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## 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

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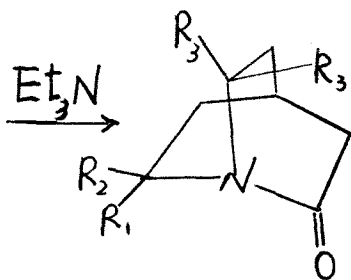
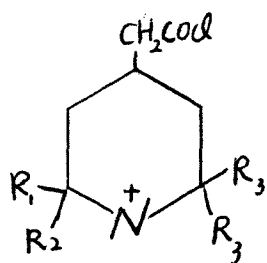
## I. INTRODUCTION

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<sup>1,2</sup>. The interest in bicyclic bridgehead lactams is due, in part, to their apparent violation of Bredt's Rule. In 1938, Lukes<sup>3</sup> 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 possess 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<sup>4</sup> 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.

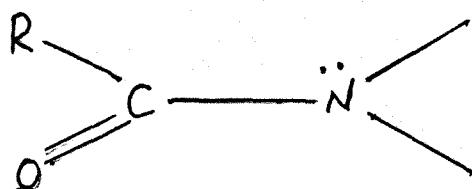
H. Pracejus<sup>5,6</sup> used ethyl chloroformate and triethylamine to react with amino acylchlorides to synthesize three derivatives of 2-quinuclidone ( 1-3 ).



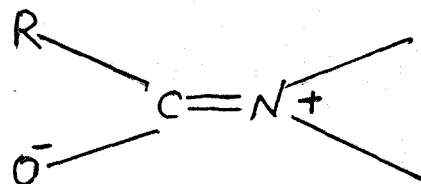
- 1,  $R_1 = R_2 = R_3 = H$
- 2,  $R_1 = R_2 = H; R_3 = CH_3$
- 3,  $R_1 = H; R_2 = R_3 = CH_3$

" 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 "<sup>7</sup>. 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



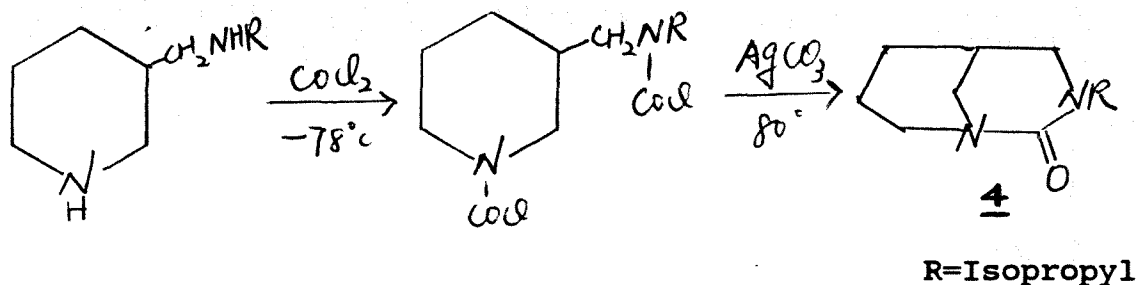
A



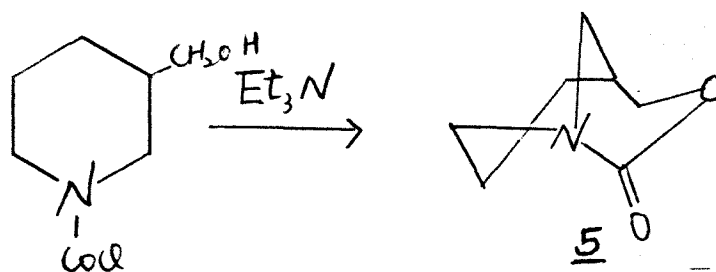
B

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<sup>8</sup>. 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 accompanied 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<sup>9</sup>,



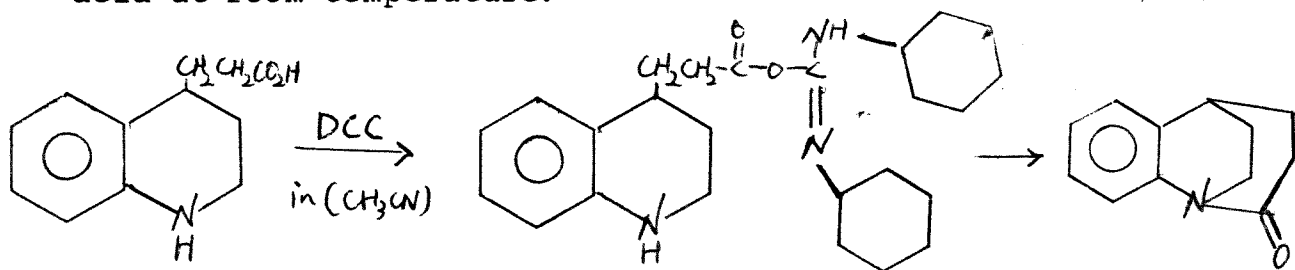
a bicyclic urea found to be stable toward boiling water, toluenesulfonic acid and phosphoric acid. The infrared carbonyl absorption at  $1650\text{ cm}^{-1}$  further indicated the strainless conformation of this compound. Buchanan<sup>10</sup> reported synthesis of 5-phenyl-1-azabicyclo[3,3,1]nonan-2-one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



Hall, Shaw, and Deutschmann synthesized the related lactam, 1-azabicyclo[3,3,1]nonan-2-one by heating the amino acid between  $180\text{--}285\text{ }^{\circ}\text{C}$  at 0.05 torr and catching the lactam in a cold receiving flask<sup>4</sup>. 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 ( $1680\text{ cm}^{-1}$  and  $1720\text{ cm}^{-1}$ )<sup>12</sup>. If one compare the carbonyl frequencies for 1-azabicyclo[2,2,2]octan-2-one and the corresponding ketone ( $1750\text{ cm}^{-1}$  and  $1731\text{ cm}^{-1}$ )<sup>12</sup>, 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 ( $1650\text{ cm}^{-1}$ ) 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:<sup>2</sup>



6

The unsubstituted compound was previously made by

the mixed anhydride techniques which Somayaji and Einspahr<sup>2</sup> 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<sup>13</sup> (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.<sup>14</sup>



## 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.

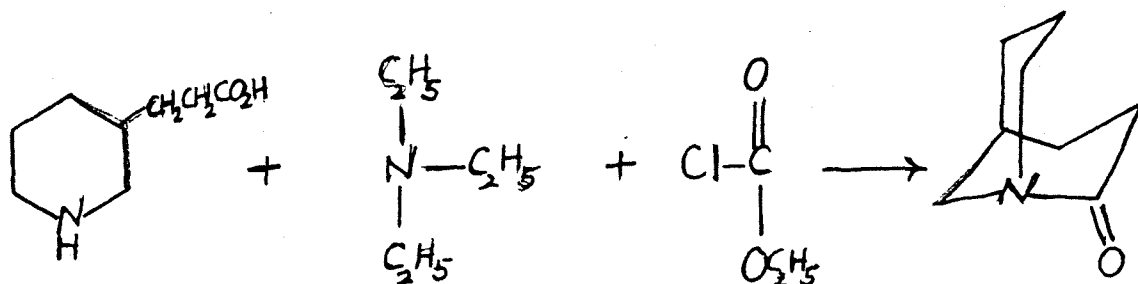
4. Ultra-Violet lamp: Model Uvsl-25 mineralight lamp.

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<sup>10,11</sup>



Weighed 405.6 milligram of  $\beta$ -(3-piperidyl) propionic acid ( mp is  $177^{\circ}\text{C}$  prepared by K. Zyla according to ref 15; The infrared spectrum is shown in Fig.1 , the homologue  $\alpha$ -3-piperidyl acetic acid was similarly prepared, mp is  $235^{\circ}\text{C} - 238^{\circ}\text{C}$ , 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  $1730\text{-}^1\text{cm}$  and  $1680\text{ cm}^{-1}$ .

\*MM of  $\beta$ -(3-piperidyl) propionic acid is 158.0 gram.

\*Density of triethylamine is 0.726.

\*Density of ethyl chloroformate is 1.135.

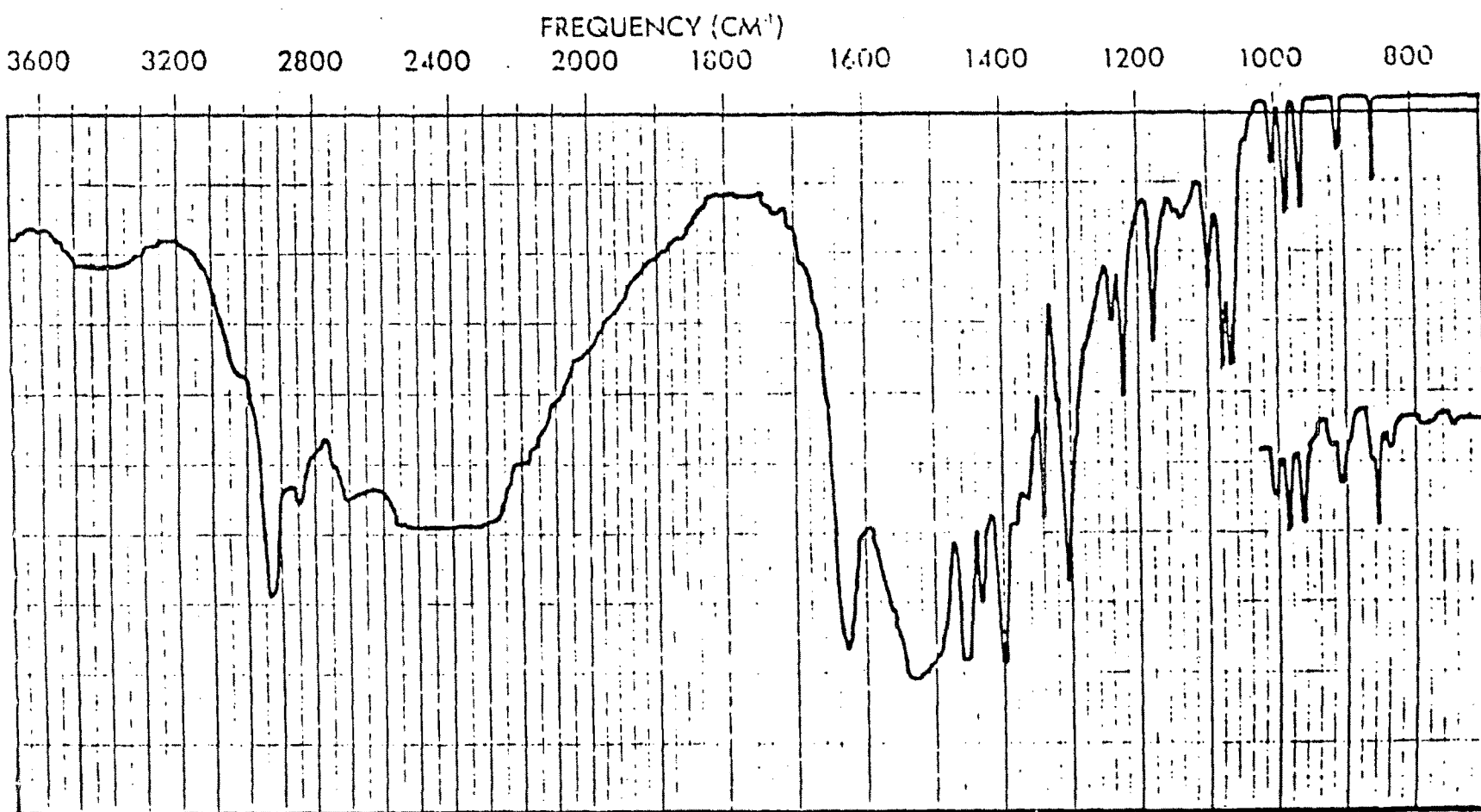


Figure 1.  $\beta$ -(3-piperidyl)propionic (KBr pellet)

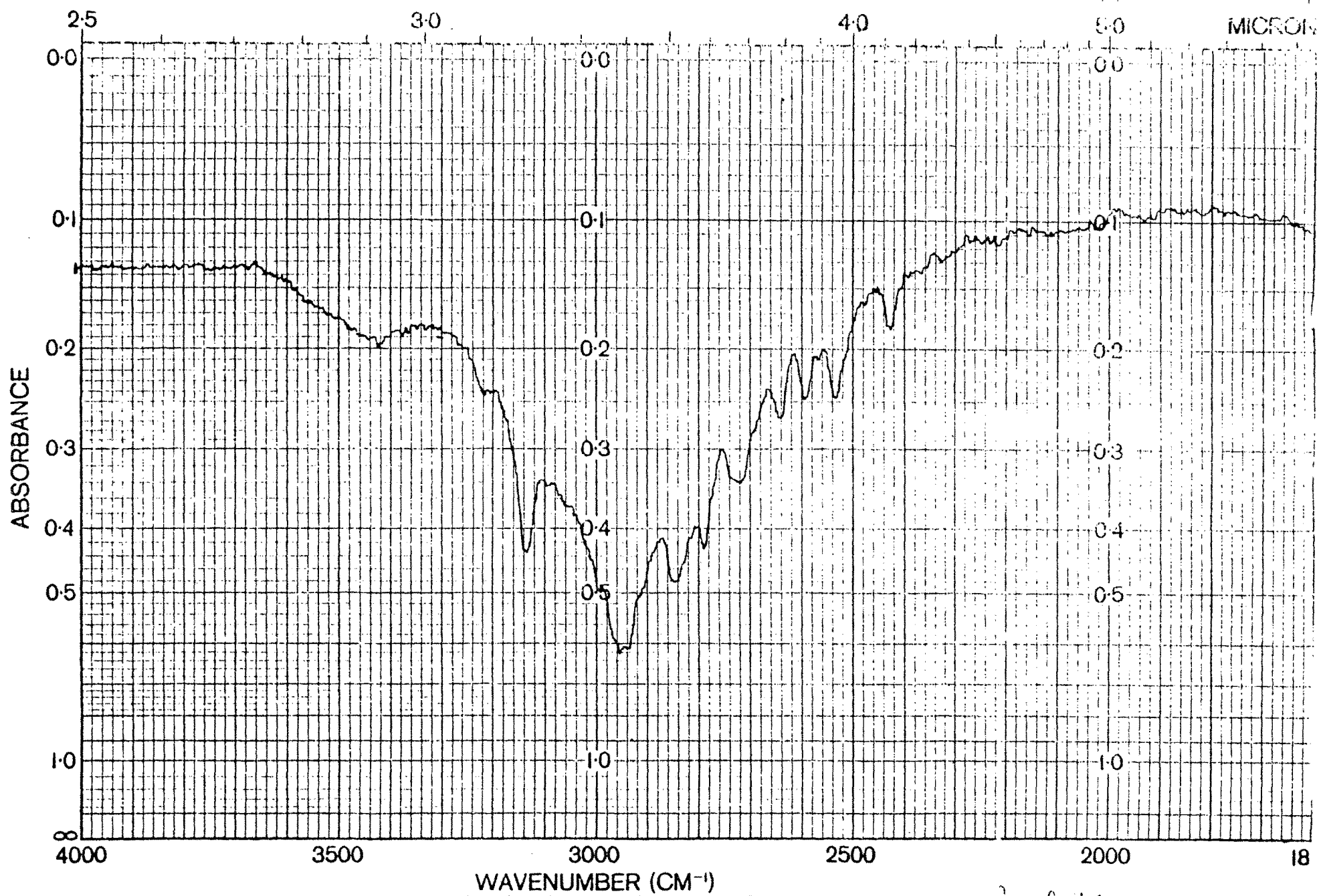
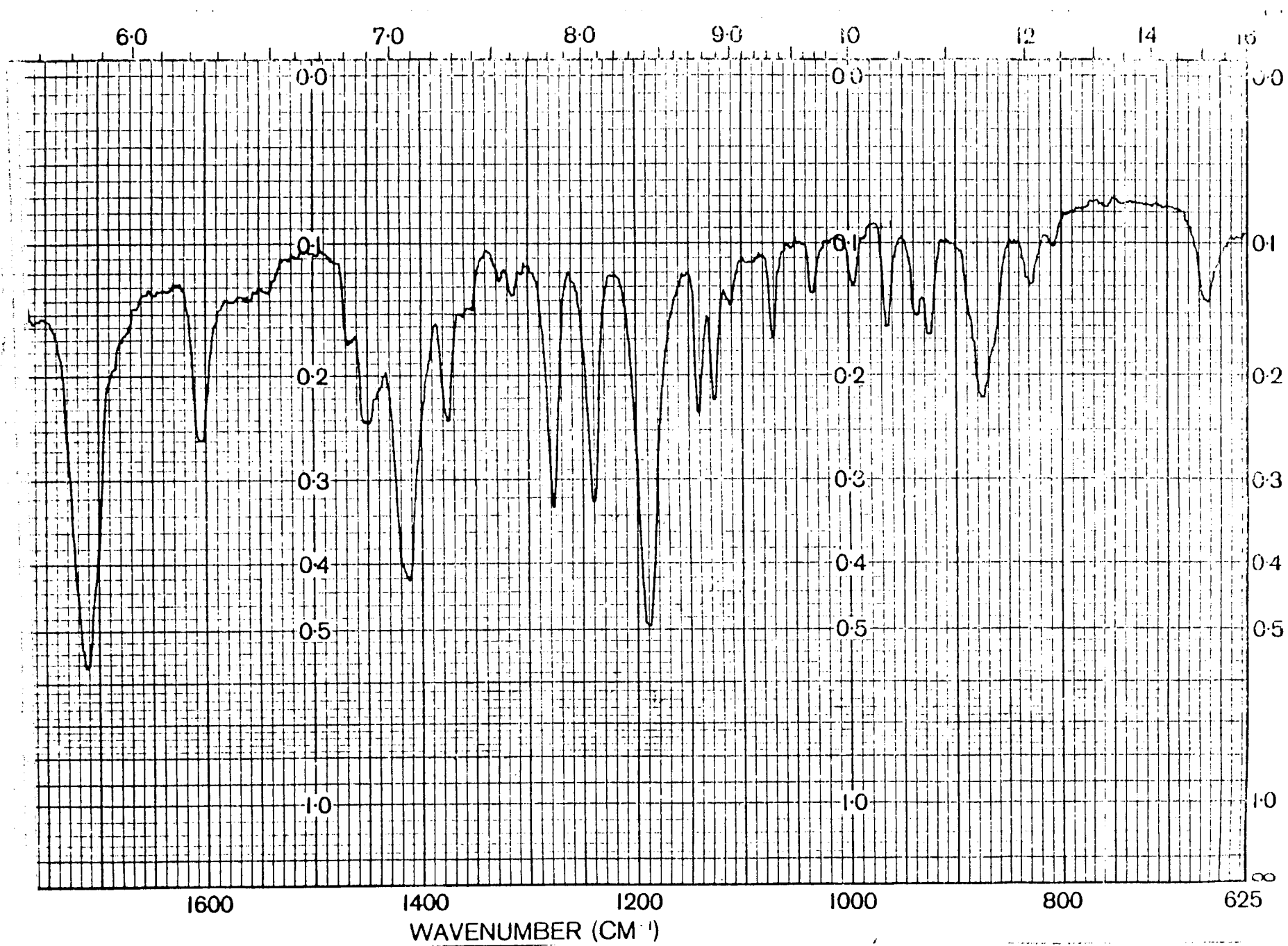


Figure 2  $\alpha$ -3-piperidyl acetic acid (KBr pellet)



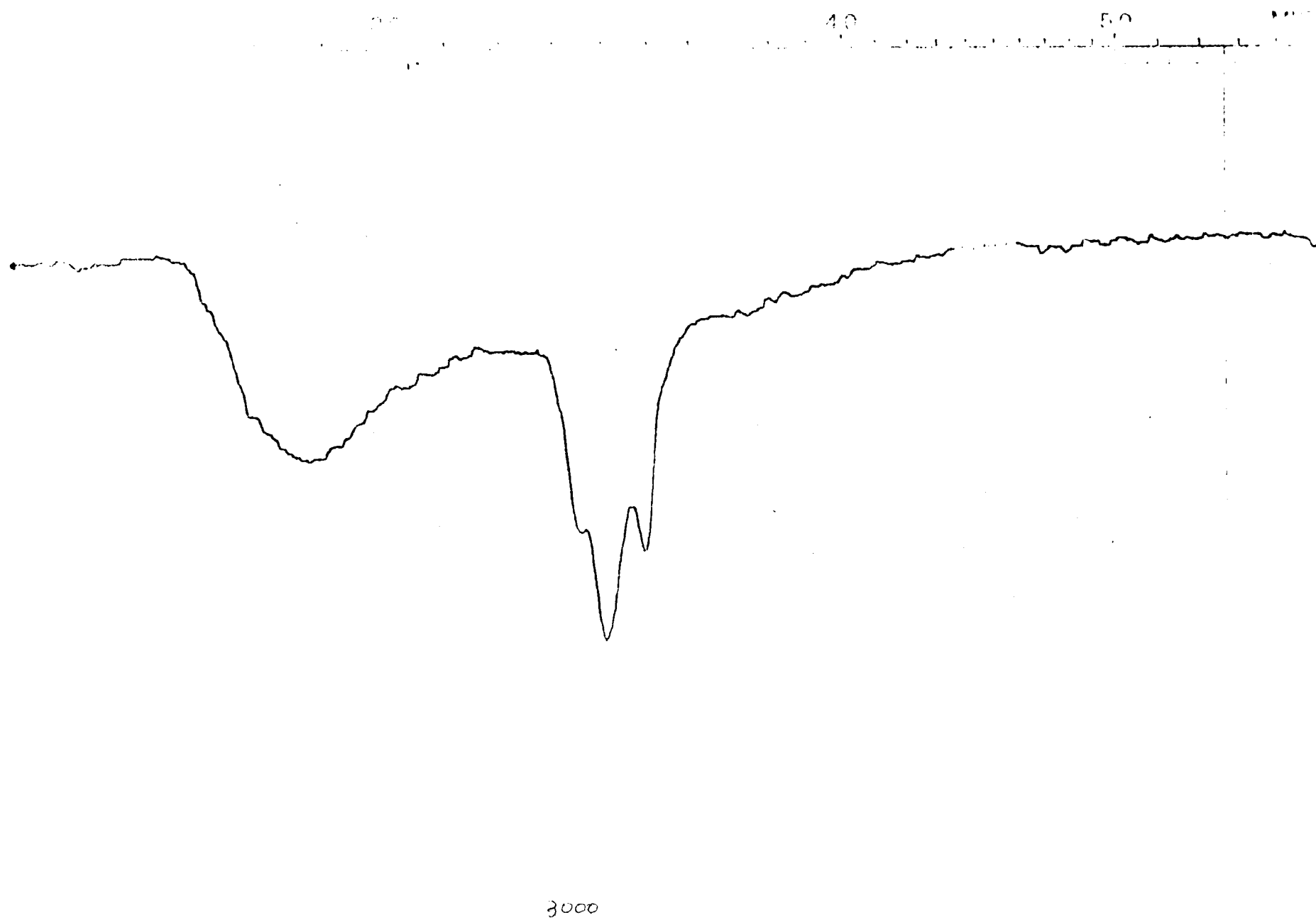


Figure 3. 1-azabicyclo(3,3,1)nonan-2-one



60

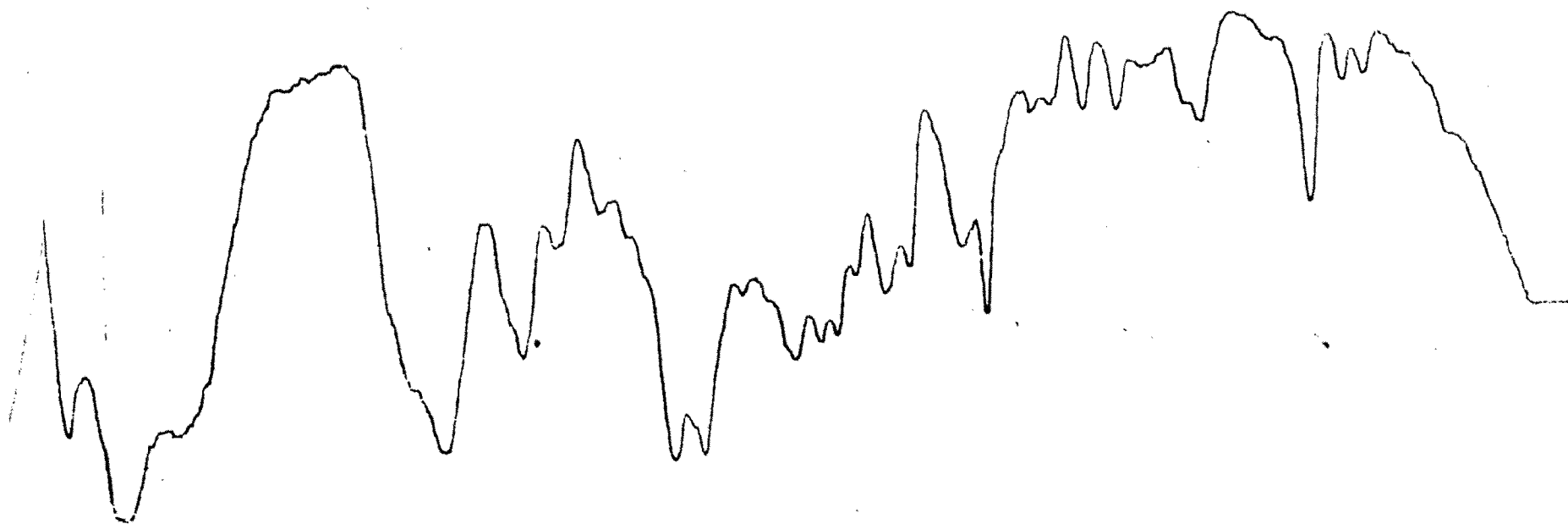
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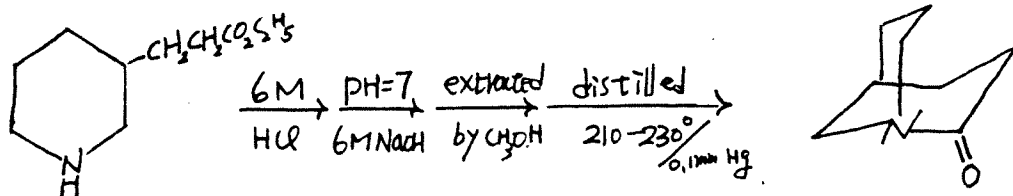
McCleod range



1600

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

2. Generation of Amino Acid from ethyl- $\beta$ -(3-piperidyl)-propionate<sup>16</sup>



Hydrolysis of ethyl- $\beta$ -(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- $\beta$ -(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<sup>-1</sup>, but it has absorption between 1200 cm<sup>-1</sup> and 1450 cm<sup>-1</sup>, and has absorption at 2100 cm<sup>-1</sup> . It could be the starting amino acid.

