CARBONIUM ION STUDIES

I. ACETYLATION OF NORBORNENE

II. DEAMINATION OF

DICYCLOPROPYLCARBINYLAMINE

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ABSTRACT

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by Russell John Poel

The purpose of this investigation was to study reactions in the norbornene and dicyclopropylcarbinyl systems which were believed to proceed through ionic mechanisms. In particular, the question of whether or not rearrangement would occur during the course of acetylation of norbornene and deamination of dicyclopropylcarbinylamine was of interest.

Norbornene was shown to react with a 1:1 complex of acetyl chloride-aluminum chloride to give 60% of a mixture of 2-chloro-3-acetylnorbornanes. Removal of halogen gave 2-exo-acetylnorbornane as the major product. The predominant product of acetylation is probably 2-exo-chloro-3-exo-acetylnorbornane. There was no evidence to support rearrangement during the course of the acetylation.

The configuration of the 2-acetylnorbornane was shown to be exo by comparison with an authentic sample prepared from 2-exo-norbornanecarbonyl chloride. The reaction between dimethylcadmium and 2-endo-norbornanecarbonyl chloride proceeds with epimerization to give 2-exo-acetylnorbornane as the major product.

The addition of acetic anhydride to a methylene chloride solution of norbornene and stannic chloride unexpectedly gave 2-exo-acetoxynorbornane.

Russell John Poel

Dicyclopropylcarbinylamine and dicyclopropylcarbinylamine-α-d_1 were prepared from the oxime by reduction with lithium aluminum hydride and deuteride, respectively. The unlabeled amine was also prepared from dicyclopropyl ketone by a Leuckart reaction. Deamination of dicyclopropylcarbinylamine in dilute perchloric acid gave dicyclopropylcarbinol as the major product. Bisdicyclopropylcarbinyl ether and an unidentified third product were probably produced during the work-up of the reaction mixture. The three products, alcohol, ether and unidentified product, were formed in a ratio of 11:4:1.

When dicyclopropylcarbinol was heated with dilute perchloric acid, rearrangement occurred. The products obtained were 2-cyclopropyltetrahydrofuran and 4-cyclopropyl-3-butene-1-ol. When dicyclopropylcarbinol was heated in a solution containing ammonia, sodium nitrite and perchloric acid, the major material recovered was unchanged alcohol. In addition bisdicyclopropylcarbinyl ether and the unidentified third product of the deamination reaction were obtained.

The n.m.r. spectra of diisopropyl ketoxime, diisopropylcarbinylamine and N-diisopropylcarbinyl benzamide show non-equivalent methyl groups. The case of the ketoxime is due to the syn and anti relationships of the methyl groups to the oxime group. Magnetic nonequivalence in the latter two cases is probably due principally to conformational preference.

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Grateful acknowledgment is also extended to Dr. William H. Reusch for helpful discussions and suggestions.

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DEDICATION

To Mary Jo, my wife, for her
patience and understanding.

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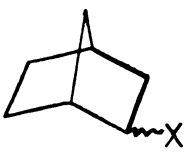
INTRODUCTION

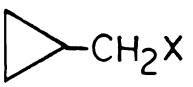
AND

HISTORICAL

The formation of carbonium ions, their nature during their often short existence, and the products to which they give rise, are subjects that have interested many chemists. Two systems which have been of particular interest are the non-classical carbonium ions which are derived from norbornyl (I) and cyclopropylcarbinyl (II) derivatives. Excellent reviews of these two systems may be found in de Mayo's Molecular Rearrangements (1,2).

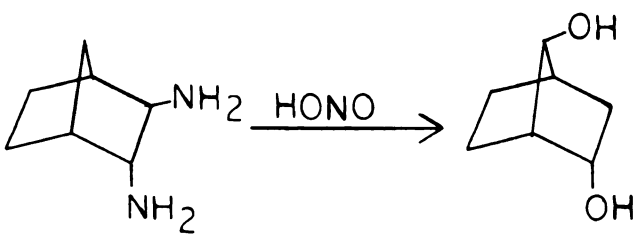


I



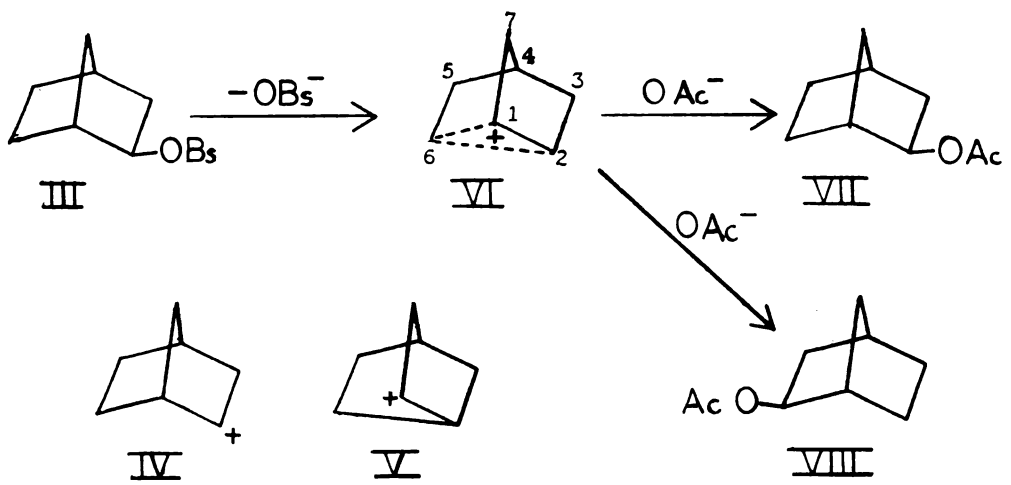
II

Because Wagner-Meerwein rearrangements are a familiar feature of the norbornyl cation and because of its well-defined geometry, the bicyclo[2.2.1] heptane ring system is of particular interest in the study of ionic processes. An early example of such rearrangements was shown by Schulze (3). The nitrous acid deamination of 2-endo-3-exo-diaminonorbornane gave 2-exo-7-syn-dihydroxynorbornane as the sole product.

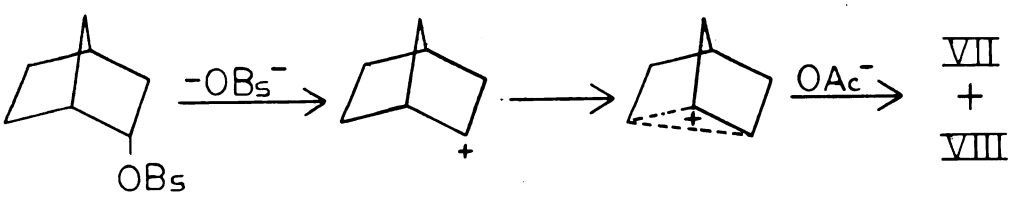


Winstein (4,5,6,7) found that the rates of solvolysis of the epimeric norbornyl p-bromobenzenesulfonates (brosylates) differ rather greatly. Exo-norbornyl brosylate (III), on treatment with potassium acetate in acetic acid, undergoes solvolysis at a rate 516 times that

of cyclohexyl brosylate. Some question remains as to whether the norbornyl system should be compared with the cyclohexyl or cyclopentyl system as it is not strictly comparable with either (8). Acetolysis of optically active brosylate resulted in complete racemization, and racemization was found to proceed faster than solvolysis. Winstein postulated that the enhanced reactivity was due to the formation of an ion significantly more stable than either of two classical ions, IV and V, and suggested the bridged intermediate ion VI. The breaking of



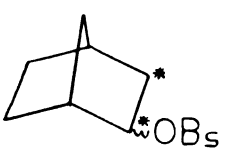
the C_1-C_6 bond to form a bridged ion with partially charged centers at C_1 and C_2 is assumed to enhance its stability and hence its rate of formation. Attack by acetate ion on VI at C_1 and C_2 would give rise to enantiomers VII and VIII. Endo-norbornyl brosylate (IX) undergoes solvolysis at a rate comparable (1.47:1) to that of cyclohexyl brosylate and also gives exo-norbornyl acetate. The reaction mechanism was interpreted as follows. Ionization of the brosylate (IX) gives the carbonium ion (IV), which then is converted to the more stable ion (VI).



IX IV VI

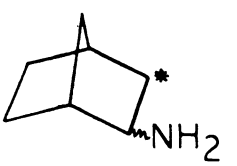
The bridged ion can than proceed to products VII and VIII. Acetolysis of optically active brosylate gave almost complete racemization (at most 7-8% retention of activity), and racemization was found to proceed at the same rate as solvolysis.

