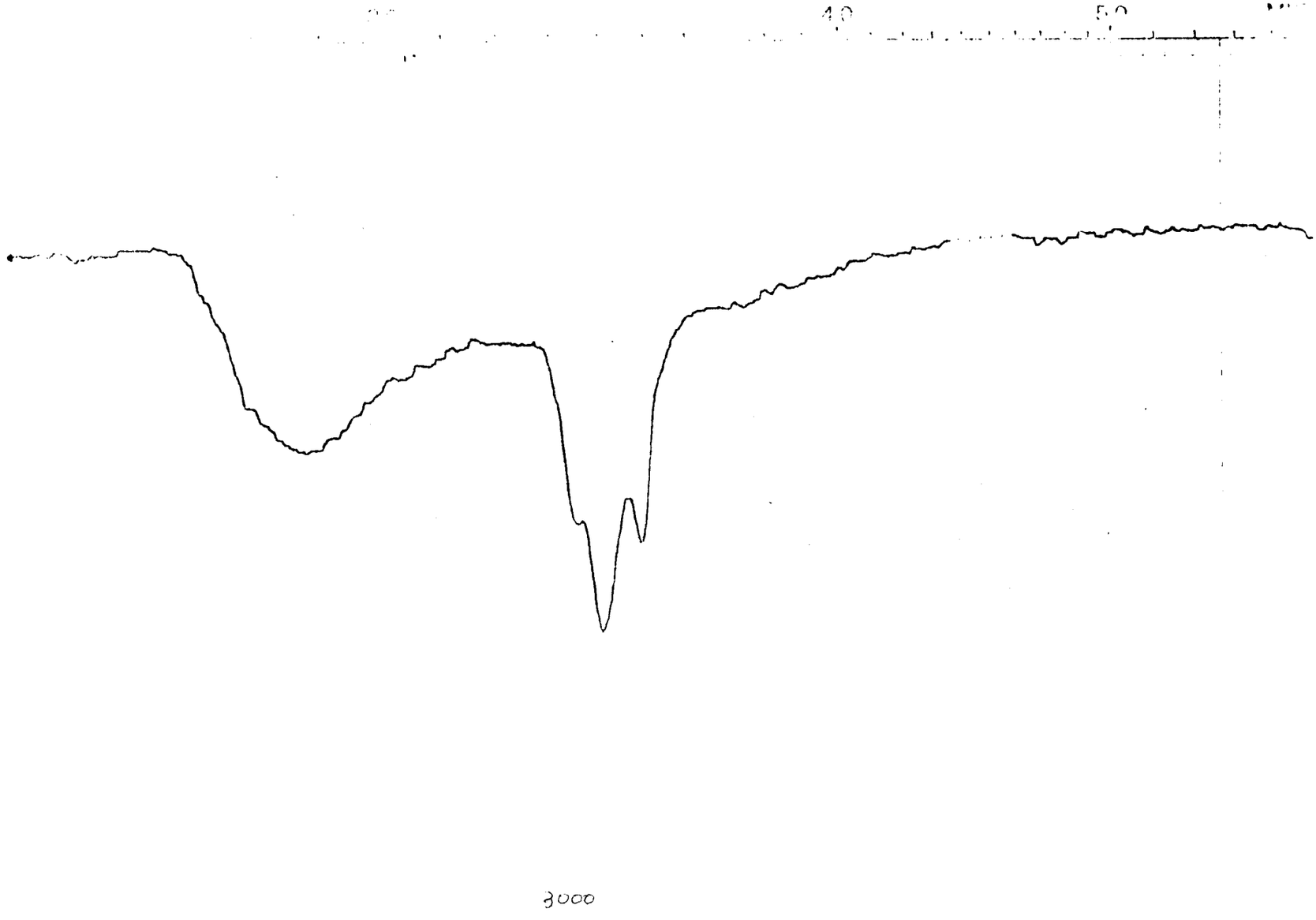


Figure 3. 1-azabicyclo(3,3,1)nonan-2-one

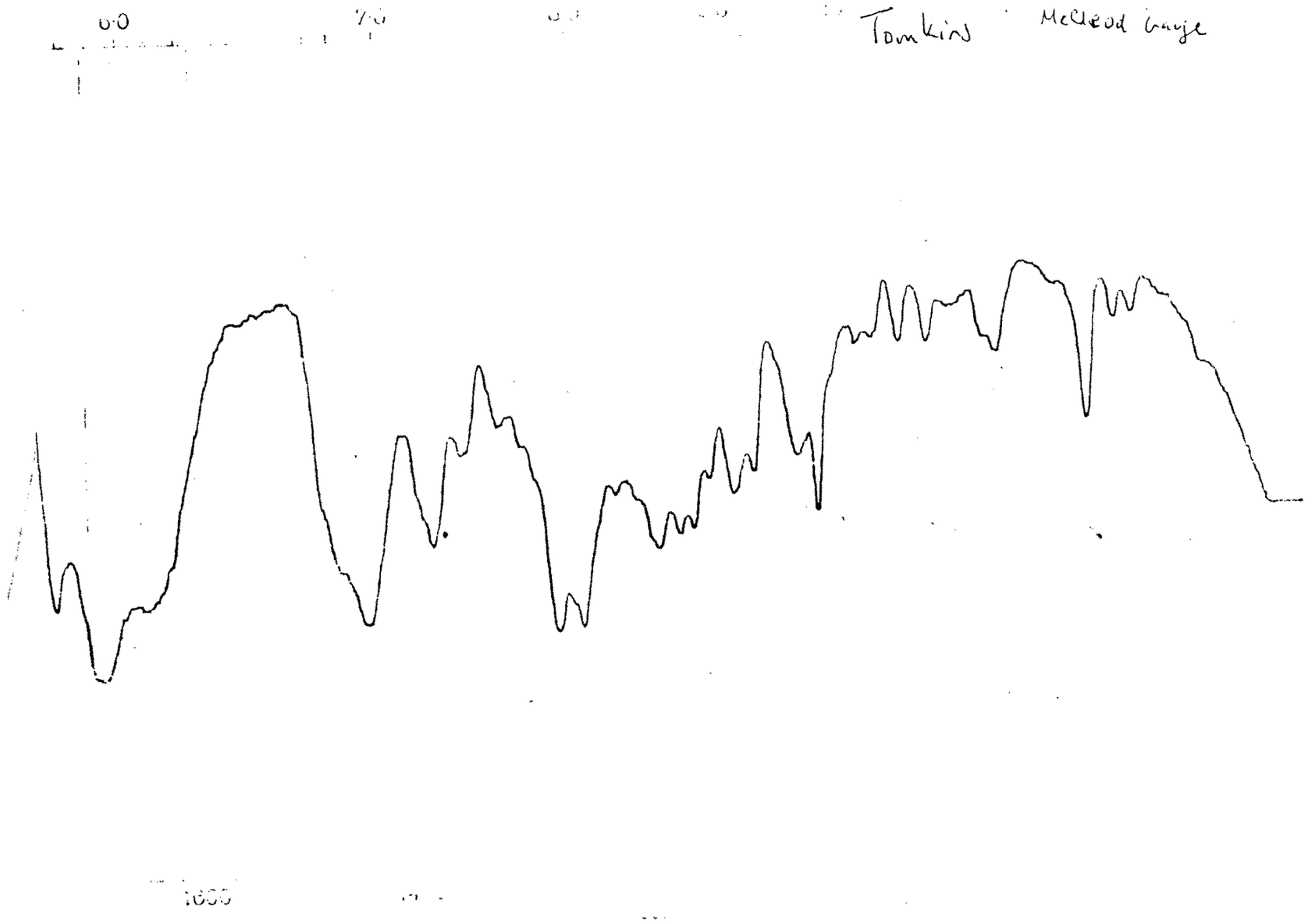
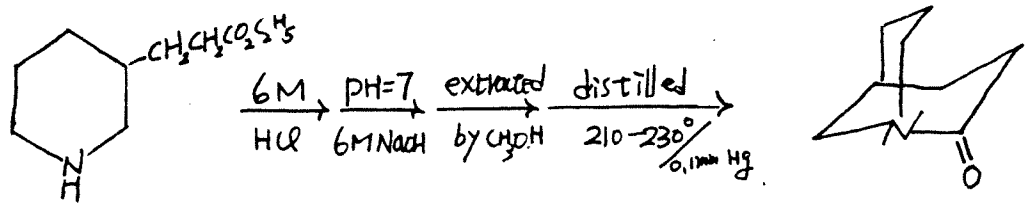


Figure 3. 1-azabicyclo(3,3,1)nonan-2-one

2. Generation of Amino Acid from ethyl-β-(3-piperidyl)-propionate[16]



Hydrolysis of ethyl-β-(3-piperidyl)propionate:

In order to make more starting amino acid, hydrolysis of ester by-products from previous reaction was performed. Take 1 gram of ethyl-β-(3-piperidyl) propionate (prepared by K. Zyla), and add 28 ml 6 M hydrochloric acid . Reflux 7 hours and allow to stand overnight.

Adjust to pH 6 using 6M sodium hydroxide. Evaporate solvent to dryness. Using methanol, extract the residue and filter it, then evaporate the solvent in vacuo and distilled at 210-230° C/0.1 mm Hg.
The resulting material is a white solid (which is left in the flask after distilling off the more volatile material). The infrared spectrum (Figure 4) of this material shows no absorption around 1700 cm^{-1}, but it has absorption between 1200 cm^{-1} and 1450 cm^{-1}, and has absorption at 2100 cm^{-1} . It could be the starting amino acid.

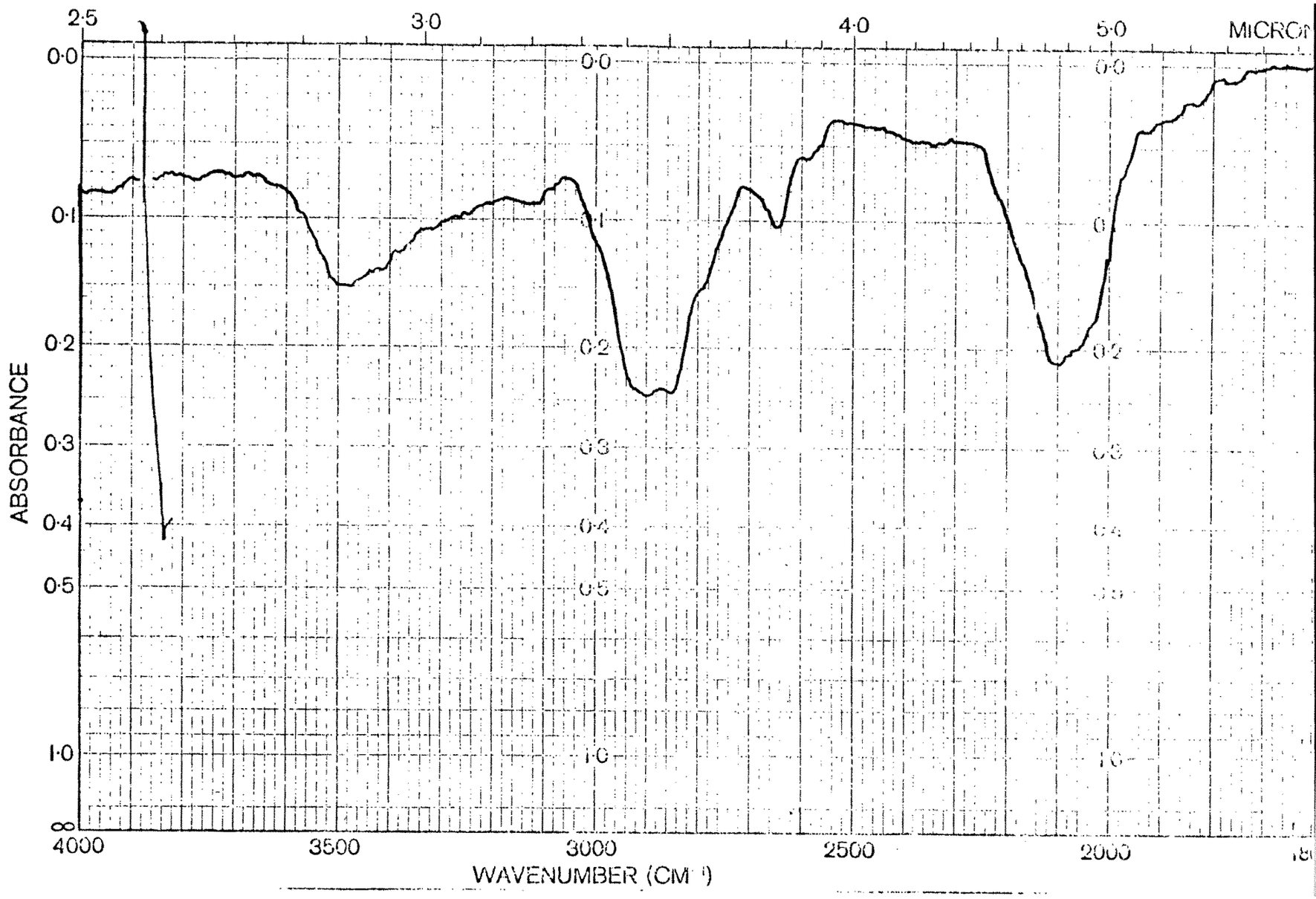
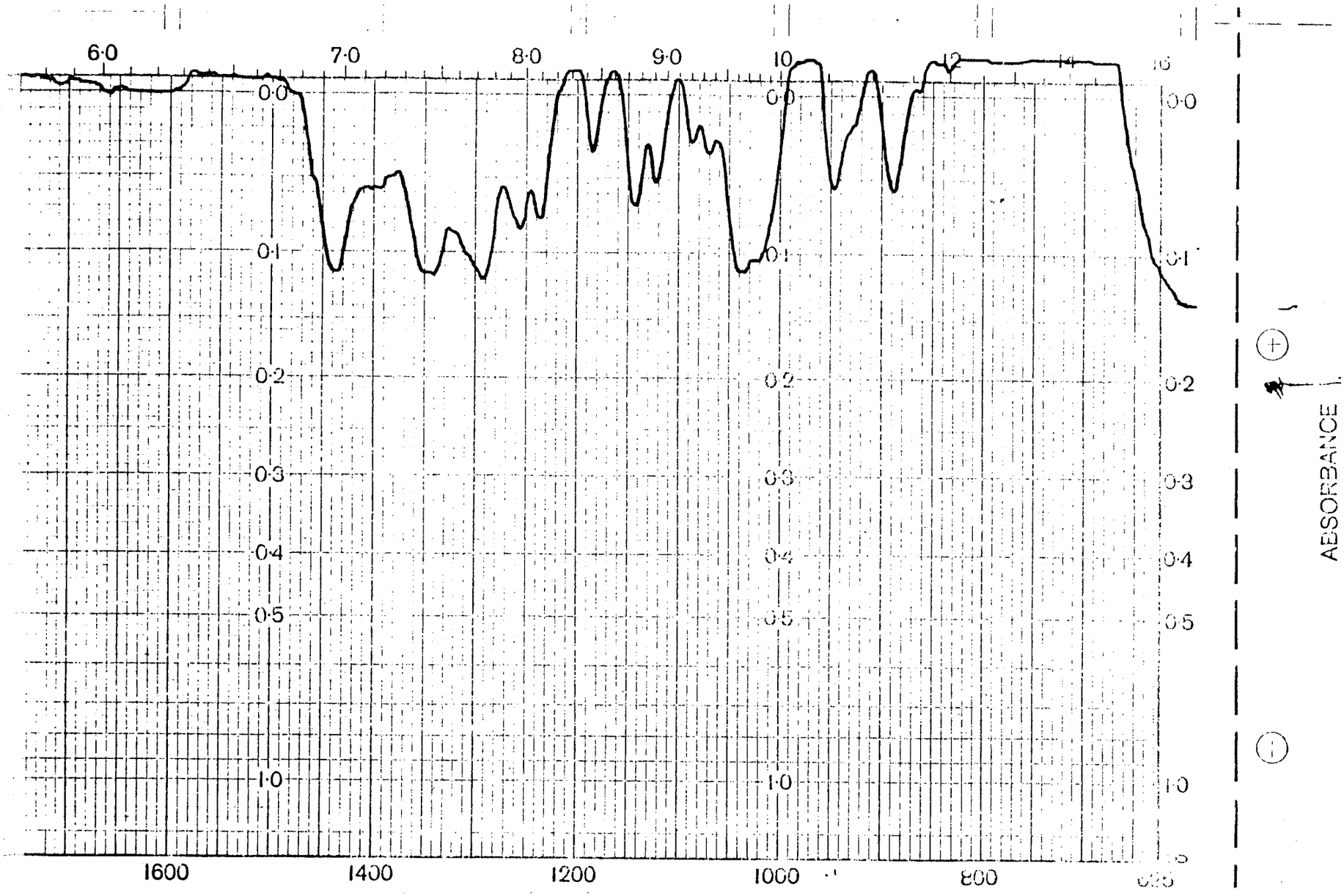
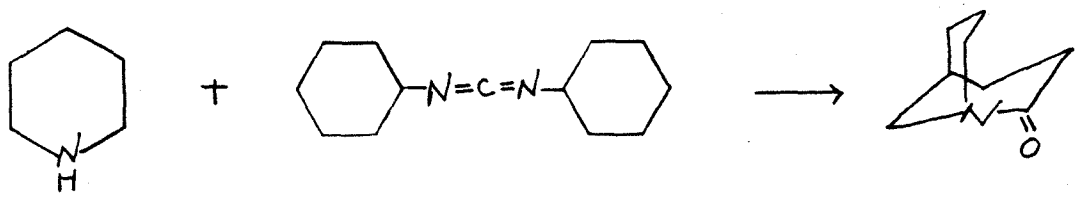


Figure 4. Mixture of starting amino acid and DCC


6·0
7·0
8·0
9·0
10
12
0·0
0·1
0·2
0·3
0·4
0·5
1·0
1600
1400
1200
1000
800
ABSORBANCE

3.Reaction with DCC[2]



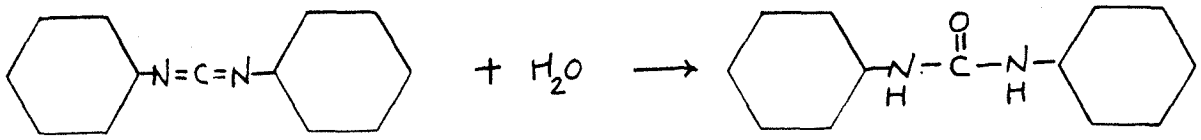
Set up a distillation apparatus using 250 ml round bottom flask (all glassware dried by putting in the oven at 150 ^{o}C for 1 hour). After putting 150 ml acetonitrile (HPLC grade) into the flask, one takes calcium hydride (CaH_2) and adds small amounts (carefully). During the addition, mix gently after each addition by swirling the flask; see if there are bubbles appearing upon addition of calcium hydride to acetonitrile. Keep adding CaH_2 until no bubbles of hydrogen are generated. At this point, the solvent is dry. Add a little more calcium hydride, then distill about 90-100 ml of dry acetonitrile. Take 4.12 gram of N,N-dicyclohexylcarbodiimide (DCC) and add to 20 ml of dry acetonitrile. Place 0.16 gram of β-(3-piperidyl)propionic acid (prepared by K. Zyla according to ref 15) in a 50 ml round bottom flask covered by glass stopper and shake for about 20 minutes. Then allow the mixture to stand for 4 hours(without stirring), then filter and evaporate the solvent. The infrared spectrum (Fig 5) shows that there is a small peak at 1680 cm^{-1} and a very strong peak at 2100 cm^{-1}. This is because excess unreacted DCC remains in the product.

The above procedure is repeated until β-(3-piperidyl)propionic acid is mixed with DCC; then let the mixture reflux 6 hours. After reflux, cool the mixture down to room temperature and allow to stand for at least 4 hours. The solution is filtered and the acetonitrile evaporated. The product is identified by infrared spectrum (Fig.6). A vacuum pump (0.12 mm) and sublimation apparatus (cooling by dry ice and acetone) were used to sublime the material for 4 hours (at room temperature). The yield is 42.3 mg . (30.2 %). Prior to vacuum sublimation, the IR spectrum of 7 (Figure 6A) shows a broad peak at 1680 cm^{-1} and broad absorption around 3500 cm^{-1}. This is due to the fact that the product contains some water. After sublimation, the IR (Figure 6B) of the product shows a stronger absorption peak at 1680 cm^{-1}, but it still has absorption at 3500 cm^{-1}.

Unfortunately, sometimes when the above procedure was repeated, the IR spectrum showed that some DCC was mixed with the product (2100 cm^{-1} absorption). Therefore, the following procedure was tried in order to remove excess DCC:

Add 40 ml 95% alcohol to the mixture of 7 and DCC, then reflux for 4 hours. Filter the solution and evaporate the alcohol. The residue was identified by its infrared spectrum. Figures 8 and 9 show that although the DCC was removed effectively by the solvent (water reacted with DCC and

became urea which is not soluble in acetonitrile, methylene chloride, chloroform, etc), the desire product (7) is also hydrolyzed by H_2O, and this is evident in Figures 8 and 9. The reaction of DCC with water is shown below



8

Thus, we attempted to use column chromatography to separate DCC and 7.

Experimentally, one combines 20 ml of acetonitrile with the mixture of 7 and DCC and filters the solution and passes it through 60 mesh silica gel (eluting solvent is 1:1 petroleum and ethyl acetate) and evaporates the eluate. Figures 10 - 11 show the differences in IR spectra before passing through the column and after passing through the column. It is very clear that DCC was separated by column successfully.