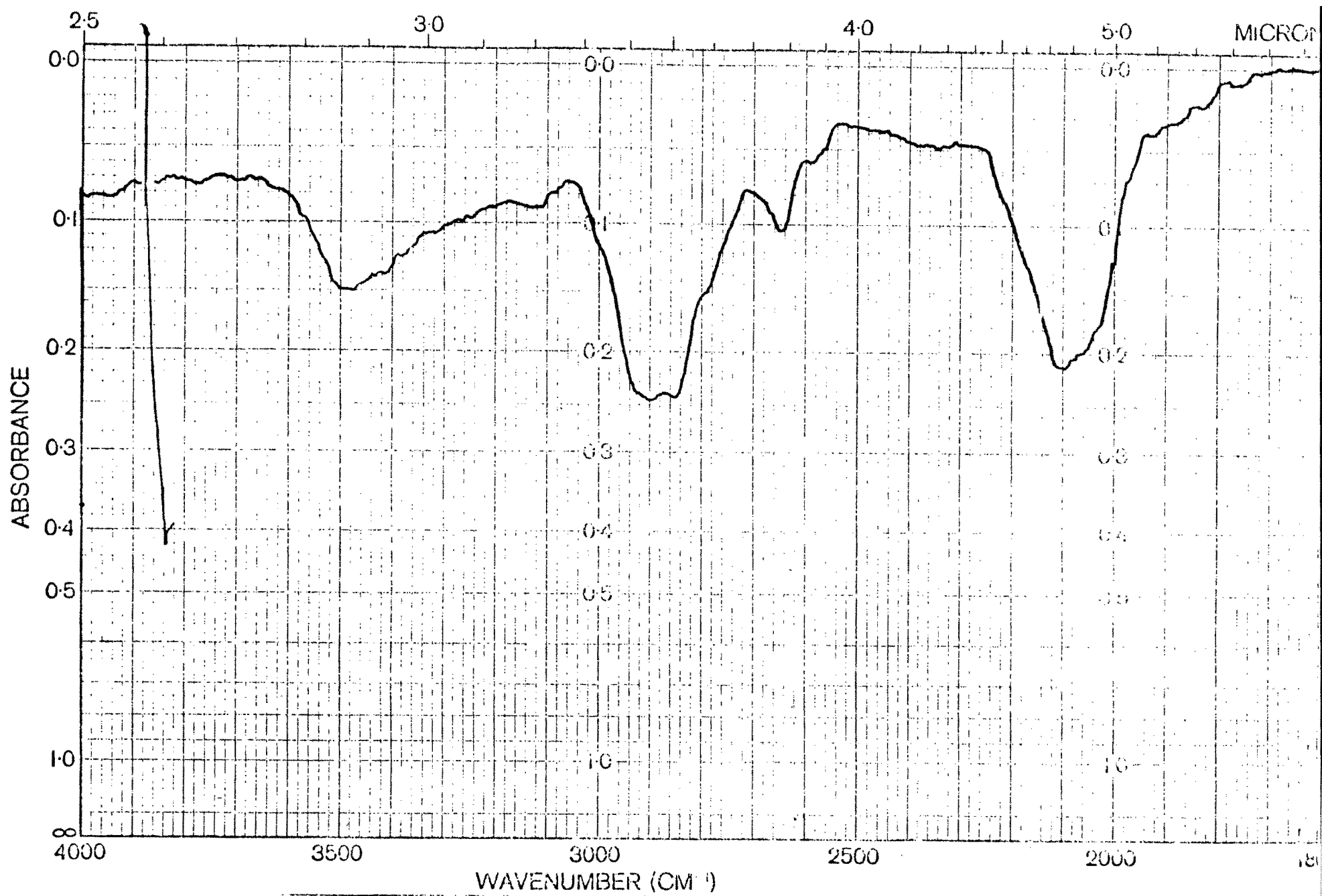
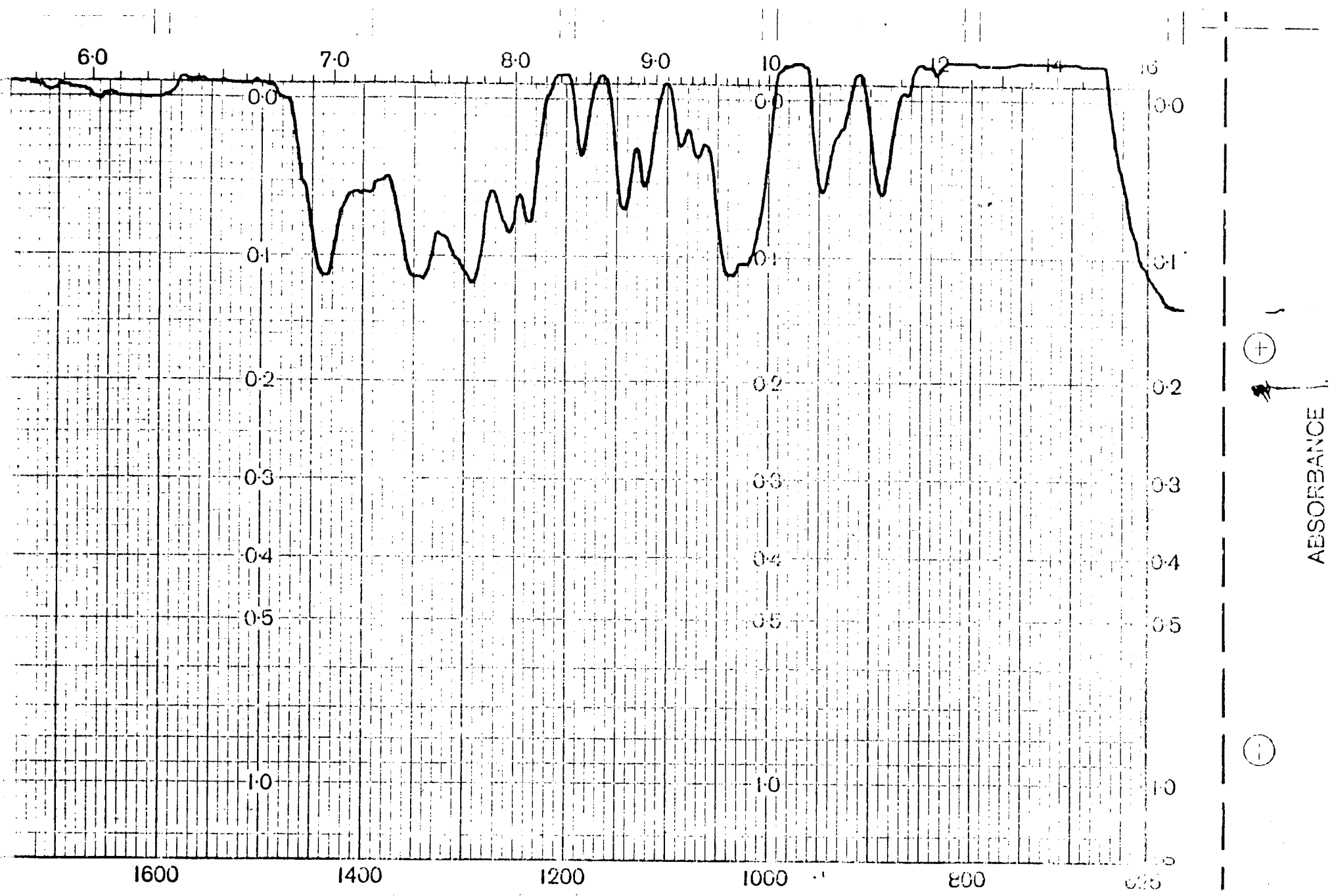
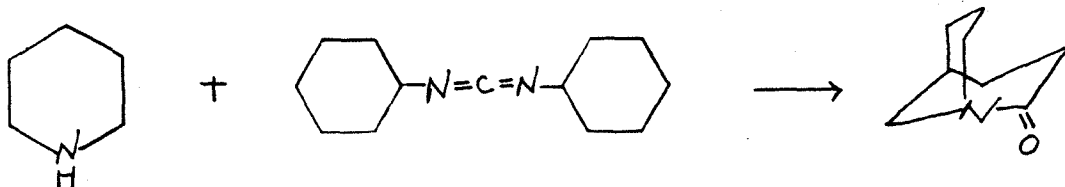


Figure 4. Mixture of starting amino acid and DCC



### 3. Reaction with DCC<sup>2</sup>



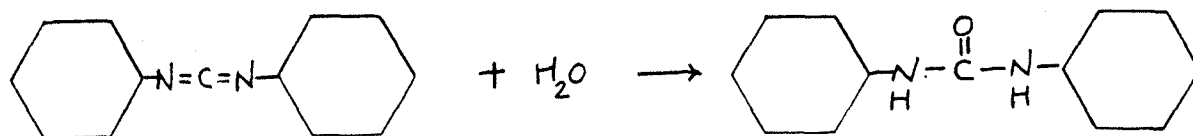
Set up a distillation apparatus using 250 ml round bottom flask (all glassware dried by putting in the oven at 150 °C for 1 hour). After putting 150 ml acetonitrile (HPLC grade) into the flask, one takes calcium hydride (CaH<sub>2</sub>) and adds small amounts (carefully). During the addition, mix gently after each addition by swirling the flask; see if there are bubbles appearing upon addition of calcium hydride to acetonitrile. Keep adding CaH<sub>2</sub> 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<sup>-1</sup> and a very strong peak at 2100 cm<sup>-1</sup>. This is because excess unreacted DCC remains in the product.

The above procedure is repeated until  $\beta$ -(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  $1680\text{ cm}^{-1}$  and broad absorption around  $3500\text{ cm}^{-1}$ . 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  $1680\text{ cm}^{-1}$ , but it still has absorption at  $3500\text{ cm}^{-1}$ .

Unfortunately, sometimes when the above procedure was repeated, the IR spectrum showed that some DCC was mixed with the product ( $2100\text{ cm}^{-1}$  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<sub>2</sub>O, 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.

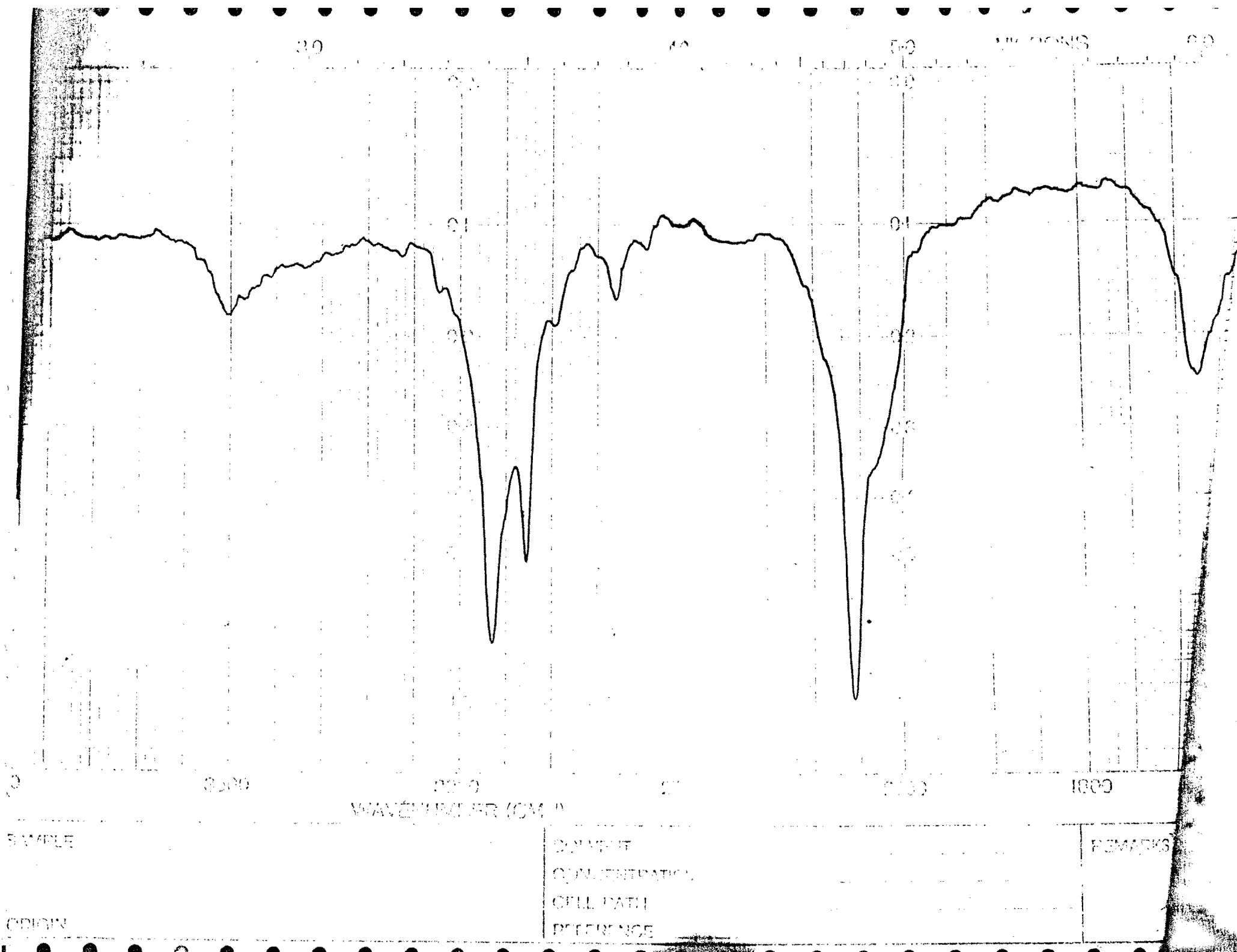
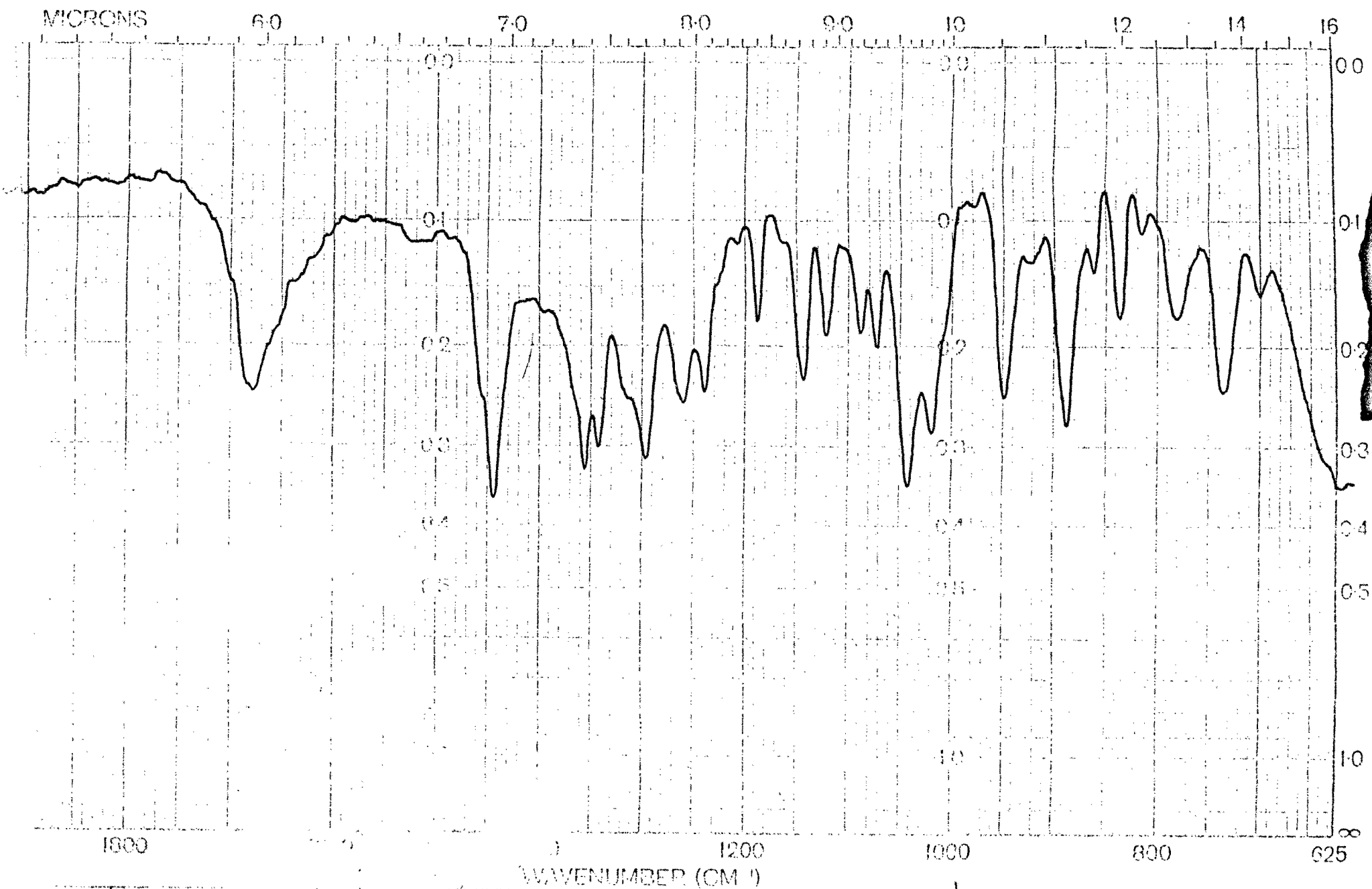


Figure 5. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC





REMARKS

C1CN2CCC1C2 + DCC  
 EVAPORATED  
 residue  
 shaking  
 4 hours

SCAN SPEED 3

OPERATOR Cu

SLIT

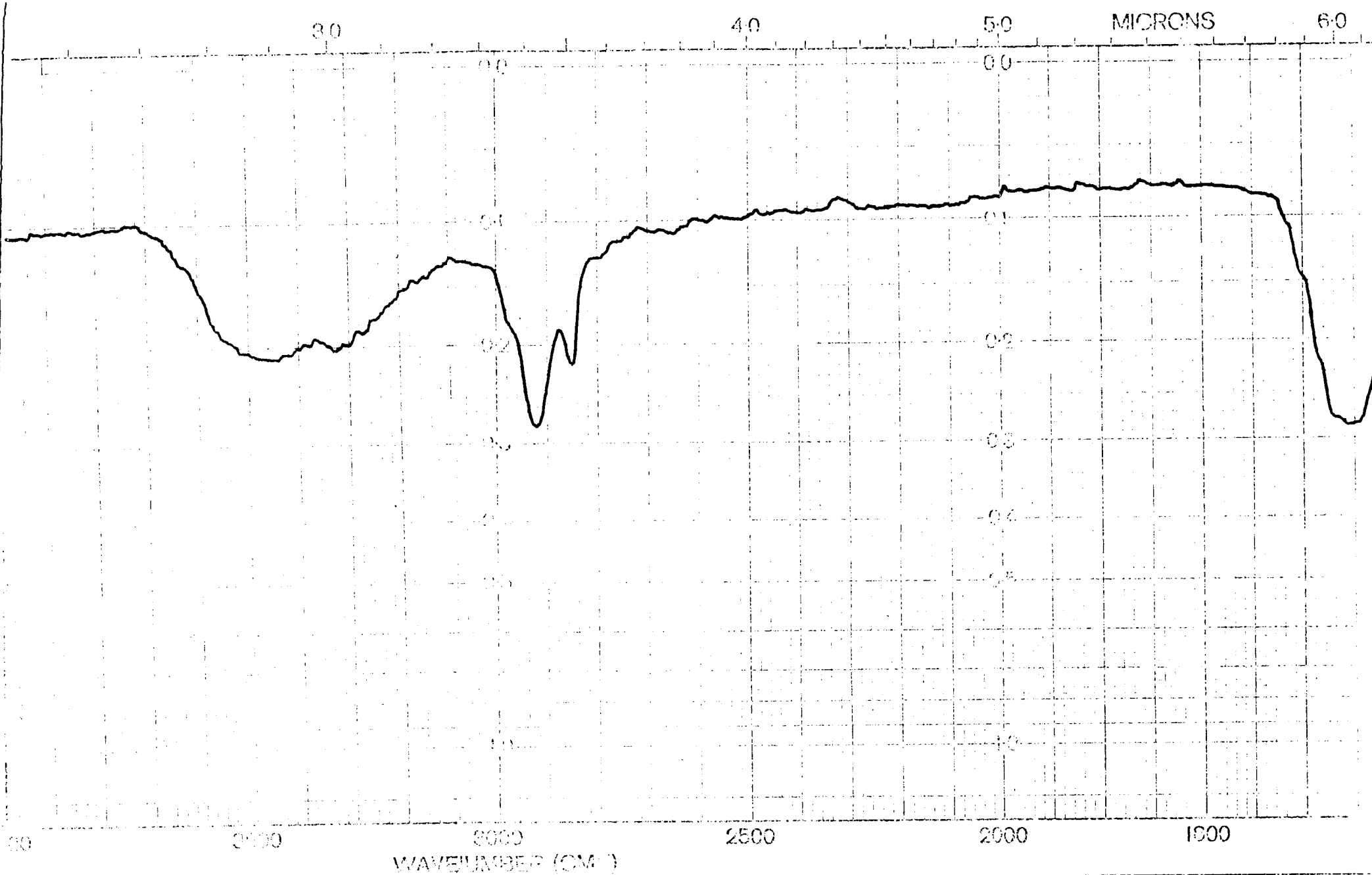
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Figure 5. Mixture of 1-azabicyclo(3,3,1)nonan-one and DCC