To test the validity of this postulated bridged ion Roberts (9) synthesized exo- and endo-norbornyl-2,3-$^{14}C_2$ brosylates (Xa,b) and exo- and endo-norbornyl-3-^{14}C amine (XIa,b). If ion VI were the only



Xa endo isomer

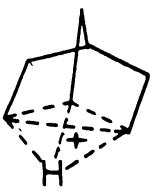
Xb exo isomer



XIa endo isomer

XIb exo isomer

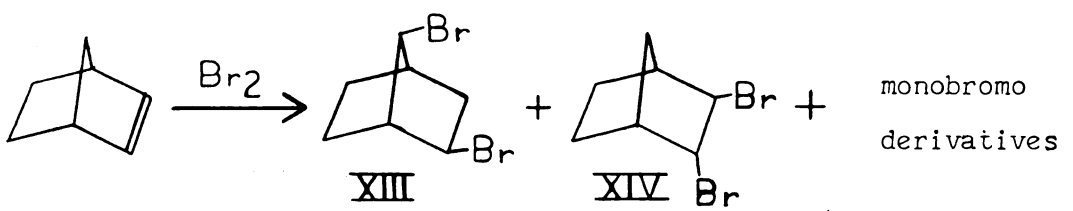
carbonium ion intermediate, the exo-norbornyl acetate obtained from solvolysis should contain equal activity at C_1, C_2, C_3, and C_7. The actual distribution found was: C_1 and C_4, 23% (C_4 probably zero); C_2 and C_3, 40%; C_5 and C_6, 15%; C_7, 23%. To account for these results Roberts suggested participation of a further intermediate ion (XII), arising from a hydride shift from C_6 to both C_1 and C_2. From the observed values of ^{14}C scrambling it was calculated that solvolysis of Xb proceeded 45% via XII and 55% via VI. In the deamination



XII

reactions of the labeled compounds the percentage of rearrangement is completely insensitive to differences in configuration or reaction medium. Furthermore, ion XII appears to be less significant in the deamination process than in the solvolysis, probably being involved no more than 20%.

Addition reactions involving the norbornene system can proceed either by a free radical process or an ionic mechanism. If the latter process is involved, addition of a cation to the double bond results in the formation of a norbornyl cation. Analysis of the products of the reaction would indicate whether ions such as VI and XII were involved. In an initial study of the bromination of norbornene Roberts (10) identified the monobromination products, 3-bromonortricyclene and exo-norbornyl bromide. The dibromide products were not identified. By dipole moment measurements and characterization of their reaction products Kwart (11) identified the dibromides as 2-exo-7-syn-dibromonorbornane (XIII) and the 2-exo-3-endo isomer (XIV).

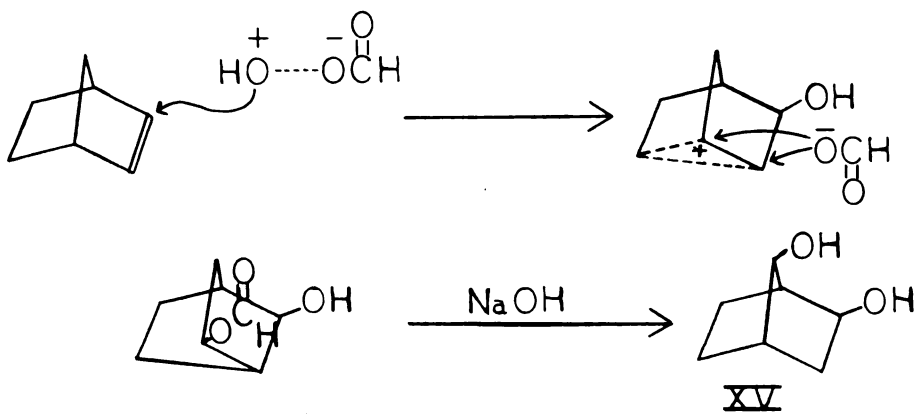


XIII XIV

The ratio of XIII to XIV, 1.8, was identical in duplicate runs. In a similar study Roberts (12) chlorinated norbornene at -75° and

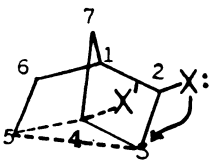
obtained 43% 3-chloronortricyclene and 37% 2-exo-7-syn-dichloronorbornane. He also added hypochlorous acid to norbornene at ice bath temperature to obtain 30% of 3-chloronortricyclene and 51% of 7-syn-chloro-exo-norborneol.

The perhydroxylation of norbornene was studied by Kwart (13) to elucidate further the steric course of addition to this unsaturated system. When norbornene was added to a solution of hydrogen peroxide in formic acid, there was isolated a single product (74%) identified as 2-exo-7-syn-dihydroxynorbornane (XV). Kwart pictured the mechanism for addition as follows:

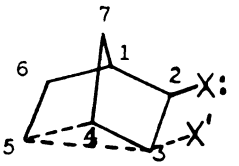


XV

In a private communication to Kwart, Winstein suggested the following. Attack of the catenoid fragment of the addition reagent on the double bond produces a bridged ion. If this catenoid fragment possesses unshared pairs of electrons, it exerts a substituent influence that may direct the course of the reaction leading to the transition state and thence to the final reaction products. This is represented in XVI. In state XVI where anionoid fragment $\ddot{X}'$ is half-bonded to C_4, bridging of the group $\ddot{X}$ at C_2 across to the adjacent C_3 position lowers



XVI



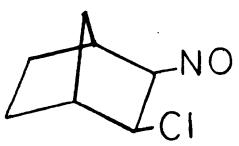
XVII

the charge density at C_3 and consequently lowers the energy of the complex as a whole. In state XVII where the anionoid fragment X' is half-bonded to C_3, bridging of the group $\ddot{X}$ to the non-adjacent C_4 is not as probable.

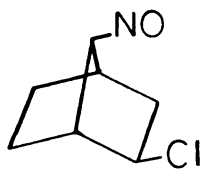
In a similar experiment Saegebarth (14) studied the tungstic acid catalyzed hydroxylation of norbornene. Isolation of the rearranged diol (XV) established the cationic nature of this reaction.

Nyce (15) studied the ionic and radical addition of deuterium bromide to norbornene and reported that a simple bridged ion could account for the distribution of deuterium in the polar addition product.

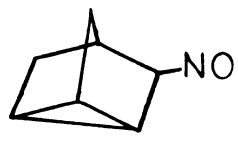
Lest one think that all previously observed ionic additions to norbornene involve rearrangement, it would be proper to include a reaction which does not involve rearrangement. The addition of nitrosyl chloride to norbornene was studied by Miller (16). This reagent presumably ionizes to give a nitrosonium ion and a chloride ion, and adds to olefins in the same direction as hydrogen chloride. If the first



XVIII



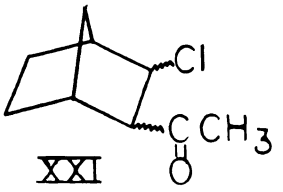
XIX



XX

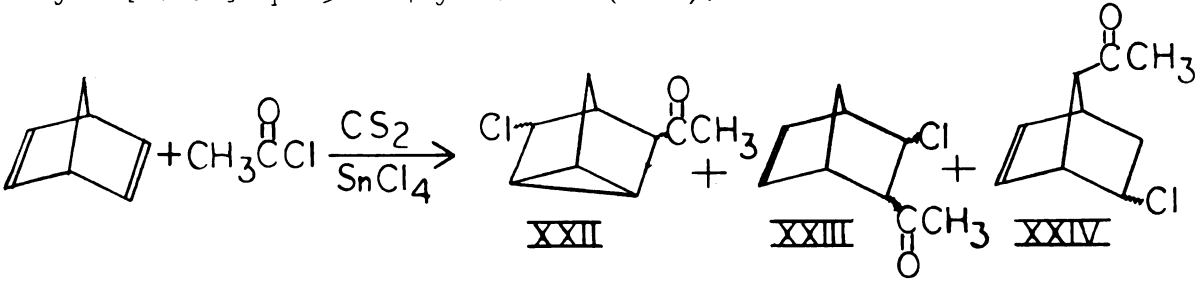
step is addition of NO^+, then products XVIII, XIX, and XX might be expected. Structure XVIII was the only product isolated (62%).

In a patent issued to the Shell Development Co., Fan (17) describes the "addition of lower aliphatic acyl halides to an ethylenically unsaturated bicyclic hydrocarbon". Addition of an equimolar mixture of norbornene and acetyl chloride to a solution of stannic chloride in carbon disulfide gave a 12% yield of methyl 3-chloronorborn-2-yl ketone (XXI). Fan suggested that XXI consists of a



XXI

mixture of the endo and exo isomers since the reaction with 2,4-dinitrophenylhydrazine gave two hydrazones. No proof of the structures was shown, nor was the possibility of a rearranged product mentioned. A similar reaction with norbornadiene yielded two fractions which were listed as "probably methyl 5-chlorotricyclo[2.2.1.$O^{2,6}$]hept-3-yl ketone (XXII), and methyl 3-chlorobicyclo[2.2.1]hept-5-en-2-yl ketone (XXIII)". The mixture also contained indications of methyl 2-chlorobicyclo[2.2.1]hept-5-en-7-yl ketone (XXIV).



XXII XXIII XXIV

Hart and Martin (18) acetylated an equilibrium mixture of nortricyclene and norbornene. The former gave methyl 2-chloronorborn-6-yl ketone which lost hydrogen chloride readily to give 1-acetylnortricyclene. Norbornene with acetyl chloride-aluminum chloride complex

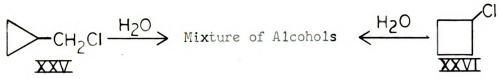
in methylene chloride, was found to give chloroketones remarkably stable to dehydrohalogenation. The structure and stereochemistry of these chloroketones was not investigated further.