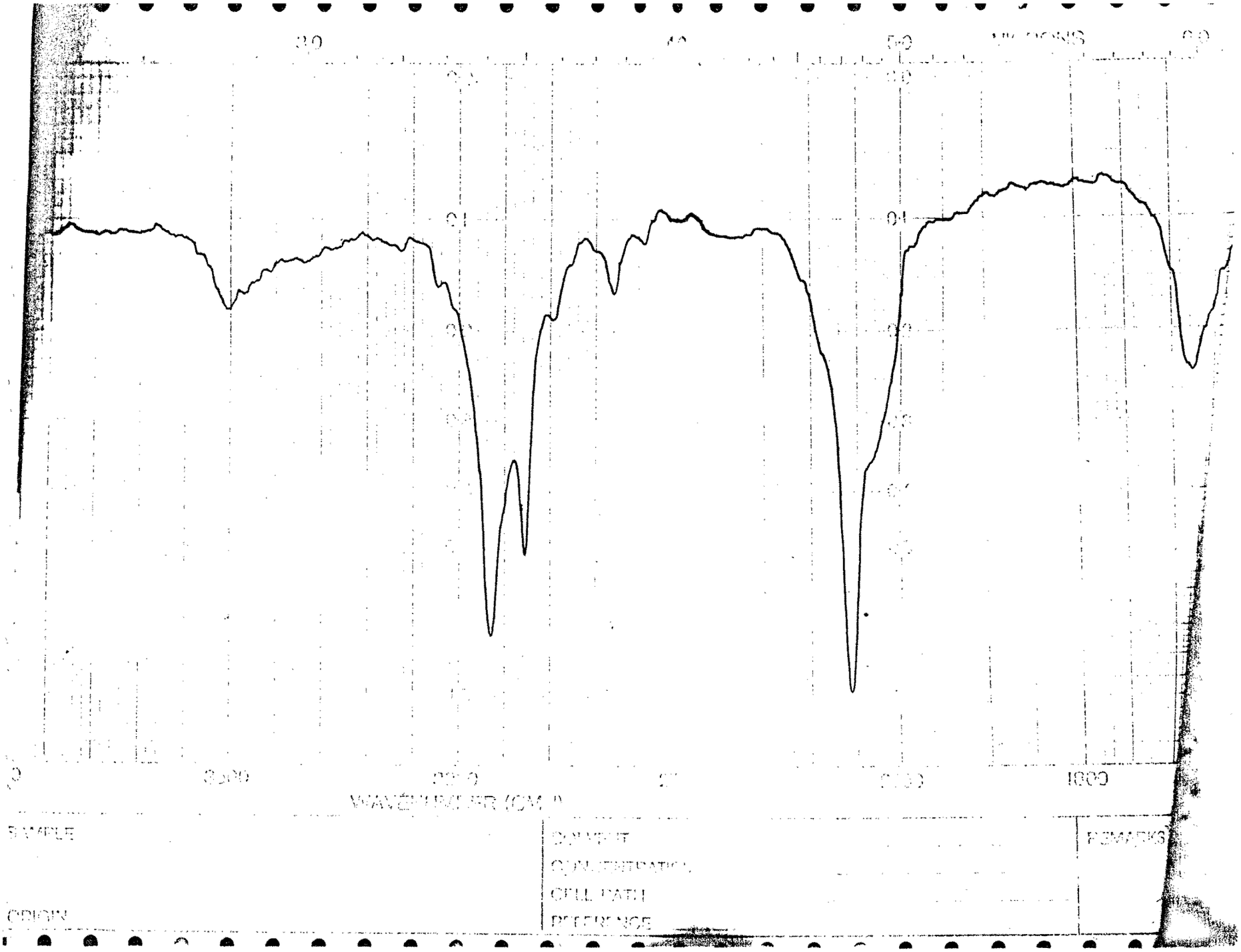


Figure 5. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC

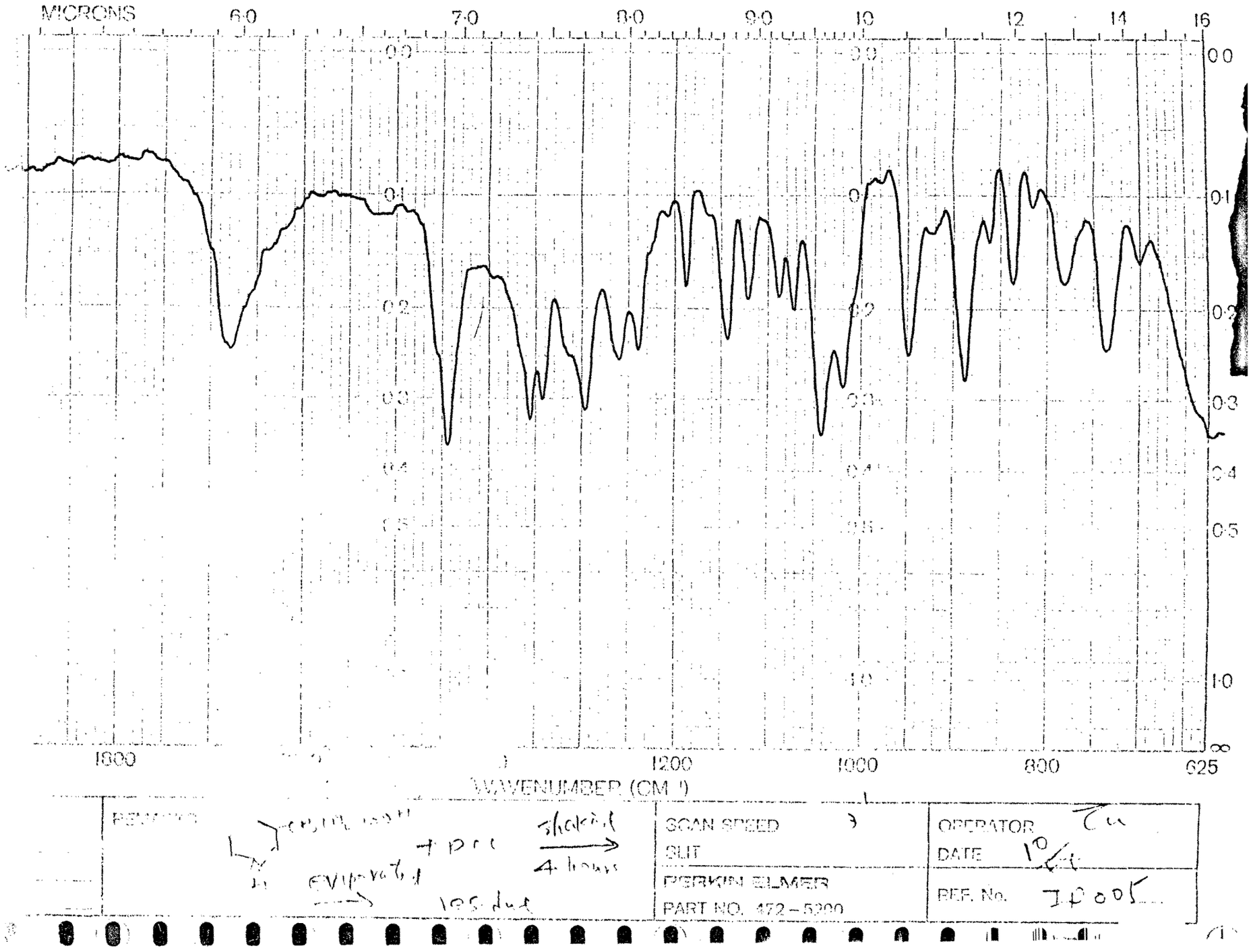


Figure 5. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC

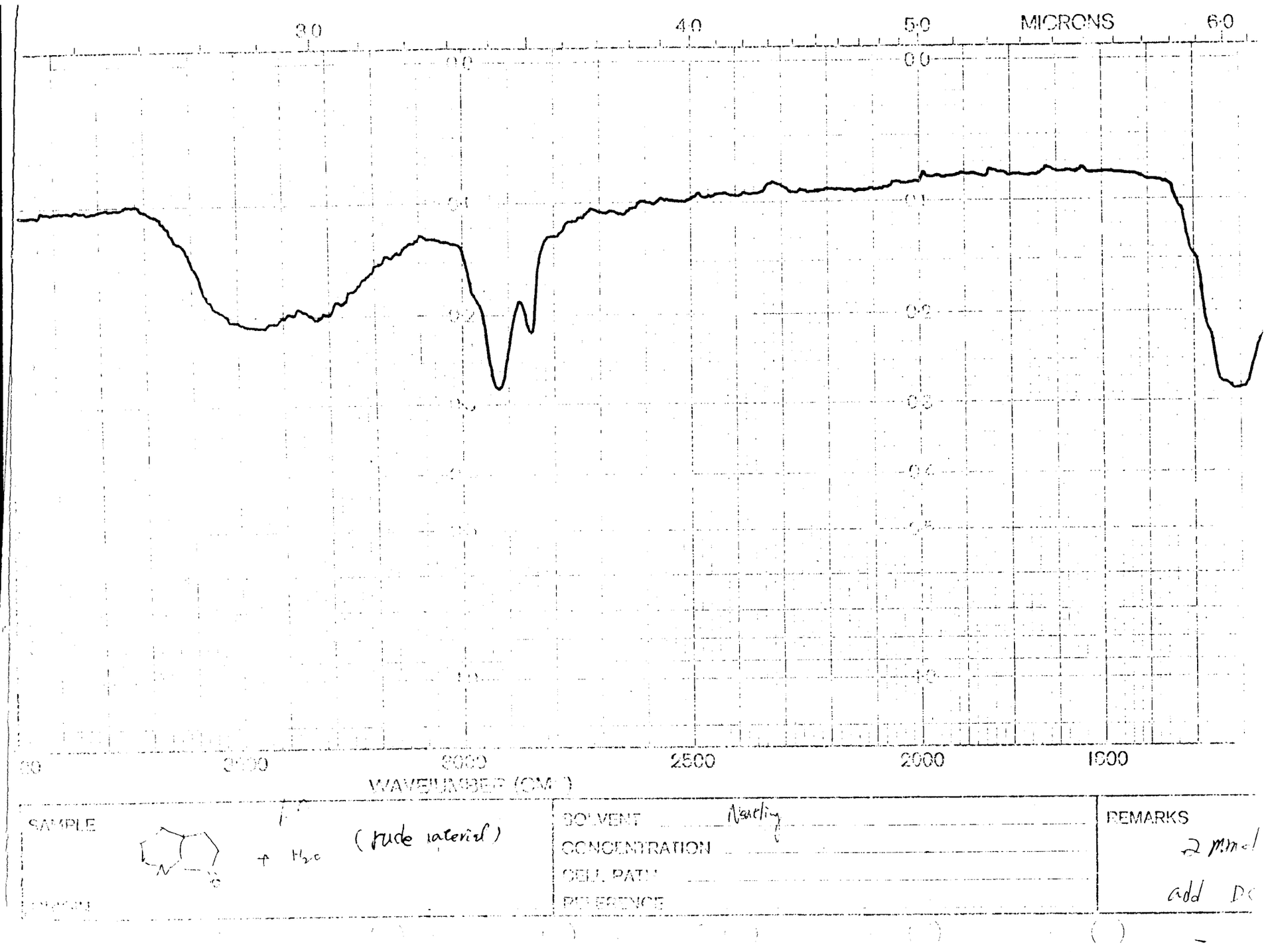


Figure 6A. 1-azabicyclo(3,3,1)nonan-one (Crude material)

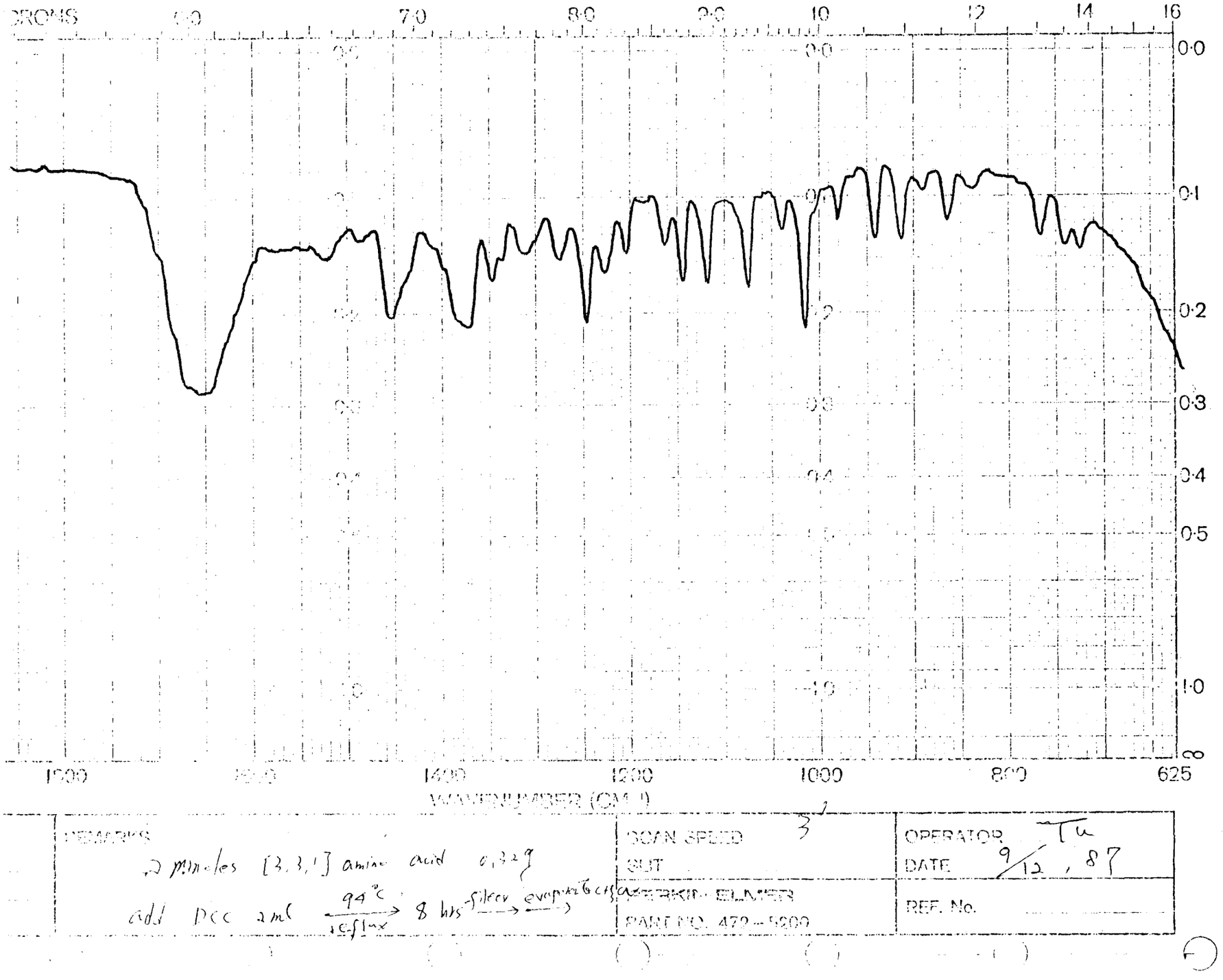


Figure 6A. 1-azabicyclo(3,3,1)nonan-one (Crude material)

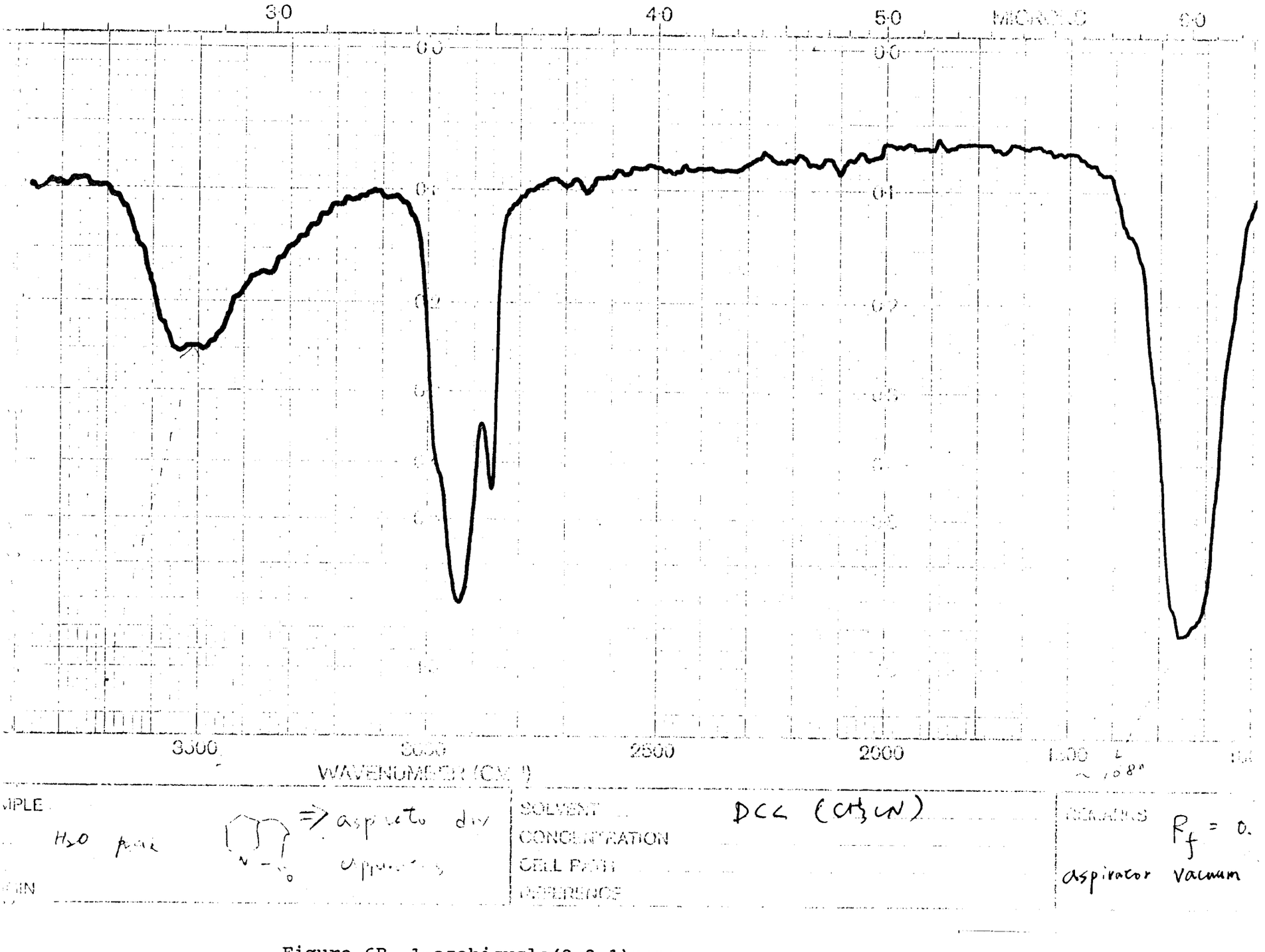


Figure 6B. 1-azabicyclo(3,3,1)nonan-one

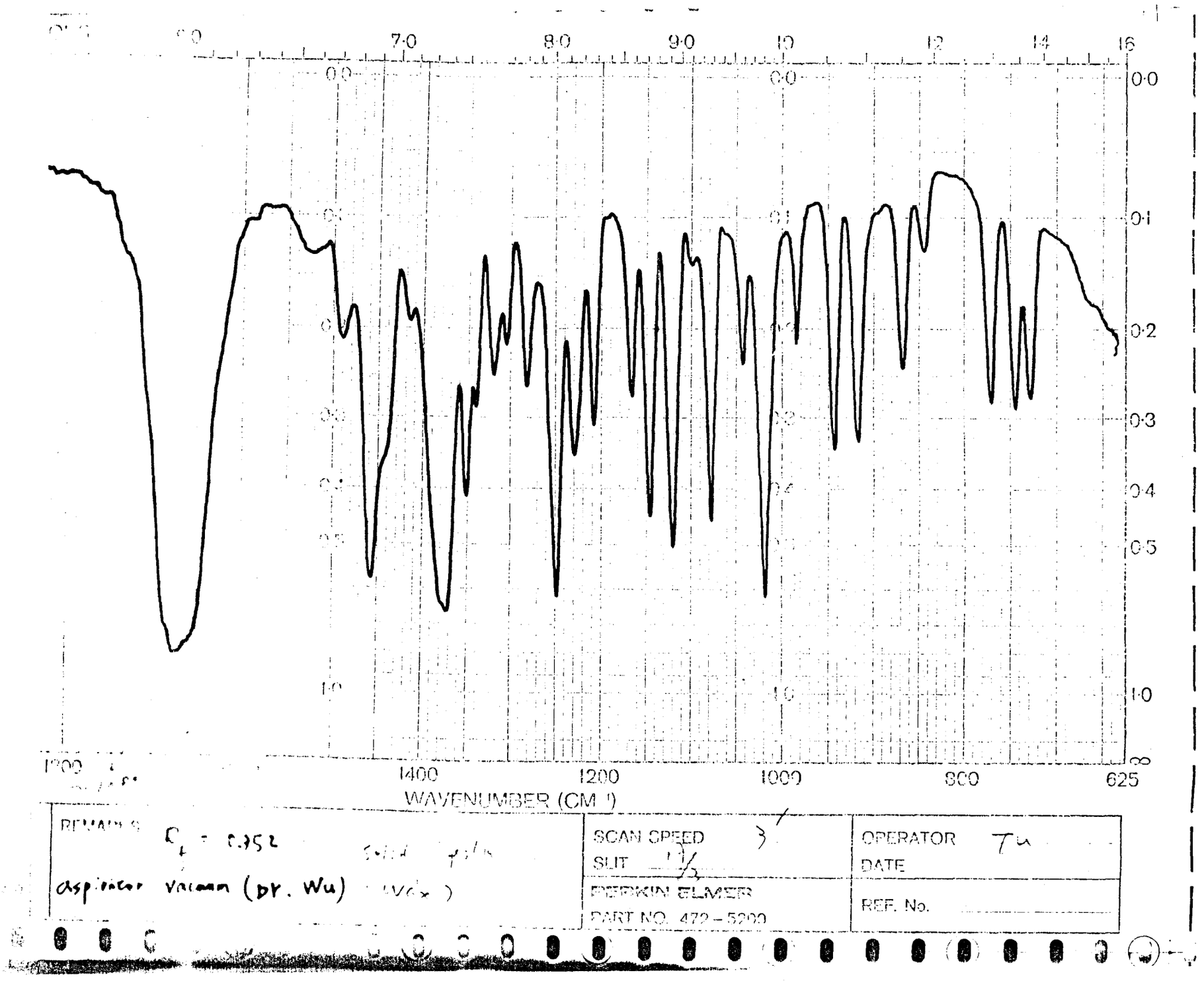


Figure 6B. 1-azabicyclo(3,3,1)nonan-one

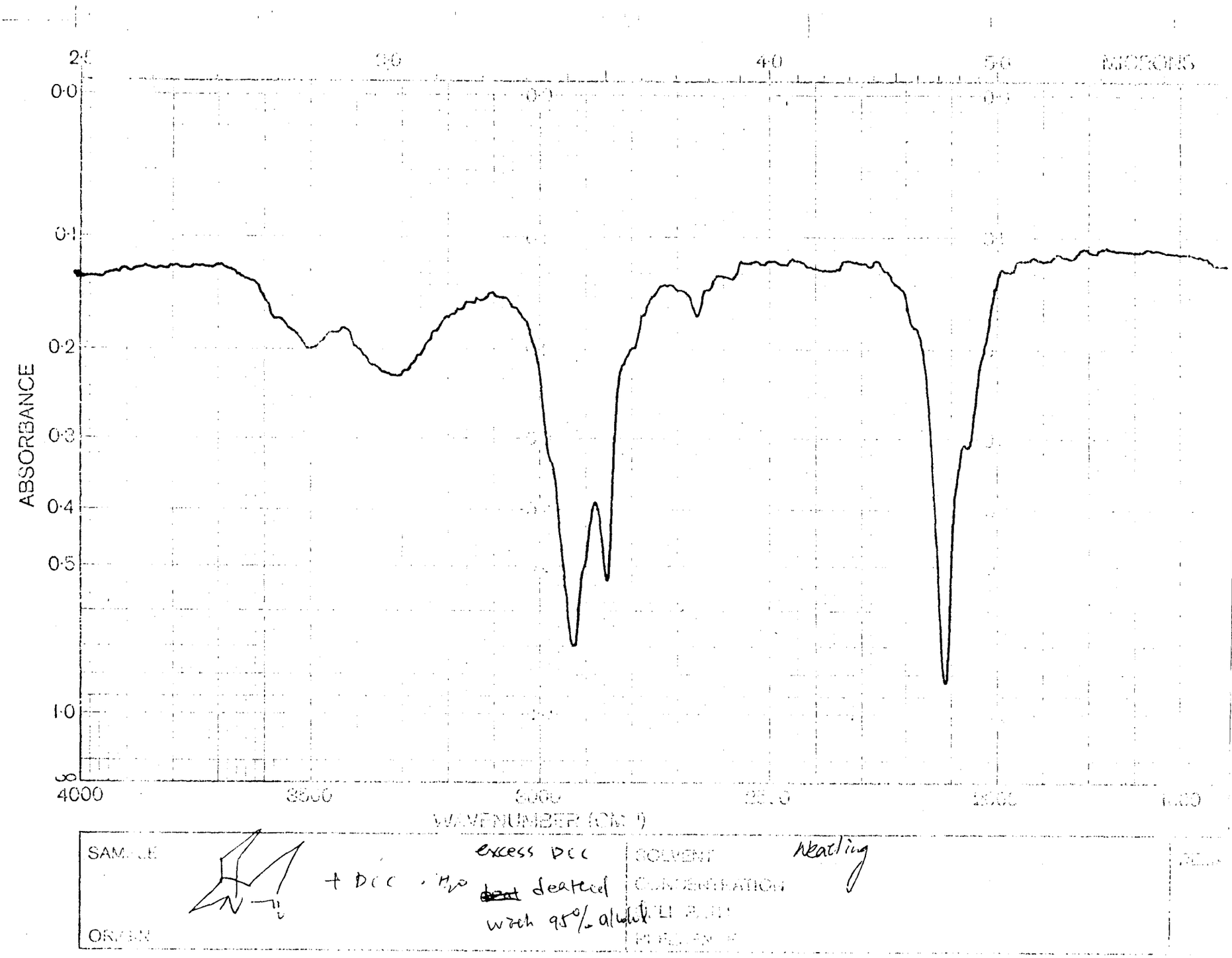
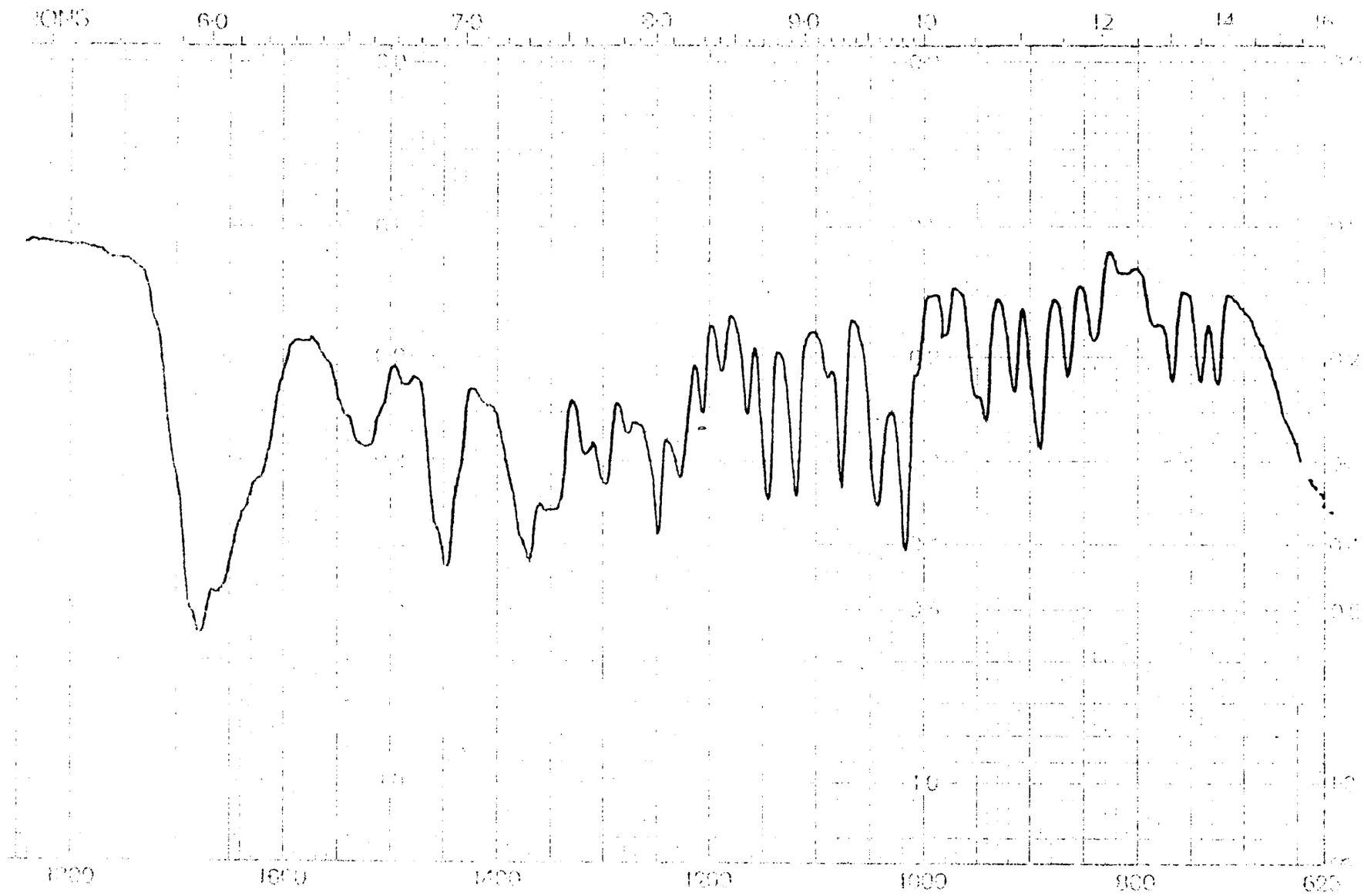
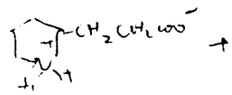