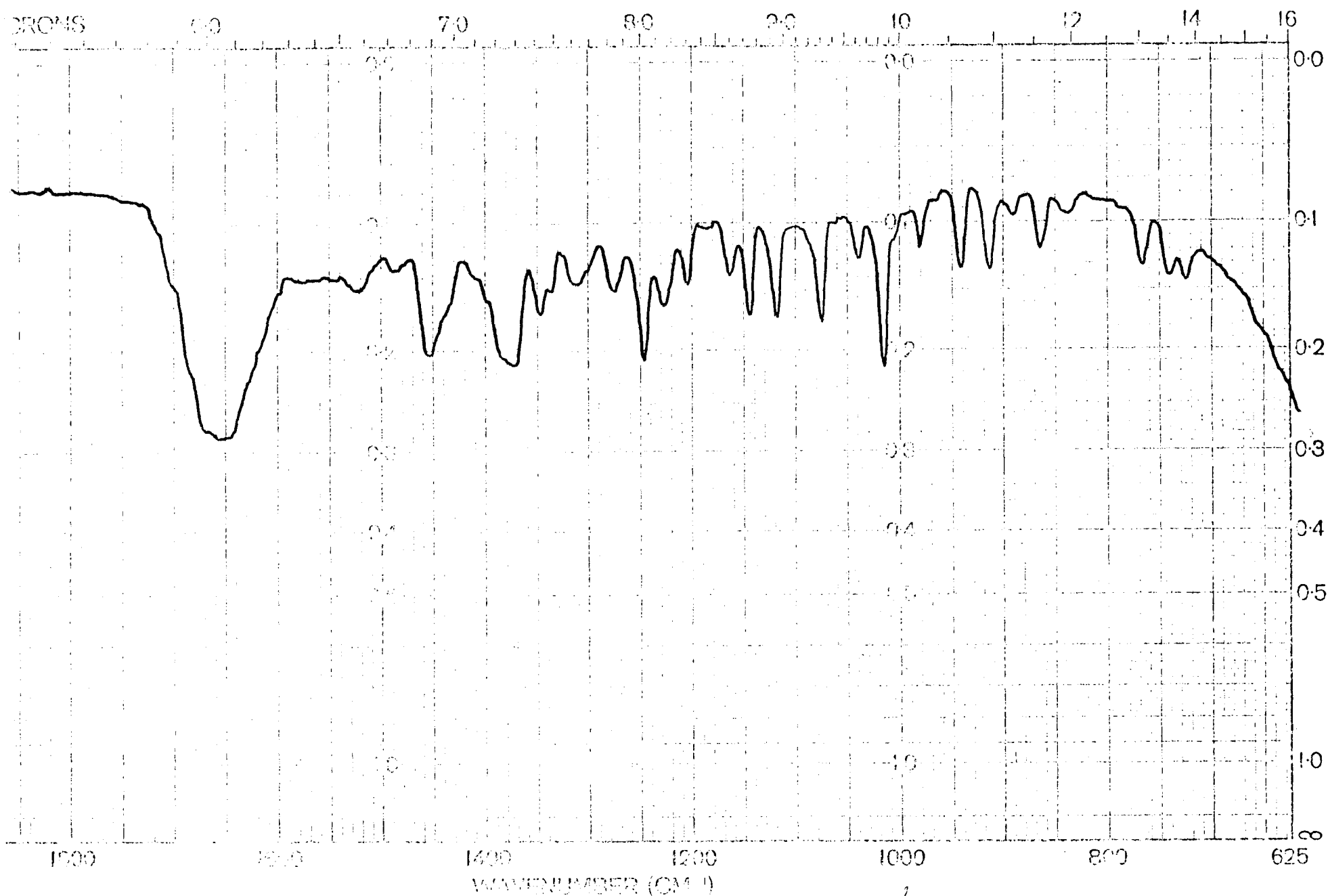
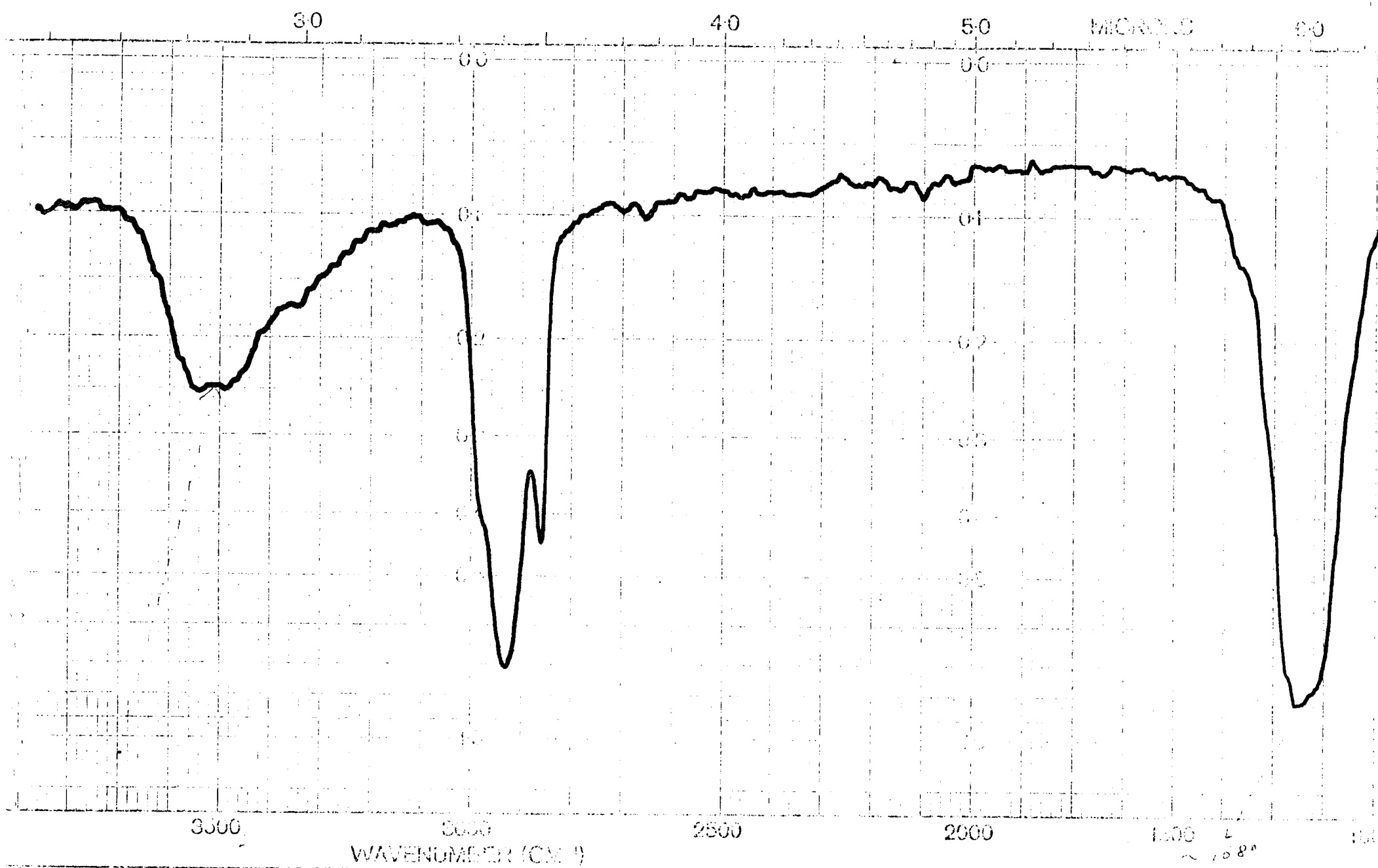
SAMPLE	 + H <sub>2</sub> O (rude material)	SOLVENT	<i>Acetone</i>	REMARKS
CONCENTRATION		CONCENTRATION		<i>2 mmol</i>
CELL PATH		CELL PATH		<i>add DC</i>
REFERENCE		REFERENCE		

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



REMARKS 2 moles [3,3,1] amino acid 0.32g add DCC 2ml $\xrightarrow[reflux]{94^\circ C}$ 8 hrs $\xrightarrow{filter}$ $\xrightarrow{evaporate}$ $\xrightarrow{60^\circ C}$	SCAN SPEED 3	OPERATOR Tu
	PERKIN-ELMER PART NO. 472-5200	DATE 9/12/87
		REF. No.

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




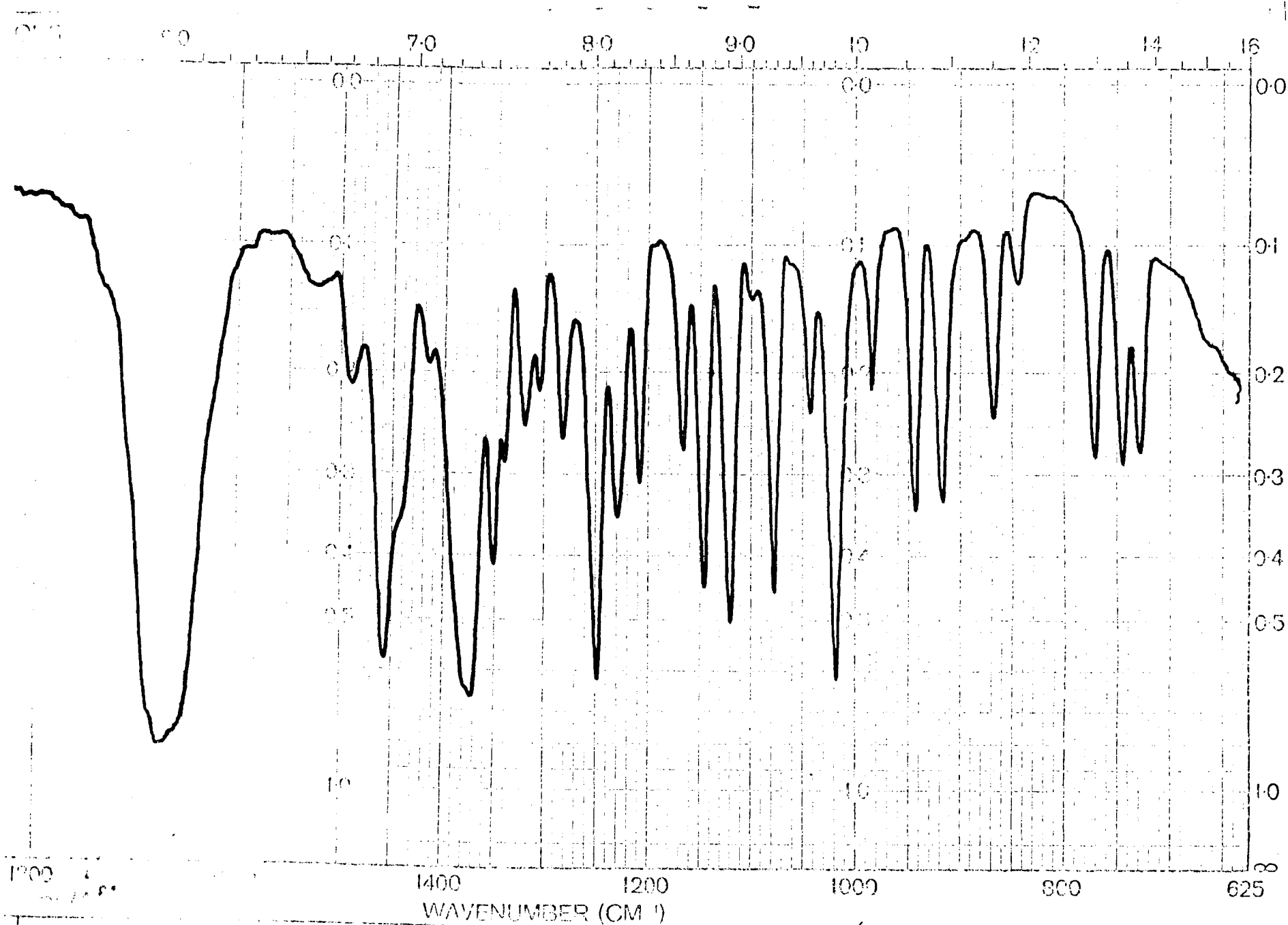
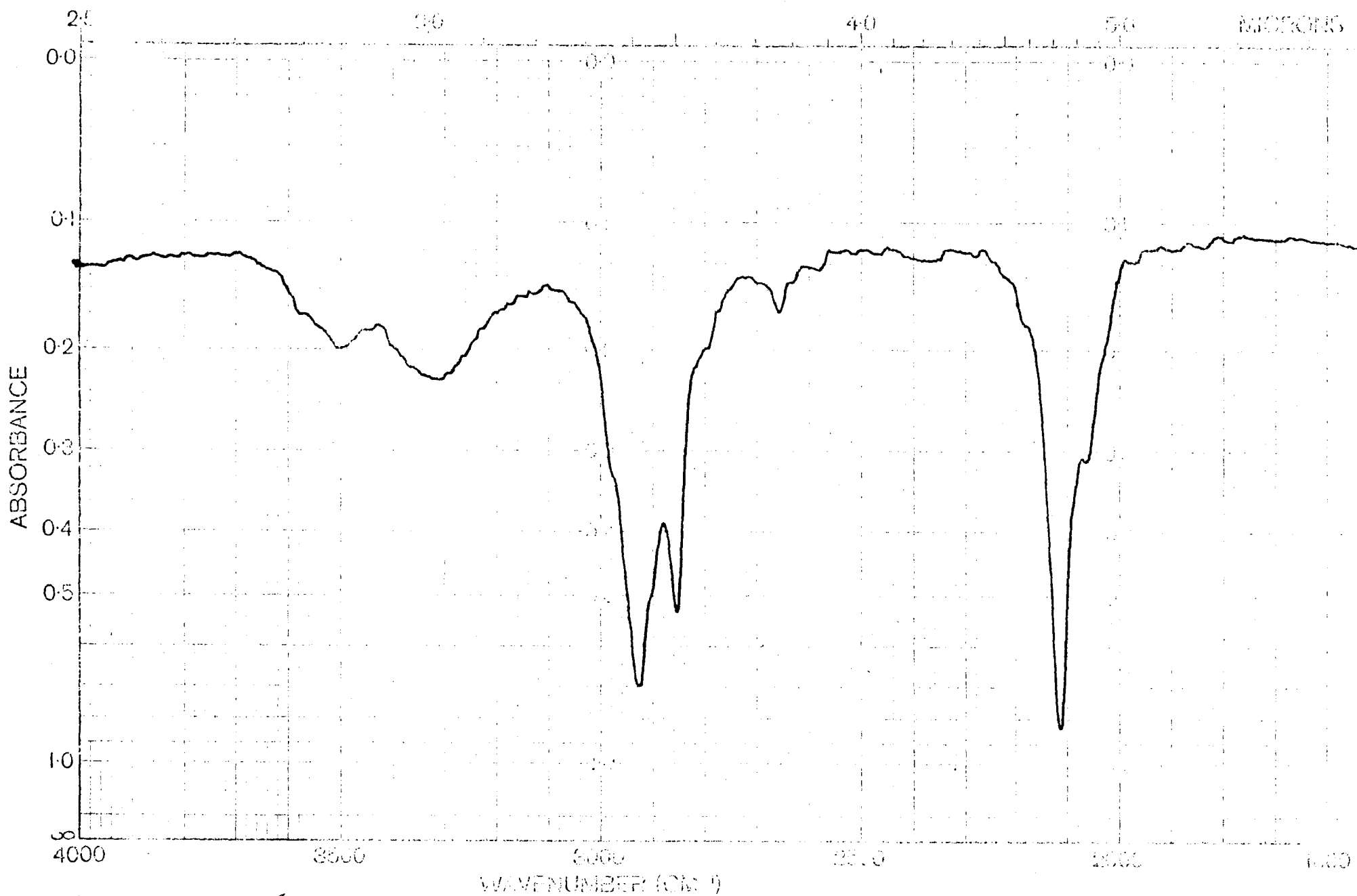
SAMPLE H <sub>2</sub> O peak	 ⇒ aspirato div aspirato	SOLVENT CONCENTRATION CELL PATH REFERENCE DCC (C <sub>2</sub> H <sub>5</sub> N)	REMARKS aspirator R <sub>f</sub> = 0. vacuum
---------------------------------	--	---	---

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



REMARKS $\epsilon_t = 0.352$ Aspirator Vacuum (Dr. Wu)	solid film (Vox)	SCAN SPEED 3 SLIT 1/2 PERKIN ELMER PART NO. 472-5200	OPERATOR Tu DATE REF. No.
--	---------------------	---	---------------------------------

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



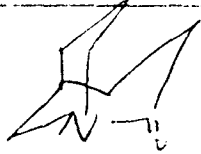
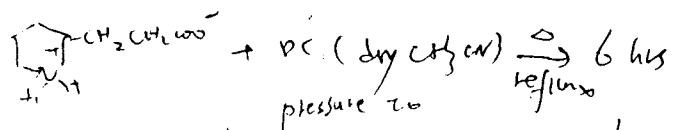
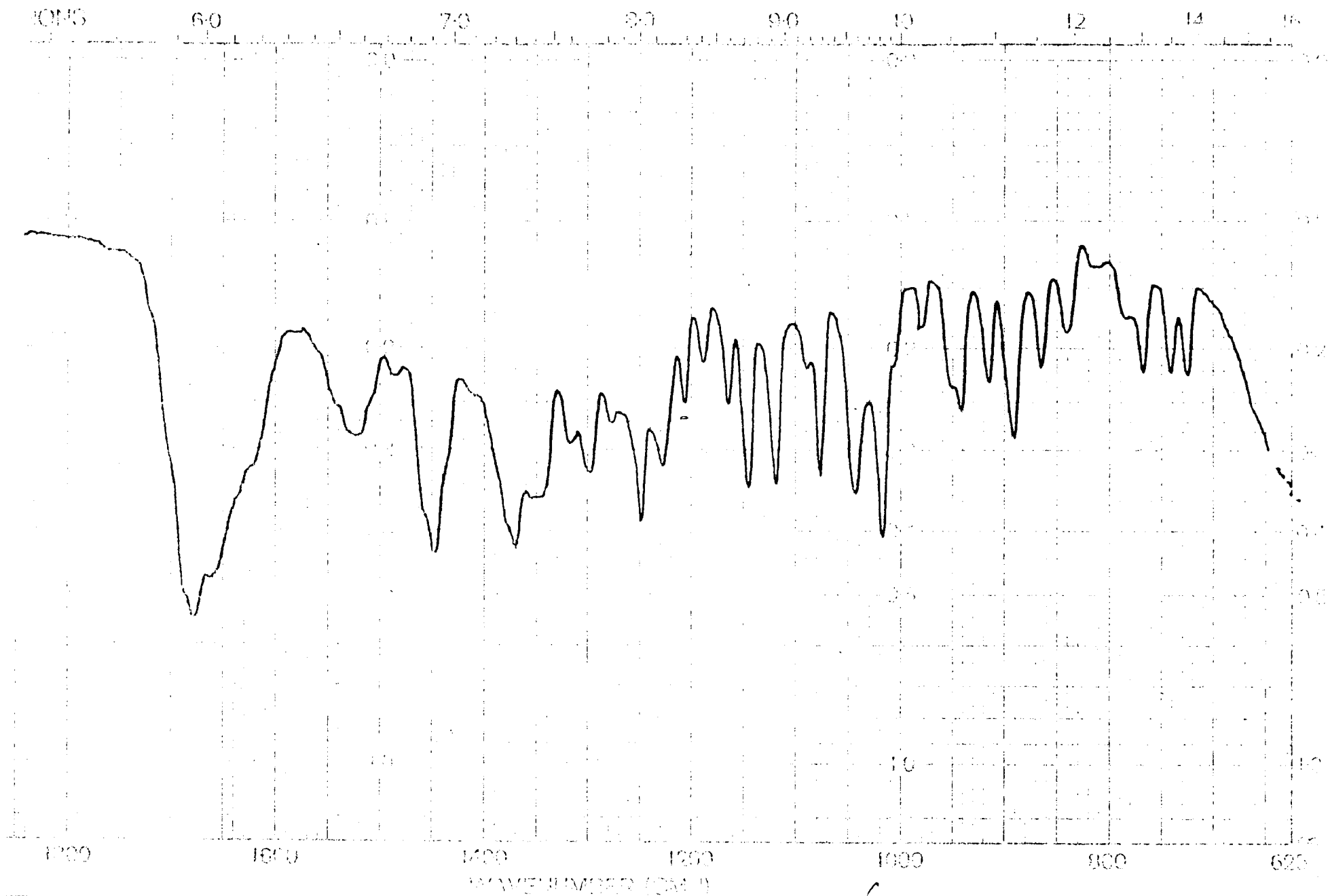
SAMPLE		excess DCC	SOLVENT	reacting
ORIGIN	+ DCC - H <sub>2</sub> O	<del>but</del> deaerated	CONCENTRATION	
		with 95% alcohol	PREPARED	

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



→ → reduce reaction → oil (yellow)  
 filter ~~Vacuum~~ pressure 20

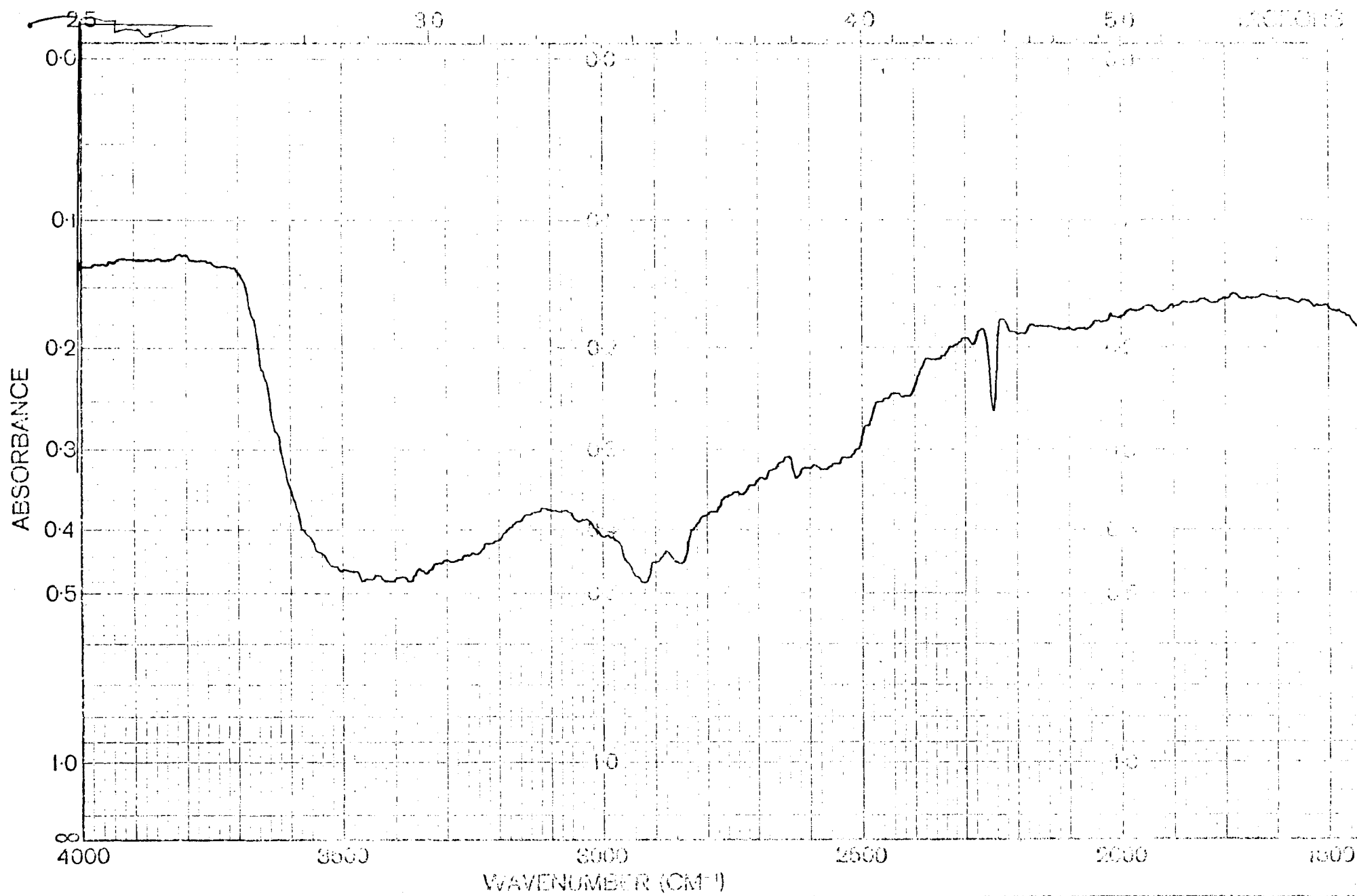
SOXHLET  
 21

PART NO. 570-5000

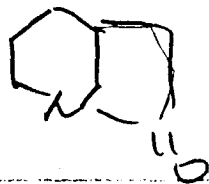
OPERATOR  
 DATE

REF. No.