One purpose of this investigation was to reinvestigate the product obtained by acetylation of norbornene. In most of the ionic addition reactions involving norbornene the rearranged product, i.e., the 2,7-isomer, was a principal, if not major, product. It was our purpose to examine the product to determine whether the aceto group was bonded to the seven position of norbornane.

In recent years considerable attention has been devoted to the nature of the carbonium ion intermediates derived from cyclopropylcarbinyl derivatives. Products obtained from reactions involving these intermediates can quite easily be rationalized mechanistically, but prediction of products a priori has been considerably more difficult. It had been reported by Demjanow (19, 20) that cyclobutyl and cyclopropylcarbinylamine, each with nitrous acid, gave a mixture of cyclobutanol and cyclopropylcarbinol. Smith (21) reported that cyclopropylcarbinol with phosphorus tribromide yielded a bromide which on successive treatment with magnesium and carbon dioxide gave allylacetic acid. Such products could be explained on the basis of classical carbonium ions.

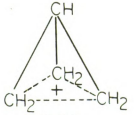
More recently Roberts attempted to determine the importance of various factors which direct the course of rearrangement in cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl derivatives. Roberts and Mazur (22) first showed that the solvolysis of cyclopropylcarbinyl

chloride (XXV) and cyclobutyl chloride (XXVI) is considerably faster than that of β-methylallyl chloride, and that the same mixture of alcohols is obtained from the solvolysis of XXV and XXVI. Similarly,

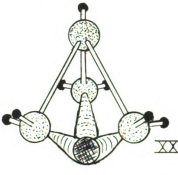


XXV XXVI

in the nitrous acid deamination of the corresponding amines essentially identical mixtures of alcohols were obtained. From these data they reasoned that the energy barrier for interconversion of the ions corresponding to the respective starting material is quite small. Here they first considered the possibility that the ions have effectively no separate existence, but are converted to an intermediate ion of the type suggested for the camphanyl cation (23). Shortly thereafter first mention was made by Roberts (24) of a tricyclobutonium ion (XXVII) as a common intermediate. M. J. S. Dewar in a private communication to Roberts suggested that XXVIIa can very reasonably



XXVII

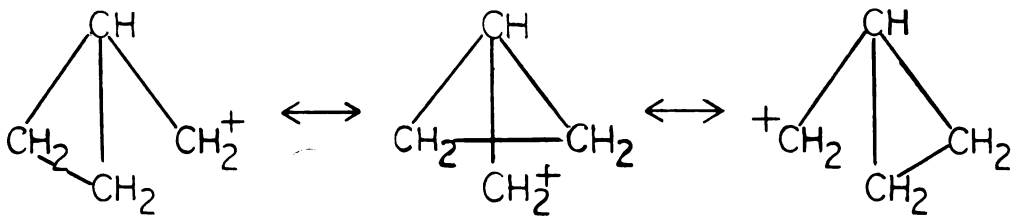


XXVII a

be formulated by the molecular orbital theory if it is considered that all of the carbon atoms use the customary sp^3 orbitals and that the methinyl group is attached to the three methylene groups by the customary σ-bonds. The three extra sp^3 orbitals of the methylene groups

are then positioned to overlap as shown, and can then form one stable molecular orbital holding two electrons, and two considerably less stable vacant orbitals.

Bergstrom and Siegel (25) reported the rapid first order ethanolysis of cyclopropylcarbinyl benzenesulfonate. They represented the cyclopropylcarbinyl cation as the hybrid XXVIII-XXX. This resonance hybrid, noteworthy for its symmetry, a factor important in



XXVIII XXIX XXX

resonance stabilization of an ion (26), explains the predominant formation of ethyl cyclopropylcarbinyl ether in the solvolysis. Nor does it preclude the possibility for rearranged products, since attack at the methinyl carbon would lead to cyclobutyl products.

A second possible pathway which would explain products obtained and the enhanced activities, involved equilibrating non-classical unsymmetrical bicyclobutonium ions (See Figure 1). If equilibration of ions XXXIa,b,c is complete before reaction with solvent (implying a low potential energy barrier between the isotope-position isomers), then the two formulations would be essentially the same. To elucidate the nature of the intermediate, Roberts (27) investigated the degree of equivalence achieved by the methylene groups during an irreversible process in a highly nucleophilic solvent, the deamination of cyclopropylcarbinylamine-α-^{14}C in aqueous perchloric acid. The distribution

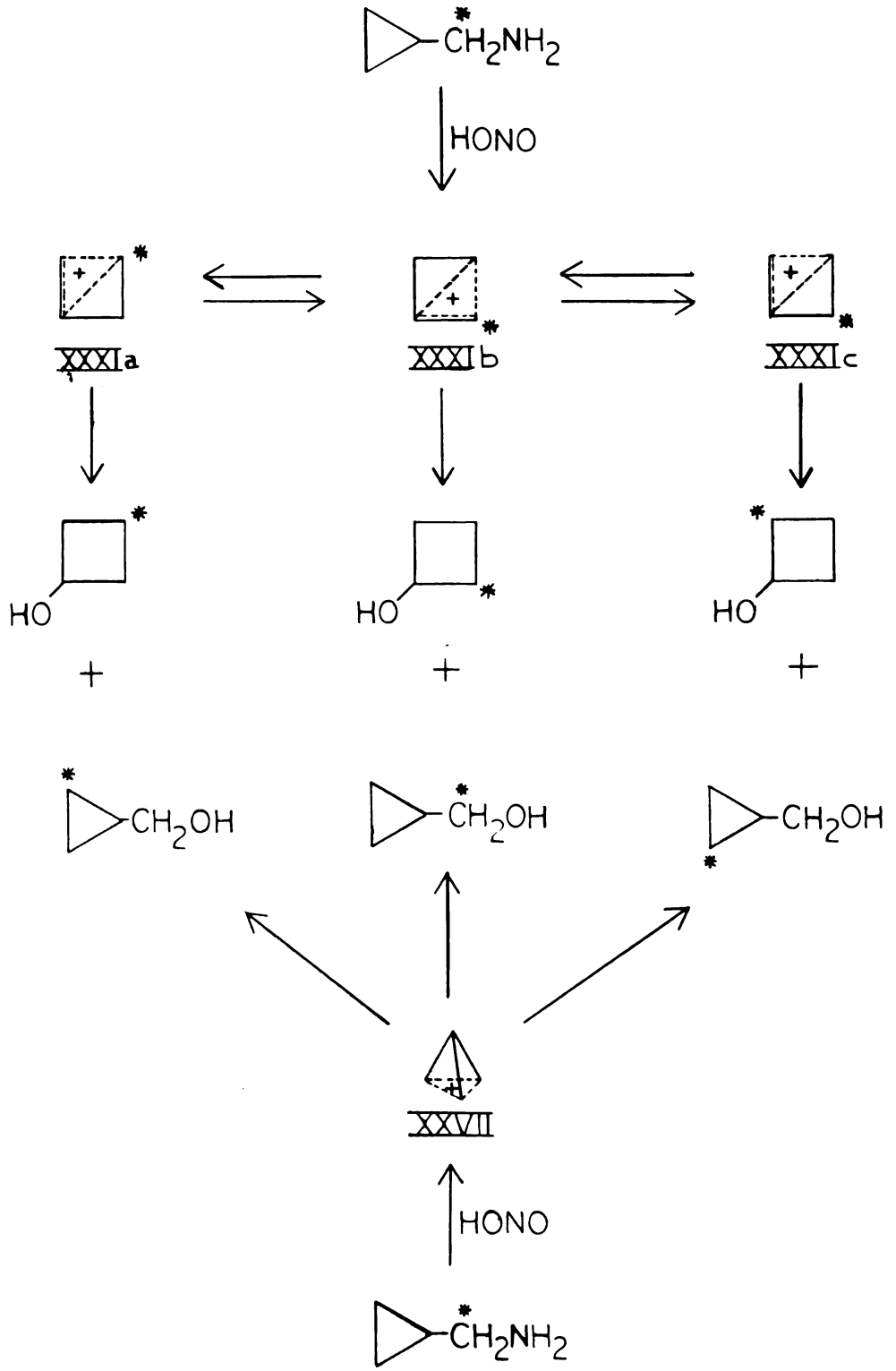
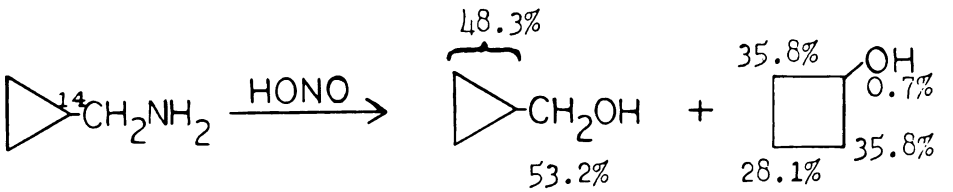


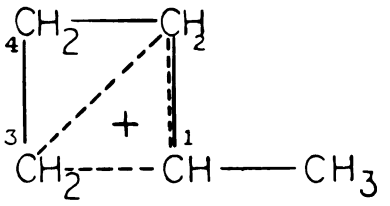
Figure 1. The ^{14}C Labeling in the Nitrous Acid Deamination Products of Cyclopropylcarbinyl-^{14}C-amine.

of the label in the two major products is shown below. The extent



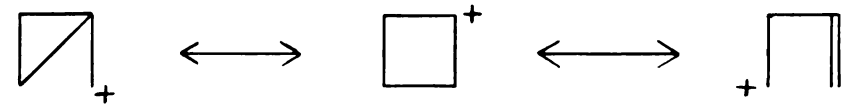
of equivalence is remarkable but by no means complete, and hence the symmetrical ion (XXVII) was ruled out as the most stable non-classical intermediate. The results can best be explained by assuming rapid but not instantaneous equilibration of three isomeric non-classical unsymmetrical bicyclobutonium ion intermediates (XXXIa-c). Symmetrical ion XXVII could still be considered as a way-point between XXXIa-c.