Figure 7. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC





$\rightarrow CH_2CH_2COO^-$ + PC (dry CH_2Cl_2) $\xrightarrow[\text{reflux}]{\Delta}$ 6 hrs

pressure to

$\rightarrow$ $\rightarrow$ reduce $\rightarrow$ oil (yellow)

filter ~~Vacuum~~

OPERATOR

DATE 21/11

REF. No. ID007

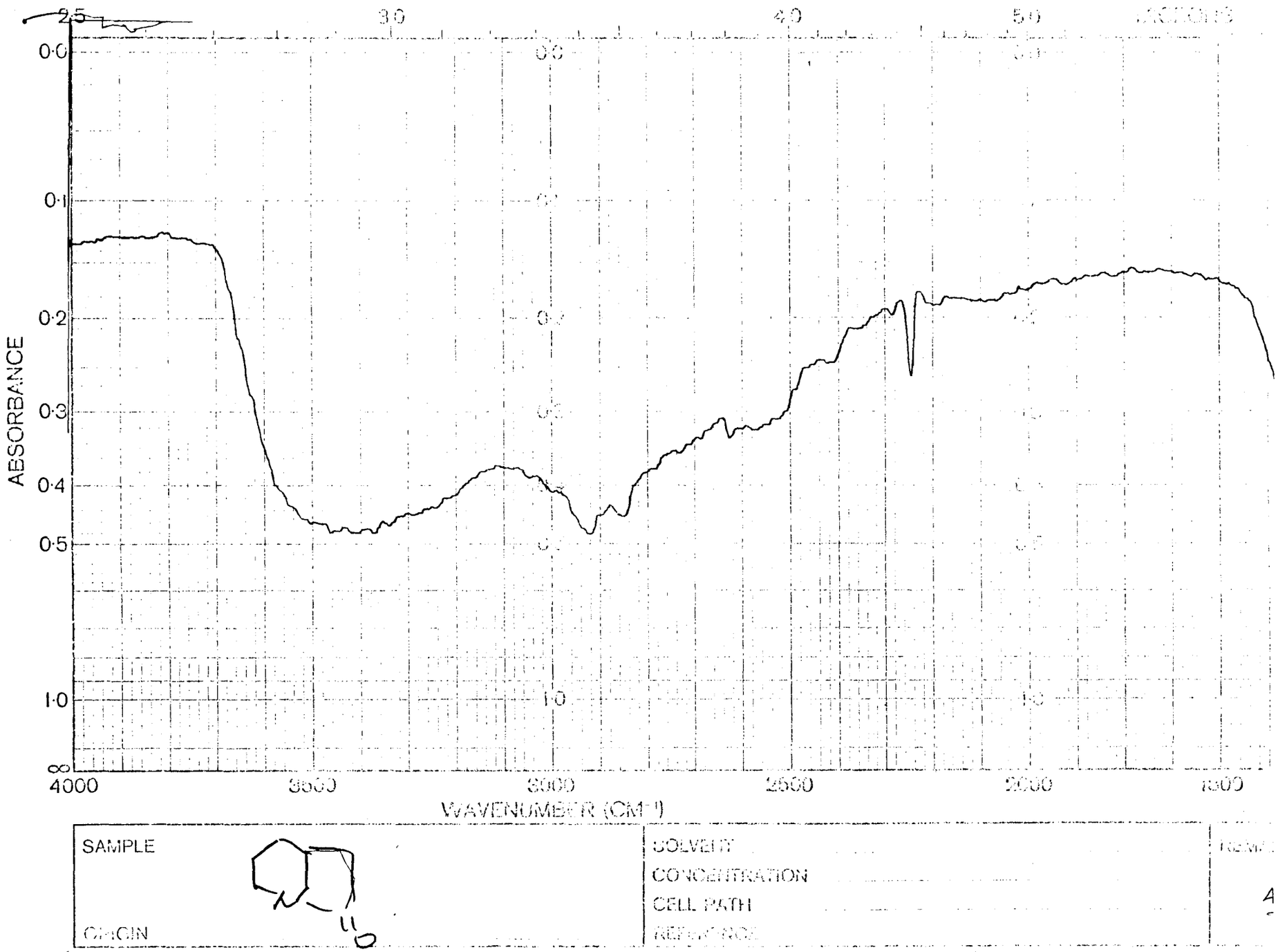


Figure 8. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC

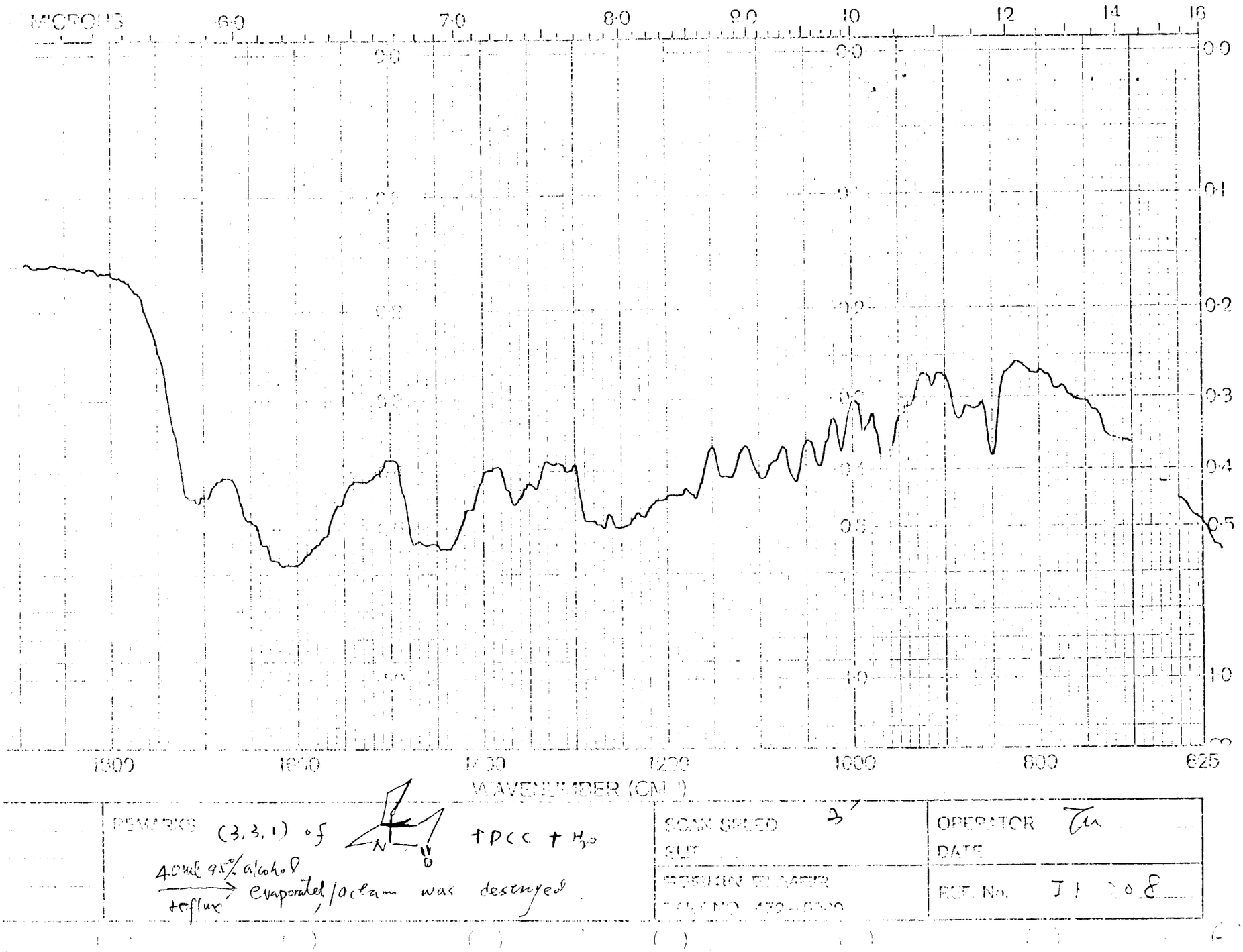


Figure 8. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC

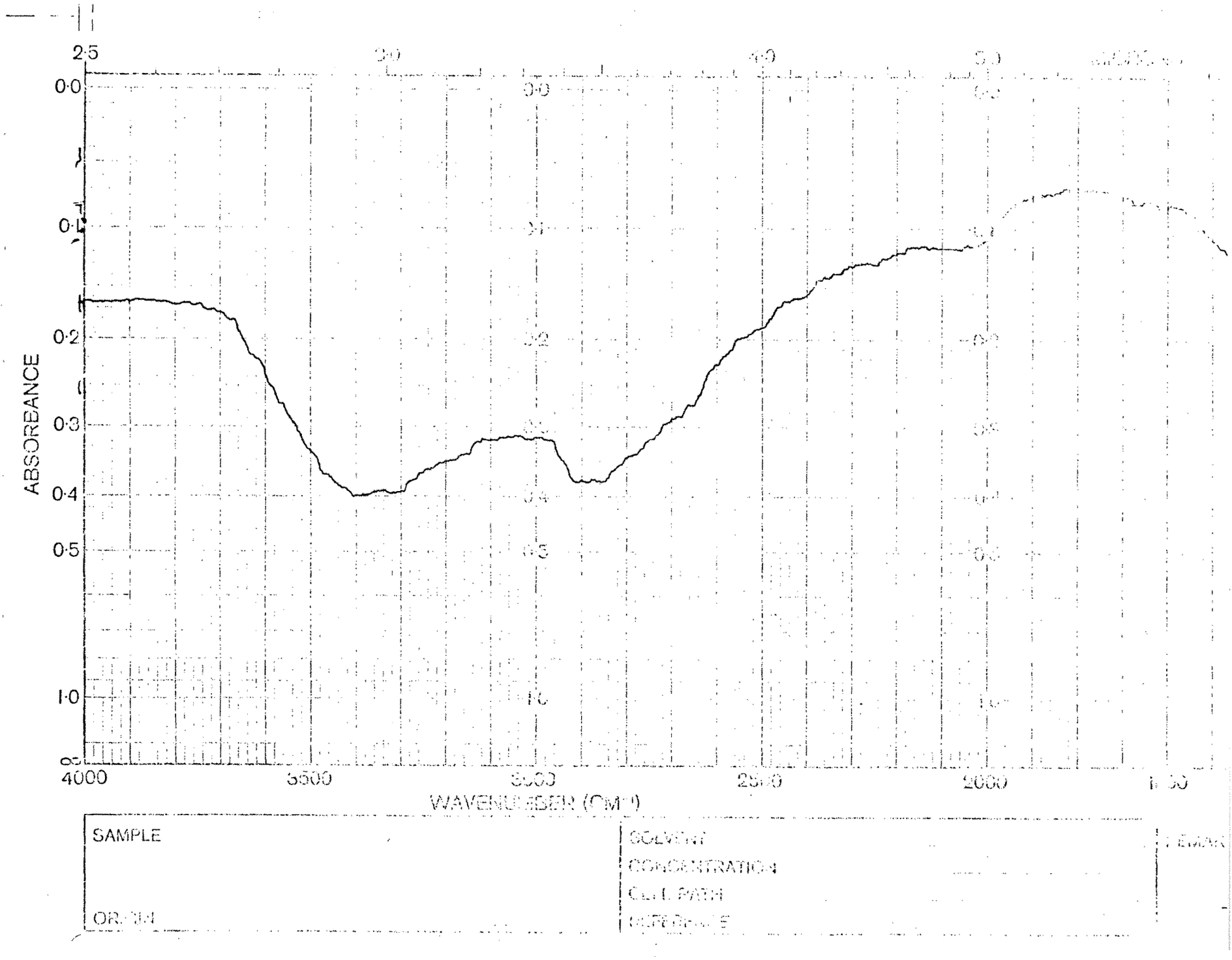


Figure 9. 1-azabicyclo(3,3,1)nonan-one
(hydrolyzed)

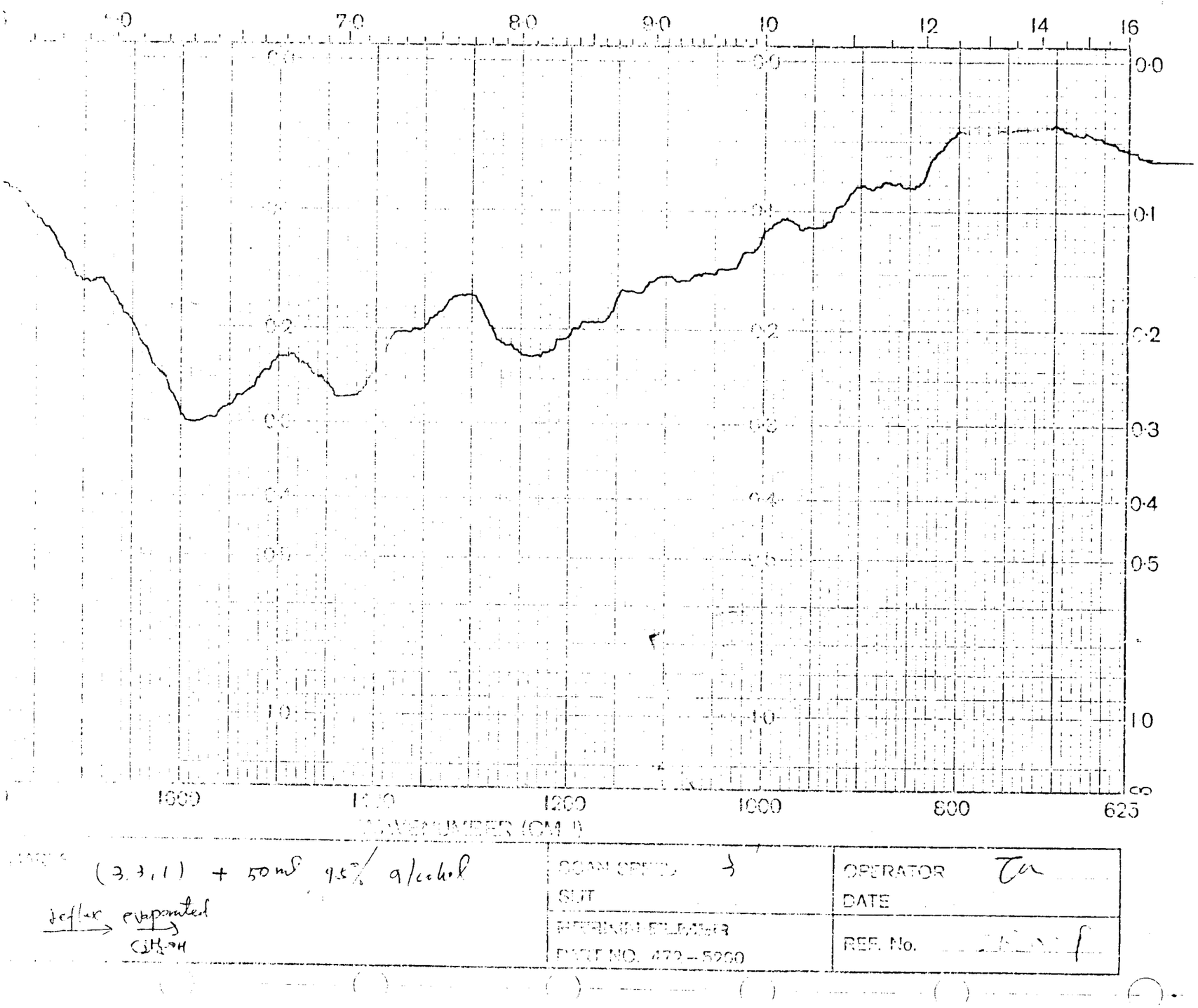


Figure 9. 1-azabicyclo(3,3,1)nonan-one (hydrolyzed)

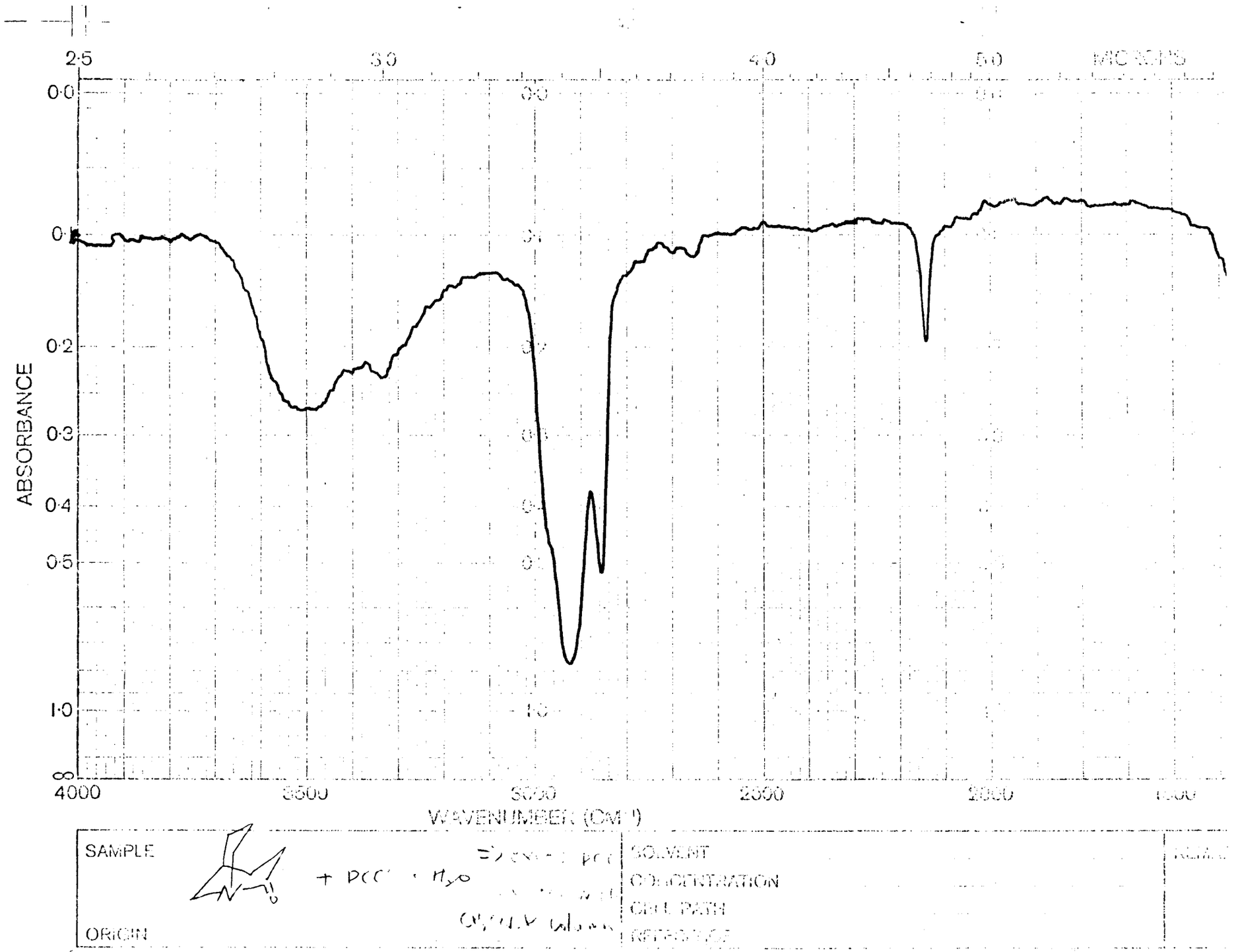


Figure 10. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC (before passing column)

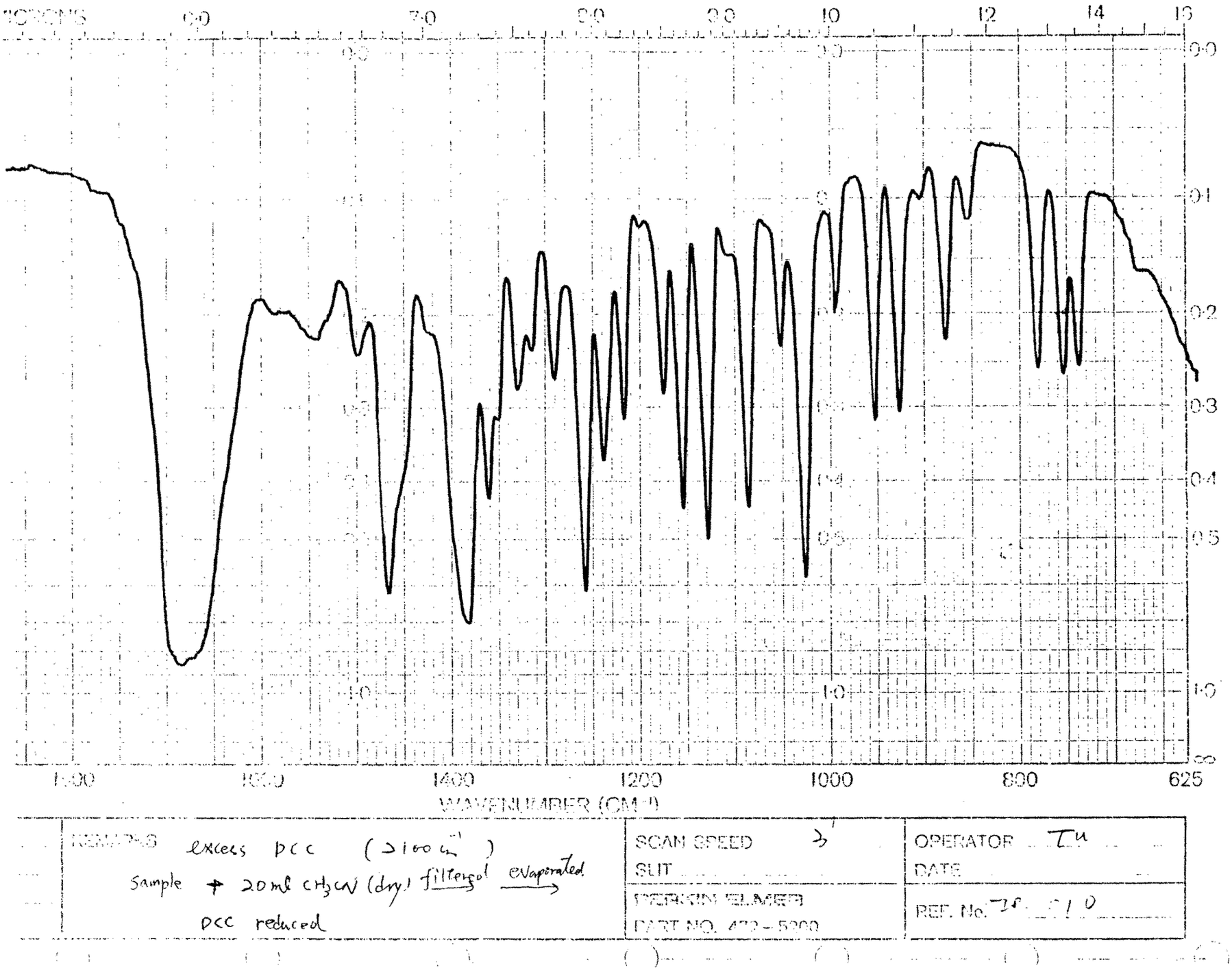


Figure 10. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC (before passing column)