21/11  
 10007



SAMPLE



CHGIN

SOLVENT

CONCENTRATION

CELL PATH

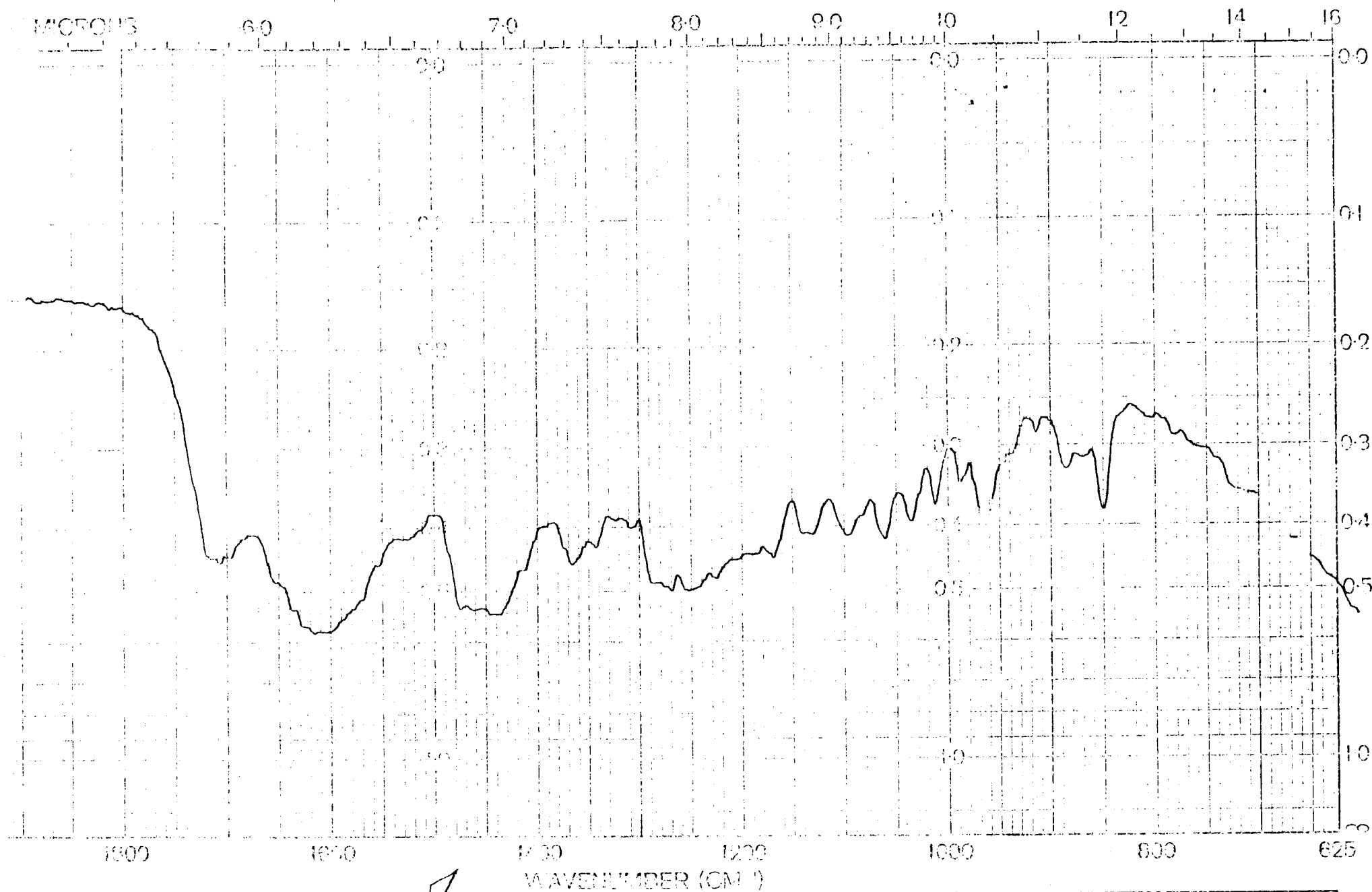
REFERENCE

REMARKS

A

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





REMARKS

(3,3,1) of C1CN2CC3CC1CC23 + PCC + H<sub>2</sub>O  
 40ml 95% alcohol  
 + reflux → evaporated, oil was destroyed

SCAN SPEED 3'

SPLIT

PERKIN ELMER

TELE NO. 472-5500

OPERATOR Tu

DATE

REF. No. JF 208

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

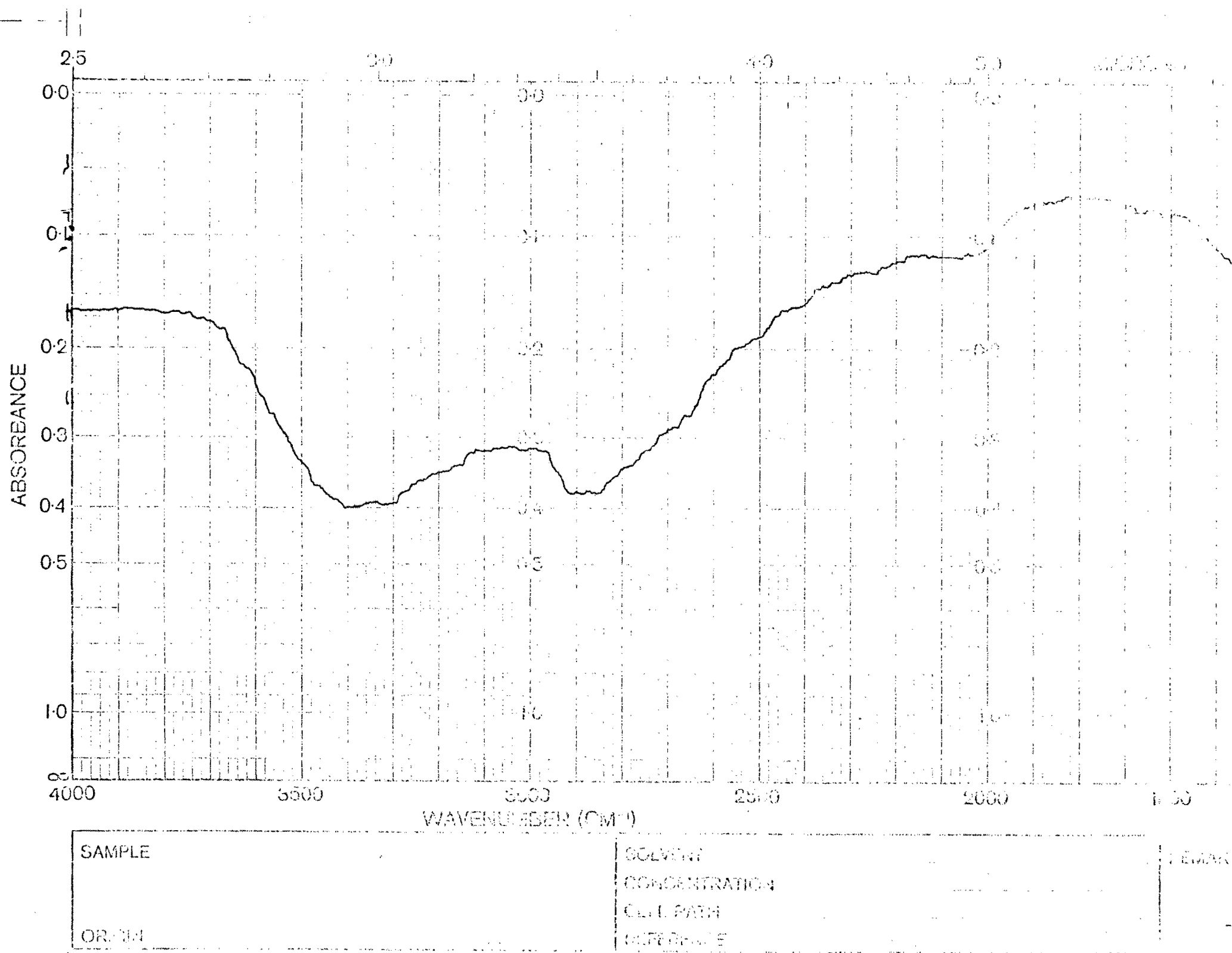
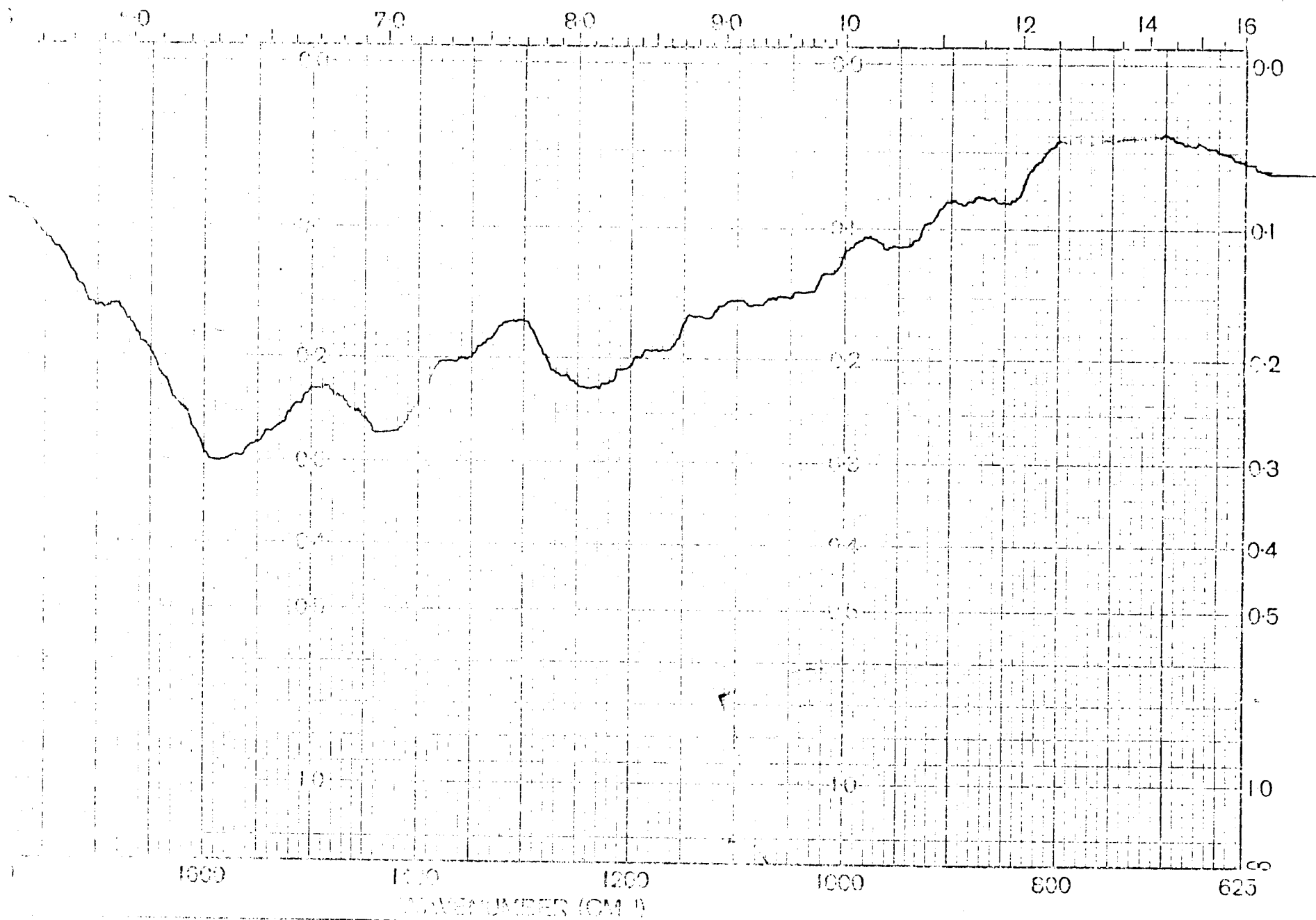
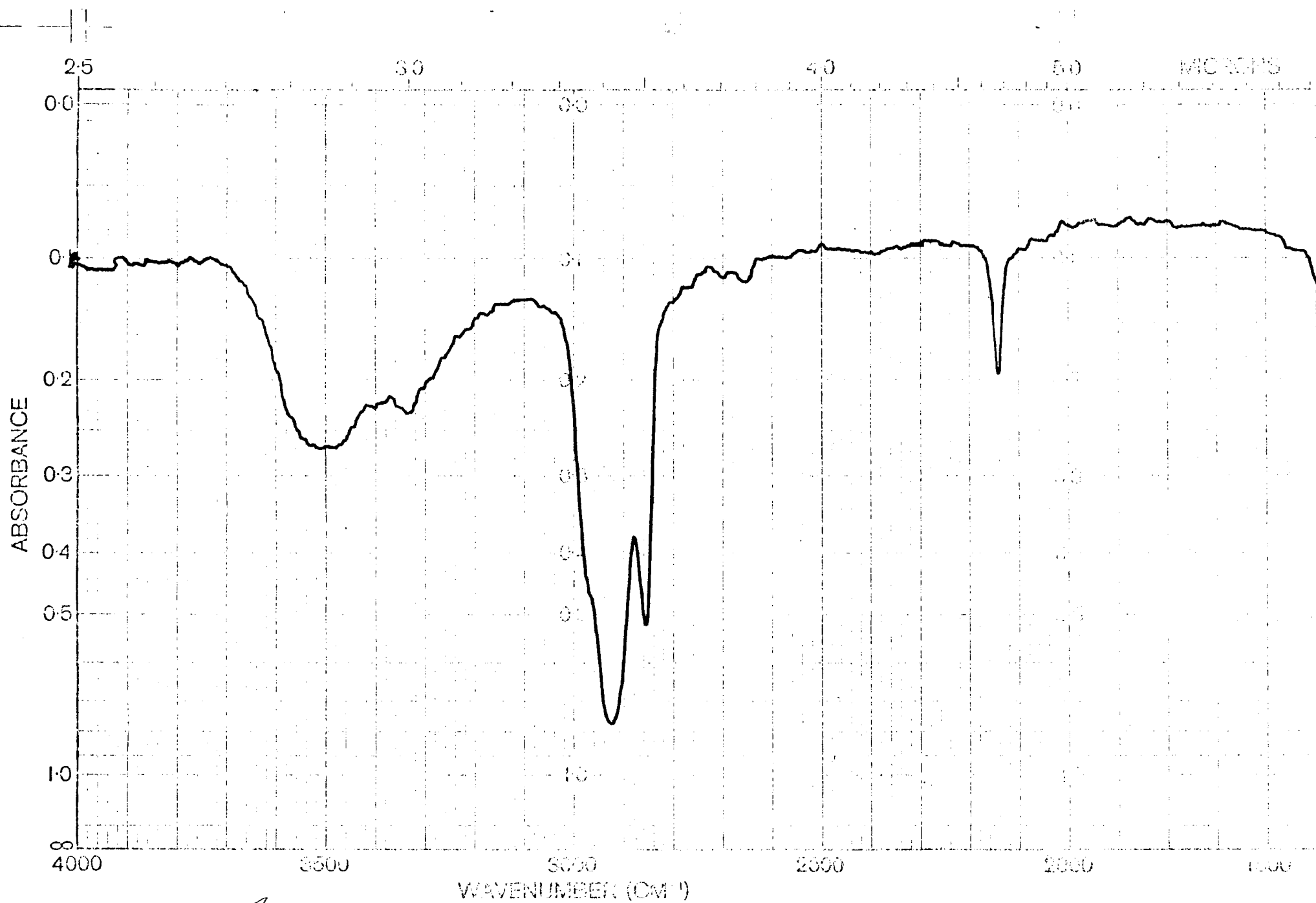


Figure 9. 1-azabicyclo(3,3,1)nonan-1-ol  
(hydrolyzed)



(3,3,1) + 50ml 95% a/cohol reflux evaporated CH <sub>2</sub> OH	SCAN SPEED 3	OPERATOR <i>Ta</i>
	SUB	DATE
	REFERENCE ELEMENT	REF. No. <i>2101 f</i>
	DATE NO. 472-5200	

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




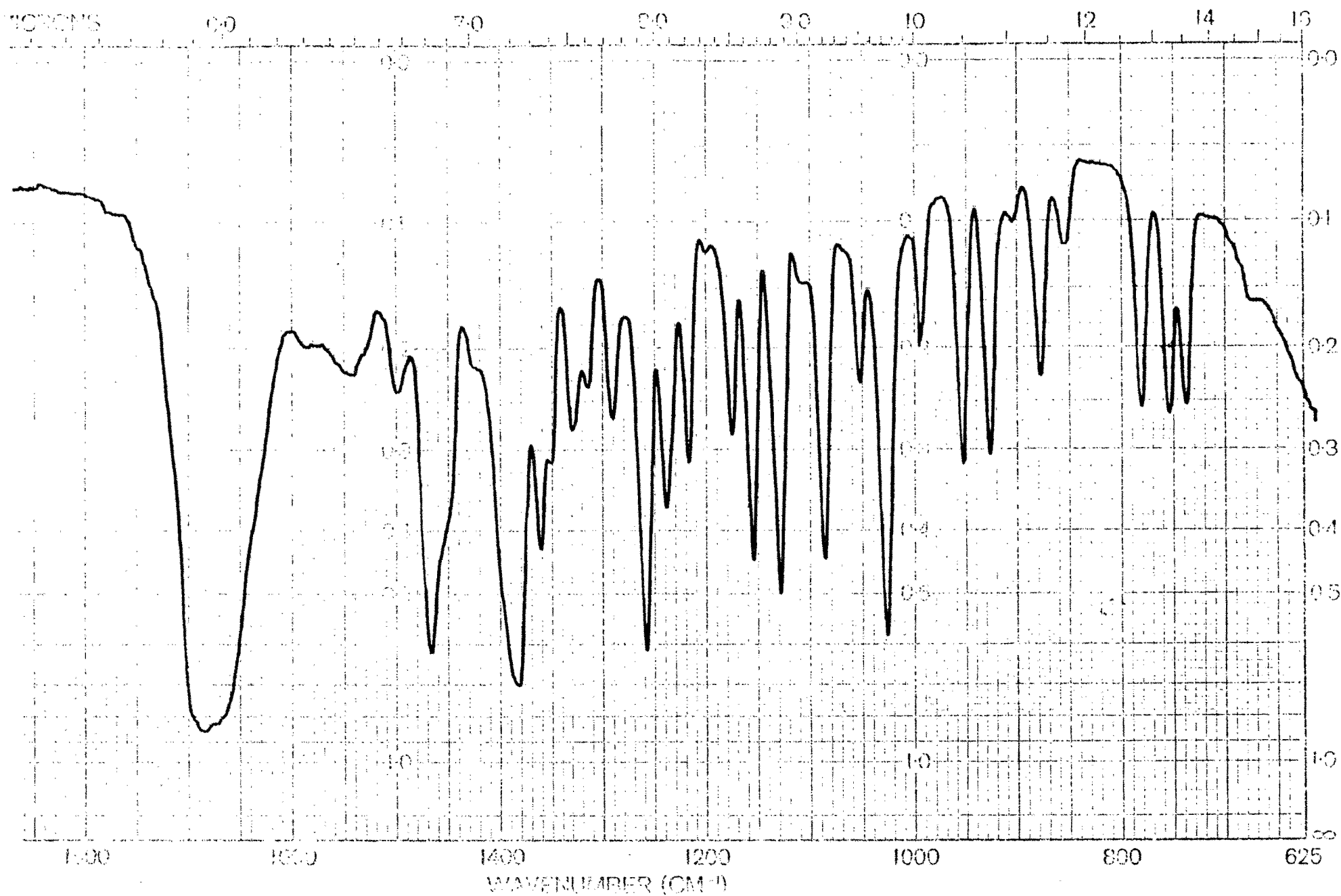
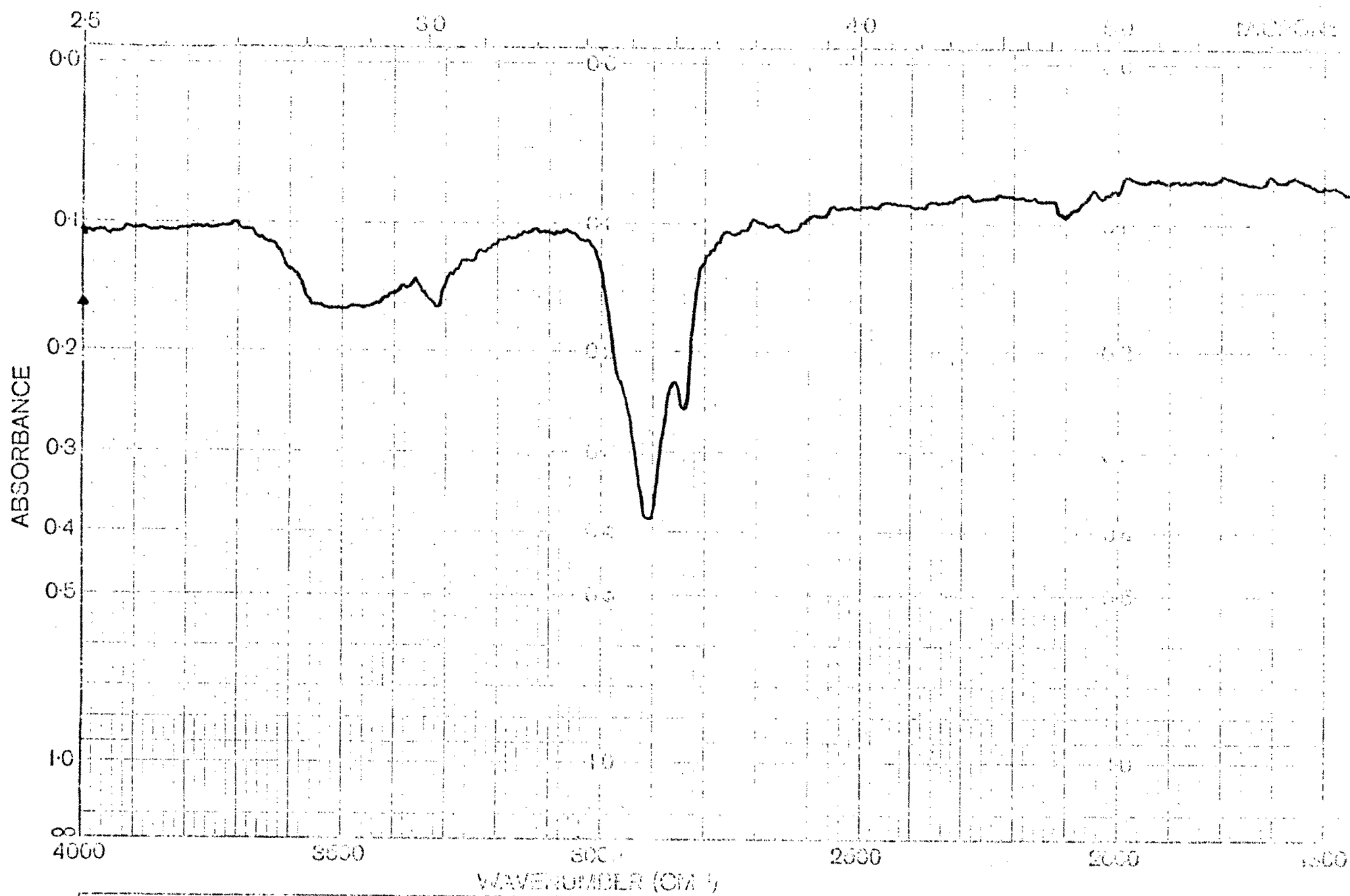
SAMPLE		+ DCC + H <sub>2</sub> O	≡ 2.5 ml per	SOLVENT		RELATIVE
ORIGIN			CM-1. V. (1000)	CONCENTRATION		
				CELL PATH		
				REFERENCE		

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



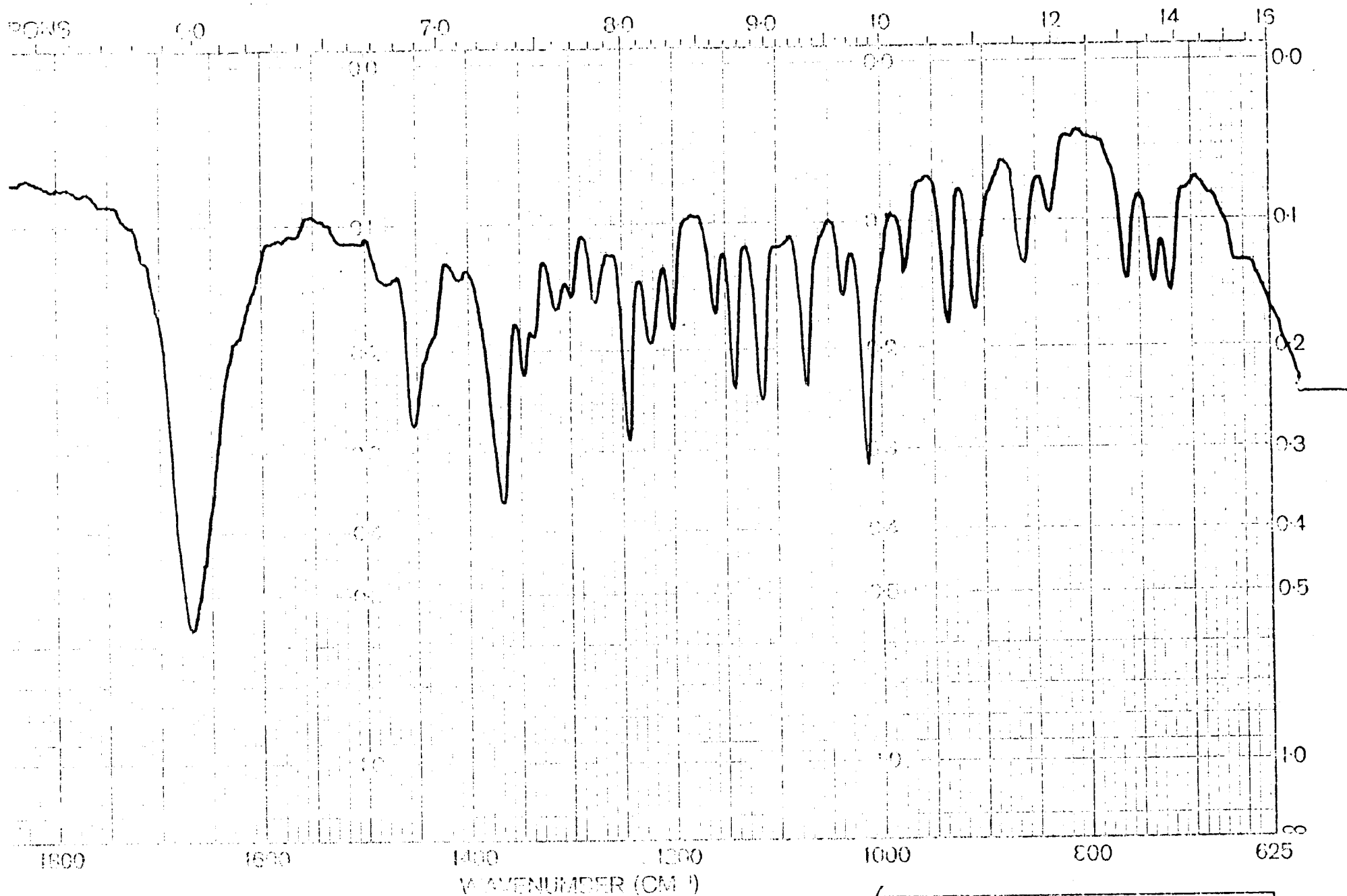
REMARKS excess DCC ( $>100 \mu^2$ ) Sample $\rightarrow$ 20ml $\text{CH}_2\text{Cl}_2$ (dry) filtered $\xrightarrow{\text{evaporated}}$ DCC reduced	SCAN SPEED $\rightarrow$	OPERATOR $\text{TL}$
	SPLIT	DATE
	INSTRUMENT ELEMENT	REF. No. $38-510$
	PART NO. 472-5200	

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



SAMPLE	<chem>C1CC2CC3CC1N2C3=O</chem>	SOLVENT	solid film.
ORIGIN		CONCENTRATION	
		CELL PATH	
		REFERENCE	

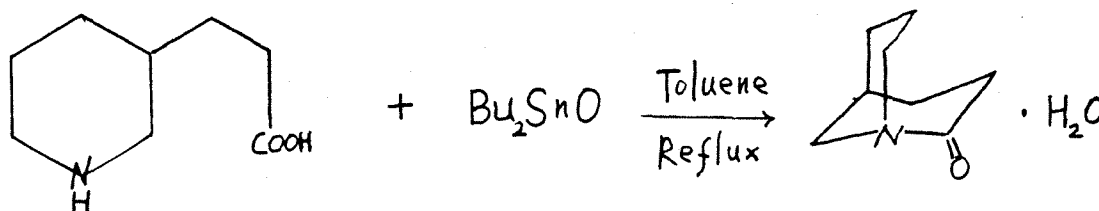
Figure 11. 1-azabicyclo(3,3,1)nonan-1-one  
(after passing column)



<p>REAGENT</p> <p><chem>C1CN2CC3CC1CC23</chem> + CH<sub>2</sub>OH</p> <p>residue</p> <p>1:1 (C<sub>12</sub>H<sub>21</sub>N<sub>2</sub>O = potassium order)</p> <p>column</p> <p>Δ 12 hrs (40°C)</p> <p>20 ml (95%)</p> <p>R<sub>f</sub> = 0.35 (15% CH<sub>2</sub>Cl<sub>2</sub>)</p>	<p>SCAN SPEED 3</p> <p>SLIT</p> <p>PERKIN ELMER</p> <p>PART NO. 472-5000</p>	<p>OPERATOR</p> <p>DATE 6/11</p> <p>RTE No. IR-042</p>

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

4. Reaction of  $\beta$ -(3-piperidyl) propionic acid  
with di-n-butyltin oxide<sup>13</sup>



A mixture of  $\beta$ -(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 seen 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  $1680\text{ cm}^{-1}$   
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.