The distribution of charge in this ion is of great importance since carbonium ions tend to react most rapidly with solvent at the positions of greatest charge density. This is a consequence of Hammond's (28) thermic postulate. The charge in the intermediate ion XXXI would seem to be located primarily at C_1 and C_2, and to a lesser, though significant, extent at C_3 as determined by the ratios of the products formed in irreversible reactions. Any change in this charge distribution could greatly influence the product distribution. That this is true was shown when Roberts (29,30) studied reactions of substituted cyclopropylcarbinyl derivatives. Of special interest here is the fact that cyclopropylmethylcarbinylamine gave cyclopropylmethylcarbinol as the exclusive product, indicating that XXXII is the most stable bicyclobutonium ion with the charge located primarily at C_1.



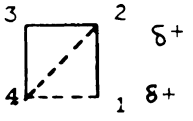
XXXII

Further evidence that there is little positive charge on the ring methylene carbon atoms of the cyclopropylcarbinyl system in the transition state was presented by Sneen (31). Phenyl substitution on the methylene carbons of cyclopropylcarbinyl β-naphthalenesulfonates produced only a very small kinetic effect. Hence, to the extent that the bicyclobutonium ion is a resonance hybride of XXXIIIa-c, form



XXXIIIa b c

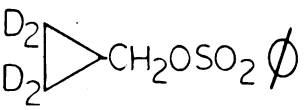
XXXIIIc contributes in only a minor way, and the bicyclobutonium ion can be simplified to:



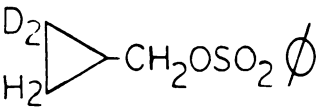
That considerably less (19%) than the theoretical amount of acid was liberated in the solvolysis of cyclopropylcarbinyl β-naphthalenesulfonates is indicative that internal return from ion pairs to less reactive isomeric esters was occurring. Further evidence for such internal return of ion pairs may be found in the hydrolysis by Roberts (32) of cyclopropylcarbinyl chloride-α-D_2. Separation of

unreacted chloride and analysis by VPC showed the chlorides, cyclopropylcarbinyl:cyclobutyl:allylcarbinyl in a ratio of 7.5:3.2:1.0, respectively. Further, it was estimated that some 24% of isotopically rearranged cyclopropylcarbinyl chloride was present in the mixture.

Further evidence by Borčić (33) for the participation of the cyclopropyl ring in the transition state of reactions of cyclopropylcarbinyl derivatives was the rate increase in ethanolysis and acetolysis of deuterium labeled benzenesulfonates, as in XXXIV and XXXV. The



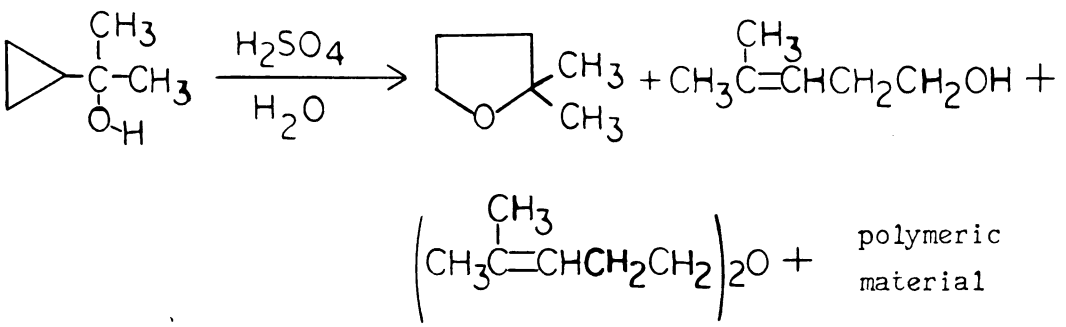
XXXIV



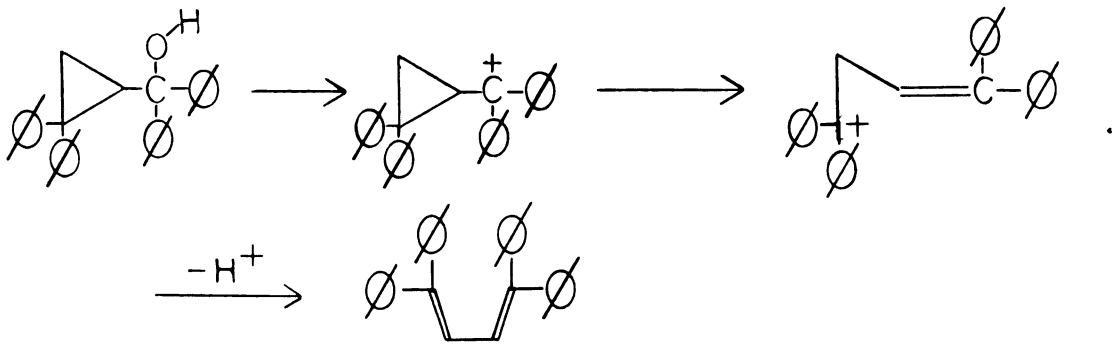
XXXV

larger isotope effect in the slower reaction, ethanolysis, is indicative of the formation of non-classical carbonium ions in the rate determining step. This is a direct application of Hammond's postulate (28).

There are several examples in the literature of compounds which, a priori, one might expect would generate rather stable carbonium ion intermediates. In fact, though a tertiary cyclopropylcarbinyl cation was generated, rearranged products were obtained. Dimethylcyclopropylcarbinol was refluxed with various concentrations of aqueous sulfuric acid by Favorskaya (34) to produce rearranged products. Walborsky (35)



studied diphenyl-2,2-diphenylcyclopropylcarbinol which, when treated with aqueous acid, boric anhydride, thionyl chloride, acetyl chloride, or acetyl chloride and pyridine, gave the rearranged product, 1,1,4,4-

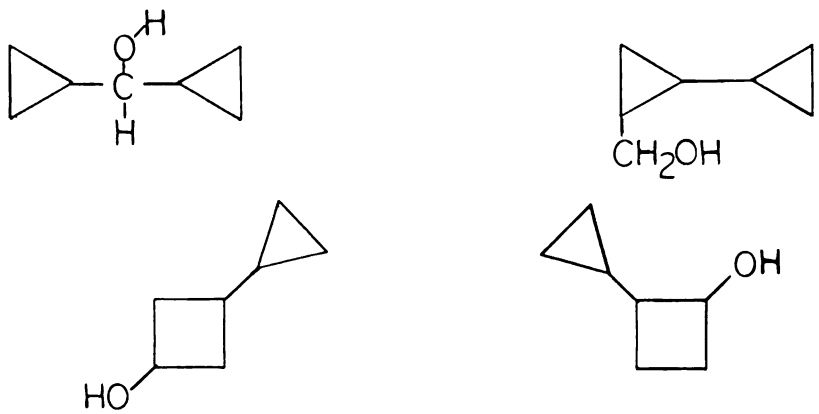


tetraphenyl-1,3-butadiene. He has suggested that relief of ring strain and the formation of the resonance stabilized diphenyl methyl-type carbonium ion are strong influences aiding ring opening. The stable nature of the extremely conjugated tetraphenylbutadiene favors its formation, by proton ejection, rather than reaction of ion with a nucleophilic reagent.

The work of Hart and Sandri (36) is of special interest with regards to our present work. In the solvolysis of p-nitrobenzoates of several cyclopropylcarbinols it was found that the effects of the cyclopropyl groups in promoting solvolysis were quite additive. Rates and products could be interpreted in terms of an ion pair mechanism which includes stabilizing the positive charge in the carbonium ion by each cyclopropyl group.