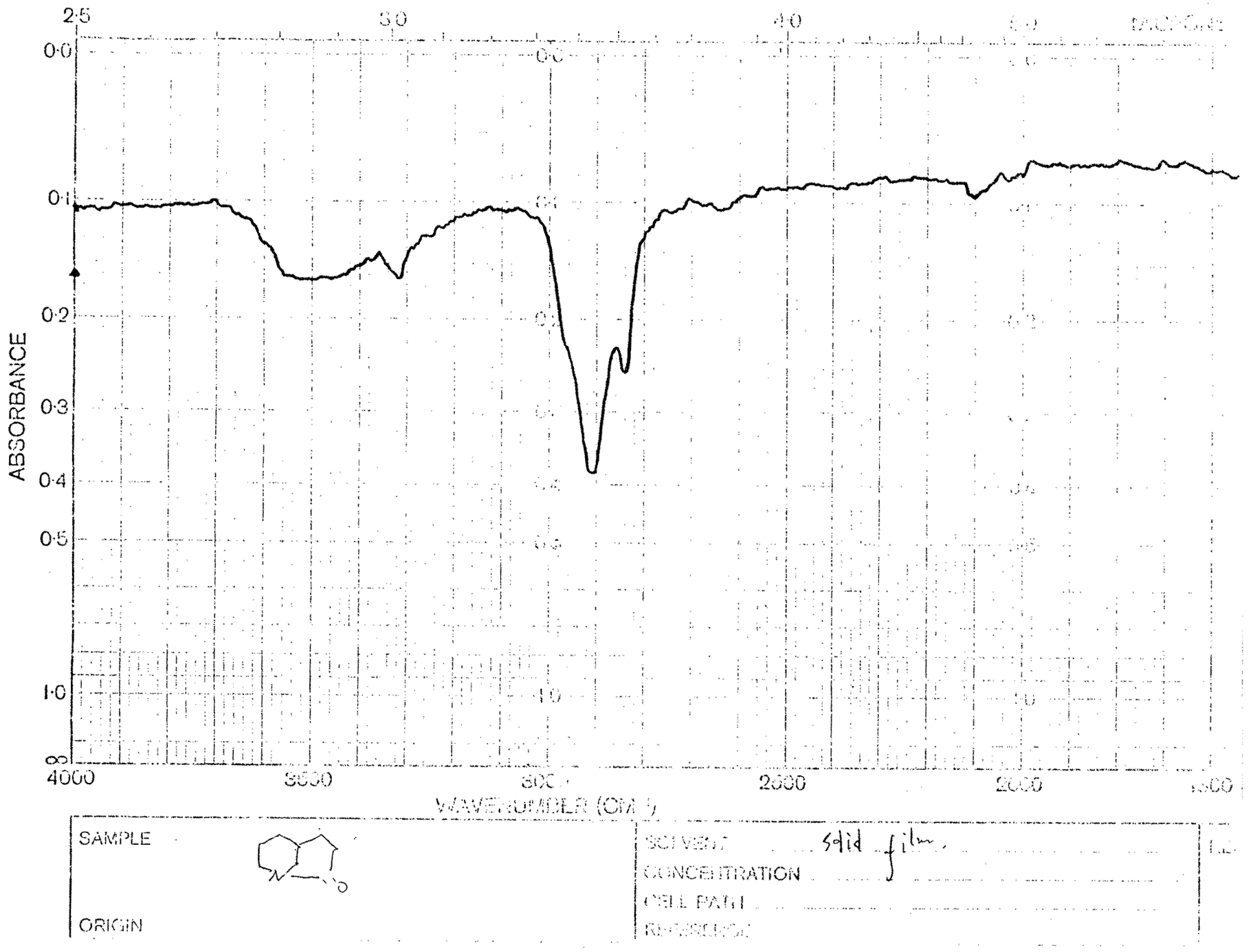


Figure 11. 1-azabicyclo(3,3,1)nonan-one
(after passing column)

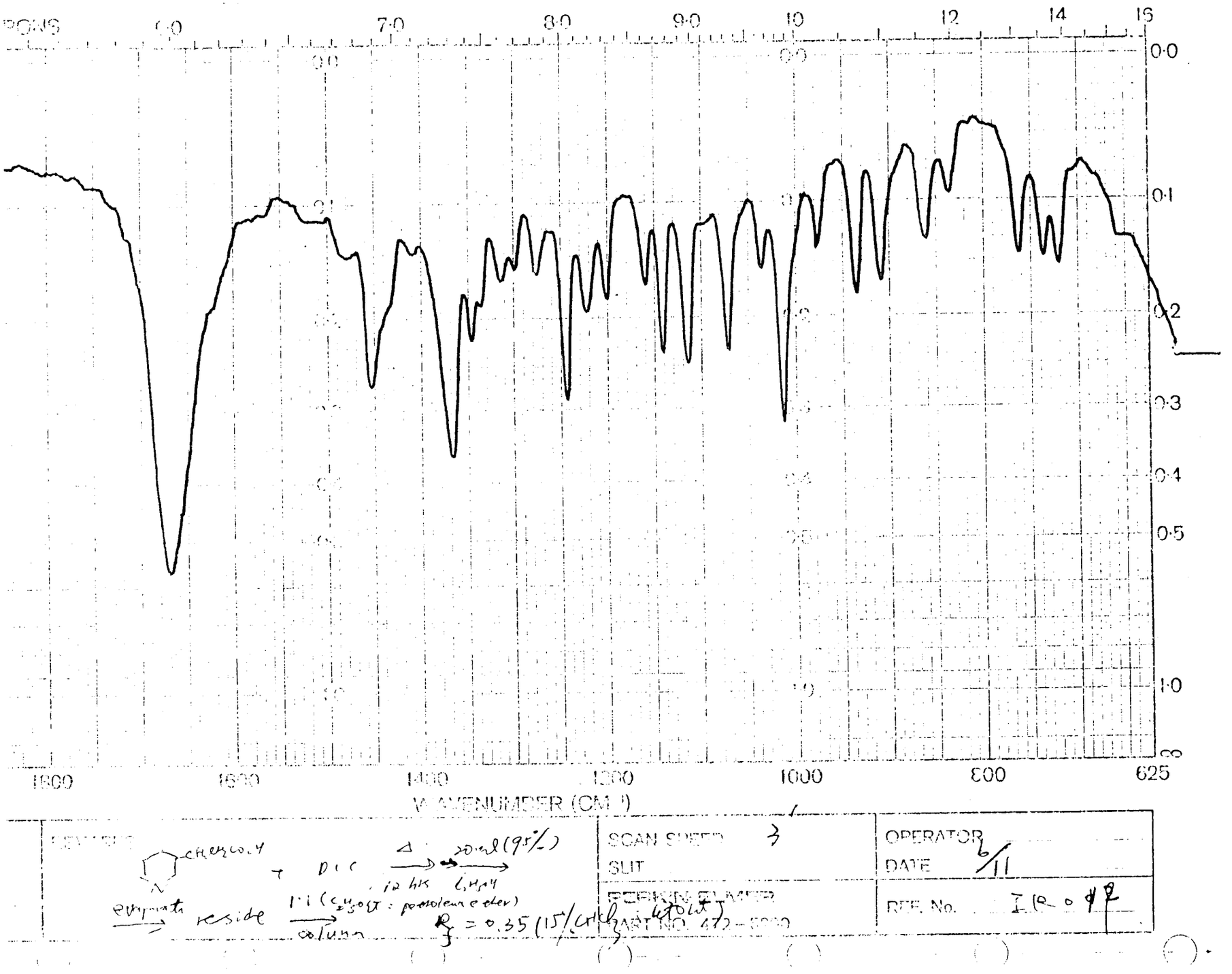
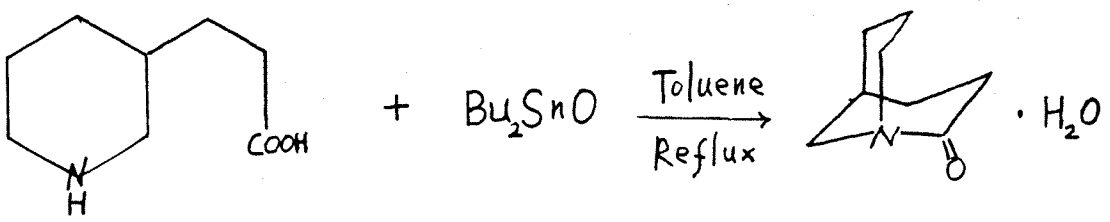


Figure 11. 1-azabicyclo(3,3,1)nonan-one
(after passing column)

4. Reaction of β-(3-piperidyl) propionic acid with di-n-butyltin oxide[13]



A mixture of β-(3-piperidyl)propionic acid [98.6 mg (0.63 mmole)] and di-n-butyltin oxide [156.8 mg (0.63 mmole)] was stirred in refluxing toluene (125 ml) for 12 hours with use of a Dean-Stark apparatus for the continuous removal of water. The solvent was removed in vacuo at room temperature and the residue taken up in 25 ml chloroform and filtered through a layer of Celite. The filtrate was concentrated by rotary evaporation and the resulting oily residue was purified using "flash chromatography"; the elution is done using 100 ml of ethyl acetate. Identities are checked by putting the sample on TLC plate to develop by solvent (15 % EtOac/ 85 %$CHCl_3$) and measure the R_f (0.35; it can be sees by UV lamp). The yield is 60.2 mg (68.5 %) from column chromatography.

The product was dried by aspirator and we obtained pure 7 as is clear from Figure 13 which shows the IR

spectrum of 7 which exhibits sharp absorption at 1680 cm^{-1} Figure 12 is the IR spectrum before the residue was taken up by chloroform; it is not pure material as shown by the very broad absorption peaks.

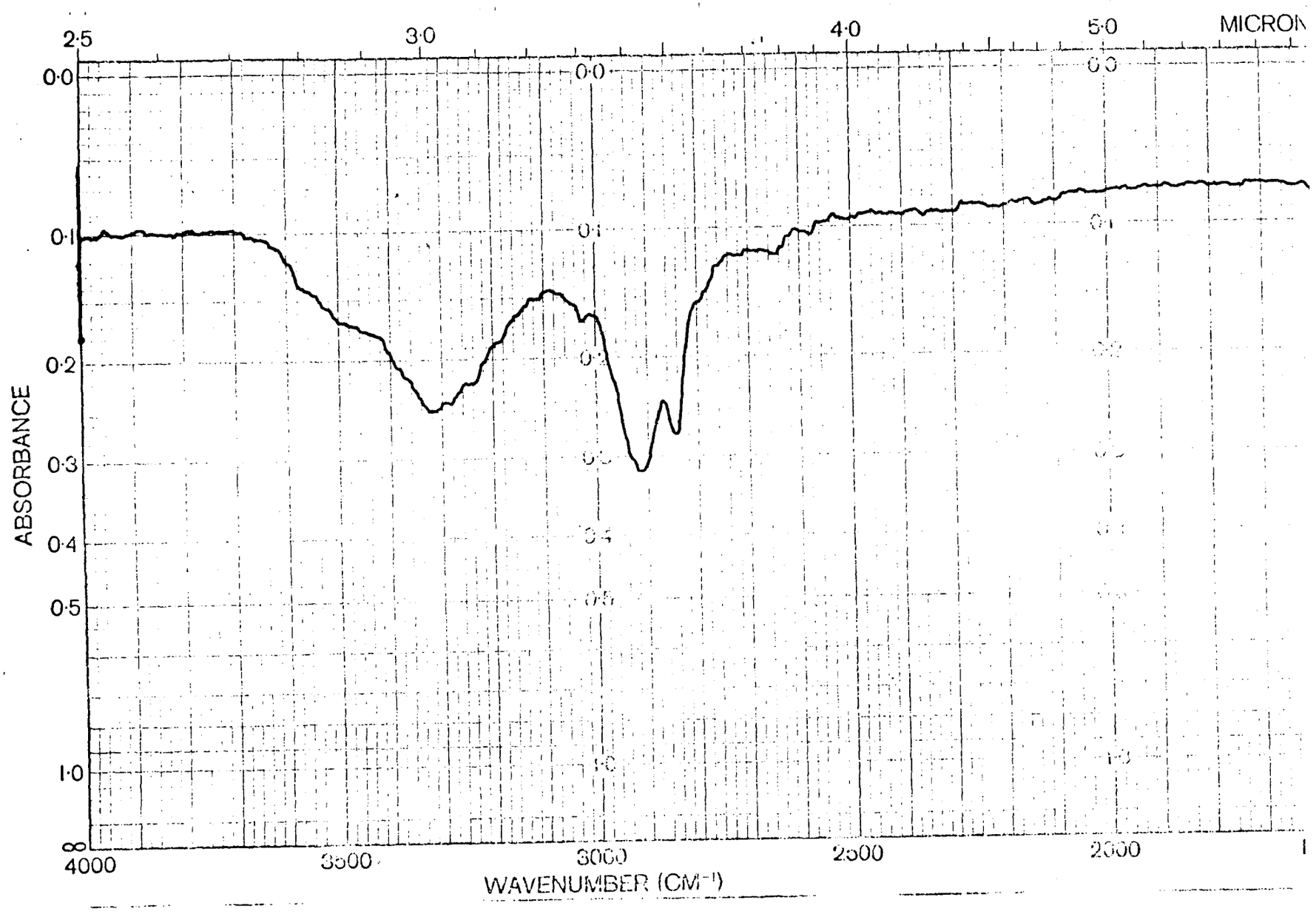


Figure 12. 1-azabicyclo(3,3,1)nonan-one (rude material ; yellow liquid)

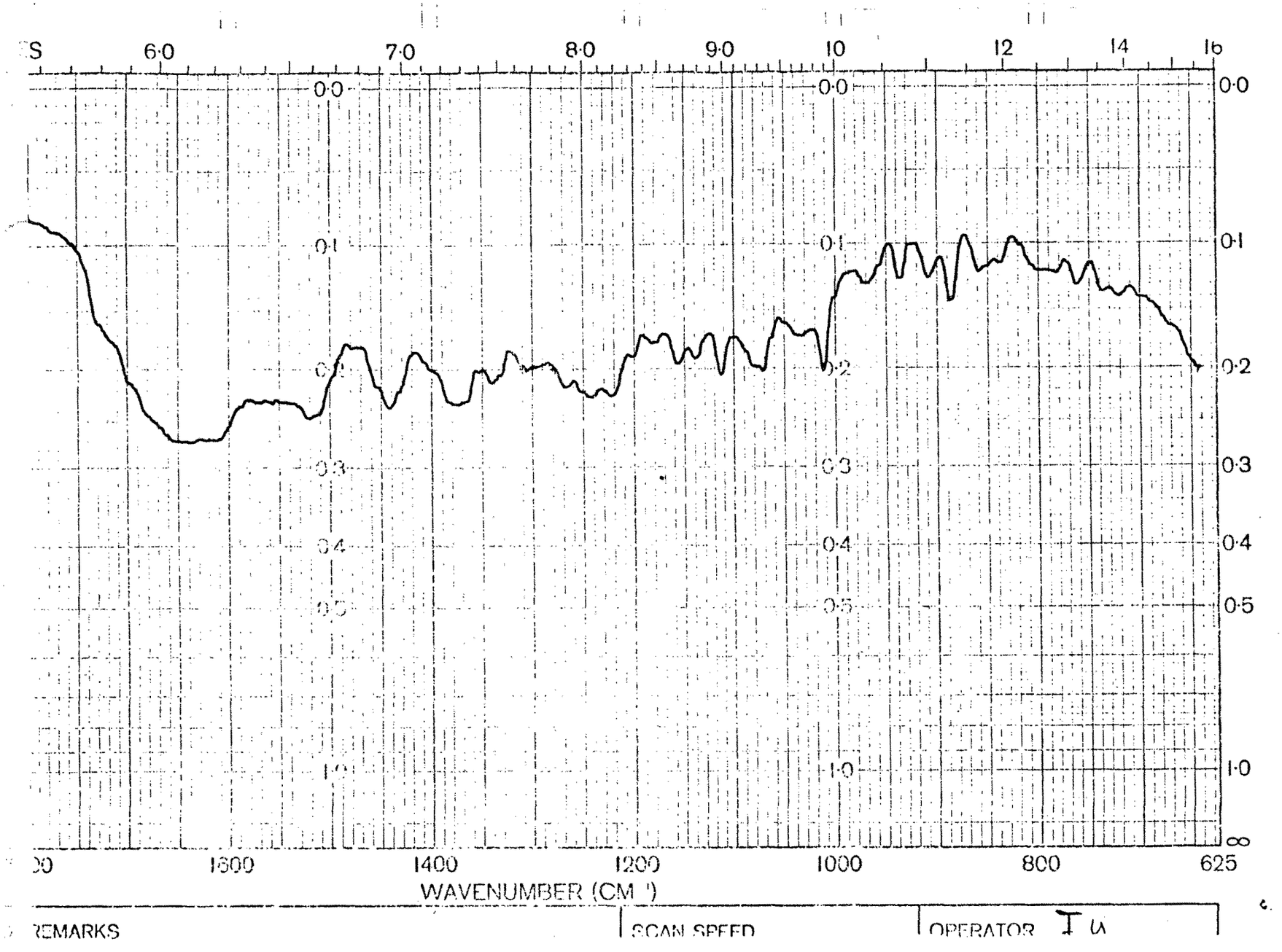


Figure 12. 1-azabicyclo(3,3,1)nonan-one (rude material ; yellow liquid)

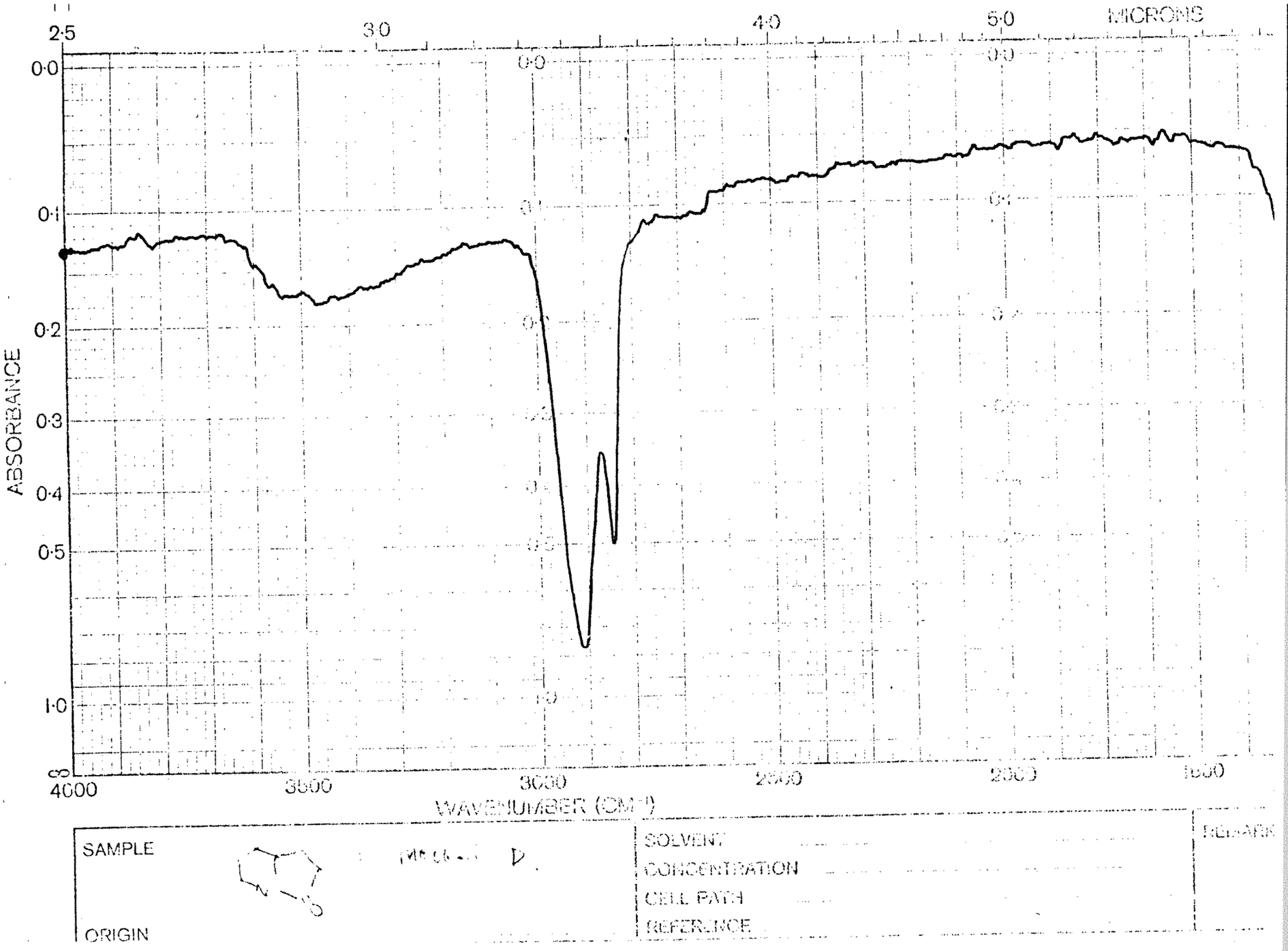


Figure 13. 1-azabicyclo(3,3,1)nonan-one (solid)

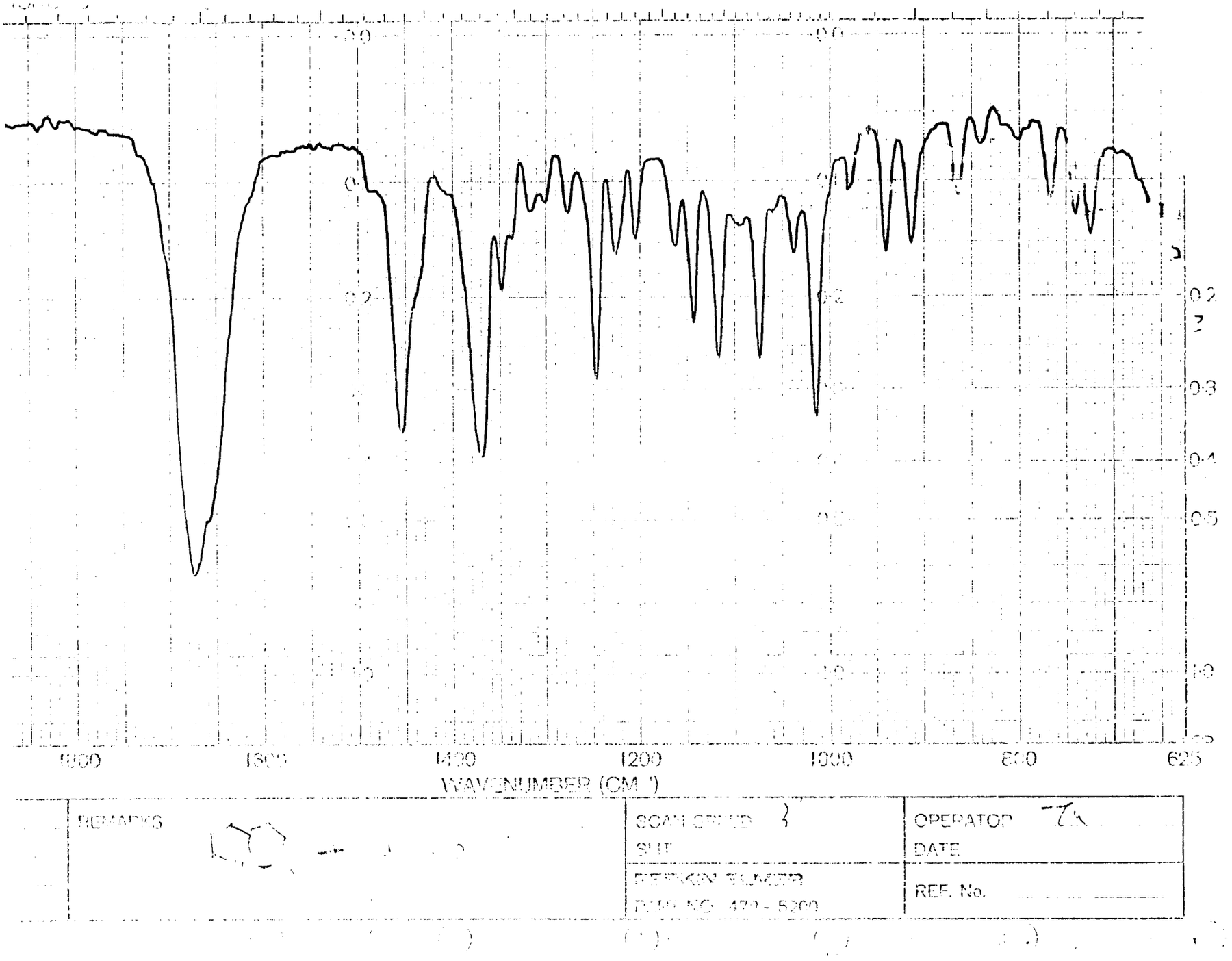


Figure 13. 1-azabicyclo(3,3,1)nonan-one (solid)