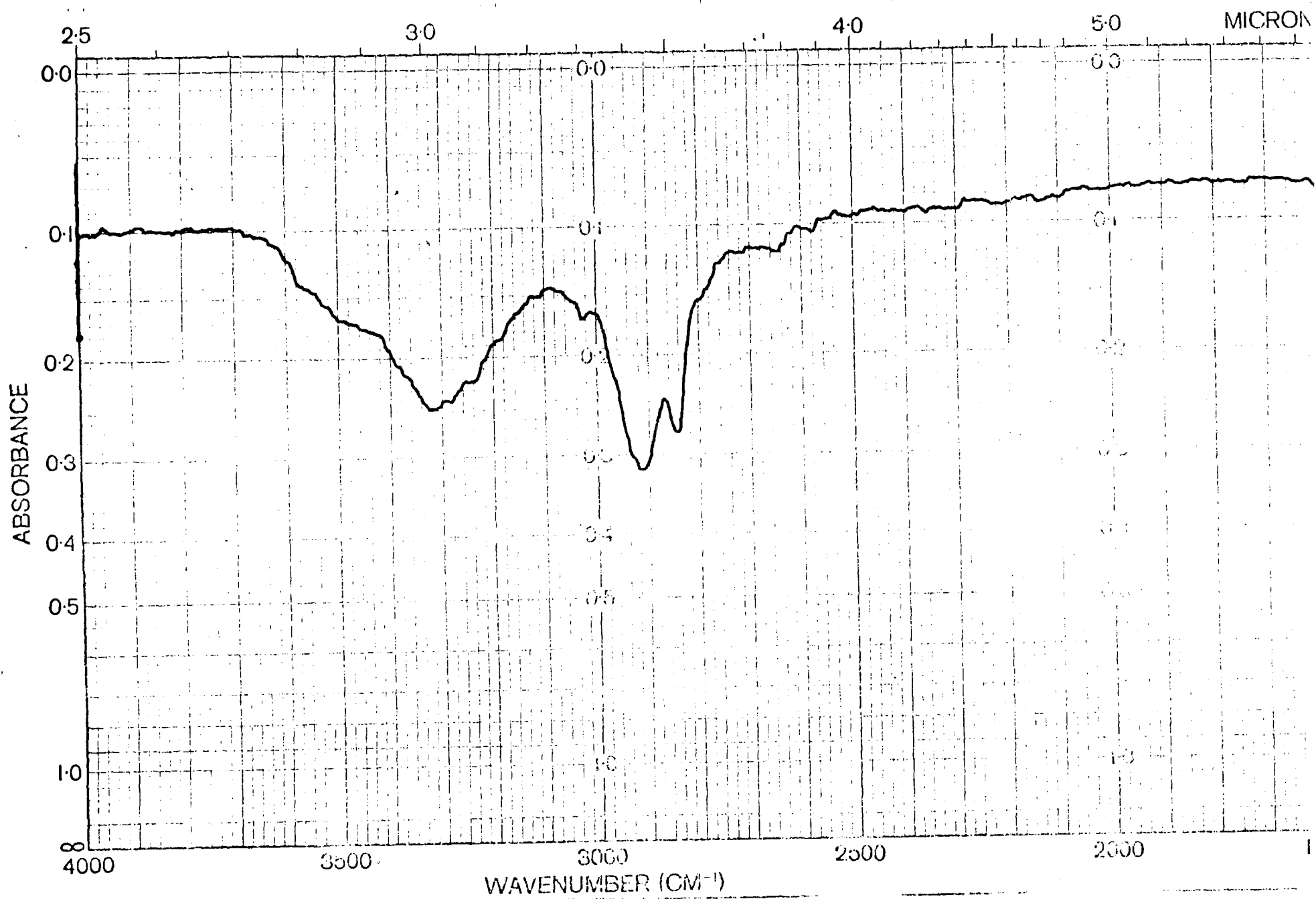


Figure 12. 1-azabicyclo(3,3,1)nonan-1-one (rude material ; yellow liquid)

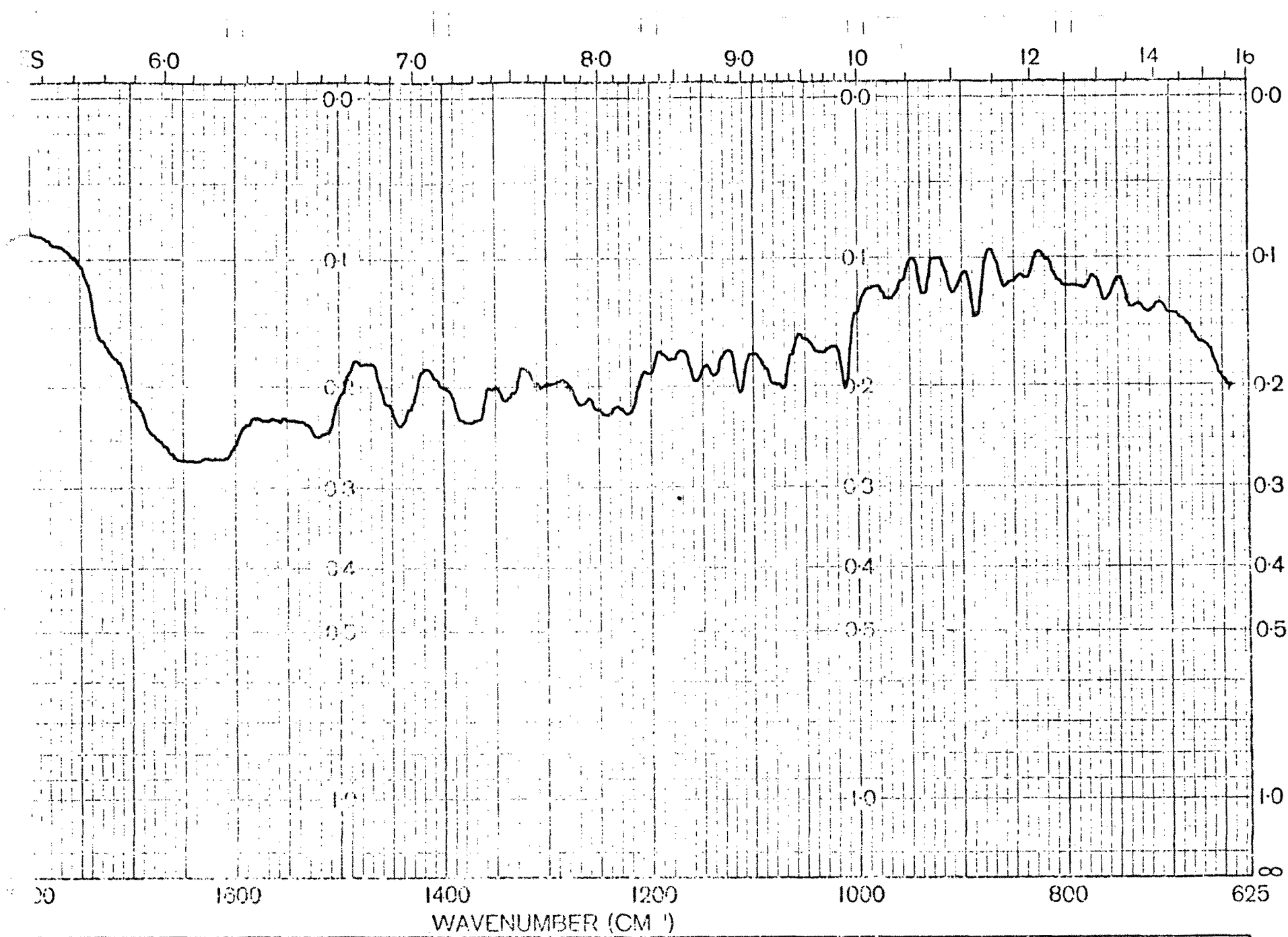
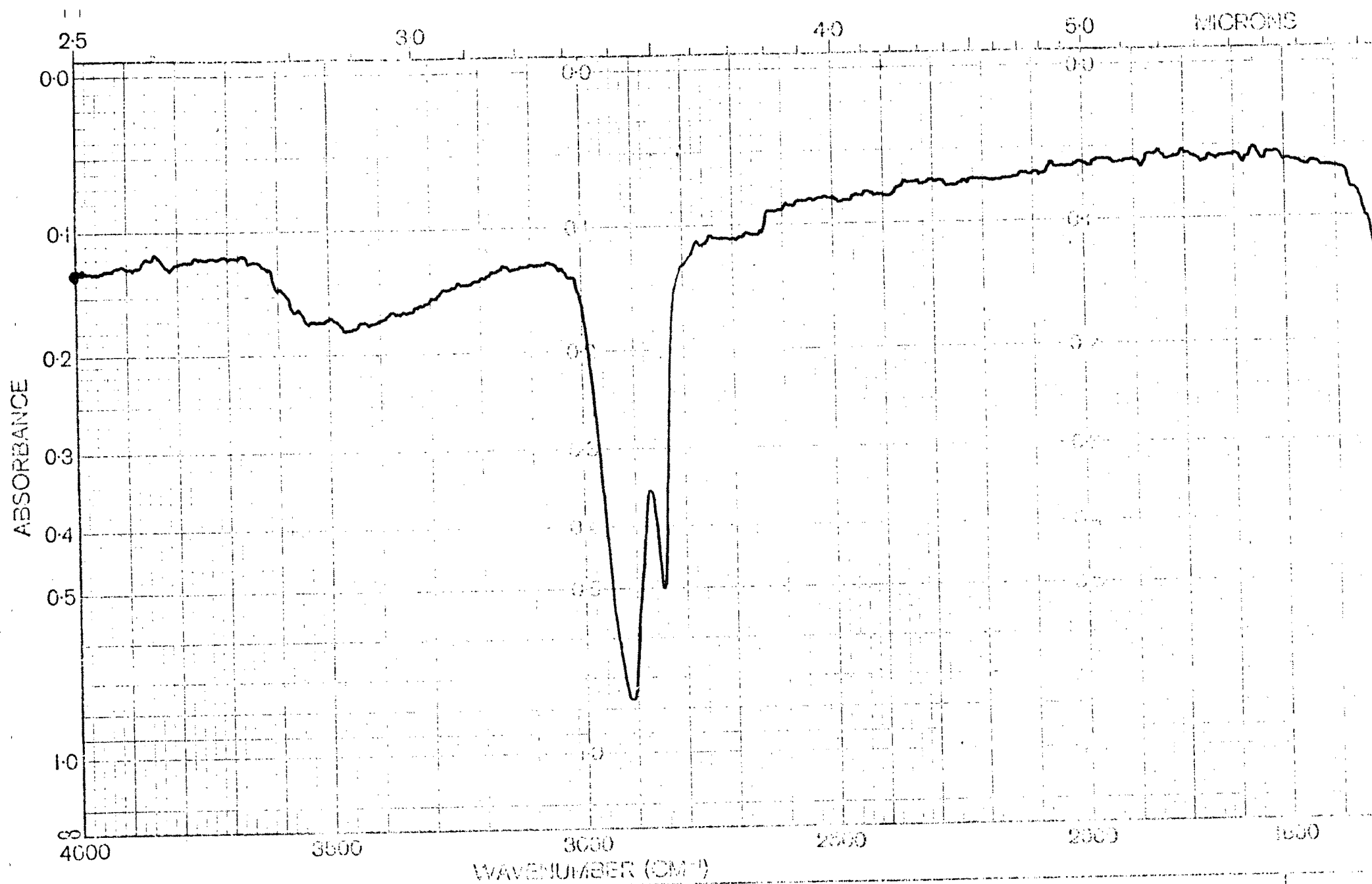


Figure 12. 1-azabicyclo(3,3,1)nonan-1-one (rude material ; yellow liquid)




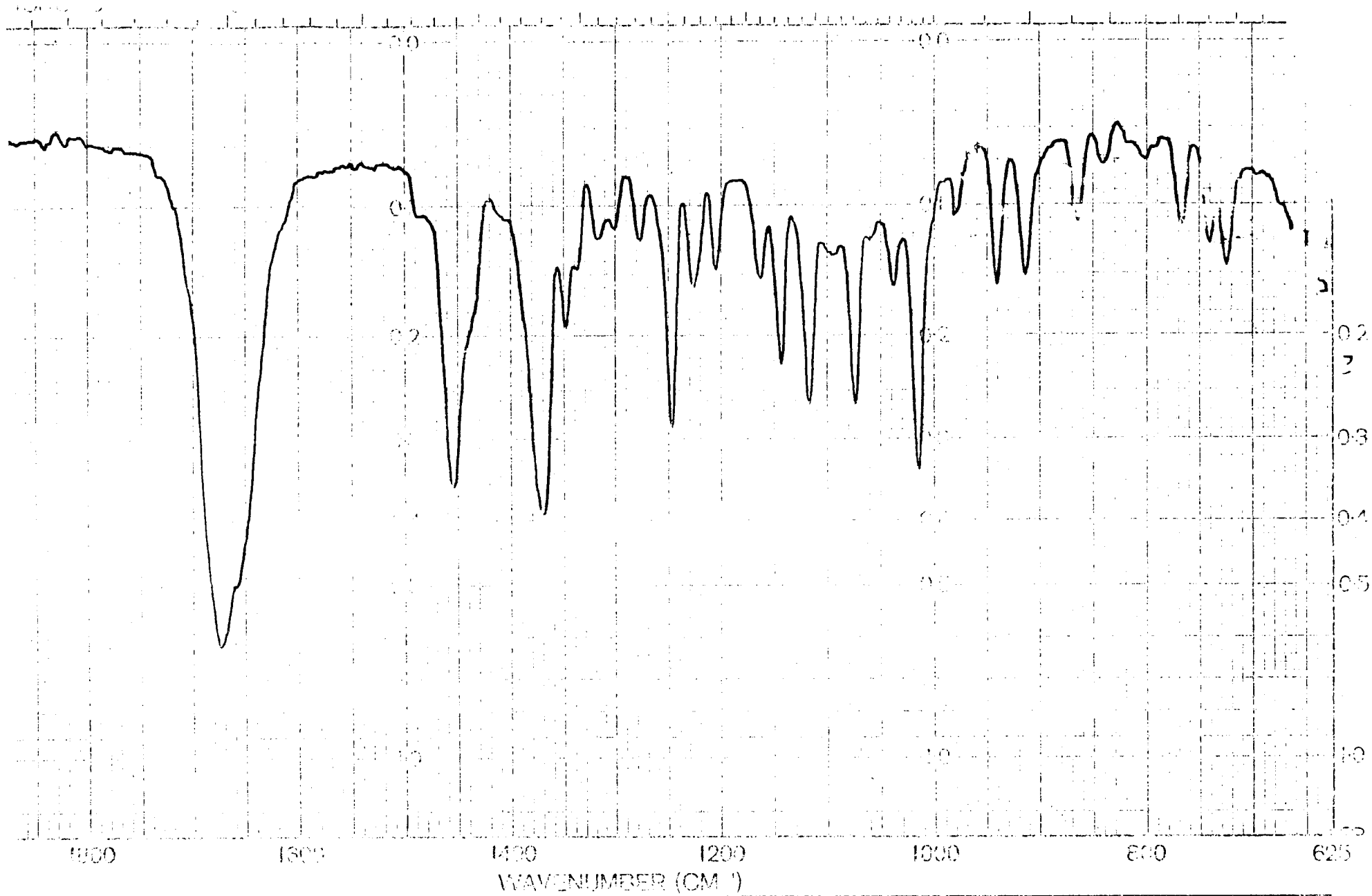
SAMPLE		SOLVENT	REMARK
ORIGIN		CONCENTRATION	
		CELL PATH	
		REFERENCE	

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



REMARKS  <chem>C1CN2CC3CC1CC2C3=O</chem>	SCAN SPEED } S/IT	OPERATOR <i>ZK</i>
	PERKIN ELMER DUO NO. 472-5200	DATE
		REF. No.

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

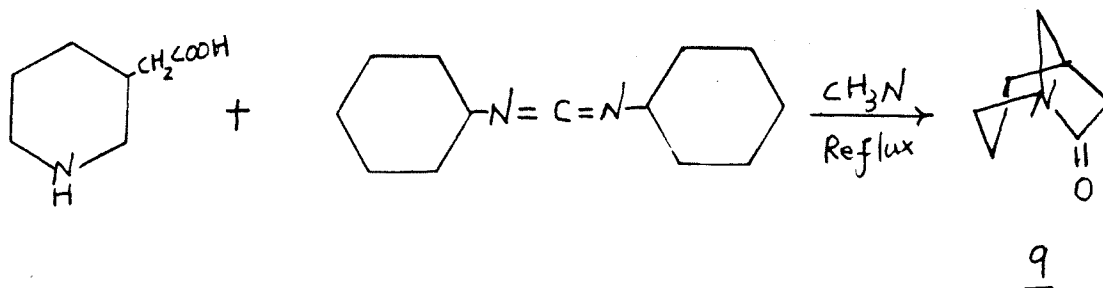
### C. " Flash Chromatography " <sup>17</sup>

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.

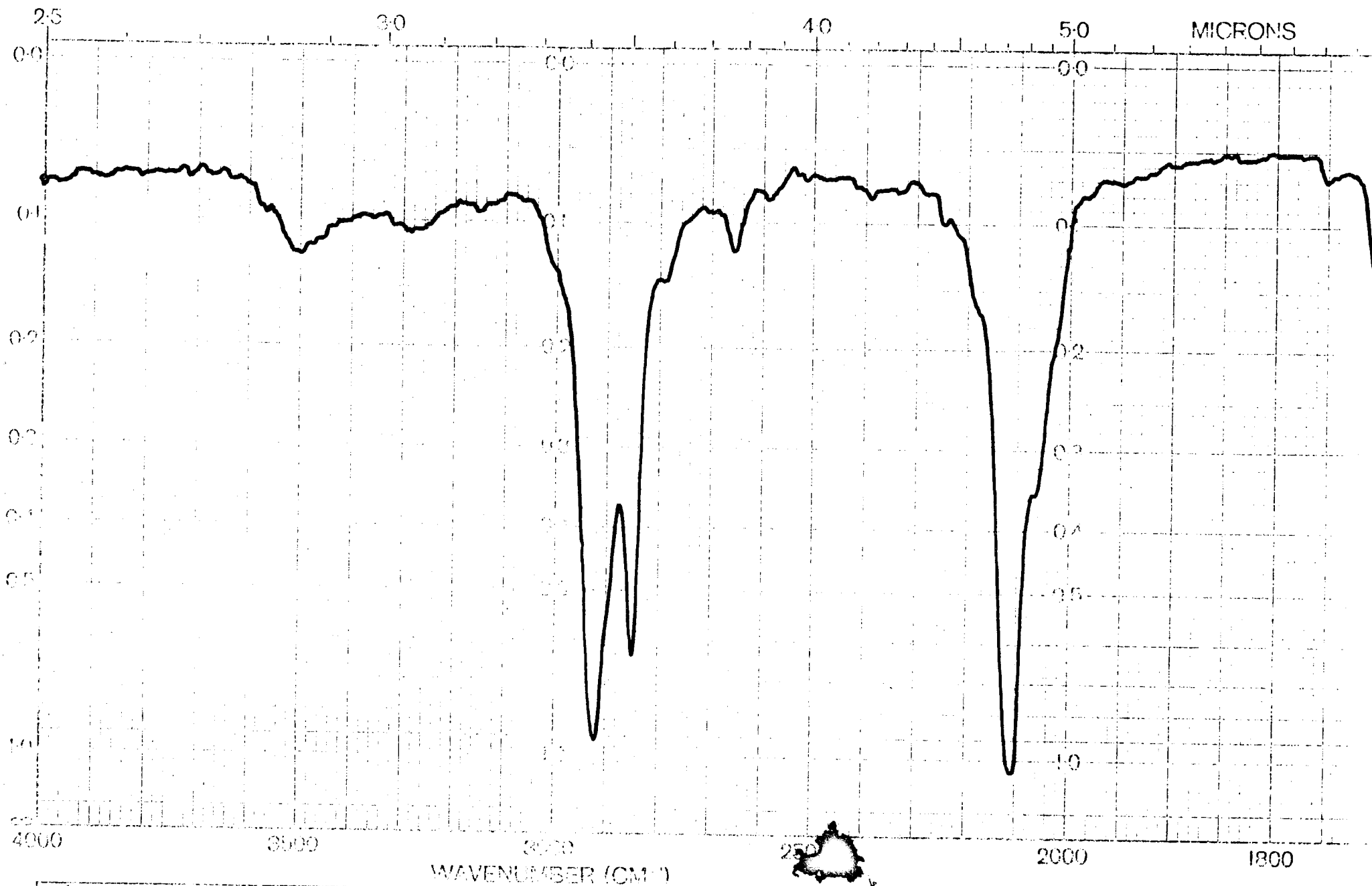
D. Attempted Synthesis of 1-AZABICYCLO(3,2,1) OCTAN-7-ONE

1. Reaction Using DCC



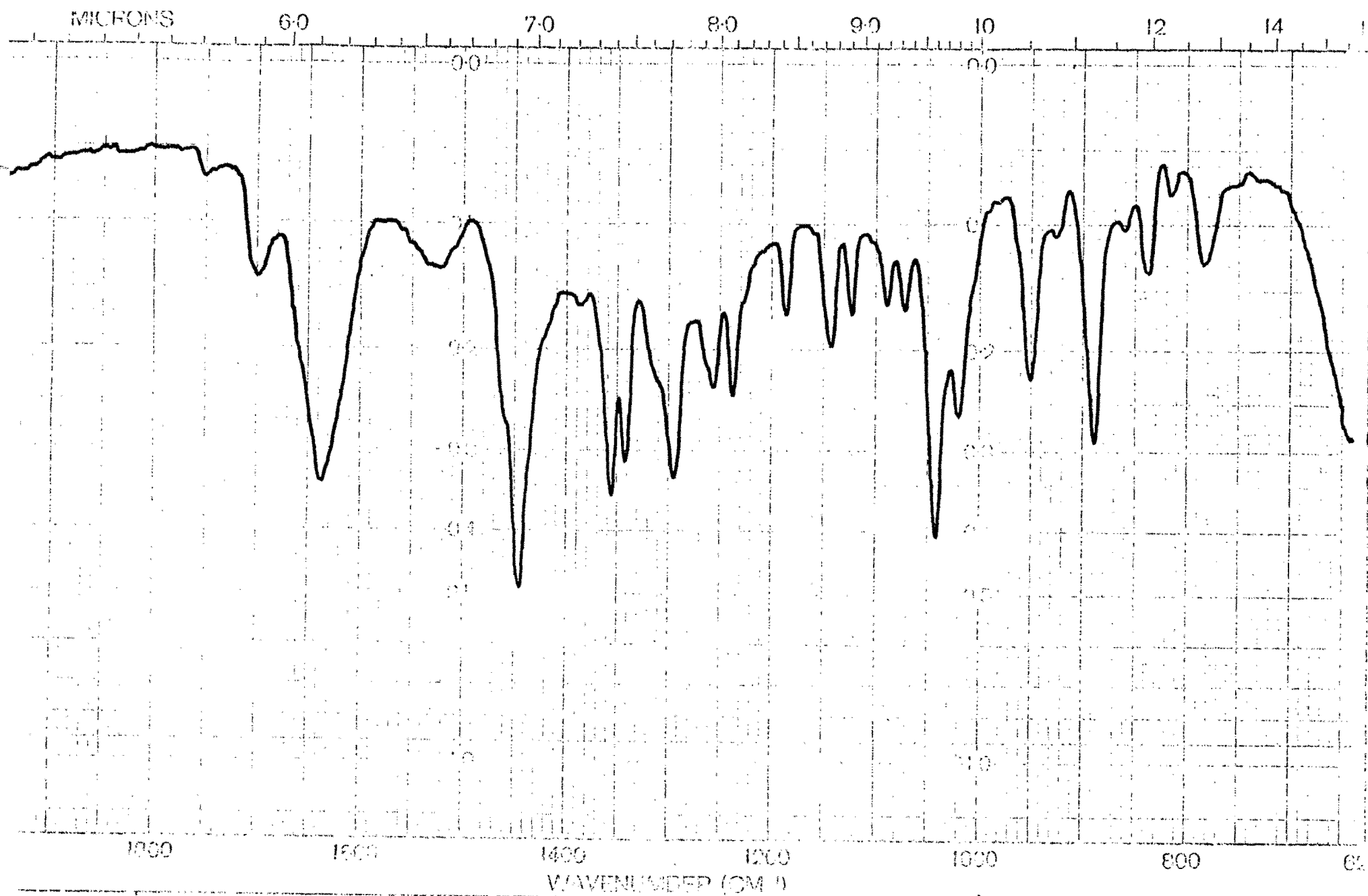
Take 0.2004 gram of 3-β-piperidyl acetic acid hydrochloride (prepared by K. Zyla according to ref 14), and added 1.94 ml of 0.575 N sodium hydroxide to neutralize hydrochloride in the starting material which contains trace water. Then use 0.1 M hydrochloric acid to adjust the pH to 7 and evaporate water 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  $1700\text{ cm}^{-1}$ , and absorption at  $1640\text{ cm}^{-1}$ ; It also shows a strong absorption at  $2100\text{ cm}^{-1}$  (DCC absorption). After being treated with flash chromatography, Figure 16 indicates the peak around  $1700\text{ cm}^{-1}$  became broader, and the DCC still remained because IR spectrum has absorption at  $2100\text{ cm}^{-1}$ . It probably is the mixture of starting amino acid and DCC.