The purpose of the second portion of this investigation was to study the synthesis and deamination of dicyclopropylcarbinylamine and to determine the influence of the second cyclopropyl group on the course

of the deamination reaction. Dicyclopropylcarbinylamine can be visualized as cyclopropylcarbinylamine labeled in the α-position with a cyclopropyl group. Reference to the labeled products in Figure 1 would suggest the following possible products. If the charge were sufficiently delocalized over the two rings, such rearranged products



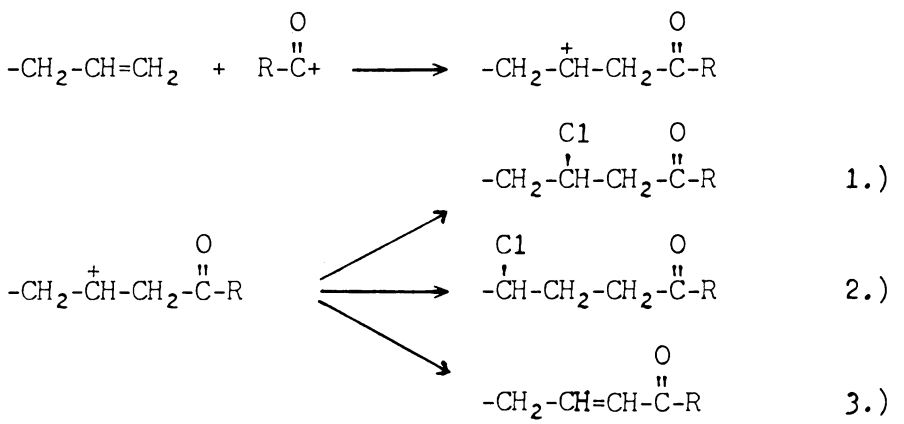
would be reasonable. If, as in the case of cyclopropylmethylcarbinylamine, the charge is sufficiently stabilized on the carbinyl carbon, no rearranged products would be expected. The possibility for a variety of products was indeed intriguing.

RESULTS AND DISCUSSION

I. Acetylation of Norbornene

A. Discussion of the Friedel-Crafts Aliphatic Ketone Synthesis

In the eighty eight years since Friedel and Crafts originally published their observations on the action of aluminum chloride in organic reactions (37), the literature of Friedel-Crafts reactions has grown like Topsy. Of great help to anyone who ventures into this field is the book recently edited by Olah (38). Most textbooks of organic chemistry in which the Friedel-Crafts reactions are discussed present a mechanism for the ketone synthesis in which the acylium ion, RCO^+, is the electrophilic reagent. Rather consistently the impression is created that the ketone synthesis involves an aromatic system and an acid halide or anhydride. Unfortunately the reaction between olefin and acylating reagent is most often overlooked, probably because it does not always proceed as smoothly as with aromatic hydrocarbons and yields can be quite low. The reaction is most conveniently affected by addition of the alkene to a solution of acyl halide-aluminum chloride complex in methylene or ethylene chloride. The acyl group combines with that carbon of the olefinic bond which holds the smaller number of alkyl groups and the resulting cation may 1.) combine with chloride ion, forming a β-chloroketone, 2.) isomerize by transfer of a hydride ion and subsequently combine with a chloride ion, or 3.) afford unsaturated ketone by loss of proton. Each of these three processes has been observed in the reaction between cyclohexene and acetyl chloride in the presence of aluminum chloride.



Nenitzescu and Balaban (39) in discussing aliphatic acylation have suggested that in non-polar media the acylating agent is present as an ion pair or as a strongly polarized complex. They further suggested that for the course of the reaction the precise nature of the intermediate electrophilic species is unimportant. In this investigation we hope to show that one of the factors which may control the course of the reaction is the nature of the electrophilic species.

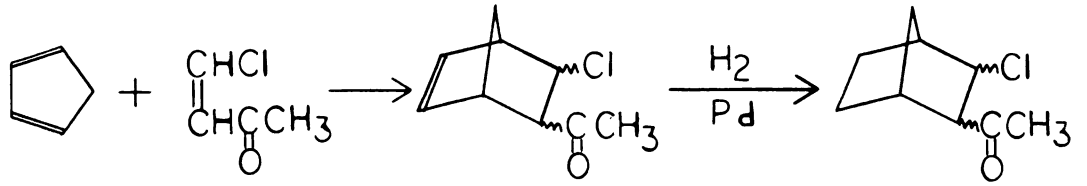
B. Acetylation of Norbornene

A preformed aluminum chloride-acetyl chloride complex in methylene chloride was treated at ice bath temperature with a methylene chloride solution of norbornene. That the chloroketone which was obtained was a mixture of isomers was evidenced by several facts. The derivatives, particularly the 2,4-dinitrophenylhydrazone, required repeated recrystallizations to obtain a sharp melting point. The carbonyl absorption band at 5.88 μ had several weak side bands, indicating more than one carbonyl. The gas chromatograph (See Figure 4)* shows one major peak and at least three others, considerably smaller

*Refer to 'EXPERIMENTAL' for all figures.

and somewhat less distinct. The product decomposed rather rapidly on standing at room temperature. Attempts to purify the material by careful fractional distillation resulted in conversion of much of the material into a glass. All samples showed a weak absorption in the infrared at 2.97 μ. However, in higher boiling fractions obtained toward the end of a distillation this became a prominent band. This could indicate that the polymer which was being formed came about by a heat induced aldol condensation.

Nesmeyanov and coworkers (40) reported the synthesis of a chloroketone, XXXVII, b.p. 84-86°, n_D^{20} 1.4915 by the following reactions:

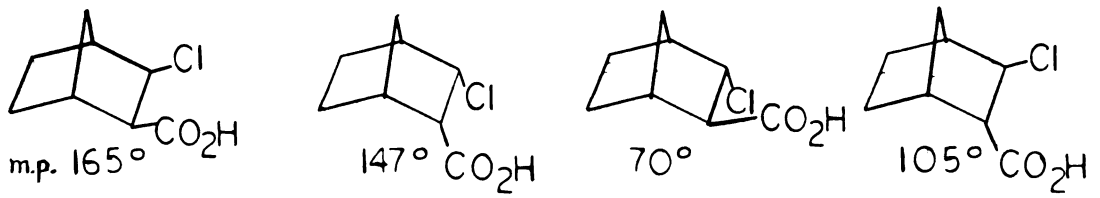


XXXVI XXXVII

No configuration was specified for XXXVII or for the starting chlorovinyl ketone. No derivatives were given for XXXVII.

The mixture of ketones described by Fan (17) gave two 2,4-dinitrophenylhydrazones (m.p. 183-184° and 157-159°). The former probably corresponds to our major product. Fan described these as the 2,3-isomers, though no configurations were ascribed to the products, and in fact, no evidence was submitted that these were 2,3-isomers.

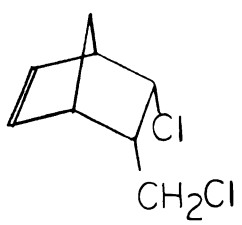
Since the isomeric 2-chloro-3-carboxynorbornanes are known compounds (41), conversion of the chloroketone to a solid acid should establish the configuration of the chloroketone if it arose from simple addition to the double bond. The chloroketone was treated

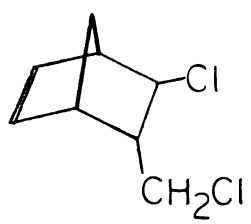


with sodium hypobromite to give a mixture of acids. A small portion of acidic material was converted to the methyl esters by treatment with diazomethane. The gas chromatograph (Figure 6) indicated a larger amount of by-product in the methyl ester than in the chloroketone. A possible explanation for this is that epimerization occurred under the basic conditions of the haloform reaction. Attempts to recrystallize the oily acid from ligroin and benzene were unsuccessful. When water was used as a recrystallization solvent, a very small amount of crystals was obtained. The greater portion remained as an oil. Observation of the melting point through a microscope seemed to indicate two kinds of crystals, one that melted at 147-149° and the larger amount which melted at 160-163.5°. This would indicate that the major acid was 2-exo-chloro-3-exo-carboxynorbornane, m.p. 165°, and the other 2-endo-chloro-3-endo-carboxynorbornane, m.p. 147°.

Several attempts to remove the halogen from the chloroketone and the chloroacid, and hence reduce the number of possible stereoisomers, were equally unsuccessful. Dehydrohalogenation with potassium t-butoxide was unsuccessful. A small amount of unchanged starting material was recovered, while the remainder polymerized in the distilling flask. Attempted reductive dehalogenation of the chloroacid using phosphorus and hydriodic acid and using zinc, acetic acid and hydrochloric acid were equally unsuccessful. In both cases sodium fusion

of the oily acid showed it to be still rich in chlorine. Attempts to remove the chlorine from the chloroketone by hydrogenolysis (low pressure hydrogenation over platinum black) also failed. Marvel, et al., reported that a more active catalyst was obtained by adding a small amount of concentrated hydrochloric acid to the hydrogenation mixture. With this they were able to remove halogens from aromatic systems. This modification also failed. It might be expected that a β-chloroketone would lose hydrogen chloride rather readily to form an α,β-unsaturated ketone. However, the difficulty with which chlorine is removed from the norbornane nucleus is not without precedent. The chlorine in the Diels-Alder adduct (XXXVI) and the corresponding saturated product (XXXVII) obtained by Nesmeyanov, et al., could not be replaced by hydrogen either by catalytic hydrogenation or with zinc dust or a zinc-copper couple. Tweedie (43) studied several 5-chloro-6-chloromethylnorbornenes. Lithium aluminum hydride converted





the chloromethyl group to a methyl group but did not remove the chlorine from the ring. Reduction to 5-methylnorbornene was complete using sodium in t-butyl alcohol.