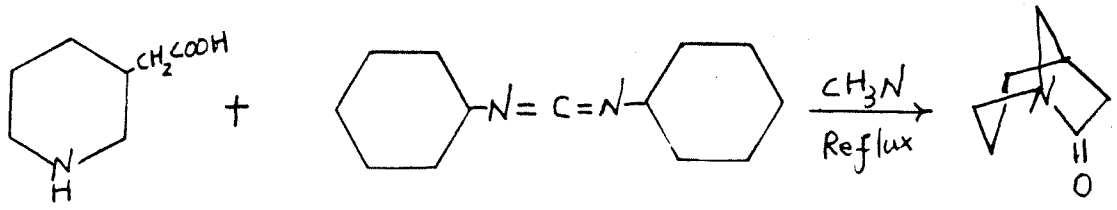
C. " Flash Chromatography "[17]

Into a 10 mm diameter and 50 cm length chromatography tube, place a small plug of glass wool just above the stopcock. A smooth 0.3 cm layer of 50-100 mesh sand to cover the bottom of the column and then 40-63 mesh silica gel (dry) is poured into the column to reach a depth of 15 cm. With the stopcock open , the column is tapped vertically on the bench top to pack the gel. Next a 0.3 cm layer of sand is carefully placed on the flat top of the dry gel bed and the column is clamped on the bottom for pressure packing and elution. Then ethyl acetate is poured over the sand to fill the column completely. The needle valve of the flow controller is opened all the way (the flow controller is fitted tightly to the top of the column and secured with strong rubber bands.). The main air line valve which leads to the flow controller is opened slightly and put a finger fairly tightly over the bleed port (Figure 27) at the same time. The purpose is to cause the pressure above the adsorbent bed to climb rapidly and compress the silica gel as solvent is rapidly forced through the column. It is very important to keep the pressure until all the air is expelled and the lower part of the column is cool; otherwise the column will fragment and should be repacked . The pressure is then placed onto the adsorbent bed by partially blocking the bleed port (Figure 27). The top of the silica gel should not be allowed to run dry. Next our lactam is applied by pipette

predissolved in 20 ml of ethyl acetate and eluted to the top of the adsorbent bed and the flow controller is briefly placed on the top of the column to push all of the lactam into the silica gel. Control the eluting speed at 5.1 cm/min by flow controller. If done carefully, there is little chance of failure.

D. Attempted Synthesis of 1-AZABICYCLO(3,2,1) OCTAN-7-ONE

1. Reaction Using DCC



9

Take 0.2004 gram of 3-β-piperidyl acetic acid hydrochloride(prepared by K.Zyla according ref 14), and added 1.94 ml of 0.575 N sodium hydroxide to neutralize hydrochloride in the start material which contains trace water. Then use 0.1 M hydrochloric acid to adjust the pH to 7 and evaporate water by rotary evaporation. The residue is dissolved in 20 ml of dry acetonitrile in a 100 ml of round bottom flask. One ml of DCC solution (preparation as described before) was added into the flask. Shake and reflux 6 hours, then filter and evaporate the solvent. Figure 14 shows the IR spectrum , which has a small peak at 1700 cm^{-1} , and absorption at 1640 cm^{-1} ; It also shows a strong absorption at 2100 cm^{-1} (DCC absorption). After being treated with flash chromatography, Figure 16 indicates the peak around 1700 cm^{-1} became broader, and the DCC still remained because IR spectrum has absorption at 2100 cm^{-1}. It probably is the mixture of starting amino acid and DCC.

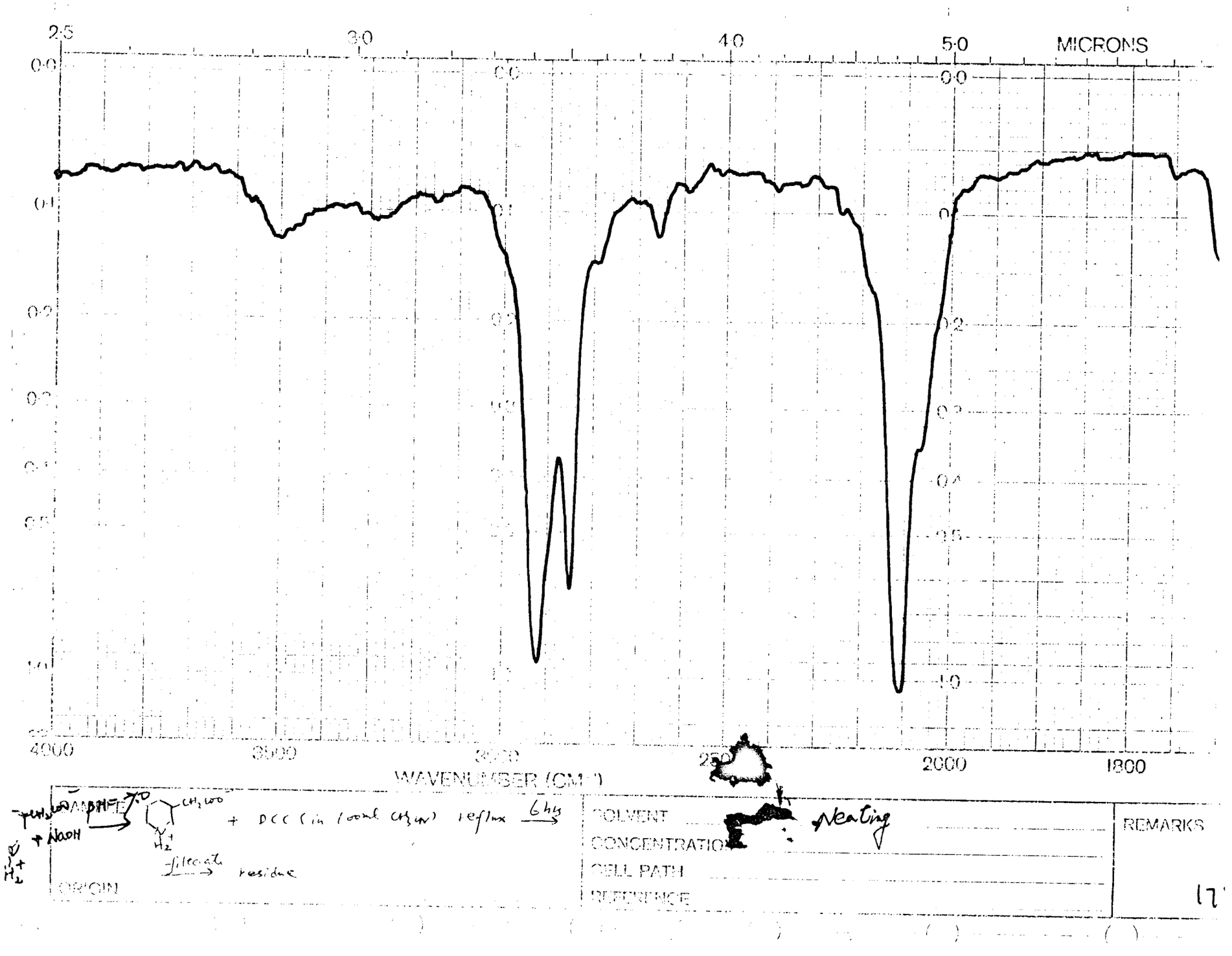


Figure 14. Mixture of 3-β-piperidyl acetic acid and DCC

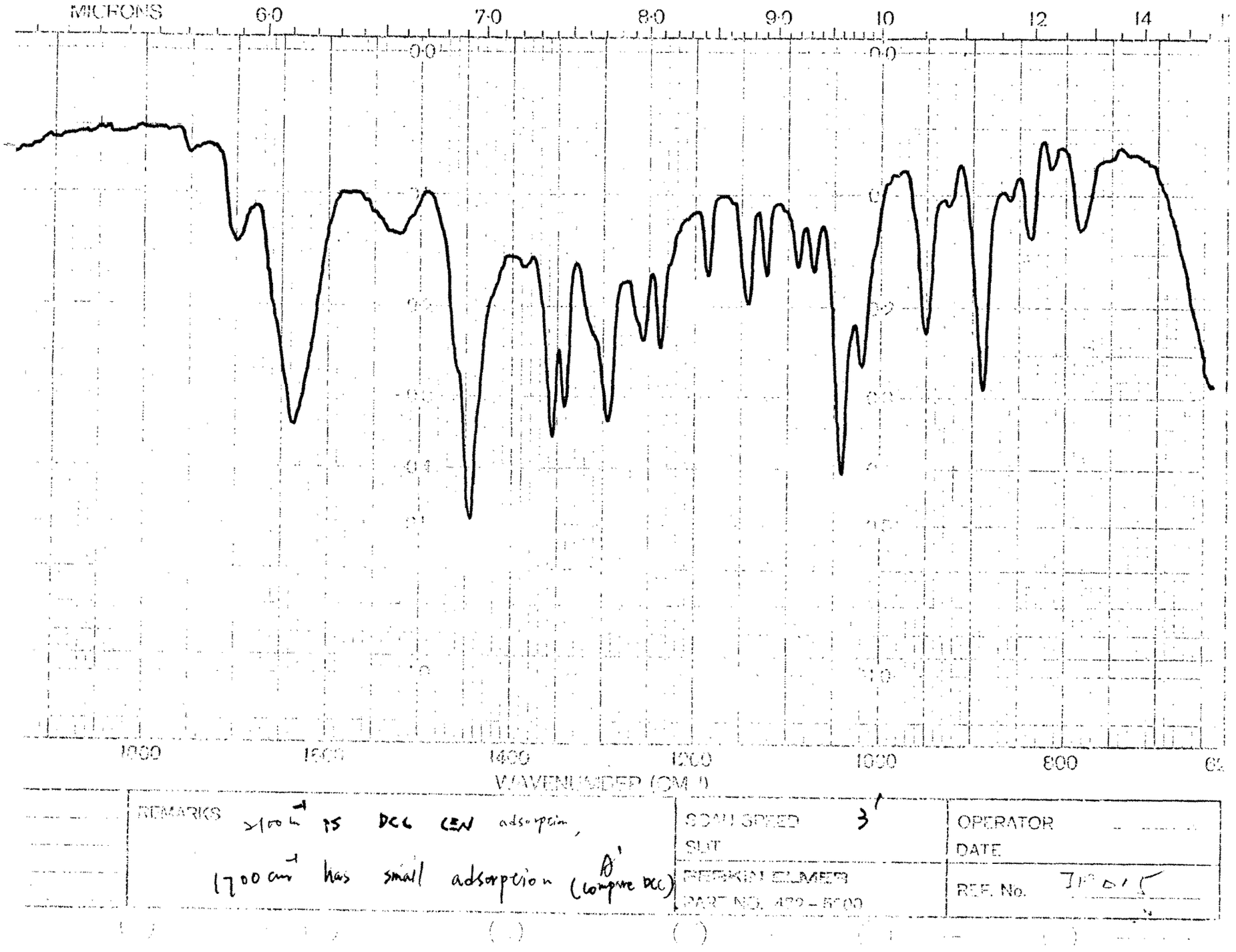


Figure 14. Mixture of 3-β-piperidyl acetic acid and DCC

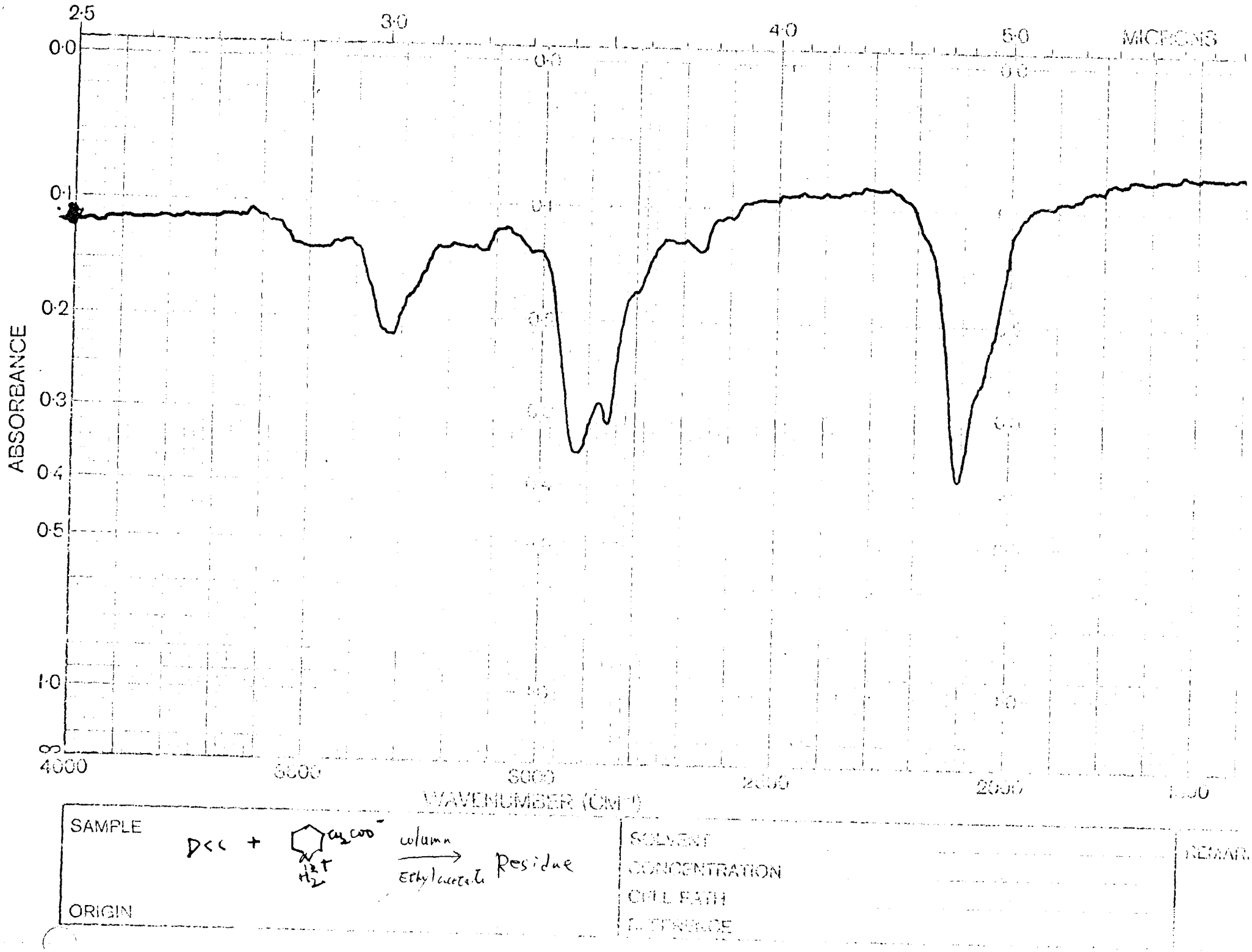


Figure 15. Mixture of 3-β- piperidyl acetic acid and DCC (after passing column)

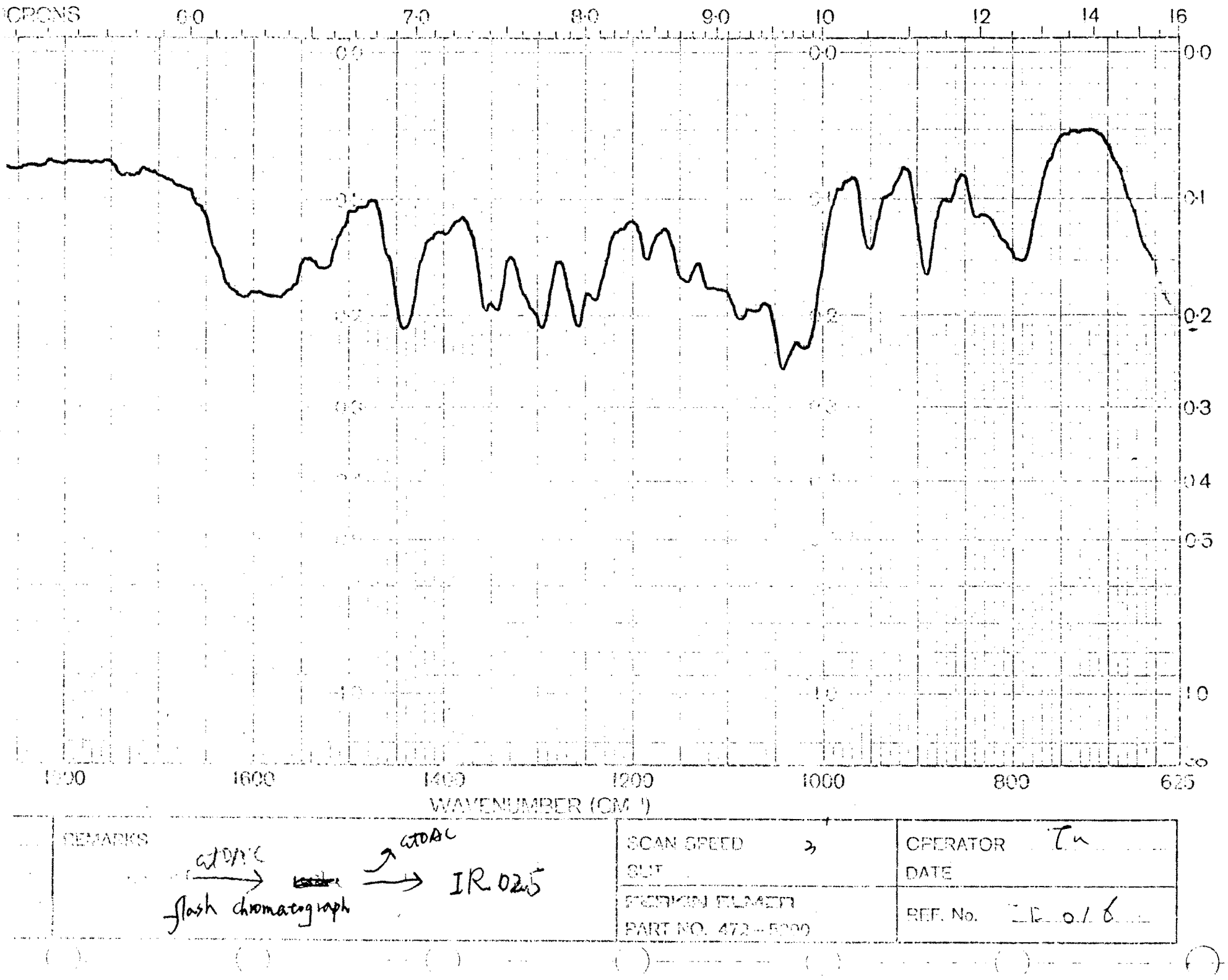
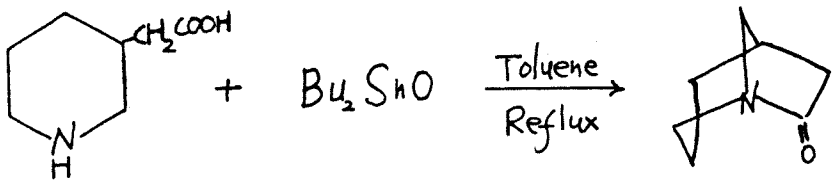


Figure 15. Mixture of 3-β- piperidyl acetic acid and DCC (after passing column)

2. Reaction with di-n-butyltin oxide



9

Place 180 mg of 3-β-piperidyl acetic acid hydrochloride into a 500 ml round bottom flask, and add 1 ml of 1 M sodium bicarbonate to the flask to neutralize the hydrochloride. Evaporate water using a rotoevaporator. Add 248.9 mg (1 mmole) di-n-butyltin oxide and 125 ml toluene into the flask; reflux 12 hours using a Dean-Stark apparatus. Evaporate toluene and to the residue 20 ml chloroform. This chloroform solution is filtered through a layer of Celite. Evaporate the chloroform with the rotary evaporation then use "flash chromatography" to purify the product. the eluting solvent is ethyl acetate (100 ml). The IR spectrum (Fig. 16) shows there is no absorption around 1753 cm^{-1} (which is predicted by reference 7). It probably is the starting amino acid.

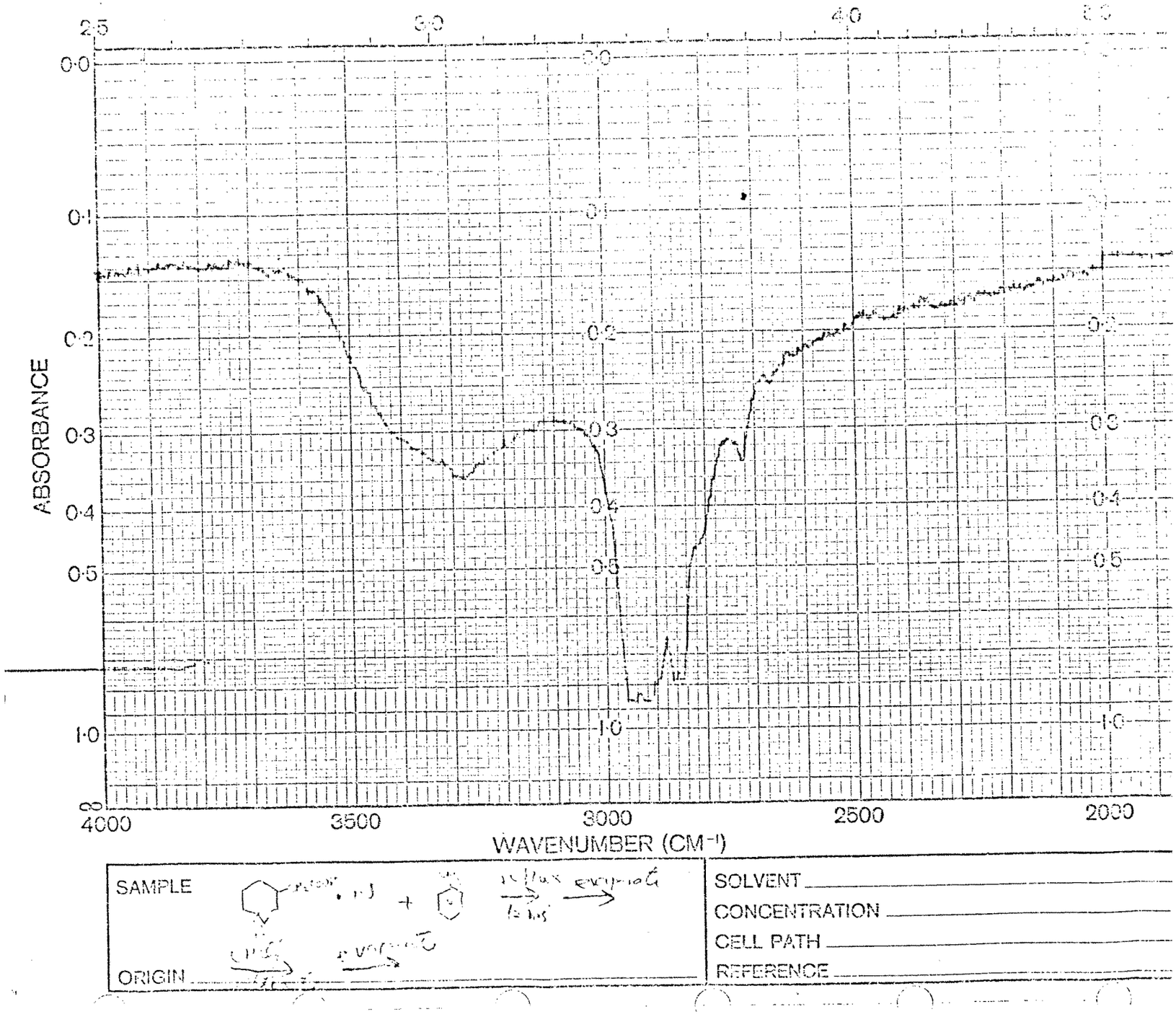


Figure 16. Starting amino acid (probably).