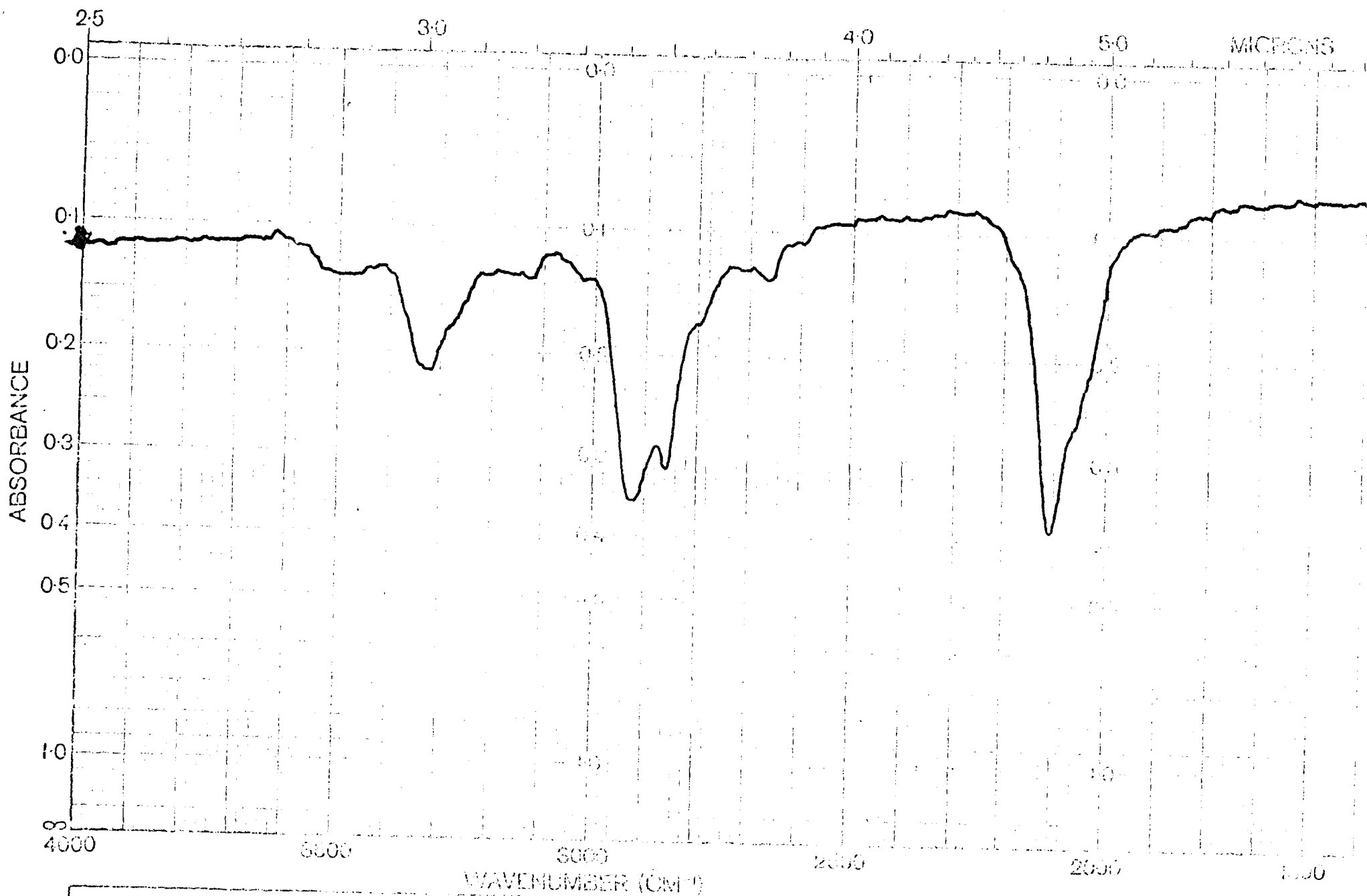
<p> <chem>CC(=O)OCC1CCNCC1</chem> + DCC (in 100ml CH<sub>2</sub>Cl<sub>2</sub>) reflux <math>\xrightarrow{6\text{hrs}}</math>  <i>trans</i> + NaOH <math>\xrightarrow{H_2}</math> <chem>CC(=O)OCC1CCNCC1</chem> <math>\xrightarrow{\text{filtrate}}</math> residue         </p>	<p>           SOLVENT _____ <i>neat</i>            CONCENTRATION _____            CELL PATH _____            REFERENCE _____         </p>	<p>REMARKS</p>
---	---	----------------

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



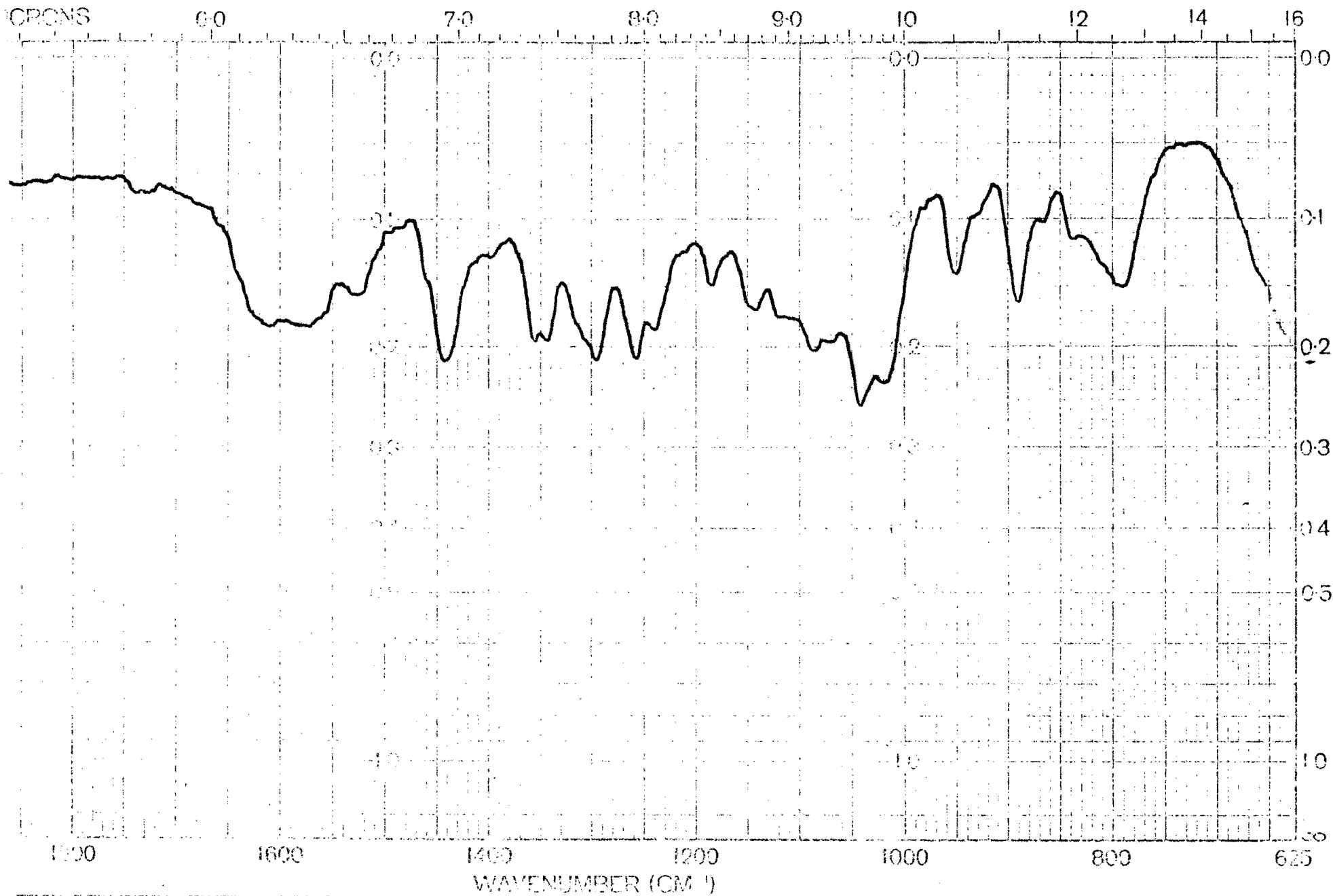
REMARKS $>100 \mu^{-1}$ is DCC (CN) adsorption, $1700 \text{ cm}^{-1}$ has small adsorption (compare DCC)	SCAN SPEED 3'	OPERATOR
	SLIT	DATE
	PERKIN ELMER PART NO. 472-5100	REF. No. J10015

Figure 14. Mixture of 3- $\beta$ -piperidyl acetic acid and DCC



SAMPLE	DCC + <chem>C1CCN(CC1)CC(=O)O</chem>	column	Residue	SOLVENT		REMARK
ORIGIN		Ethyl acetate		CONCENTRATION		
				CELL PATH		
				REFERENCE		

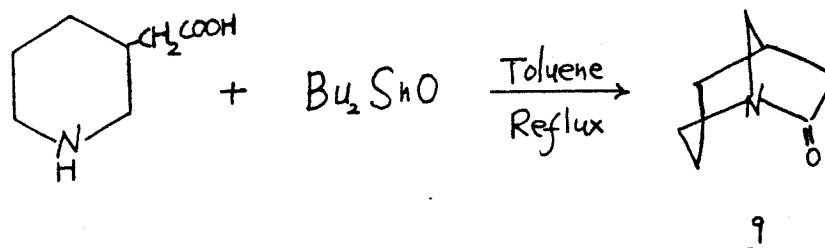
Figure 15. Mixture of 3- $\beta$ - piperidyl acetic acid and DCC (after passing column)



REMARKS <i>ADAC</i> <i>flash chromatograph</i> <i>ADAC</i> <i>IR. 025</i>	SCAN SPEED <i>3</i>	OPERATOR <i>Tu</i>
	SUT	DATE
	PRECISION ELEMENT PART NO. 472-5200	REF. No. <i>IR 016</i>

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

## 2. Reaction with di-n-butyltin oxide



Place 180 mg of 3- $\beta$ -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  $1753\text{ cm}^{-1}$  (which is predicted by reference 7). It probably is the starting amino acid.

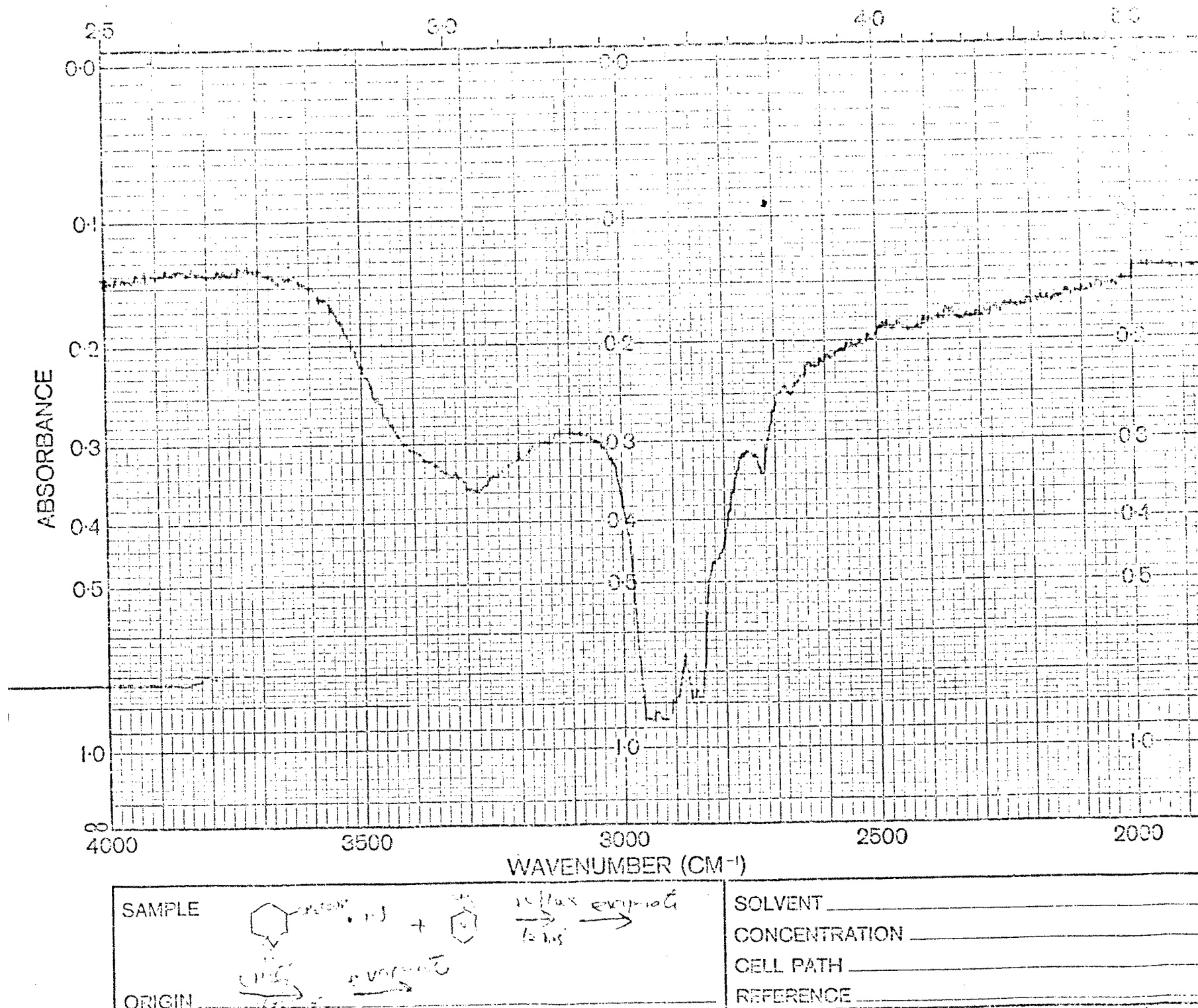
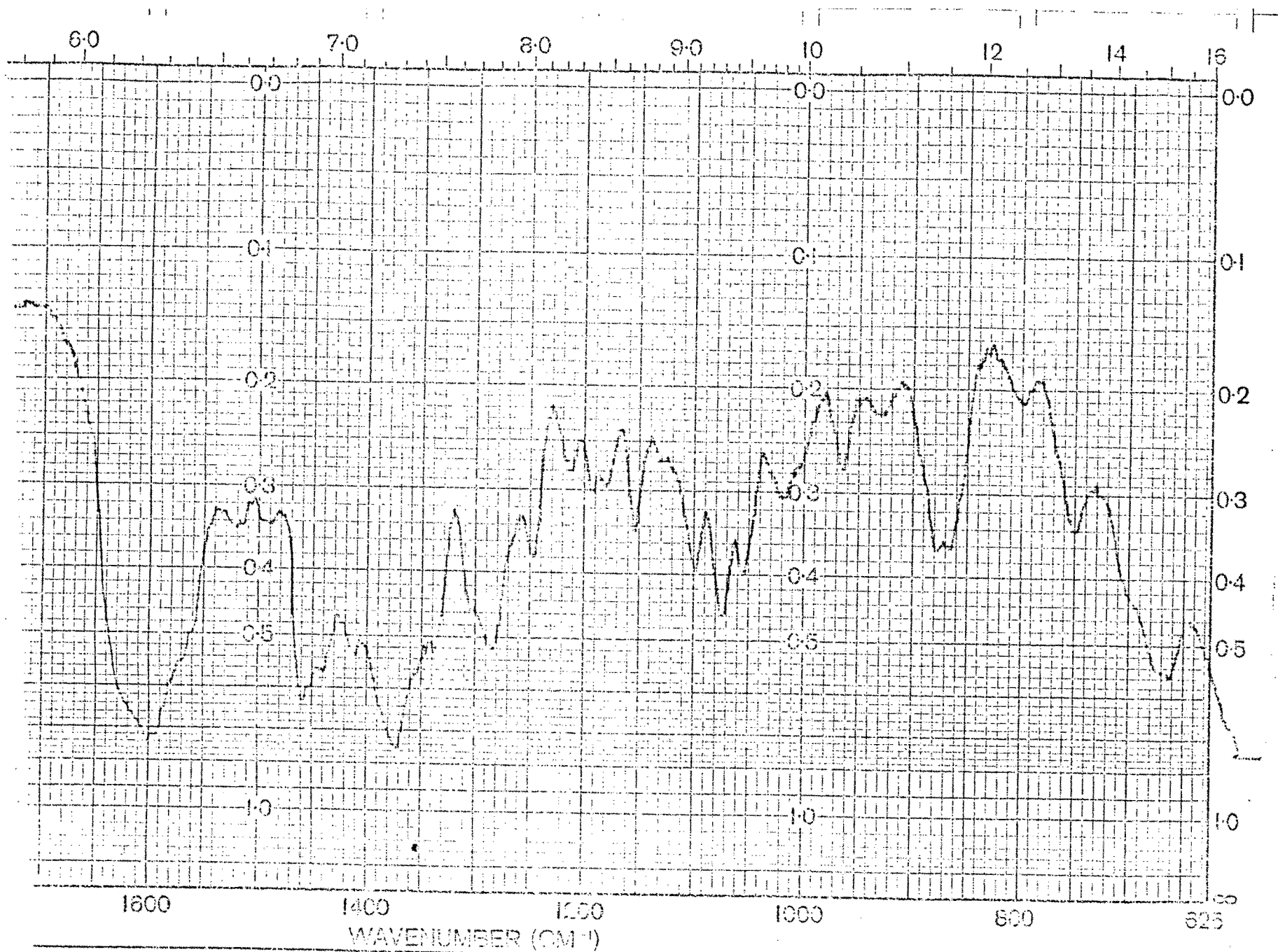


Figure 16. Starting amino acid (probably).

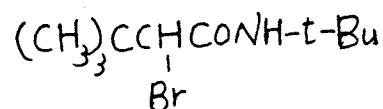
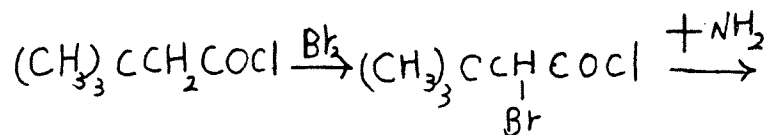


SCAN SPEED .....	OPERATOR <u>Tu</u>
SPLIT .....	DATE <u>2/10</u>
REFRACTION INDEX .....	REF. No. <u>IR 015</u>
SAMPLE NO. <u>170-1-100</u>	

Figure 16. Starting amino acid (probably).

E. Synthesis of 1,3-Di-t-butylaziridinone<sup>14</sup>

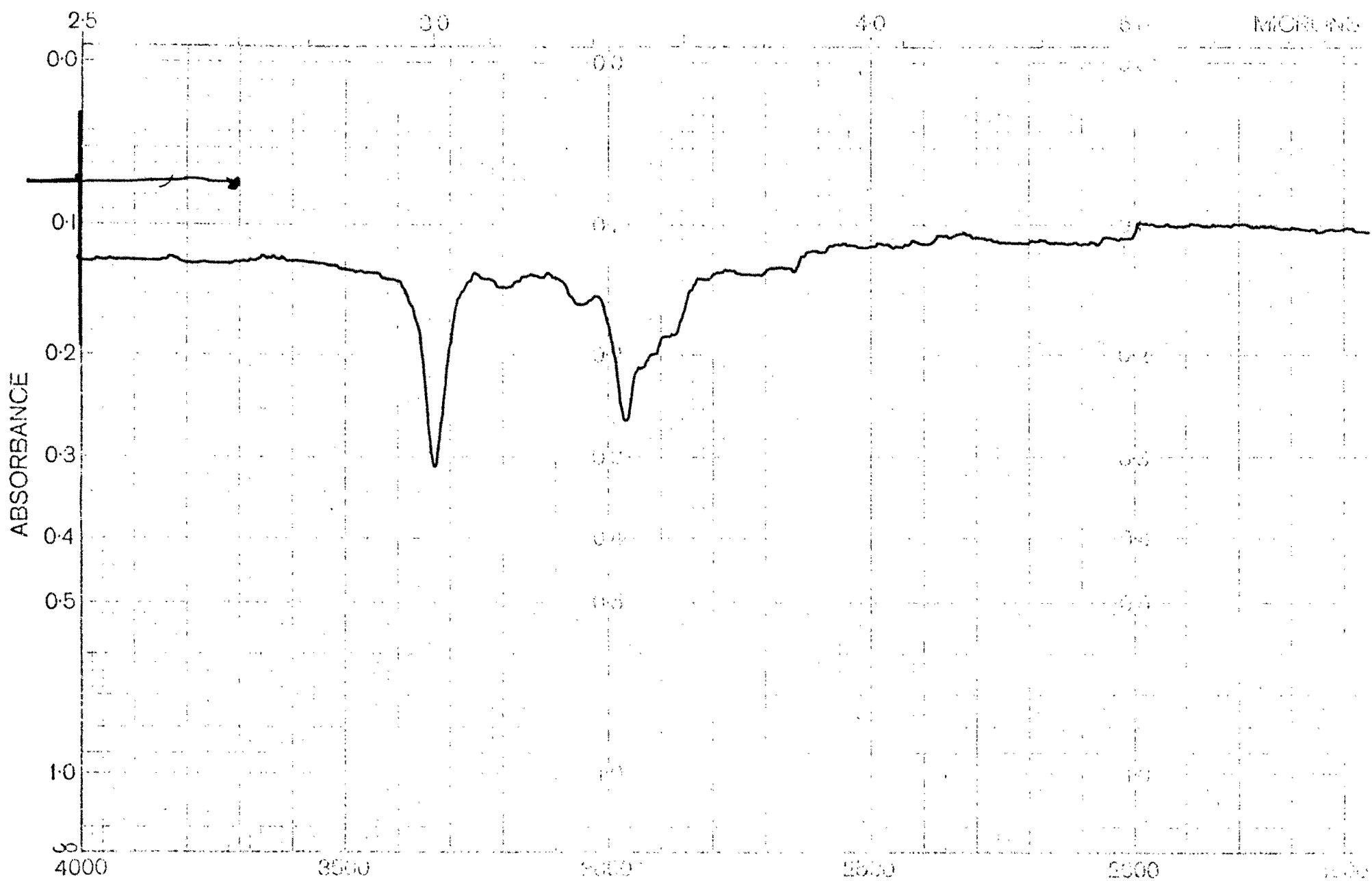
1. 2-Bromo-3,3-dimethyl-N-t-butylbutyramide



10

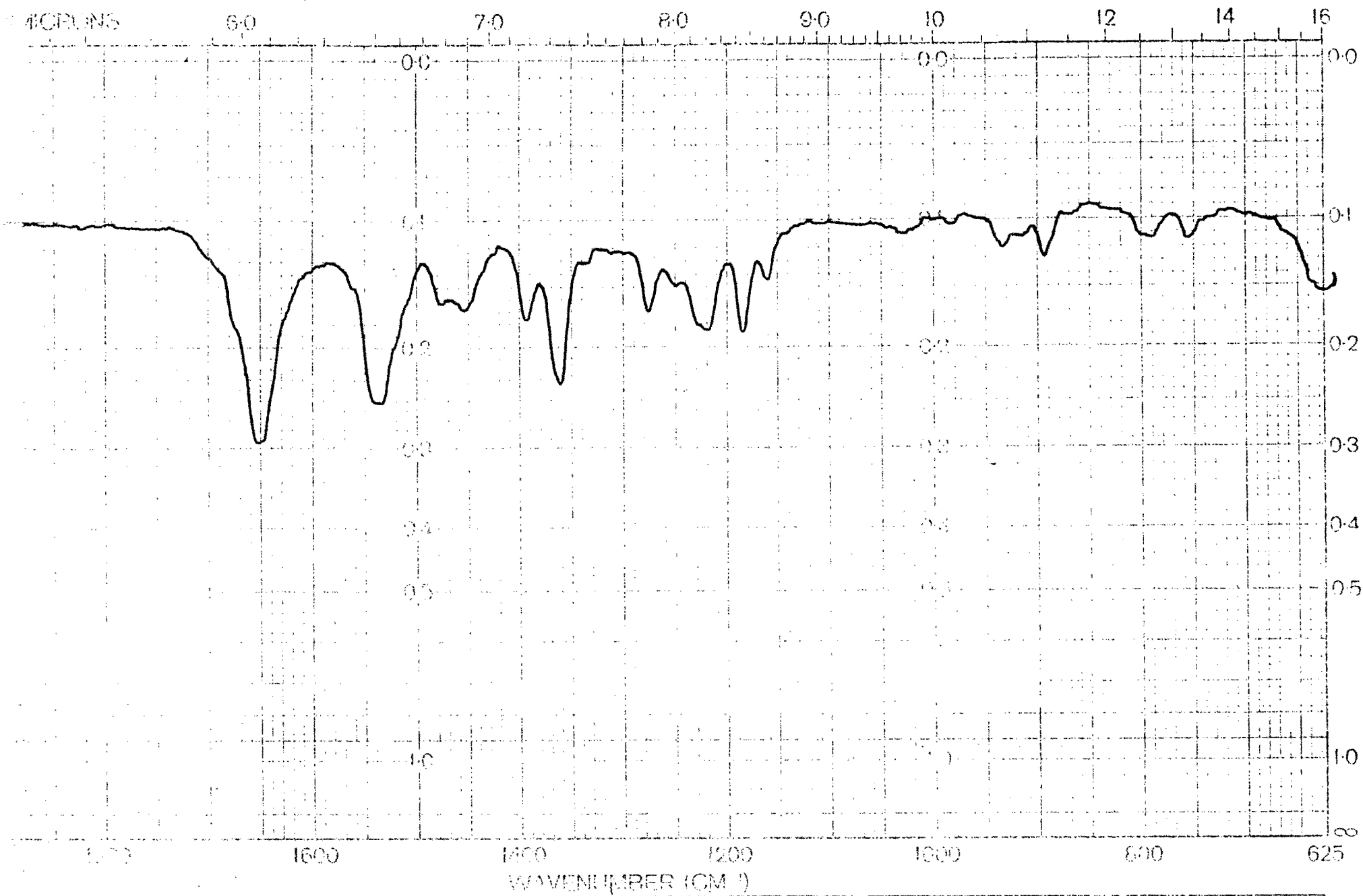
Bromine (1.6 ml, 29 mmoles) was added to a solution of 3.5 g (26 mmoles) of 3,3-dimethylbutyryl chloride in 7 ml of carbon tetrachloride, and the resulting solution was refluxed until the bromine color disappeared (about 4 hr). The solution was then added to an ice-cold solution of 6.3 ml (60 mmoles) of t-butylamine in methylene chloride (100 ml), it shows 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 separated. The methylene chloride solution was washed with hydrochloric acid (0.1 M) 30 ml, 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 °; infrared (CCl<sub>4</sub>): 3340, 2960, 1650, and 1560 cm<sup>-1</sup> (Figure 17).