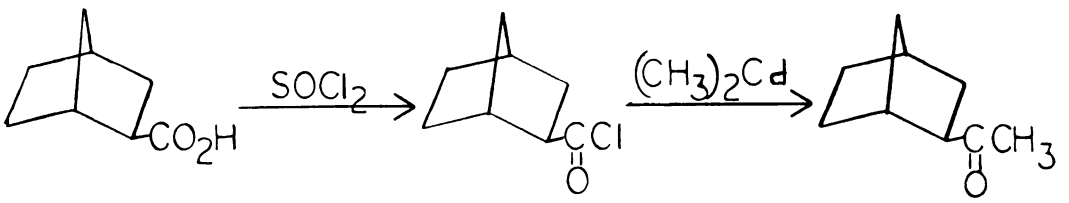
Removal of the chlorine from the chloroketone and simultaneous reduction to the alcohol was accomplished by two procedures, Tweedie's sodium and t-butyl alcohol procedure and the Raney alloy reduction of Papa (44). The methylnorbornylcarbinol (less than 5% lower boilers),

n_D^{25} 1.4832-1.4840, obtained from both reactions was identical. The uniformity of the gas chromatographic peak would indicate either that the two isomers had identical retention times or more likely that under the strongly basic conditions of the reaction the more stable epimer was almost the exclusive product.

Methylnorbornylcarbinol was oxidized with chromic acid to give 2-acetylnorbornane. The refractive index of this sample (n_D^{25} 1.4710) was identical with that reported by Berson (45) for 2-exo-acetylnorbornane. Two methyl peaks (ca. 4:1) at τ 7.94 and τ 7.97 were observed in the n.m.r. spectrum (Figure 11). Refer to the following discussion for assignment of these peaks.

C. Proof of Configuration of the Acetyl Group

To establish the identity of the acetylnorbornane obtained from the chloroketone an independent synthesis of 2-exo- and 2-endo-acetylnorbornane was attempted. A procedure similar to that of Berson (45) was employed though the experimental work was performed before Berson's work was noticed. The reaction sequence is shown below. The pure



endo- and exo-norbornanecarboxylic acids were prepared from appropriate Diels-Alder adducts. Reaction of the norbornanecarboxylic acids with thionyl chloride gave their respective acid chlorides. The epimeric purity of the acid chlorides was established by Chloupek (46) by

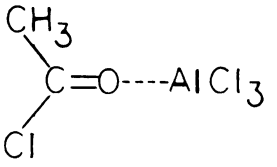
hydrolysis to the original acids and gas chromatographic analysis of the methyl esters. The epimeric purity of the ketone Berson obtained from exo-acid chloride was shown by the following facts. The melting point of the semicarbazone was unchanged by recrystallization. Oxidation with perbenzoic acid in chloroform, a reaction that would be expected to retain epimeric configuration, produced exo-norbornyl acetate uncontaminated with its endo isomer. The physical constants (m.p. of the semicarbazone, n_D^{25}, and b.p.) of the acetylnorbornane obtained in this investigation were identical to those reported by Berson for 2-exo-acetylnorbornane. A further exacting criteria of epimeric purity can be found in the chemical shifts of the methyl peaks in the n.m.r. spectrum. The magnetic environment of a methyl group in an exo-acetyl group would be expected to be different from that of the methyl in an endo-acetyl group. The n.m.r. spectrum (Figure 11) showed a small peak at τ 8.00 (less than 10% endo isomer) and the major methyl peak at τ 7.98. Berson reported that the ketone prepared from the endo-acid chloride was a mixture of epimers with the endo isomer apparently predominant. Both the procedure reported by Berson and that in this investigation used an excess of dimethylcadmium. An apparently very significant difference was the length of reaction between dimethylcadmium and acid chloride, two hours in Berson's procedure and eight hours in this investigation. The acetylnorbornanes obtained from endo- and exo-acid chlorides had identical retention times on a gas chromatographic column. The melting points of the semicarbazones were identical and showed no depression on mixing. Most significantly similar methyl peaks were observed in the n.m.r.

spectrum, the larger peak at lower fields and the smaller peak (15-20%) at higher fields. This would indicate that the endo-acetylnorbornane epimerized under the influence of the basic dimethylcadmium. The extended reaction time in this investigation allowed for a more complete conversion to the exo-isomer. Berson suggested two possible reasons for the difference in behavior of the two acid chlorides toward dimethylcadmium. Either the rates of formation of an enolic intermediate from either species during contact with the organometallic are comparable, but the rate of the enol –> exo reaction is much faster than that of the enol –> endo reaction, i.e., the equilibrium favors exo material, or the rate of enolization of endo material is faster than that of exo, perhaps because of the sterically more exposed position of the C_2 hydrogen in the former. Any choice between these two arguments would be speculative, though I tend to favor the former. Fortunately the favored isomer was the same one as that which was formed predominantly from the chloroketone so that identity could be established.

In review then, it appears that the two major products of the acetylation of norbornene with aluminum chloride and acetyl chloride were 2-exo-chloro-3-exo-acetylnorbornane and 2-endo-chloro-3-endo-acetylnorbornane, the former isomer being the predominant product. This chloroketone mixture was converted to a similar exo and endo mixture of acetylnorbornane. The configuration of this product was shown by comparison with an authentic sample.

The absence of rearrangement would suggest that the attacking species is not an acylium ion and that a norbornyl cation is not

involved in this reaction. Hart and Schlosberg (47) have substantiated the absence of the acylium ion in non-polar media. The chemical shift of the methyl group in the acetyl chloride-aluminum chloride complex in carbon tetrachloride did not change from its position when not complexed with aluminum chloride. This would suggest the absence of a positive charge on the carbonyl carbon. On the basis of infrared data Cook (48) reported that in solvents of low dielectric constant no ions have been detected in solution and that the acetyl chloride and aluminum chloride existed in a donor-acceptor complex (XXXVIII). In this complex the carbon-chlorine bond is thought to



XXXVIII

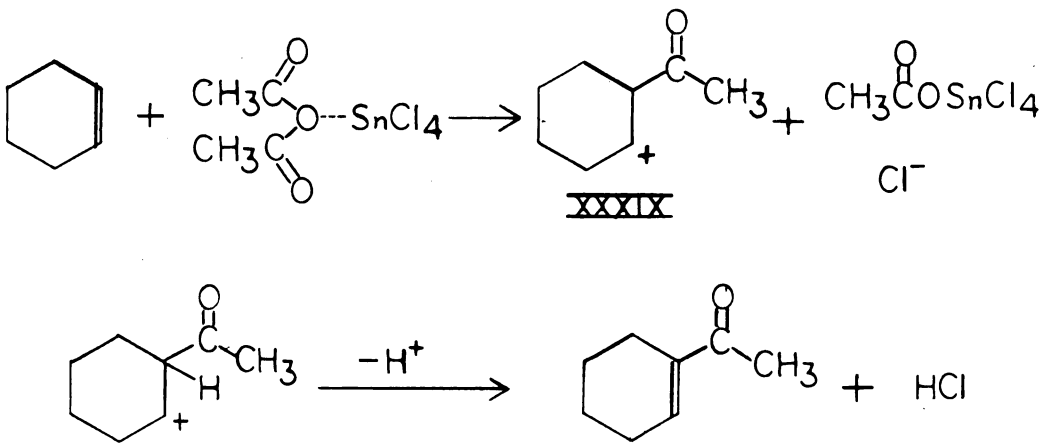
be weakened. This would have the effect of lowering the activation energy of the reaction between complex and olefin. The apparent cisoid nature of the substituents on the norbornane nucleus would suggest a four center transition state in which the carbon and chlorine are bonded simultaneously to the olefin. The much greater preference for the exo configuration would be expected because of the sterically favored approach from the top side of the double bond.

II. Stannic Chloride Catalyzed Reaction Between Norbornene and Acetic Anhydride

Several problems were encountered rather consistently when acetyl chloride and aluminum chloride were used to acetylate norbornene. The yields were often quite poor and rather variable depending upon the temperature of the reaction and the method of distillation. Elaborate distillation apparatus generally resulted in more extensive decomposition. The product of the reaction, a chloroketone, decomposed (darkened and polymerized) upon standing.

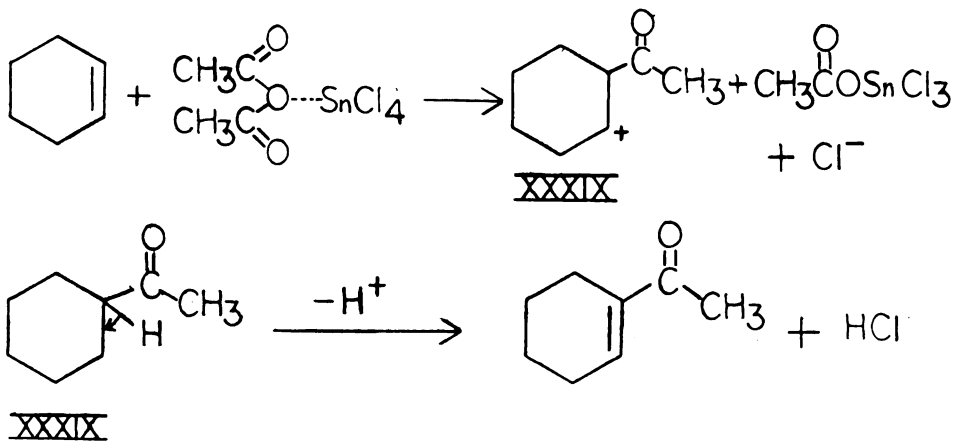
Several authors (49,50) have suggested the use of acetic anhydride in combination with stannic chloride as the acetylating agent for olefins. In the case of cyclohexene several advantages were noticed. Reaction conditions were more easily reproducible and the experimental procedure was simpler. The product, 1-acetylcyclohexene, was produced directly, thus eliminating a dehydrohalogenation step. Finally, the product was purer. This was noted by the constancy of the refractive index during distillation, by failure of the sample to darken during standing, and by complete absence of chlorine. Royals and Hendry (49) found that the most advantageous variation in experimental procedure was to add dropwise acetic anhydride to a mixture of cyclohexene and stannic chloride during a short reaction time at room temperature.