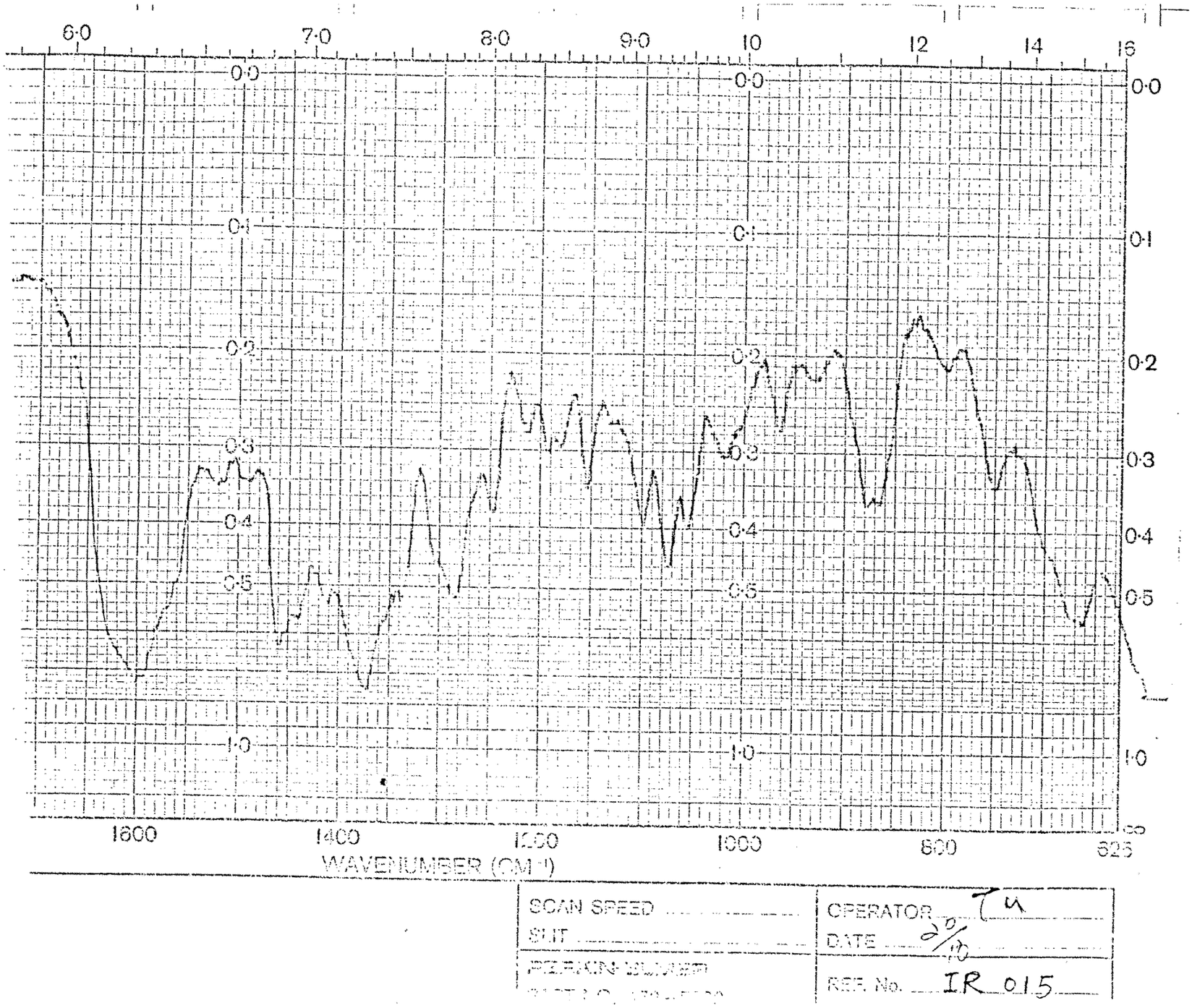
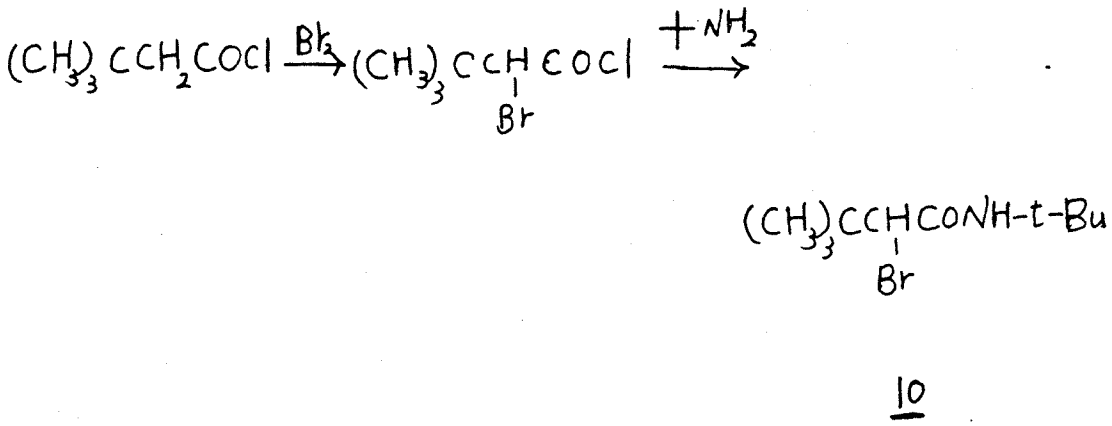


Figure 16. Starting amino acid (probably).

E. Synthesis of 1,3-Di-t-butylaziridinone[14]

1. 2-Bromo-3,3-dimethyl-N-t-butylbutyramide



10

Bromine (1.6 ml, 29 mmoles) was added to a solution of 3.5 g (26 mmoles) of 3,3-dimethylbutyryl chloride in 7 ml of carbon tetrachloride, and the resulting solution was refluxed until the bromine color disappeared (about 4 hr). The solution was then added to an ice-cold solution of 6.3 ml (60 mmoles) of t-butylamine in methylene chloride(100 ml), it showes large white precipitate which is the mixture of t-butylamine chloride and 2-Bromo-3,3-dimethyl-N-t-butylbutyramide 10. When the addition was complete, water was added and the layers were seperated. The methylene chloride solution was washed with hydrochloric acid(0.1 M) 30ml, aqueous sodium hydroxide(0.1 M) 30 ml, and distilled water 60 ml. Evaporation of the methylene chloride solution gave 5.02 g (78%) of 10: mp 152-156 ^{o}; infrared(CCl_4): 3340, 2960, 1650, and 1560 cm^{-1} (Figure 17).

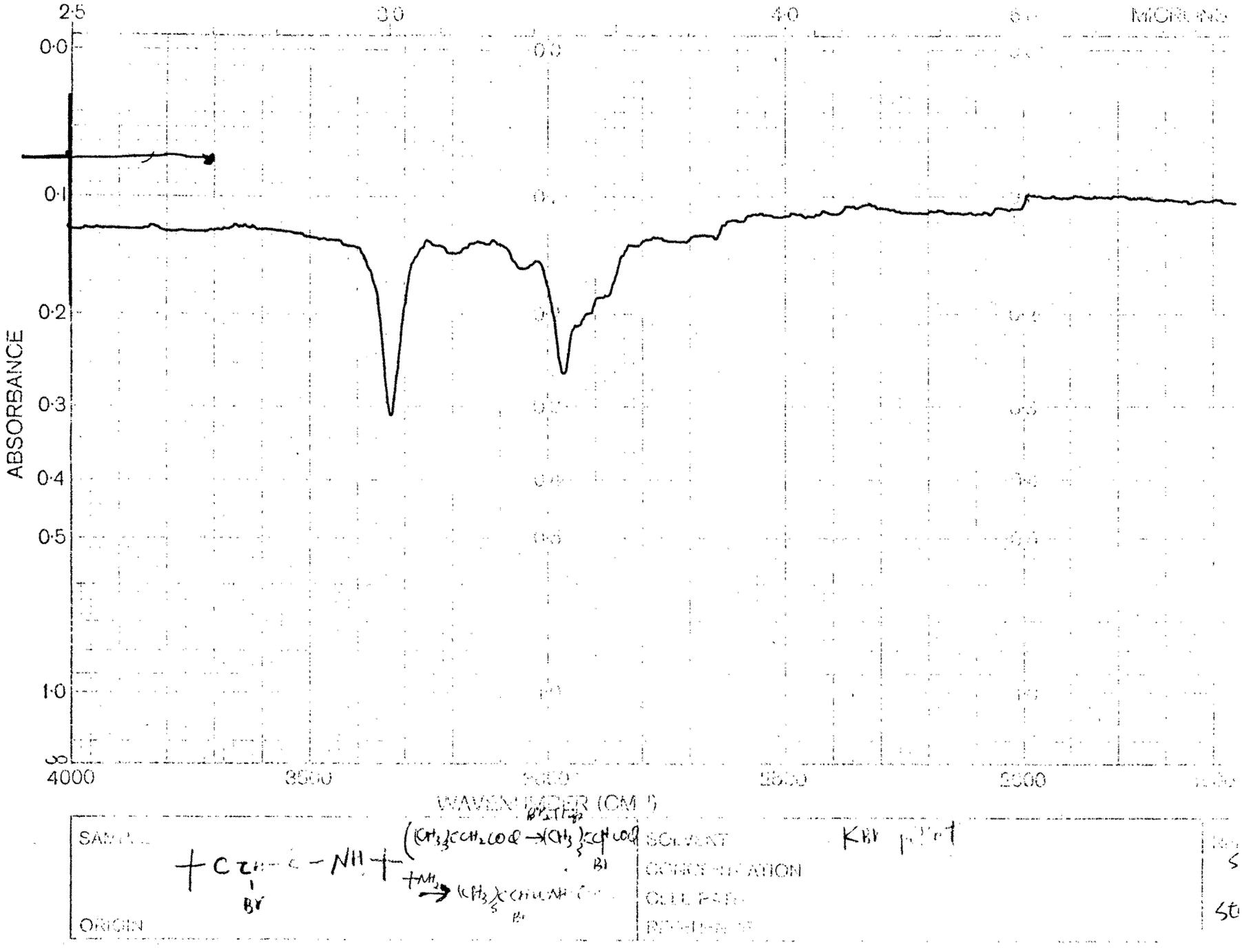


Figure 17. 2-Bromo-3,3-dimethyl-N-butylbutyramide (liquid)

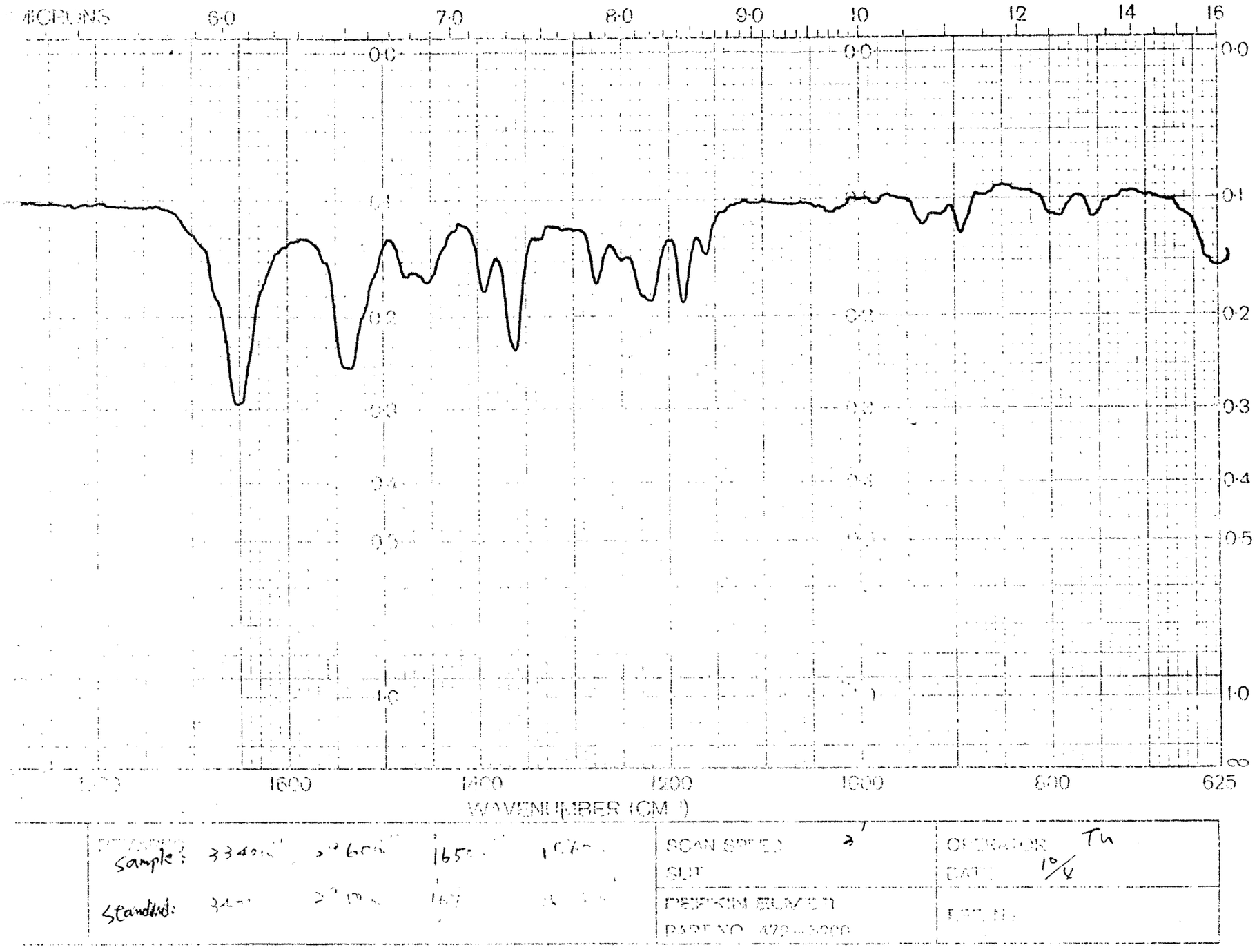
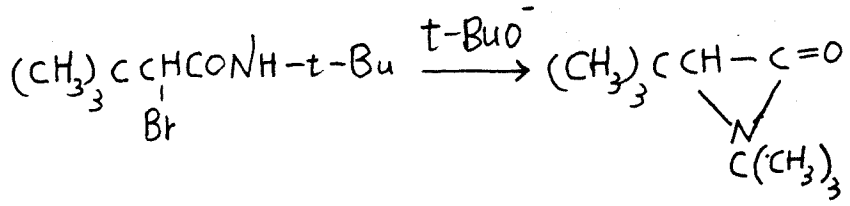


Figure 17. 2-Bromo-3,3-dimethyl-N-butylbutyramide (liquid)

2. 1,3-Di-t-butylaziridinone



10 11

A solution of 3.12 g (0.012 mole) of the α-bromo amide in 500 ml of ether was cooled to 0° in an ice bath, and 2.01 g (0.018 mole) of potassium t-butoxide was added. After 15 min of stirring, an infrared spectrum of the solution showed that the α-lactam formation was complete. The solution was filtered under nitrogen pressure and the resulting cloudy solution was evaporated. The residue was taken up in petroleum ether, placed in centrifuge tubes, and cooled to - 20°. Centrifugation gave a clear solution which on evaporation yield 1.2 g (59%) of the α-lactam. Further purification could be obtained by column chromatography on a column of "ASTM" 100 mesh silicic acid with 95% benzene 5% ethyl acetate as the moving phase. Spectral data showed: infrared (liquid film): 2960 and 1835 cm^{-1}. It makes no obvious difference before passing through column and after passing through column (Figure 18 and 19).

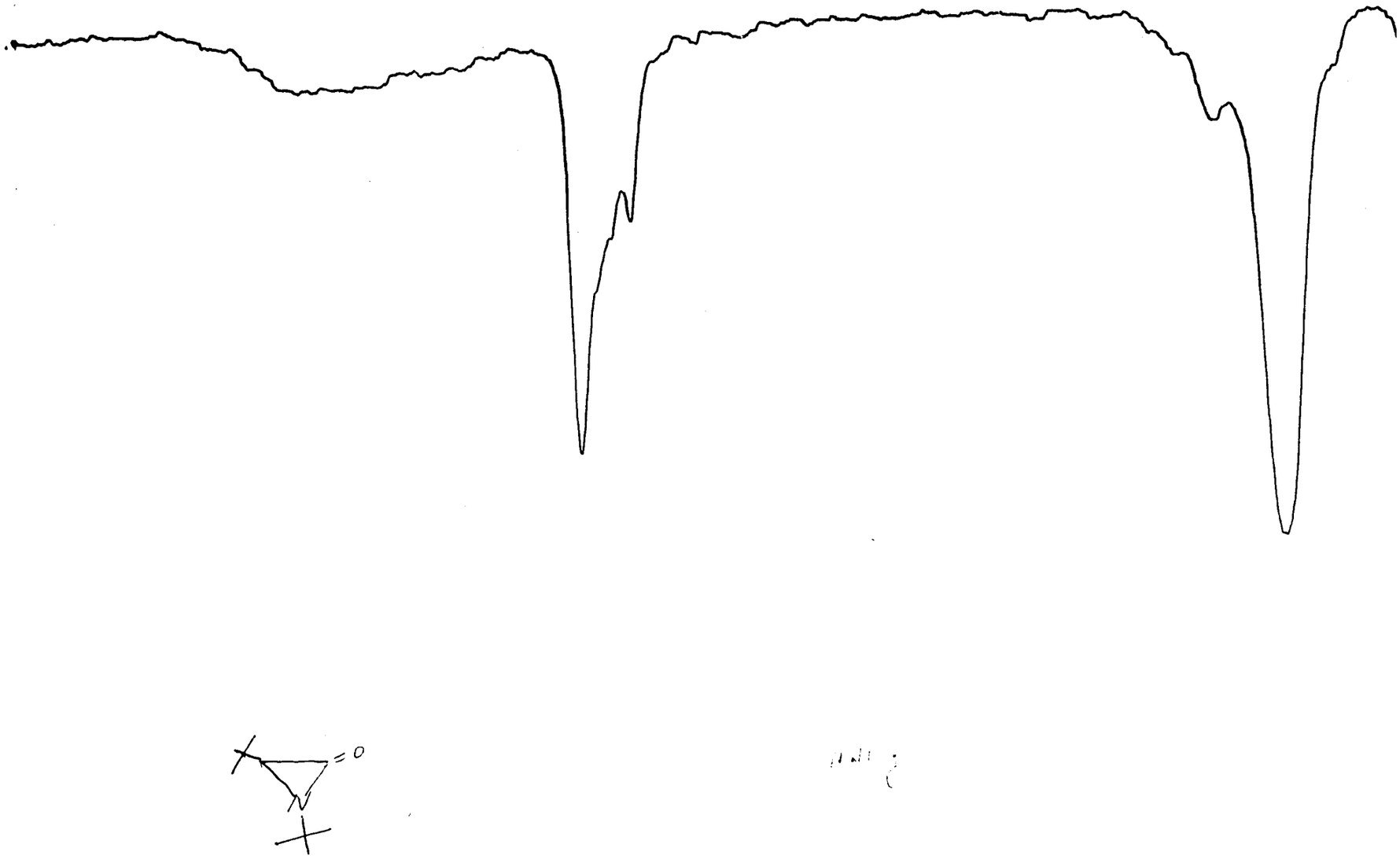


Figure 18. 1,3-Di-t-butylaziridinone (before passing column, liquid)

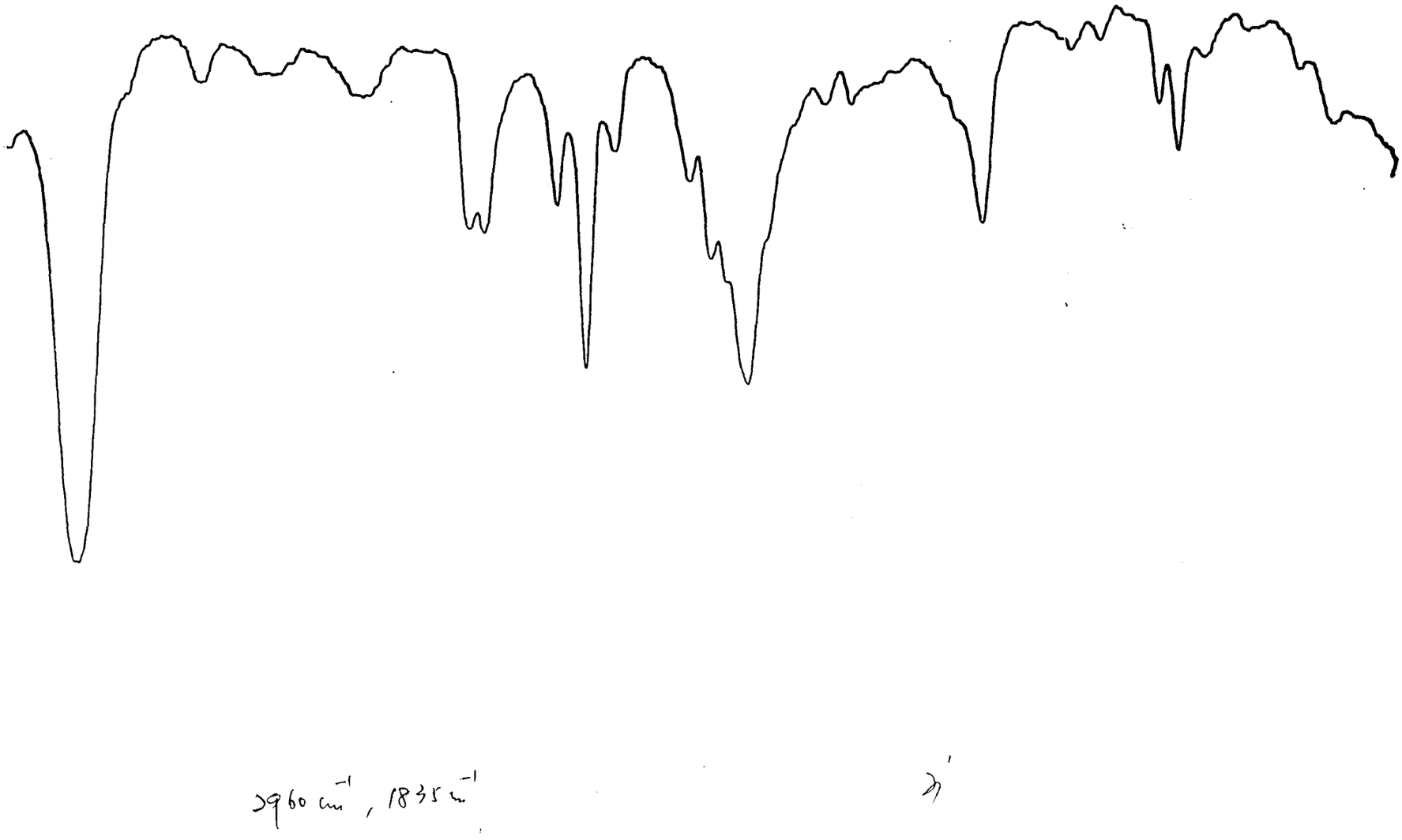


Figure 18. 1,3-Di-t-butylaziridinone (before passing column, liquid)