WAVENUMBER (CM <sup>-1</sup> )			
SAMPLE	$(CH_3)_2CH_2CO_2 \rightarrow (CH_3)_2CHCO_2$ BT	SOLVENT	KBr pellet
ORIGIN	$+NH_2 \rightarrow (CH_3)_2CHNH_2$ BT	IDENTIFICATION	5
		CELL PATH	50
		REFERENCE	

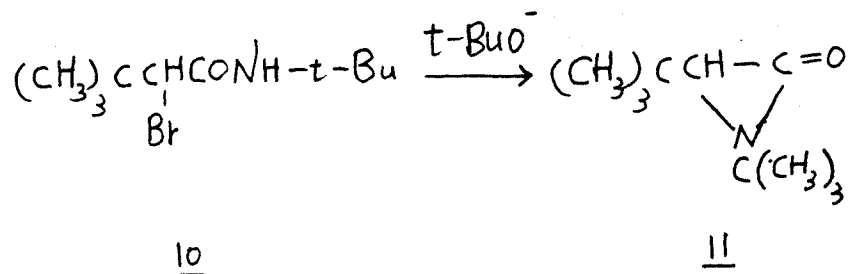
Figure 17. 2-Bromo-3,3-dimethyl-N-butylbutyramide (liquid)



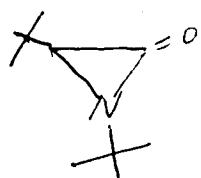
Sample:	33400	22600	16500	10700	SCAN SPEED	2	OPERATOR	Tu
Standards:	3200	22100	1600	1000	SPLIT		DATE	10/4
					DISPERSION ELEMENT		EXT. NO.	
					PART NO.	472-2000		

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

## 2. 1,3-Di-t-butylaziridinone

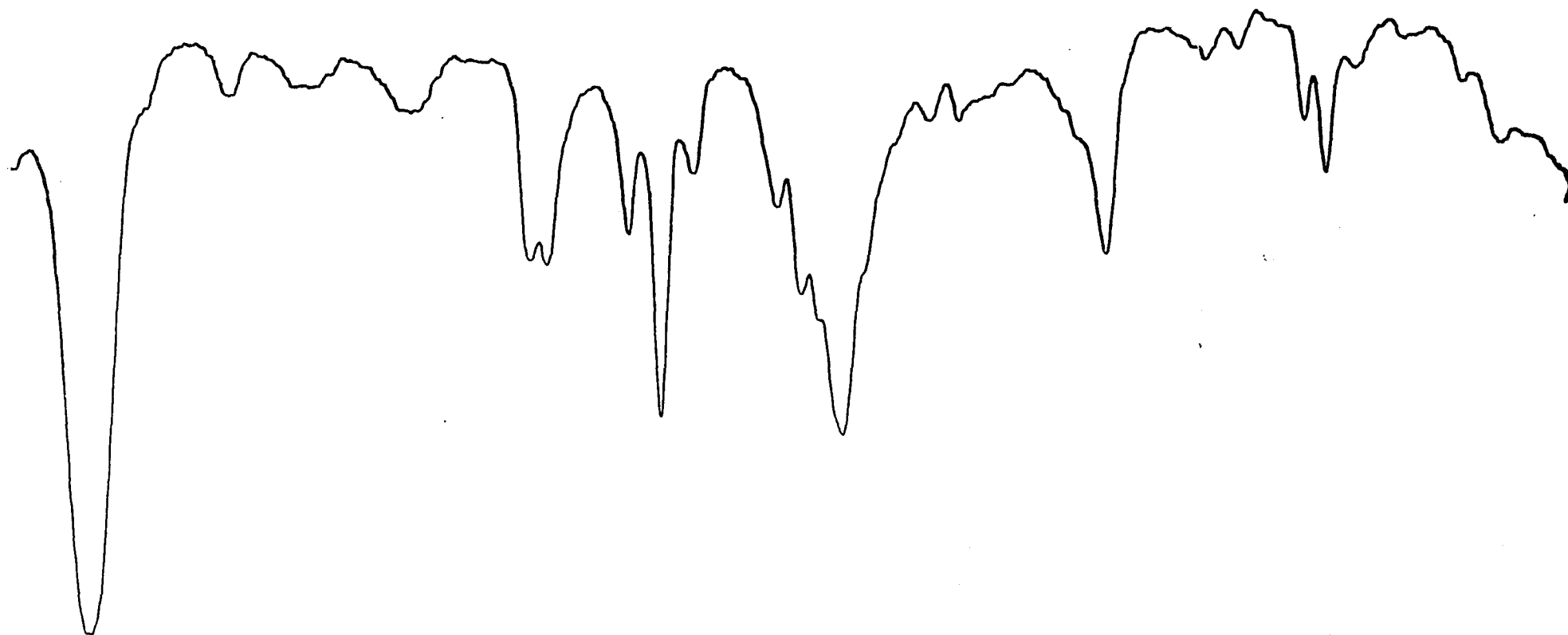


A solution of 3.12 g (0.012 mole) of the  $\alpha$ -bromo amide in 500 ml of ether was cooled to 0° in an ice bath, and 2.01 g (0.018 mole) of potassium t-butoxide was added. After 15 min of stirring, an infrared spectrum of the solution showed that the  $\alpha$ -lactam formation was complete. The solution 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  $\alpha$ -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  $\text{cm}^{-1}$ . It makes no obvious difference before passing through column and after passing through column (Figure 18 and 19).



1050

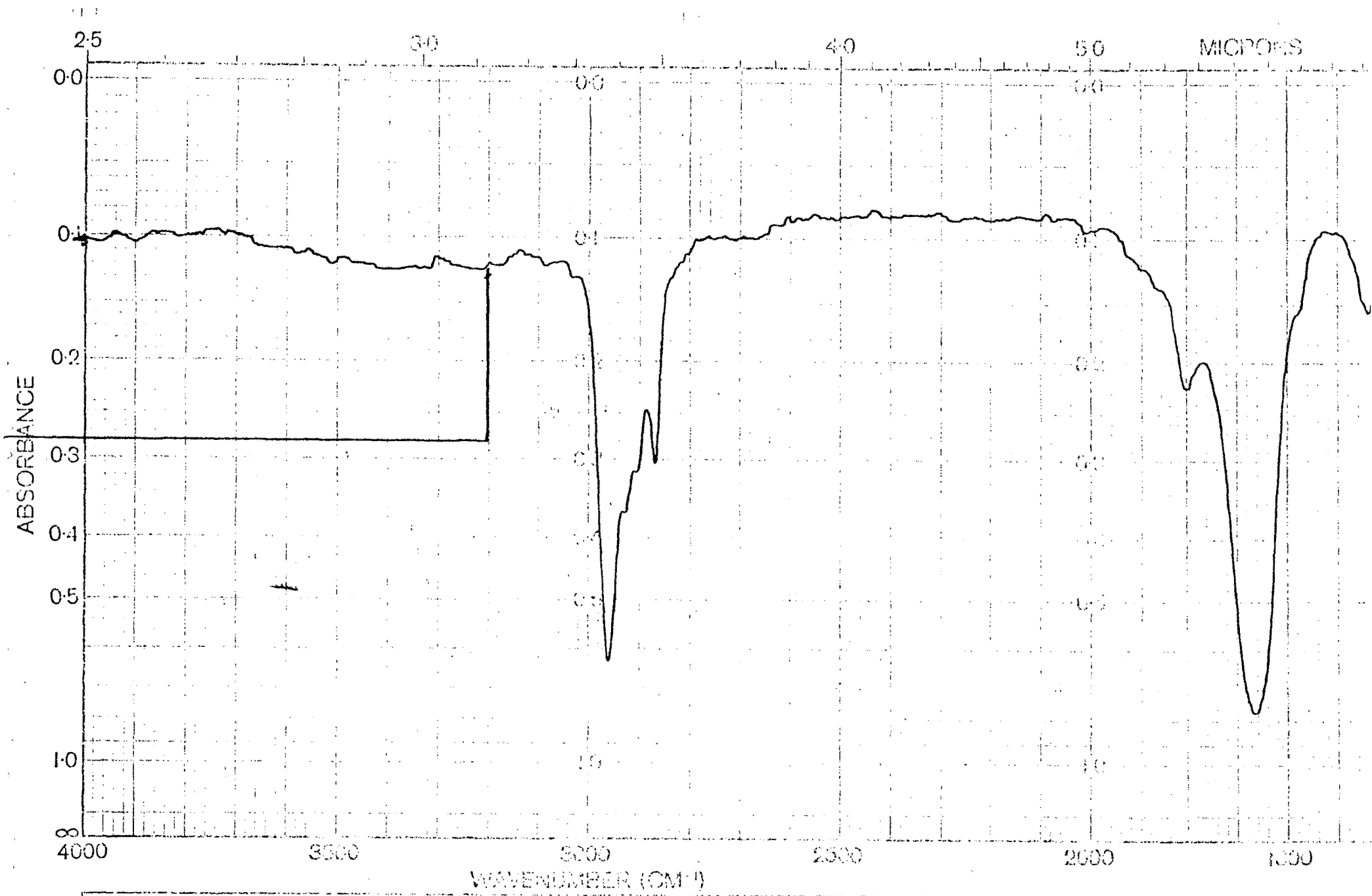
Figure 18. 1,3-Di-t-butylaziridinone (before passing column, liquid)



2960  $\text{cm}^{-1}$ , 1835  $\text{cm}^{-1}$

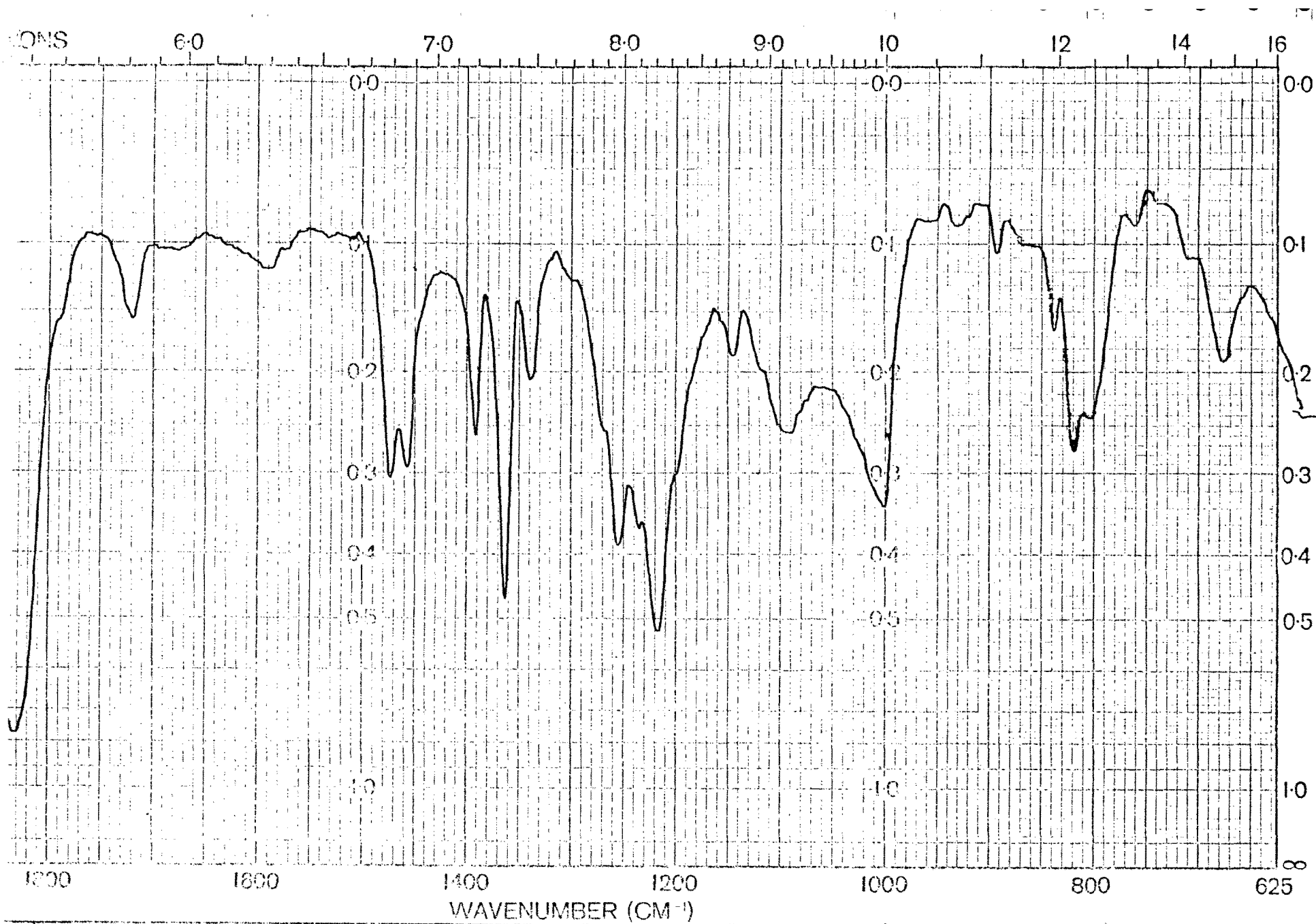
2

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



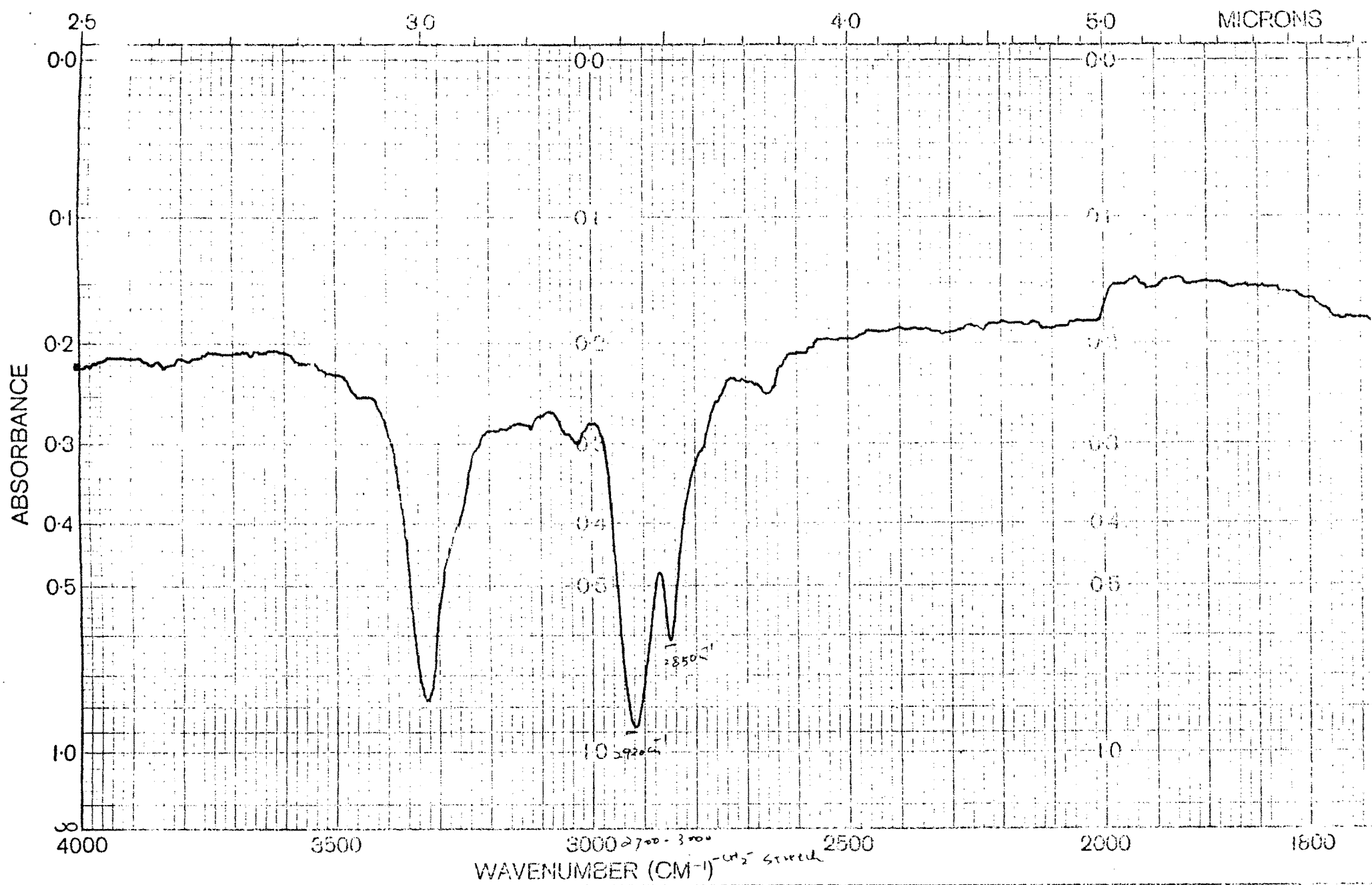
SAMPLE		SOLVENT CONCENTRATION CELL PATH REFERENCE	REMARKS
ORIGIN			95

Figure 19. 1,3-Di-t-butylaziridinone (after passing column, liquid)



REMARKS 2960 $\text{cm}^{-1}$ , 1835 $\text{cm}^{-1}$ 95% benzene 5% ethyl acetate (100ml) 100 mesh silical gel	SCAN SPEED 3	OPERATOR <i>tu</i>
	SLIT	DATE
PERKIN-ELMER PART NO. 472-5200	REF. No.	

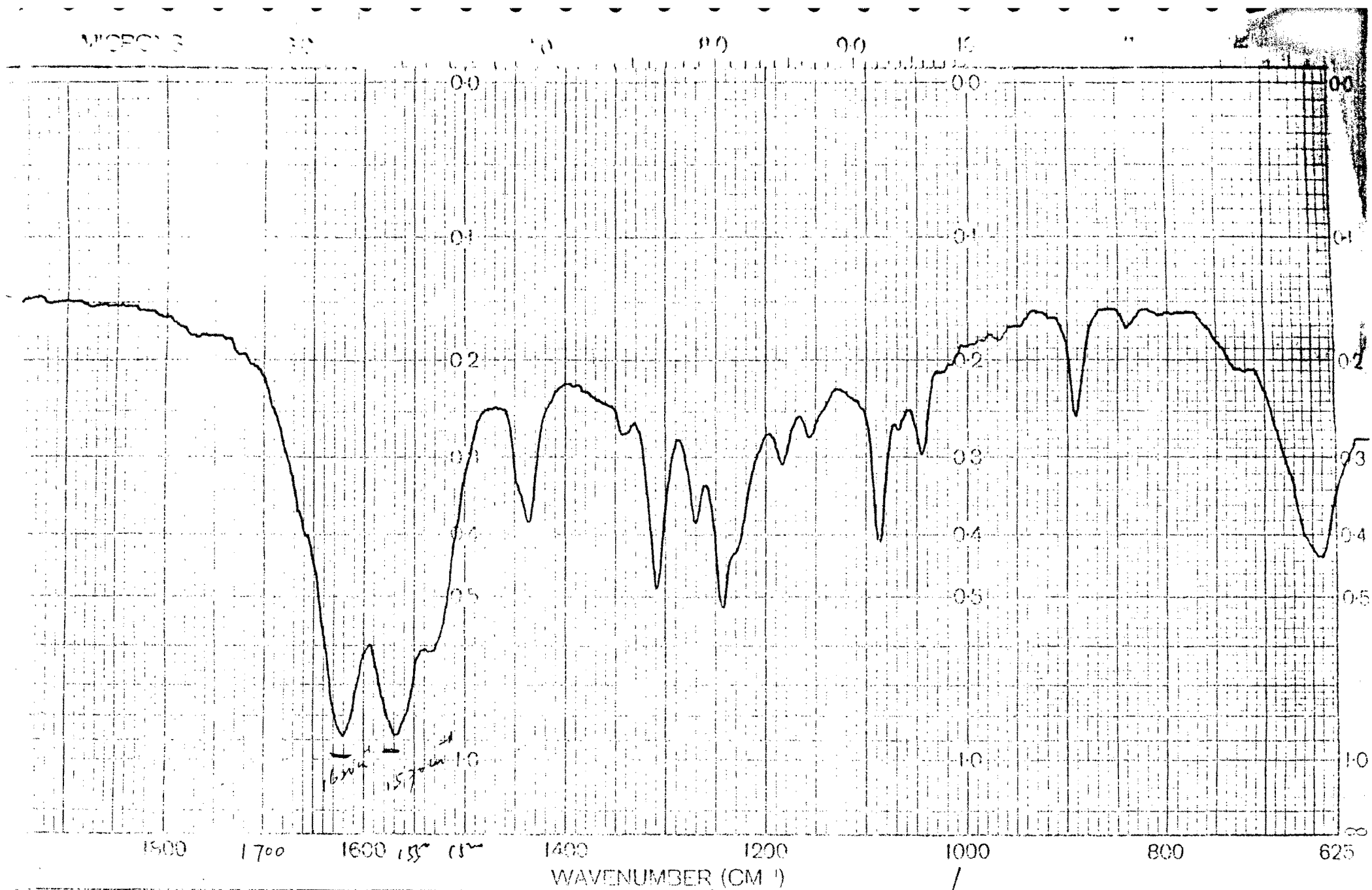
Figure 19. 1,3-Di-t-butylaziridinone (after passing column, liquid)



SAMPLE	method 3	Urea of DCC	SOLVENT	KBr - pellet	REMARK
	Solid of result (white)		CONCENTRATION		
ORIGIN	<chem>CNC(=O)N</chem>		CELL PATH	<chem>C1=CC=CC=C1N=C=N1 + H2O -&gt;</chem>	II
			REFERENCE		

Figure 20. Urea of DCC (white solid)





REMARKS $\text{CH}_3\text{COOH}$ $\text{C}_6\text{H}_5\text{NH}_2 + \text{DCC (C}_6\text{H}_5\text{N}_2\text{O)}$ $\xrightarrow[\text{Vacuum}]{\Delta}$ $\text{C}_6\text{H}_5\text{NHCO}$	SCAN SPEED 3	OPERATOR Tu
	SLIT	DATE 12-29-86
It should be <chem>C1=CC=CC=C1NC(=O)NC1=CC=CC=C1</chem>	PERKIN ELMER	REF. No. IR 089
	PART NO. 472-5200	

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  $\beta$ -(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  $\beta$ -(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  $\text{cm}^{-1}$ .

#### IV DISCUSSION

1. In 1979, Shaw synthesized 7 under high vacuum and high temperature to remove water from  $\beta$ -(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  $\beta$ -(3-piperidyl) propionic acid; the resulting N,N-dicyclohexylurea, which is not soluble in acetonitrile, is easy to remove by filtration.

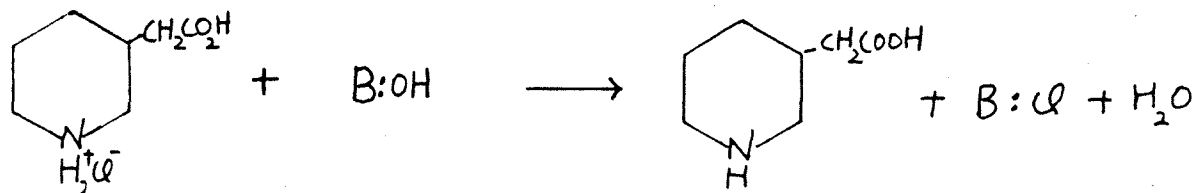
Using DCC reaction with 1,2,3,4-Tetrahydroquinoline-4-propanoic acid one can obtain 2,3,4,5-Tetrahydro-2-oxo-1,5-ethanobenzazepine (6) in very high yield (>90%)<sup>2</sup>.

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  $\beta$ -(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  $\beta$ -(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.