The mechanism proposed for this reaction is similar to that proposed for the aluminum chloride-acetyl chloride reaction.



If the same intermediate ion is postulated here as was proposed for the other reaction, the question could be raised as to why it does not combine with chloride ion to give chloroketone. The same overall results would be obtained as if the reaction had been effected with acetyl chloride. The difference is probably due to the following. Acetate ion, whether actual or potential, is present in the acetic anhydride mixture. If ion XXXIX combines with any anion, it would be with the more nucleophilic acetate rather than chloride. The ester then formed could lose the acetoxy group in the workup.

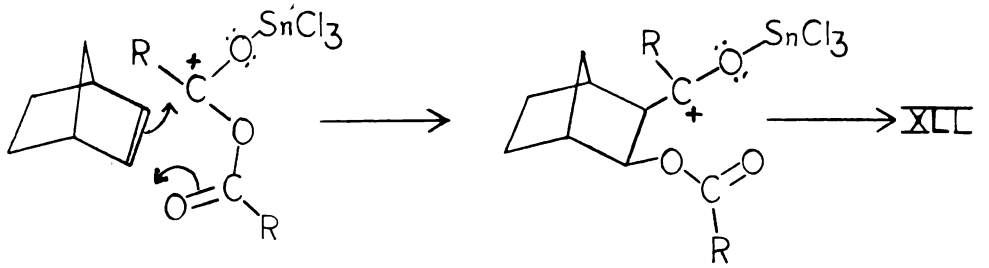
With respect to norbornene, then, two possible modes of addition might be expected. If the reaction involved an ionic intermediate similar to XXXIX, one might expect the formation of a rearranged product (XL). The rearranged product would not lose acetic acid as



XXXIX

XXXIX

readily as would the product from simple addition of acetic anhydride to the C_2 and C_3 positions. A second possible pathway suggested by Royals involved a cyclic intermediate (no carbonium ion intermediate). This could give rise to 2-acetylnorbornene, XLI, by loss of acetic acid during the work up.

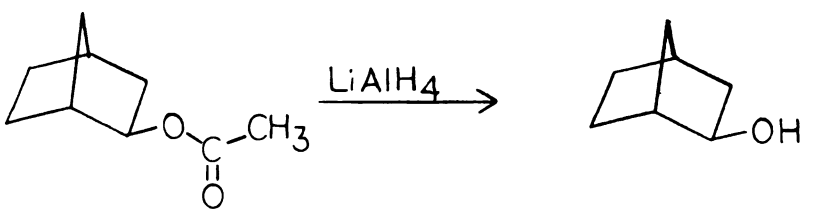


XLI

As suggested by Royals, acetic anhydride was added to a solution of norbornene and stannic chloride in methylene chloride. The exothermic reaction was maintained at room temperature by cooling in an ice bath. The distillable material obtained from this reaction contained three minor lower boiling substances and 88% of a colorless liquid, b.p. 69° at 6 mm., n_D^{25} 1.4569. A considerable amount of polymeric material was produced as with the acetyl chloride-aluminum chloride reaction. The product did not color upon standing at room

temperature and the refractive index remained constant over an extended period. The analyst suggested that the ascending carbon values of the microanalysis would indicate the possibility of changing composition (See experimental section). The constancy of the refractive index over an extended period would suggest that this was not the case. Rather surprisingly the data corresponded to neither one of the expected products. Structure XL would be expected to show two carbonyl absorptions in the infrared, one for the ester carbonyl and the other for the ketone. Structure XLI would be expected to show absorption around 6.1 μ attributable to the carbon-carbon double bond. All such phenomena were distinctly absent. The infrared spectrum (Figure 12) was characterized by two intense absorption bands, one at 5.82 μ (carbonyl stretching frequency) and a broader band from 8.05-8.14 μ (carbon-oxygen single bond stretching frequency). The n.m.r. spectrum (Figure 13) integrated very sharply for an H_{14} compound. Though the splitting patterns in norbornane derivatives are not very well defined, from the chemical shifts and the area under each peak the structure could be deduced as an acetoxynorbornane. A multiplet centered at τ 5.52 suggested a tertiary hydrogen adjacent to an acetoxy group. A rather broad peak at τ 7.82 was due to two tertiary bridgehead hydrogens and the very sharp singlet at τ 8.14 to the methyl hydrogens. The chemical shifts of the remaining eight hydrogens of the norbornane nucleus were quite close together but could be divided into three groups (5:2:1). The methylene bridge hydrogen anti to the acetoxy group should be less deshielded by the carbonyl than the other and would appear at higher fields (τ 8.98). The peak at τ 8.82 is

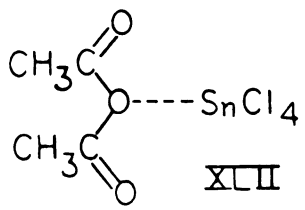
probably due to either of the pairs of similar exo and endo methylene hydrogens. The remaining multiplet is composed of the methylene group adjacent to the acetoxy group, the bridge methylene hydrogen syn to the acetoxy group (both types deshielded by the carbonyl group), and the remaining pair of similar methylene hydrogens (either exo or endo). Reduction of the acetoxynorbornane with lithium aluminum hydride to the known 2-exo-hydroxynorbornane established the position and configuration of the acetoxy group.



With the experimental evidence available one can at best conjecture as to the mechanism by which 2-exo-acetoxynorbornane is formed. From the nature of the product it seems to involve some type of nucleophilic attack by acetate ion, actual or potential, on a polarized double bond. Similarly, it could be pictured as an electrophilic attack by a polarized olefin on acetic anhydride. In an analogous reaction (50) very small amounts of cyclohexyl acetate were isolated as by-product in the synthesis of 1-acetylcyclohexene. The only experiment in which this by-product was formed in large amount was when cyclohexane was added to a mixture of acetic anhydride and stannic chloride.

Of interest in postulating a mechanism is the nature of the interactions between catalyst and olefin, and between catalyst and acetylating agent. It is probable that stannic chloride and acetic anhydride would interact in much the same way as aluminum chloride

and acetyl chloride (48). In a non polar solvent such as methylene chloride no discrete ions exist and the two reagents probably exist in the form of a donor-acceptor complex (XLII). In this complex the



XLII

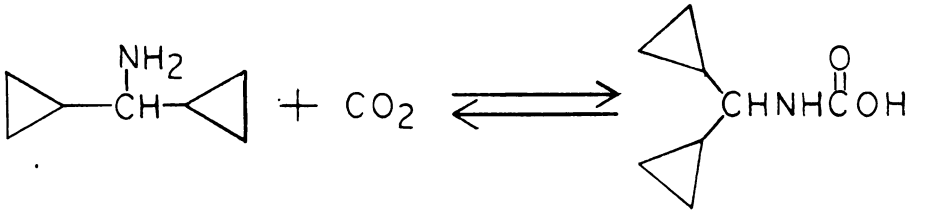
carbon-oxygen bond would be weakened. This would have the effect of lowering the activation energy for the reaction between complex and olefin. This type interaction, however, would favor formation of an α,β-unsaturated ketone.

The product can best be explained as resulting from a weak interaction between catalyst and olefin. Most studies of the interaction of Lewis acids with olefins were carried out in the presence of a third substance, a co-catalyst. Olah and Meyer (51) state that all reported examples of complex formation of olefins with Lewis acid halides or even with Bronsted acids in the absence of a co-catalyst can be interpreted as π-complexes. No ionic species are formed and hence the complexes are inactive as polymerization catalysts for excess olefins. Norbornene, however, is not a typical olefin in that the double bond is in a highly strained ring system. It is probably not necessary to postulate formation of an actual ion as the electrophilic reagent which attacks acetic anhydride. The electrophile could be pictured as a double bond polarized by stannic chloride. Further work is necessary to establish the nature of these interactions and the mechanism for this reaction.