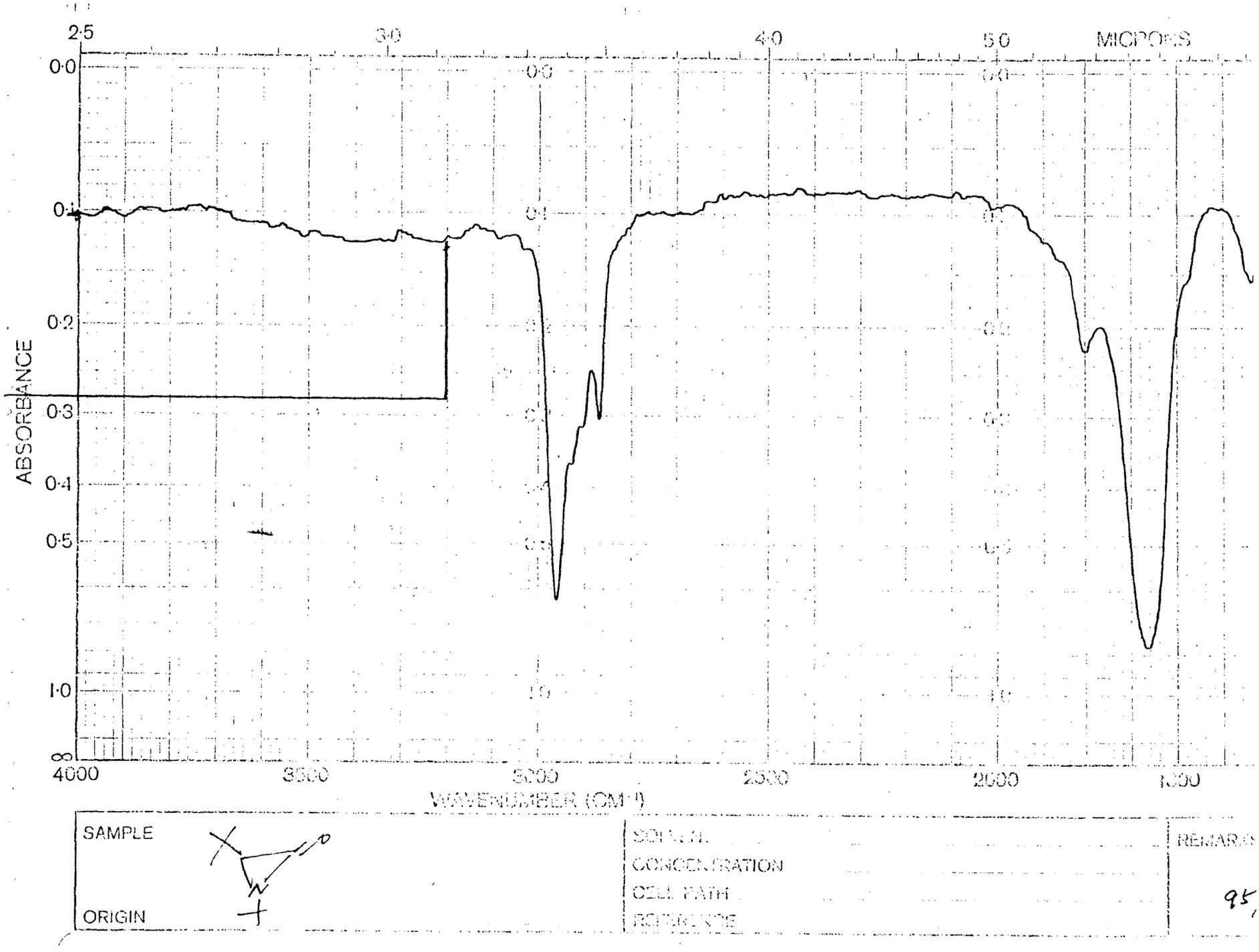


Figure19. 1,3-Di-t-butylaziridinone (after passing column, liquid)

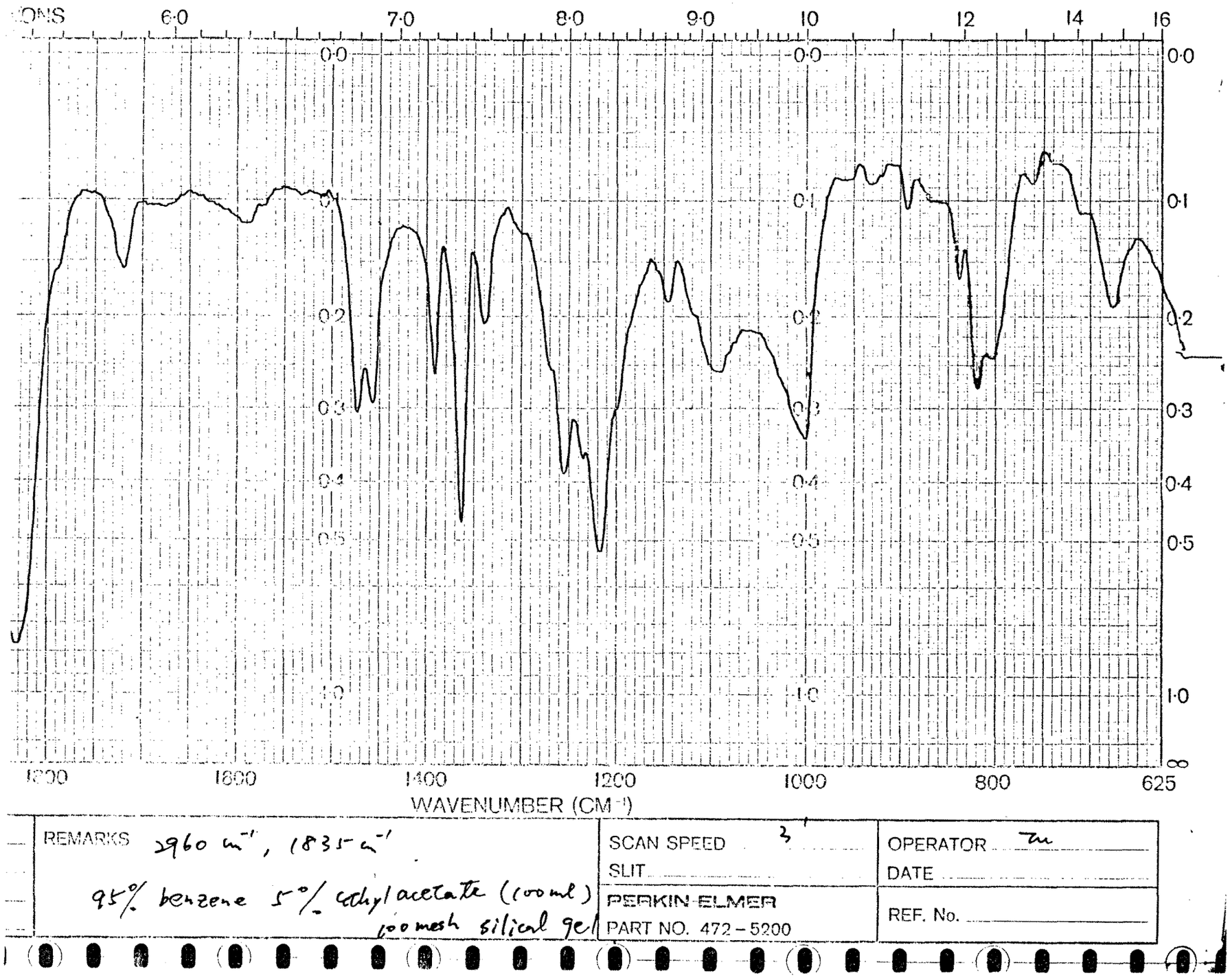


Figure19. 1,3-Di-t-butylaziridinone (after passing column, liquid)

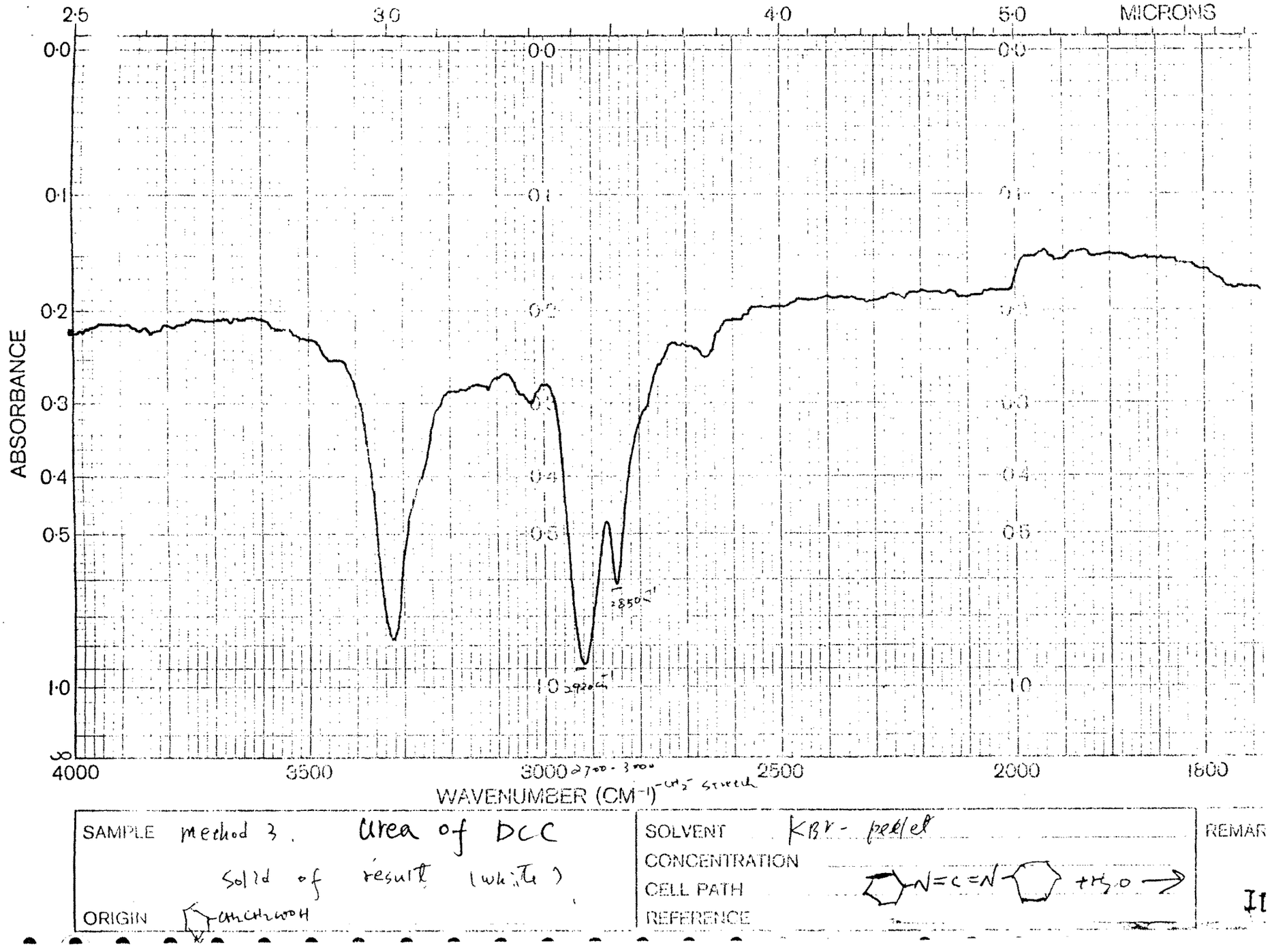


Figure 20. Urea of DCC (white solid)

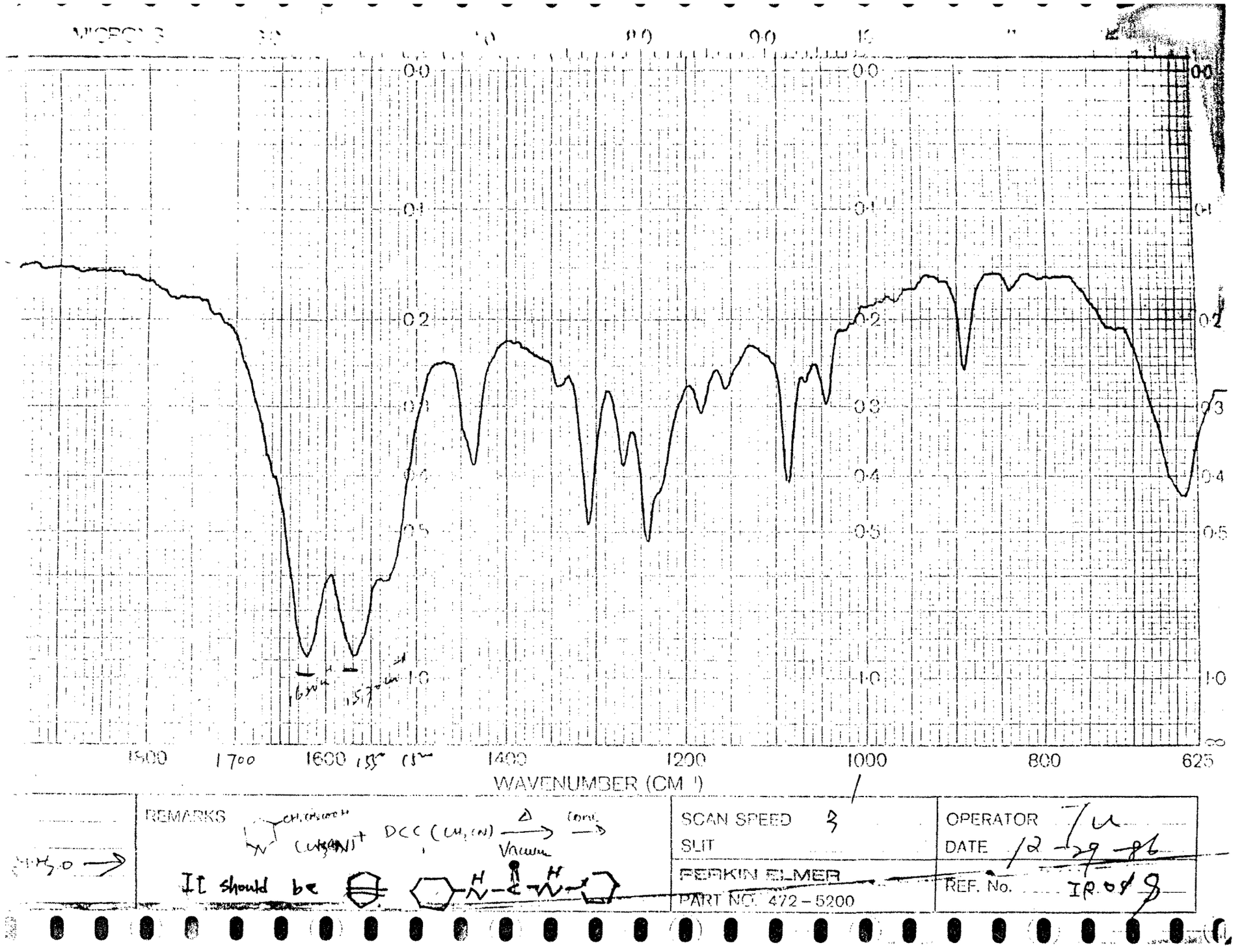


Figure 20. Urea of DCC (white solid)

III RESULTS

According to the experimental results described in Section II, we can synthesize 1-azabicyclo(3,3,1)nonan-2-one very conveniently from β-(piperidyl)-3-propionic acid using either DCC or di-n-butyltin oxide. The difference in these procedure is that with DCC synthesis can be done in a short time (around 4 hours); however, with di-n-butyltin oxide one obtains higher yield (68%). Both procedures produce much higher yields than the Hall procedure. The reaction of β-(piperidyl)-3-propionic acid with triethylamine and ethyl chloroformate (mixed anhydride route) also produces 1-azabicyclo(3,3,1)nonan-2-one (7), but it is rather impure. Although 1-azabicyclo(3,2,1)octan-7-one was not obtained by the reactions with DCC or di-n-butyltin oxide, the resulting highly viscous material suggests polymer which might have resulted from intermediary of this compound.

The synthesis of 1,3-Di-t-butylaziridinone is satisfactory, compare its IR spectrum with standard IR spectrum , both have strong absorption at 2960 and 1835 cm^{-1}.

IV DISCUSSION

1. In 1979, Shaw synthesized 7 under high vacuum and high temperature to remove water from β-(3-piperidyl)propionic. The yield is only 7% and the main product is undesired polyamide. However, a change of method such as reactions using DCC or di-n-butyltin oxide provide high yields. The mixed anhydride technique also provides a higher yield than that obtained by Shaw. This illustrates that high temperature does not favor the formation of this strained bridgehead lactam. DCC is a good reagent to apply in the synthesis of peptides. In this synthesis, DCC absorbs water and this is accompanied by cyclization of β-(3-piperidyl) propionic acid; the resulting N,N-dicyclohexylurea, which is not soluble in acetonitrile, is easy to remove by filtration.

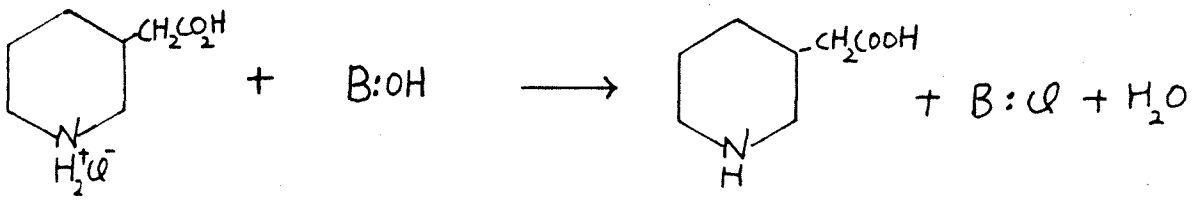
Using DCC reaction with 1,2,3,4-Tetrahydroquinoline-4-propanoic acid one can obtain 2,3,4,5-Tetrahydro-2-oxo-1,5-ethanobenzazepine (6) in very high yield (>90%)[2].

When using DCC to form 1-azabicyclo(3,3,1)nonan-2-one (7), there are two possibilities that one may consider:

one is excess DCC in the product; another is excess water in the product. If there is excess water in the product, then the aspirator does not remove water effectively. Apparently the water molecule is tightly held. If DCC is found in the product, if one first tries to use 95% alcohol to remove this impurity(small amounts of water react with DCC to form urea), it will also destroy the product. If one tries to remove DCC by differential solubilities in organic solvents, success does not appear achievable. However, Flash chromatography(1:1 petroleum and ethyl acetate) provides excellent separation.

The use of di-n-butyltin oxide to react with β-(3-piperidyl)propionic acid requires a Dean-Stark apparatus to remove water. Generally, it needs to reflux at least 12 hours to complete reaction and remove water (which is produced by -(3-piperidyl)propionic acid. The purpose of adding a large excess of the solvent,toluene (125 ml) is that it will increase the rate of intramolecular cyclization and reduce the rate of intermolecular cyclization.

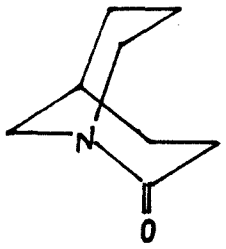
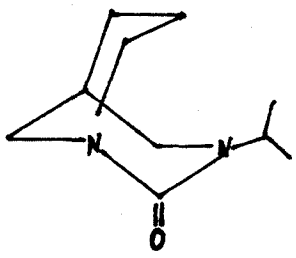
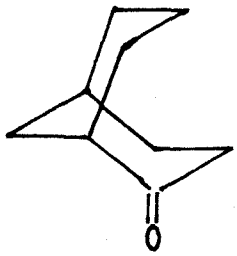
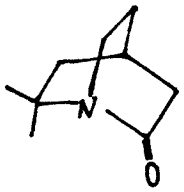
2. When trying to use DCC or di-n-butyltin oxide to react with β-3-(piperidyl)acetic acid to synthesize 9, one must neutralize β-3-(piperidyl)acetic acid hydrochloride with base ,

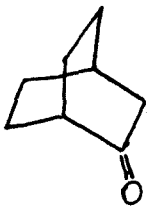


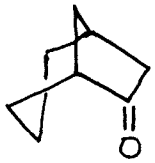
because if there is hydrochloride remaining in the starting material it would adversely affect the reaction. Upon adjusting pH around 7, and evaporating water and then proceeding under cyclization conditions, one does not obtain the desired product (it should have absorption at 1750 cm^{-1})[7] , According to reference 2, Somayaji adjusted pH to 5, and easily synthesized 2,3,4,5-Tetrahydro-2-oxo-1,5-ethanobenz-azepine (6). 1-Azabicyclo(3,2,1)octan-7-one has more strain energy than 7, therefore possibly making the reaction more difficult. Once 9 were formed, it might polymerize to relieve its strain. The IR absorption expected for 9 around 1750 cm^{-1} is due to decreased stabilization, thus supporting this view.

3. If we refer to the observations below which relate structure and IR adsorption, we can realize the relation between the effect of resonance stabilization and Infrared Carbonyl Absorption of bicyçlic lactam.

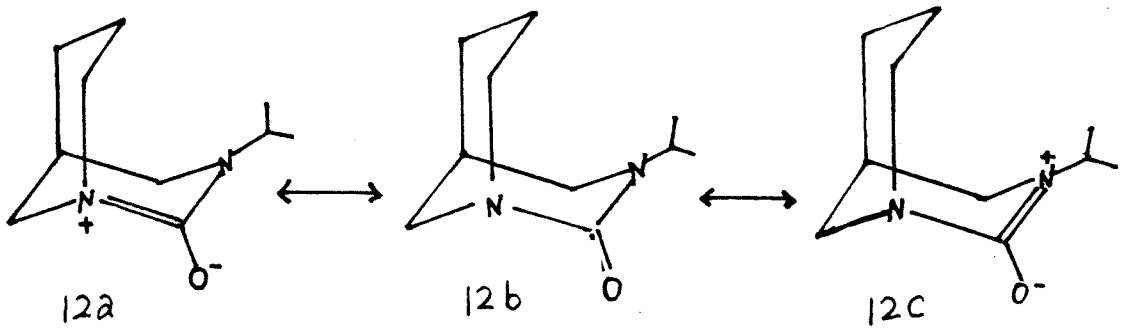
Effect of Resonance Stabillization on Infrared Carbonyl Absorption of Bicyclic Lactam[1]

	Structure	C=O Absorption (cm^{-1})
7		1680
12		1650 (Hall and Johnson 1972)
13		1711 (Marvell et al.1966)
14		1733 (Pracejus 1959)

15  1731 (Zbinden and Hall 1960)

16  1695 (Fales 1958)

Inspection of above reference that 13 shows a significantly higher carbonyl absorption than 7, indicating 7 has substantial resonance. In addition, the constant increase of approximately 30 cm^{-1} between the carbonyl absorption frequencies of 7, 12, and 13 suggests that 12a and 12c contribute equally to the stabilization of 12a:

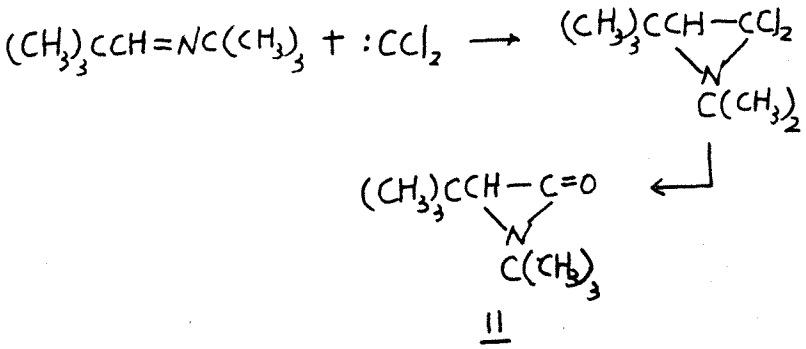


This is contrary to the assumption that an extra electron donating atom is necessary for the stabilization of this structure which was raised by Hall and Johnson in 1972. On the other hand, the approximately equal carbonyl absorption frequencies of compounds 14 and 15 showed very little resonance stabilization in the highly strained quinuclidone 14. Since that resonance stabilization is dependent on effective p-orbital overlap, it seems reasonable to conclude that the flexible, strain-free structures 12a and 7 has lower carbonyl absorptions to let carbon skeleton have ability to twist and bend for a maximum overlap. However, structure 14 has a rigid boat structure, it strictly limits the moiety of N-C=O into one position with approximately zero p-orbital

overlap. Besides, the carbonyl absorption frequency of 14 is slightly higher than corresponding ketone of 15, that is because nitrogen will withdraw electron under the absence of back donation of electrons by resonance. Comparing 1-azabicyclo(3,2,1)octan-7-one (9) to 1-azabicyclo(3,2,1)octan-2-one (16), 9 has almost 60 cm^{-1} more absorption frequencies than 16, This can be explained due to the strong strain conformation makes the nitrogen of 9 desires to withdraw electron and cause the double bond between carbon and oxygen become shorter, therefore its carbonyl absorption frequency is higher than 16.