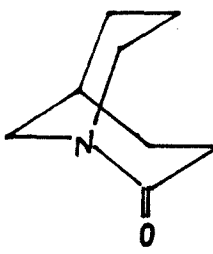
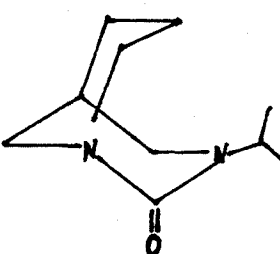
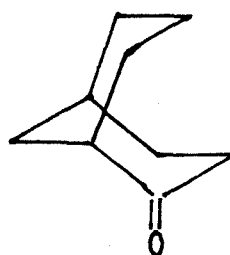
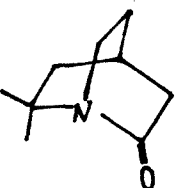
2. When trying to use DCC or di-n-butyltin oxide to react with  $\beta$ -3-(piperidyl)acetic acid to synthesize 9, one must neutralize  $\beta$ -3-(piperidyl)acetic acid hydrochloride with base ,



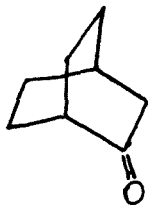
because if there is hydrochloride remaining in the starting material it would adversely affect the reaction. Upon adjusting pH around 7, and evaporating water and then proceeding under cyclization conditions, one does not obtain the desired product (it should have absorption at  $1750\text{ cm}^{-1}$ )<sup>7</sup> , 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  $1750\text{ cm}^{-1}$  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 bicyclic lactam.

Effect of Resonance Stabilization on Infrared Carbonyl Absorption of Bicyclic Lactam<sup>1</sup>

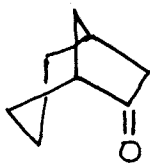
Structure	C=O Absorption (cm <sup>-1</sup> )
7 	1680
12 	1650 (Hall and Johnson 1972)
13 	1711 (Marvell et al. 1966)
14 	1733 (Pracejus 1959)

15



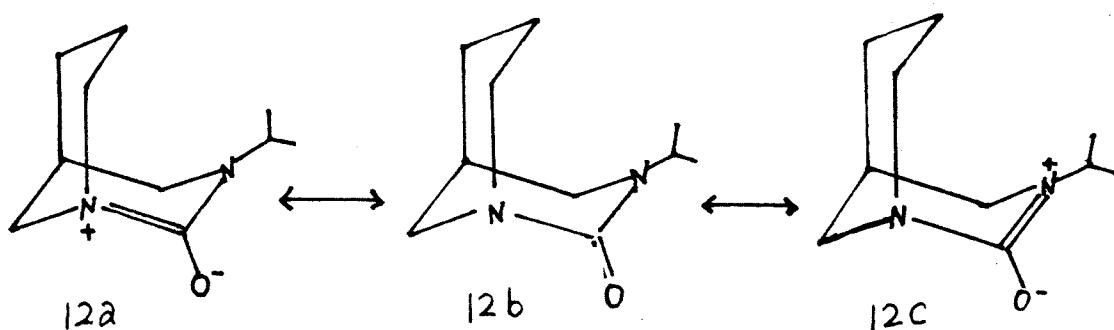
1731 (Zbinden and Hall  
1960)

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  $30\text{ cm}^{-1}$  between the carbonyl absorption frequencies of 7, 12, and 13 suggests that 12a and 12c contribute equally to the stabilization of 12a:



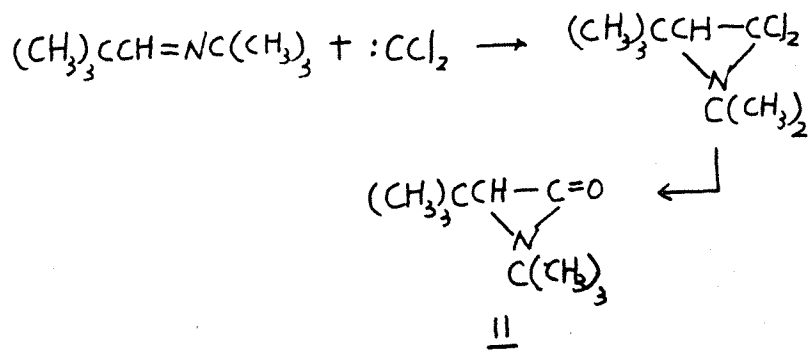
This is contrary to the assumption that an extra electron donating atom is necessary for the stabilization of this structure which was raised by Hall and Johnson in 1972. On the other hand, the approximately equal carbonyl absorption frequencies of compounds 14 and 15 showed very little resonance stabilization 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  $60\text{ cm}^{-1}$  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, aqueous 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:<sup>18</sup>



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  $1835 \text{ cm}^{-1}$ , 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 successfully, 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.

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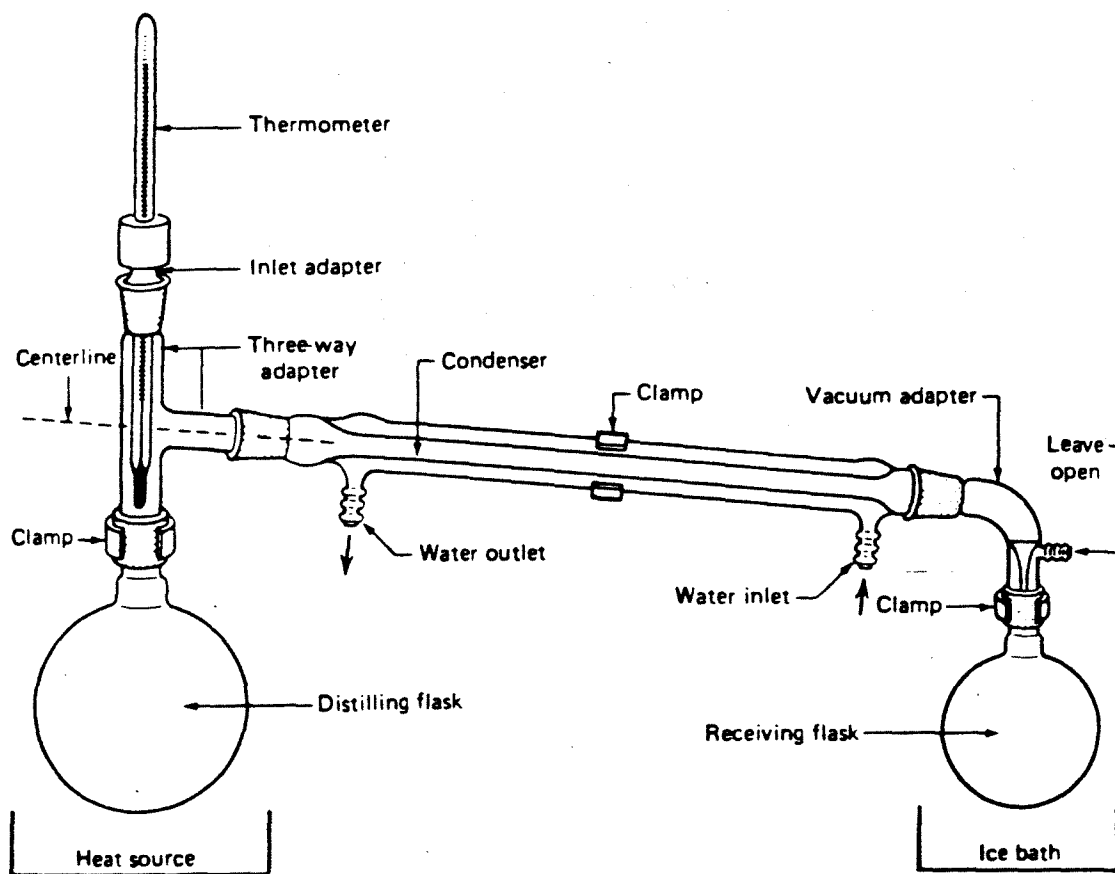


Figure 21. Distillation Apparatus

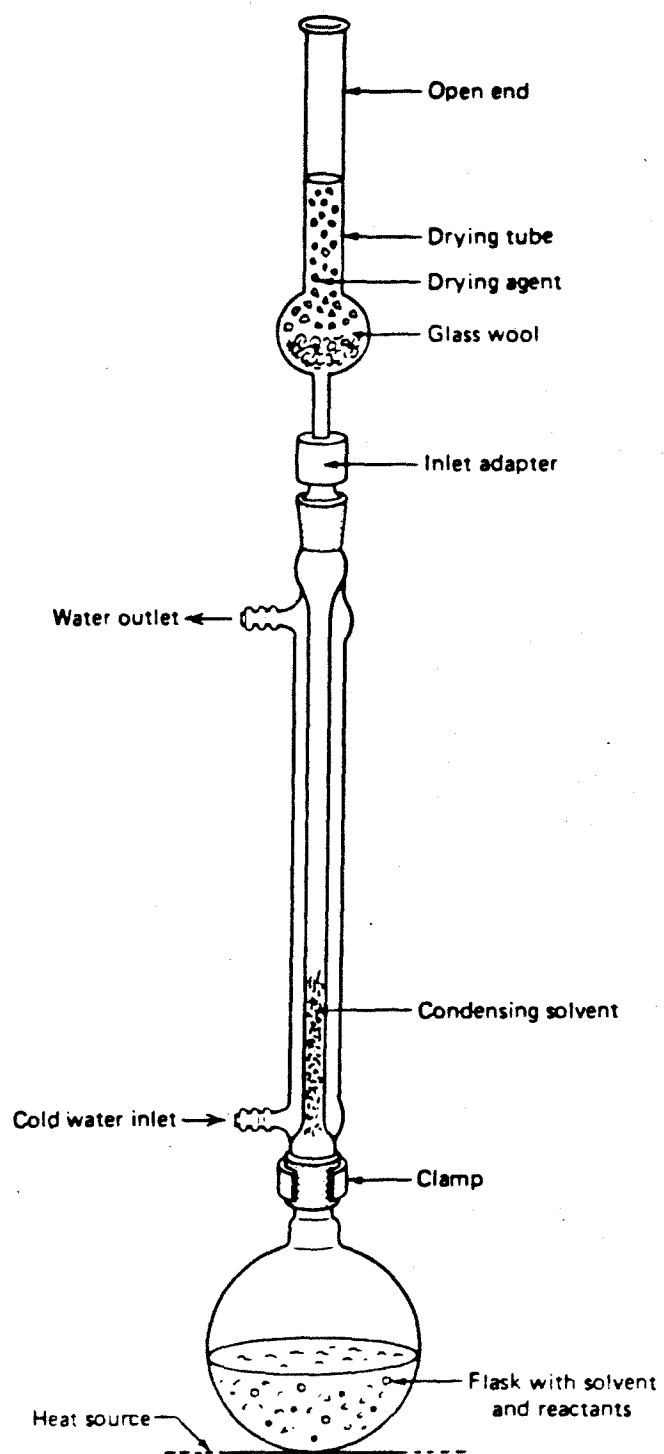


Figure 22. Reflux Apparatus

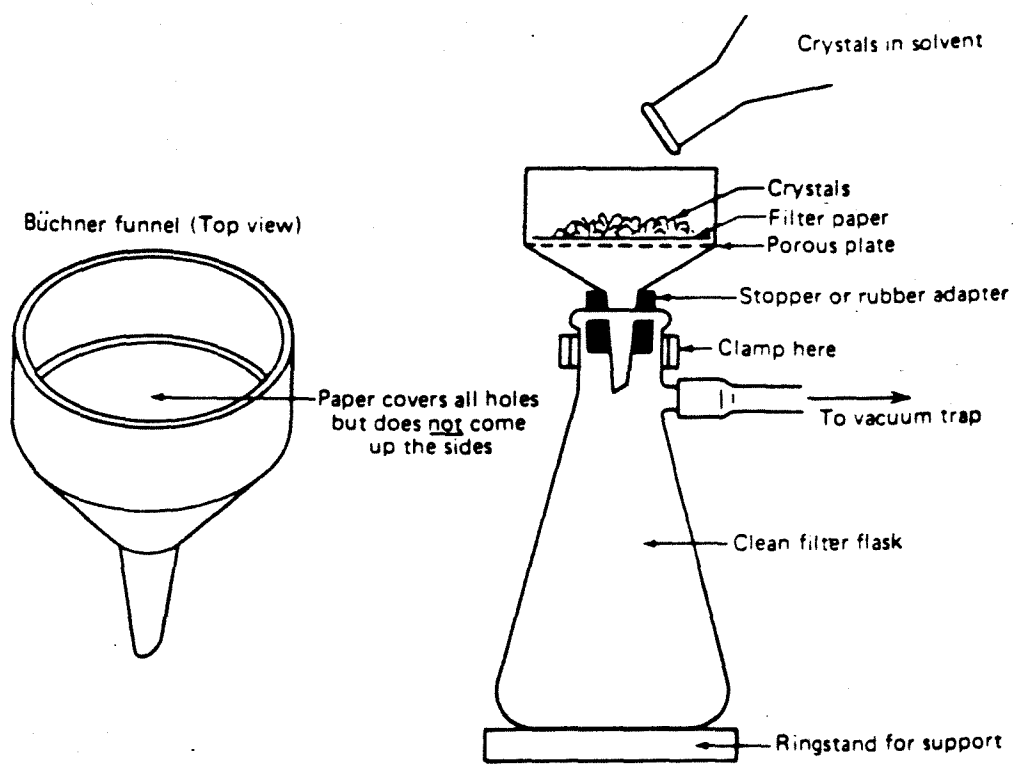


Figure 23. Filtration (suction) Apparatus



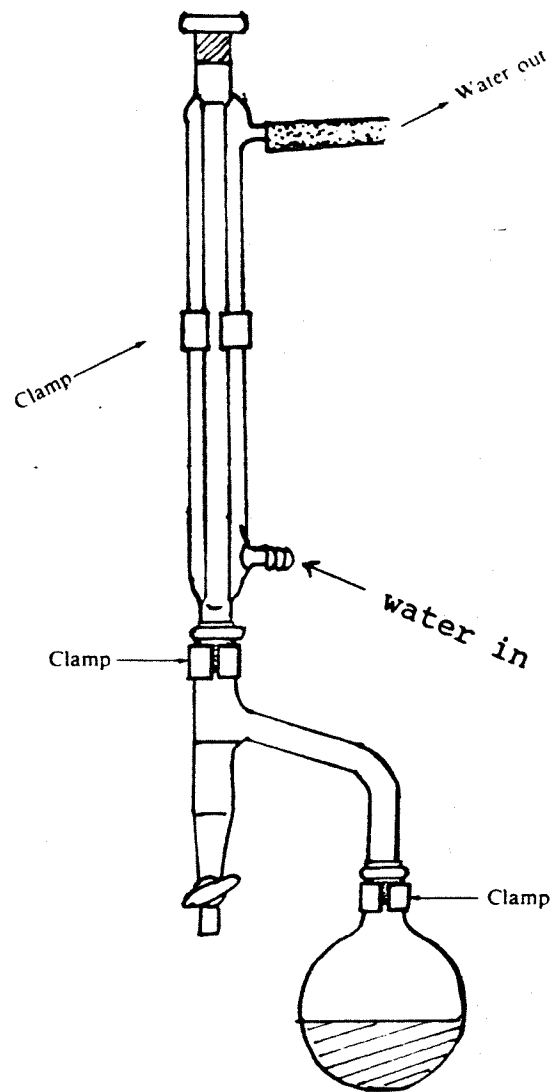


Figure 24. Dean-Stark Apparatus

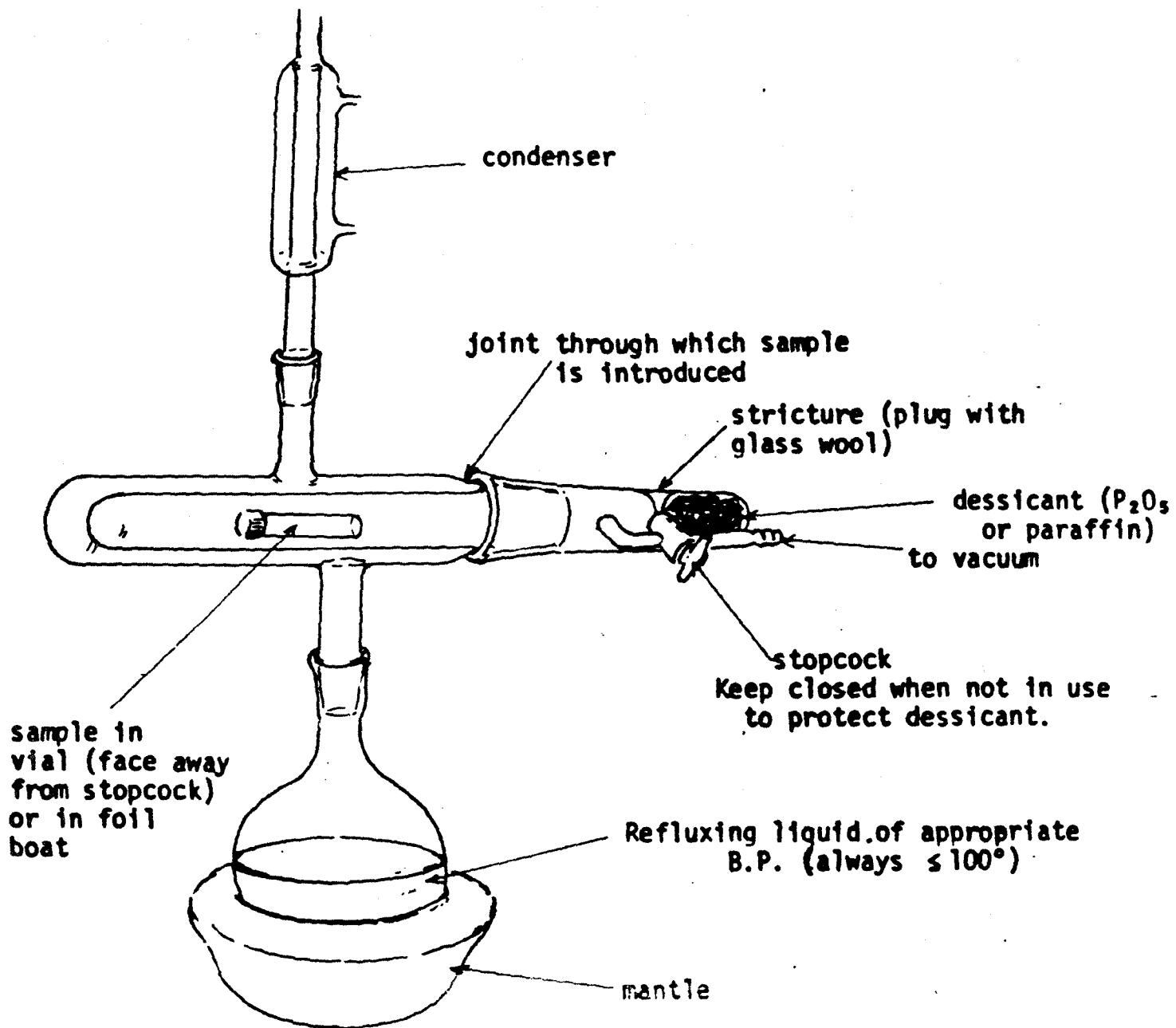


Figure 25. Aspirator Apparatus

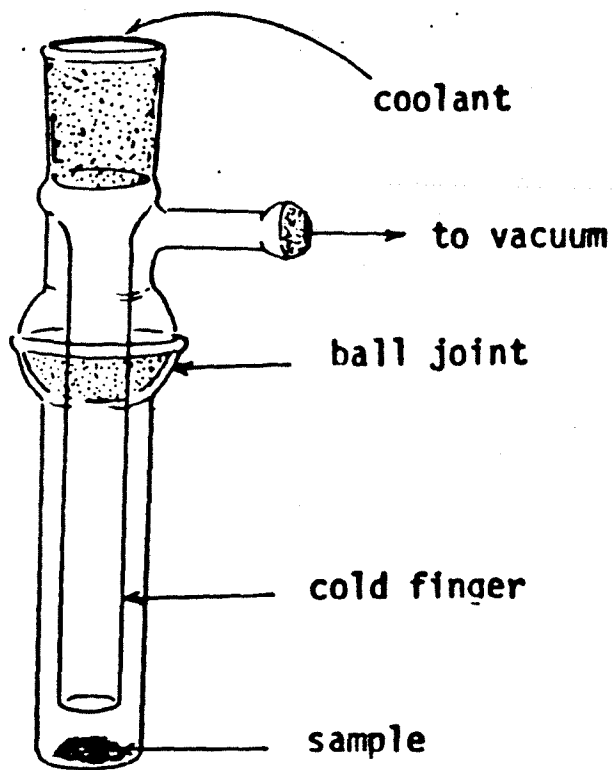


Figure 26. Sublimation Apparatus

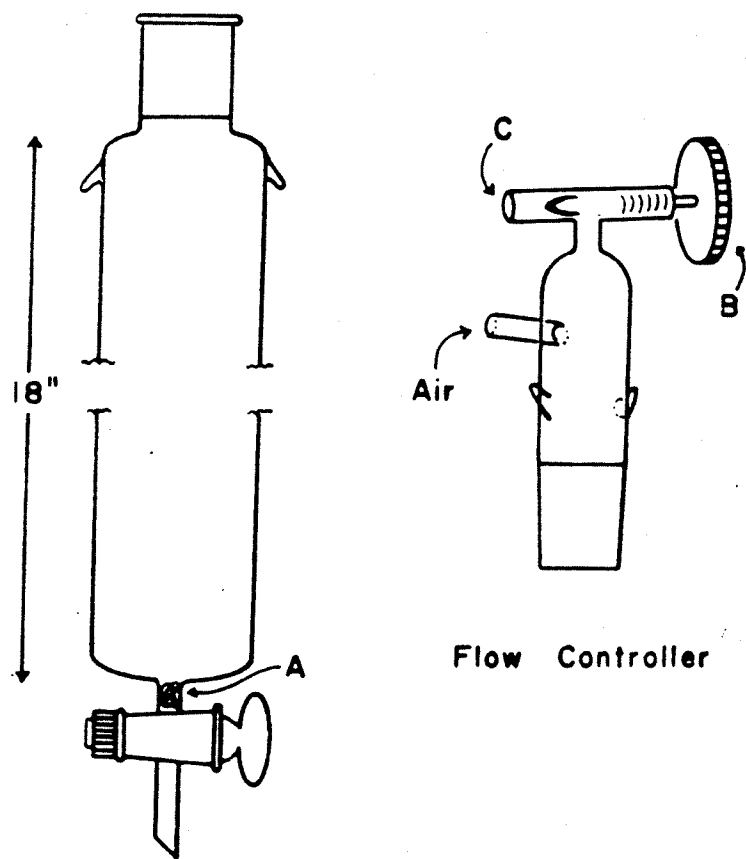


Figure 27. Flash Chromatography

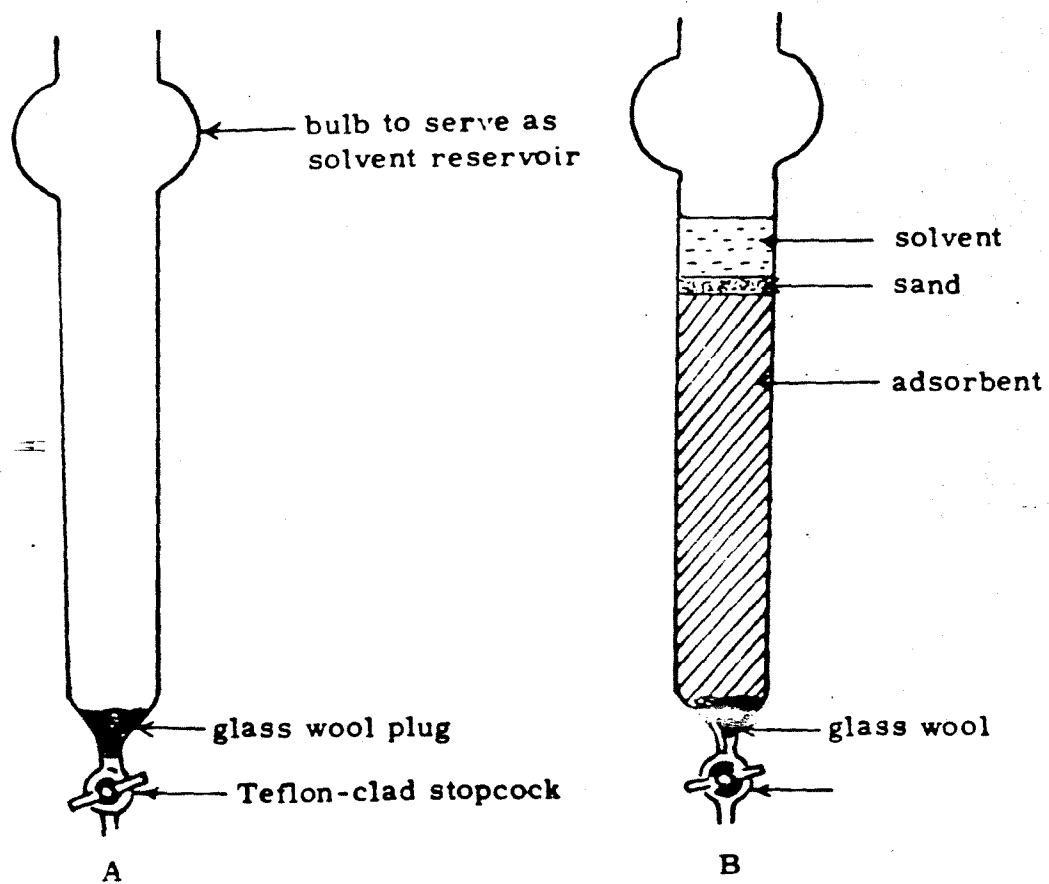


Figure 28. Apparatus of Column Chromatography