4. Before synthesizing 1,3-Di-t-butylaziridinone 11, we synthesized its precursor 2-Bromo-3,3-dimethyl-N-t-butylbutyramide 10. In this procedure, 10 dissolved in methylene chloride solution, and is used hydrochloric acid, aquious sodium hydroxide to wash, This purpose is to take away excess t-butylamine. After adding potassium t-butoxide etc procedures, and proceeding centrifugation will obtain 11 which exits in clear solution, the bottom of centrifuge tubes have white precipitation material, which could be potassium bromide.

The other route to try to synthesize 10 from N-neopentylidene-t-butyl-amine also can obtain 10, but in very low yield (1-5%). The reaction is shown below:[18]



11

The low yield is probably due to steric hindrance of dichlorocarbene addition to the imine by the t-butyl groups.

As to check the carbonyl absorption frequency of 11, it is at 1835 cm^{-1}, the reason is because that high steric hindrance makes a twist structure and shortens the distance of C=O.

VI CONCLUSION

Two new method for preparation of 1-azabicyclo(3,3,1)nonan-one have been found. This compound can be used to measure the heat in hydrolysis and combustion, it will produce more exothermic heat than unstrained lactam.

Bridgehead lactam may be useful in pharmaceuticals, because some drugs, like penicillins etc are known to be very biologically active as the lactam linkage is strained.

The synthesis of 1-azabicyclo(3,2,1)octan-7-one was not obtained successfuly, it is possible that 1-azabicyclo(3,2,1) has strong driving force to back its starting material -3-piperidyl acetic acid as it is formed.

References

1. H. K. Hall, Jr., A. El-Shekeil, J. Org. Chem 1980,45,5325.
2. V. Somayaji; and R.S. Brown, J. Org. Chem 1986, 51,2676.
3. R. Lukes, Collect.Chem. Commun, 1938,10,848.
4. H.K. Hall, Jr.; Shaw,R.G; Deutschmann, A, Jr., J. Org. Chem. 1980, 45,3722.
5. H. Pracejus, Chem. Ber. 1959,92,988.
6. H. Pracejus, Chem. Ber. 1965,98,2897.
7. A. Greenberg " Molecular Structure and Energetics ", Vol.7, VCH pub., New York, in press.
8. L. Pauling, The Nature of the Chemical Bond, Third Ed., Cornell University press, New York, 1960, p.281-282.
9. H.K. Hall, O.E. Ekechuchwn, A, Deutschmann, Jr., C. Rose, Polym. Bull 1980,3,375.
10. G.L. Buchanan, J, Chem, Soc. Chem. Commun. 1981,814.
11. G.L. Buchanan, J, Chem, Soc. Perkin trans. 1984 1,2669.
12. L. Treschanke and P. Rademacher, J. Mol. Struct. 1985,47,122.
13. K. Stelion and M.-A. Poupart, J.Am.Chem.Soc.1983,105,7130-7138.
14. J.C. Sheehan and J.H. Beeson, J.Am.Chem.Soc. 1967,89,362-365.
15. H.K. Hall, Jr., J. Amer.Chem.Soc. 1960,82, 1209.
16. G.L.Buchanan.J.Chem. Soc Perkin Trans, 1984,1, 2669-2610.

17. W.C Still, M. Kahn, and A. Mitra J.Org.Chem, 1978, 43, 2923-2925.

18. A. G. Cook and E. K. Fields,J. Org. Chem.,1962,27,3686.

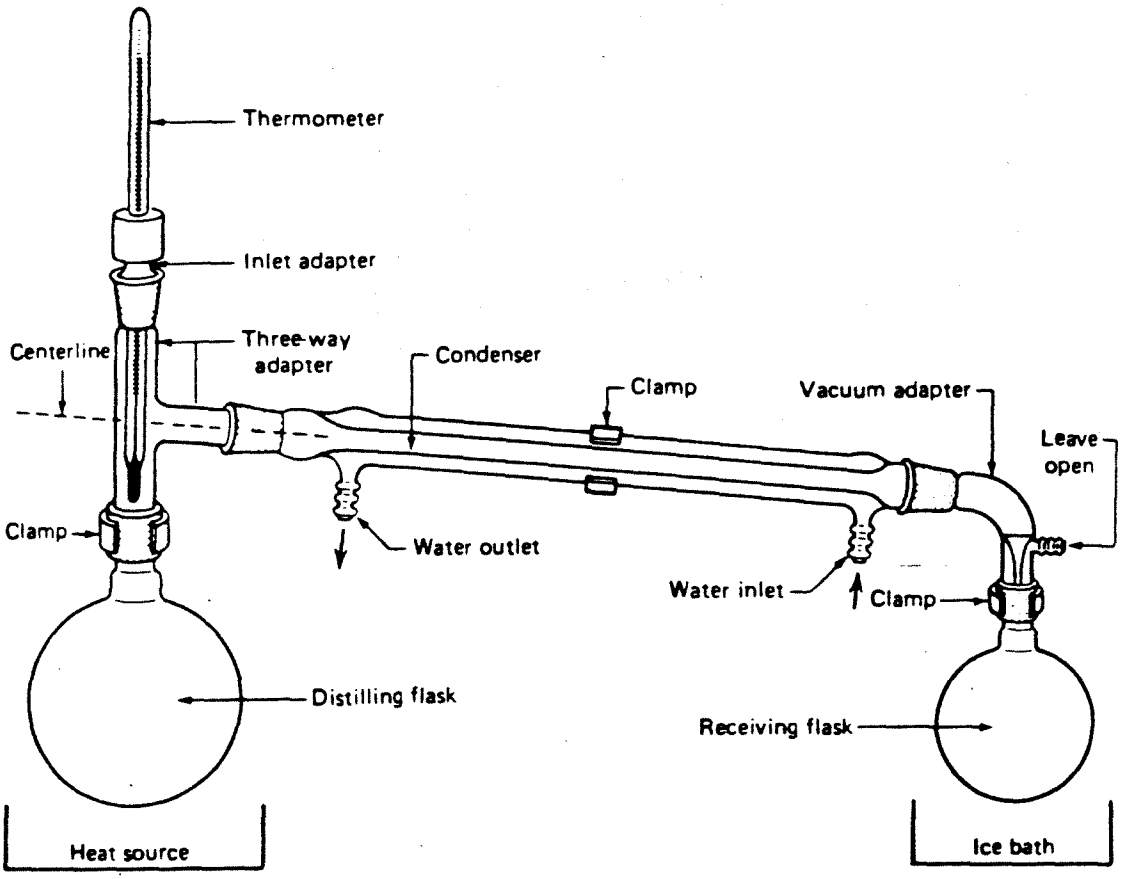


Figure 21. Distillation Apparatus

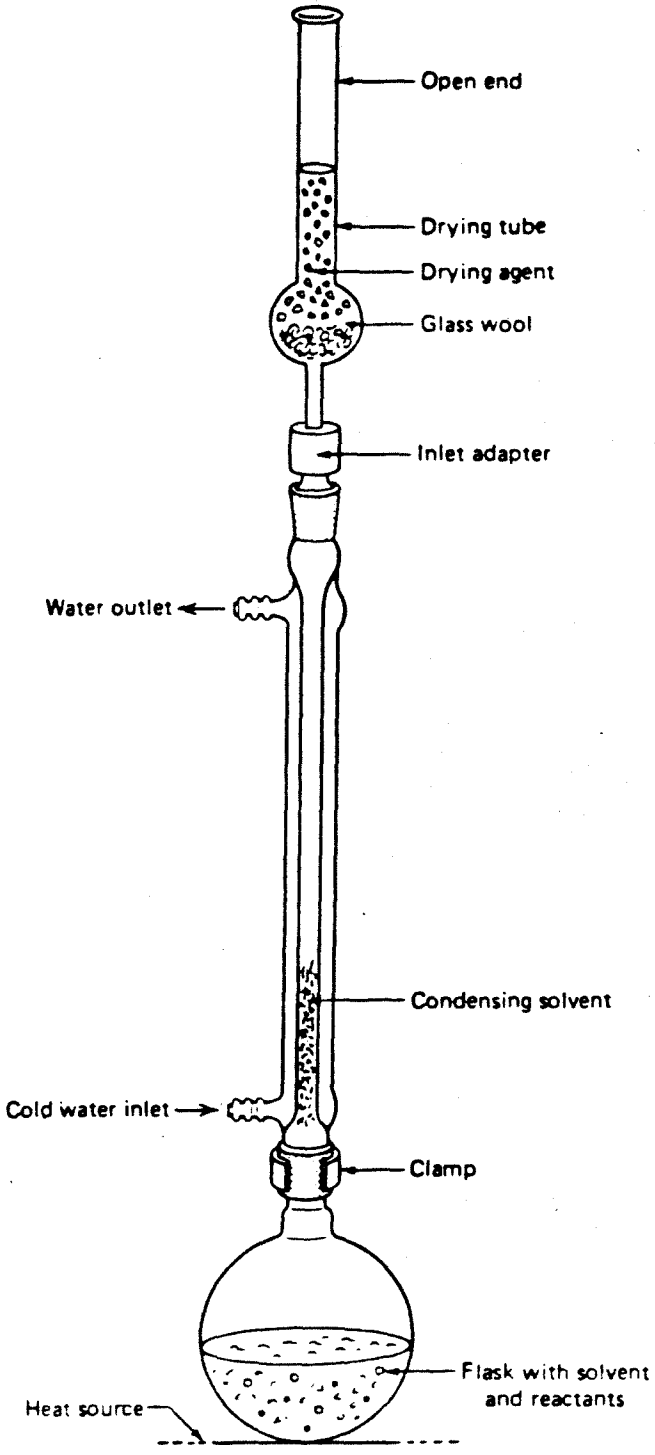


Figure 22. Reflux Apparatus

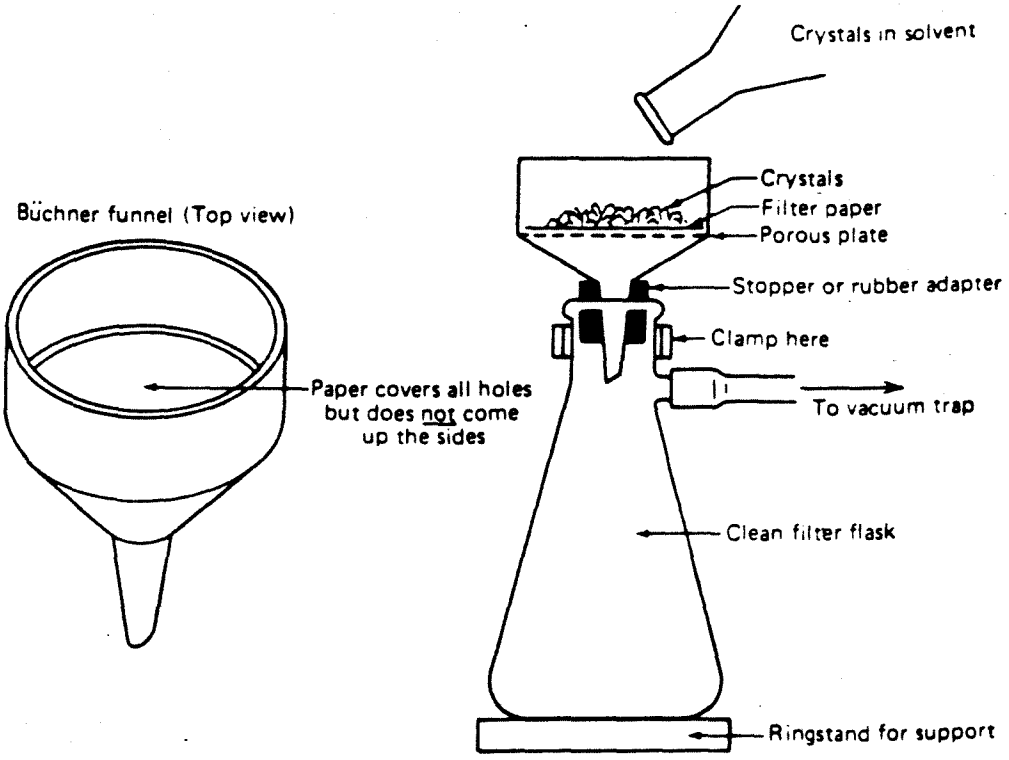


Figure 23. Filtration (suction) Apparatus

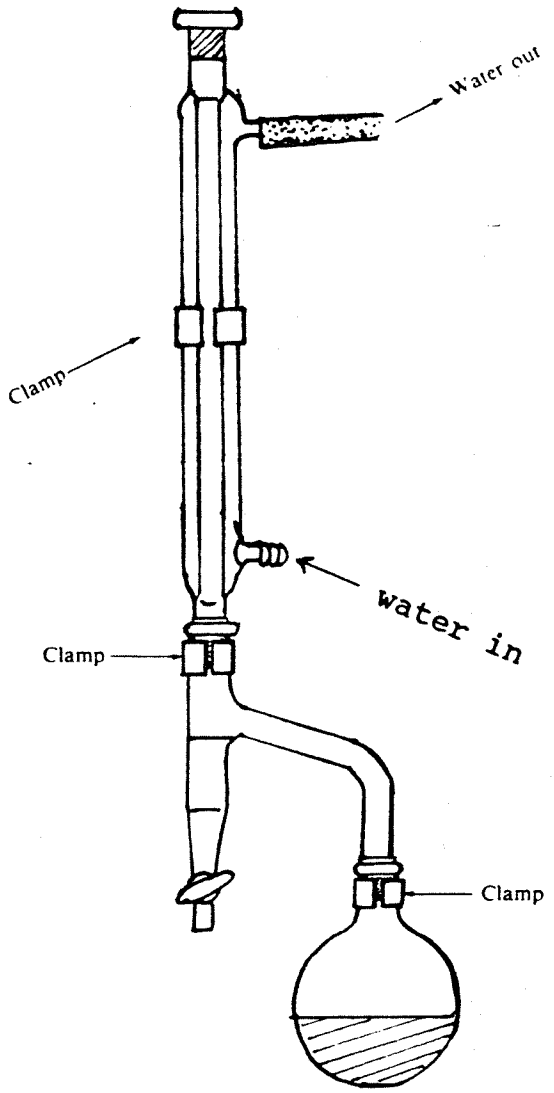


Figure 24. Dean-Stark Apparatus

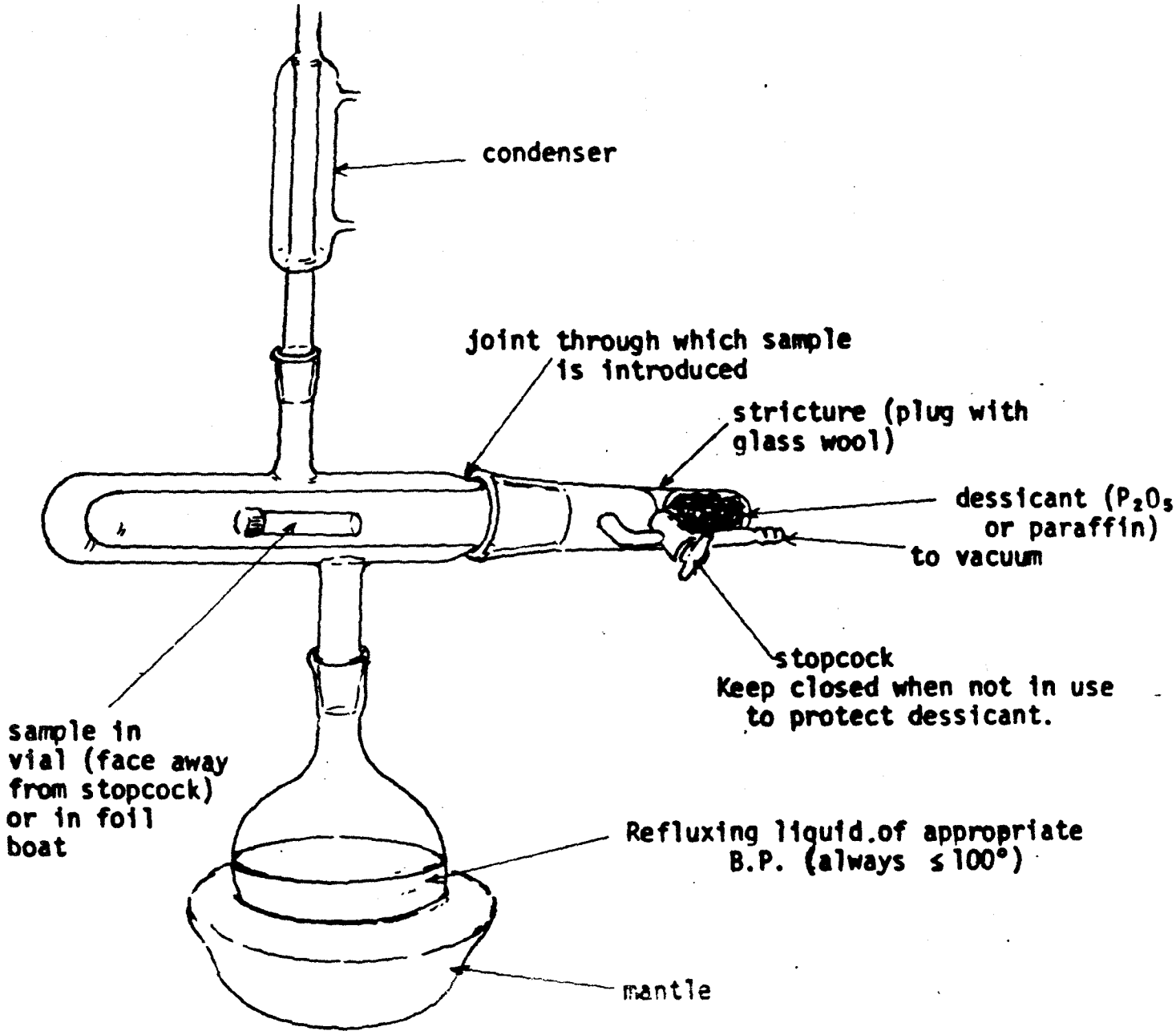


Figure 25. Aspirator Apparatus

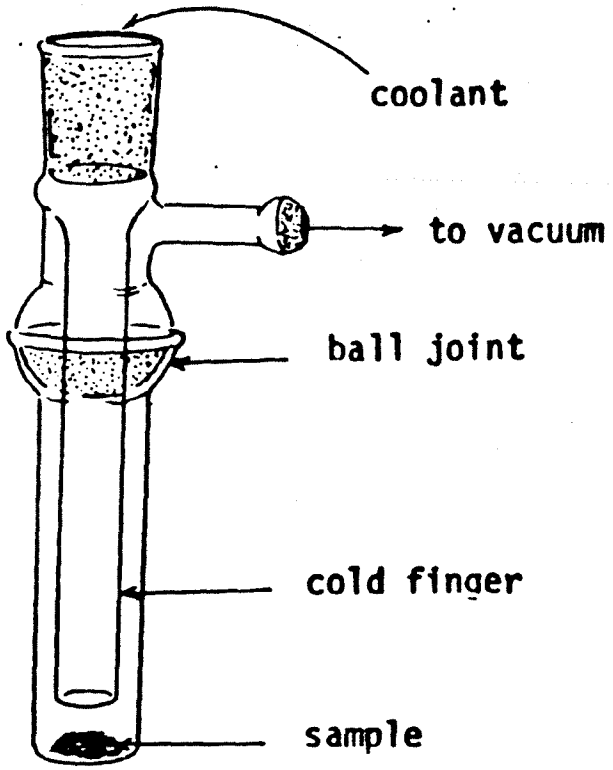


Figure 26. Sublimation Apparatus

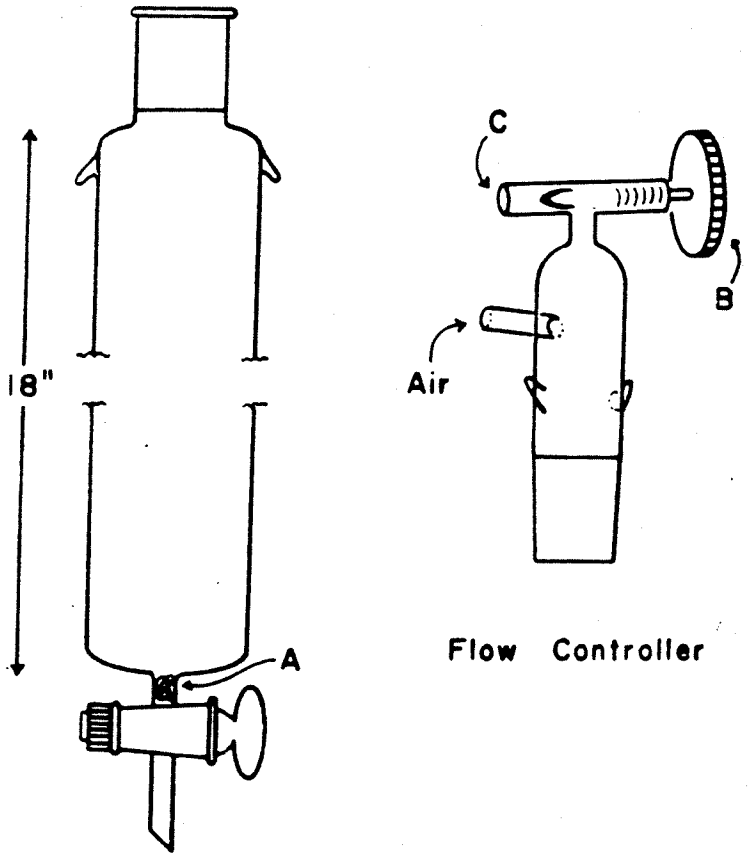


Figure 27. Flash Chromatography

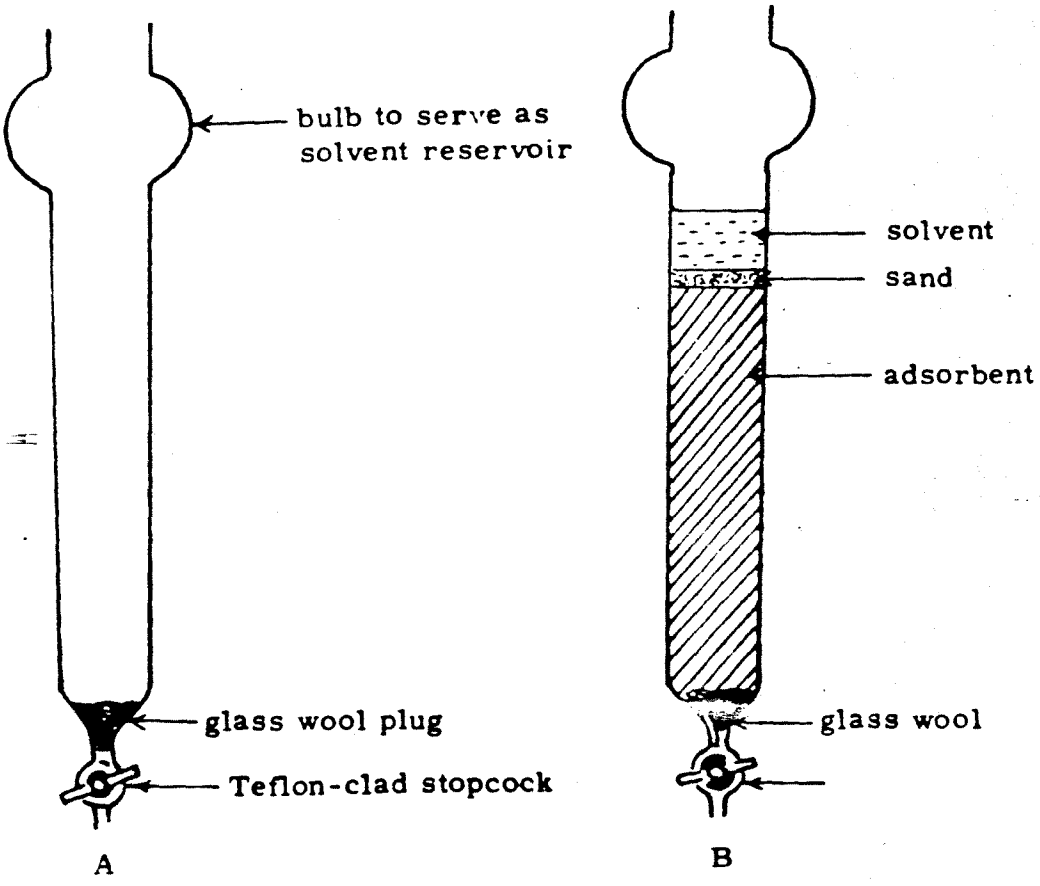


Figure 28. Apparatus of Column Chromatography