III. Deamination of Dicyclopropylcarbinylamine

A. Discussion of Synthetic Methods

The synthesis of dicyclopropylcarbinylamine was attempted by three reaction paths. Dicyclopropyl ketone was the common starting material for each. Lithium aluminum hydride reduction of the oxime gave the amine in 77% yield. Exposure of this product to the atmosphere produced a white solid. A similar solid was produced in copious amounts when a piece of solid carbon dioxide was added to the amine. This solid was probably the unstable N-alkyl carbamic acid. When

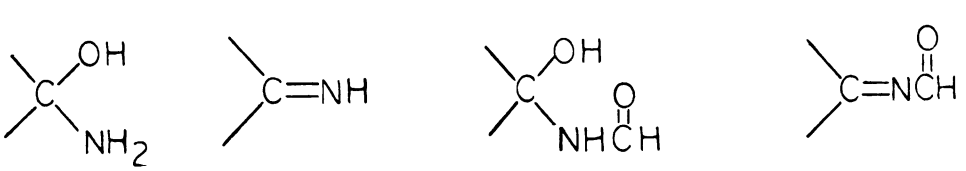


heated the solid decomposed without melting and upon standing at room temperature it would slowly disappear. The instability of carbamic acids is a well known fact since Bergmann's synthesis of peptides involves the decomposition of a carbamic acid to give the free amino acid and carbon dioxide. Gas chromatographic analysis of the amine indicated a fore shoulder (about 10%) which was very difficult to separate from the major product. Large samples decomposed in gas chromatographs. Fractional distillation through several columns was unsuccessful. Purification, essential to a study of the products of deamination, was achieved finally with the use of a spinning band column. The n.m.r. spectrum (Figure 18) was typical of cyclopropyl

compounds with complex multiplets at about τ 9.28 and τ 9.79 (cyclopropyl methinyl and methylene hydrogens respectively). The other methinyl hydrogen gave a distinct triplet at τ 8.43. The chemical shift of the amino hydrogens varied with concentration.

In a related reaction the oxime was catalytically reduced to the amine which was converted to N-dicyclopropylcarbinylacetamide by the solvent, acetic anhydride. The reduction was unusual in that the catalyst, platinum oxide, was susceptible to poisoning. Several portions of catalyst produced a larger amount of reduced product than one single portion. However, a point was reached before the theoretical amount of hydrogen was taken up when no further reaction occurred. When a bottle heater was used in an attempt to improve the yield, no reaction occurred other than reduction of platinum oxide. It was hoped that the solid amide could be obtained in a more pure form than the amine obtained from the hydride reduction. An acceptable analysis was obtained for the amide. Its n.m.r. spectrum (Figure 20) was as expected for an N-substituted acetamide. However, attempts to solvolyze the pure acetamide in aqueous and in methanolic sodium hydroxide were unsuccessful.

The third preparation was a Leuckart reaction (52) between dicyclopropyl ketone and ammonium formate. Several possible types of intermediates are shown below. No conclusive evidence was presented

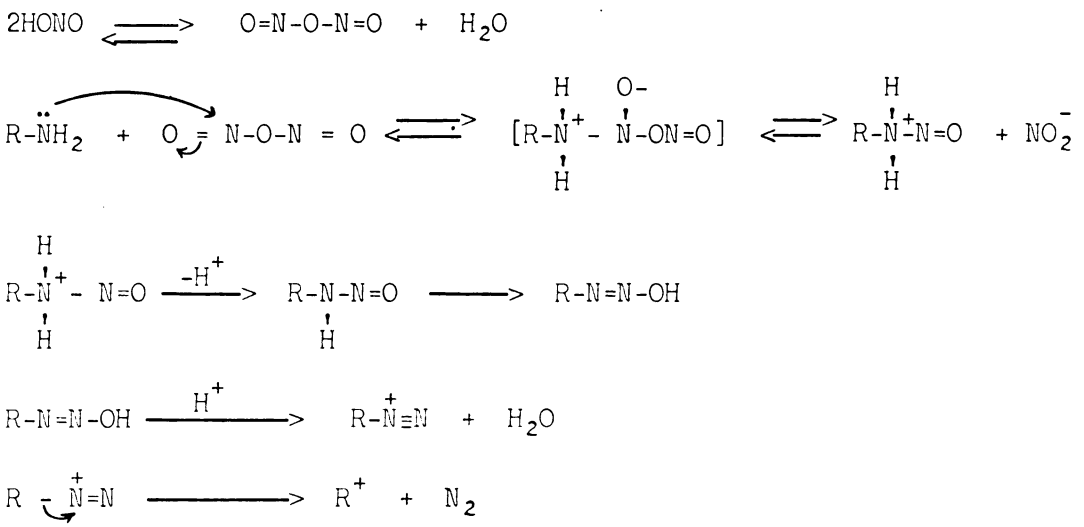


to favor one intermediate over the others. All would eventually produce N-dicyclopropylcarbinylformamide. Acidic hydrolysis of formyl derivatives is the preferred method usually giving higher yields in shorter reaction times. However, the presence of cyclopropyl rings precluded extensive refluxing in acidic media. Basic hydrolysis produced dicyclopropylcarbinylamine (44%) with an impurity similar to that from the metal hydride reduction. A modified procedure employing formamide and formic acid did not give this impurity but produced significant amounts of a secondary amine.

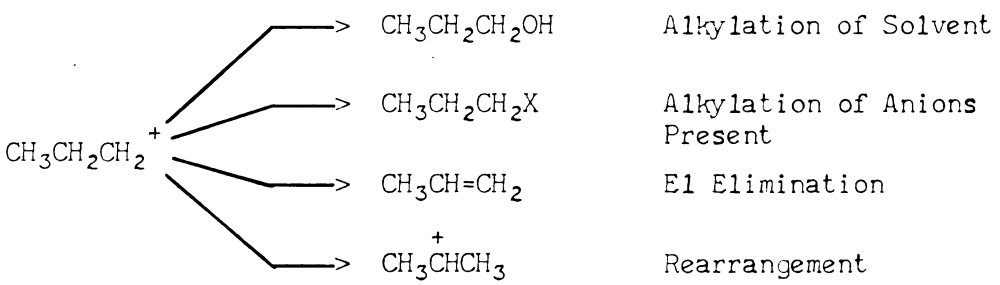
Dicyclopropylcarbinylamine-α-d_1 was prepared by reducing the oxime with lithium aluminum deuteride. Except for the presence of deuterium the product was similar in all respects to the non-deuterated sample. Integration of the methinyl hydrogen peaks indicated about 4.5% non-deuterated material corresponding to the purity of the lithium aluminum deuteride.

B. Deamination Study

The reaction of nitrous acid with aliphatic primary amines usually produces such a variety of products that it has little substantial synthetic value. The value of the reaction lies in that it provides information as to what kinds of carbonium-ion rearrangements may be expected in a given system. A rather complete discussion of the mechanism of this reaction is given by Roberts and Caserio (53). They propose the following reaction scheme for deamination of an aliphatic primary amine:



The aliphatic diazonium salt can be viewed as a combination of a carbonium ion and nitrogen which would be expected to decompose rather readily due to the considerable stability of nitrogen. In fact, they decompose so rapidly in aqueous solution that their presence can only be inferred from the fact that intermediates are formed which undergo typical reactions of carbonium ions. Roberts and Caserio state that "the reaction of a primary amine with nitrous acid is perhaps the most infallible way known to generate carbonium ions, even those which cannot be formed by solvolysis reactions of halides because of negligible S_N1 reactivity in all other known conditions." The case of the n-propyl carbonium ion may be used to illustrate the variety of reactions which may occur.



The rearranged ion undergoes reactions similar to those shown for the n-propyl cation.

Rather than the free carbonium ion, Streitwieser (54,55) has proposed that the diazonium ion is the branching point of the competing reactions. In support of this the deamination of 1-aminobutane-1-d_1 is cited. Deamination with nitrous acid in acetic acid produces a 2:1 ratio of n-butyl acetate and sec-butyl acetate. Comparison of the optical activity of n-butyl acetate obtained in this reaction with optically pure material indicated 69 ± 7% inversion of configuration and 31 ± 7% racemization. He proposed that the inversion was a result of direct displacement on the alkyl diazonium ion by solvent.

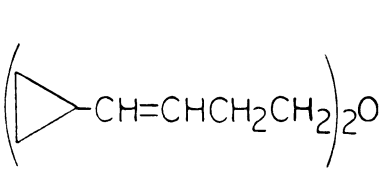
In this investigation an initial deamination was run in glacial acetic acid rather than in dilute aqueous media. It was anticipated that the acetates would have lower boiling points and viscosities than the corresponding alcohols. This would facilitate separation and identification. Gas chromatographic analysis (See Figure 23) of the products indicated the presence of twelve components in varying amounts. Most of the peaks were rather poorly resolved. No further attempt was made to identify these products.

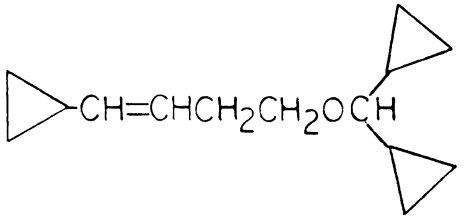
A dilute aqueous perchloric acid solution of dicyclopropylcarbinylamine was treated with sodium nitrite and the products steam distilled into a flask containing potassium carbonate. Gas chromatographic analysis (See Figure 23) indicated the presence of three products in the ratio of approximately 11:1:4. Though the retention time of the third component was considerably longer than that of the other two, distillation did not effectively separate the mixture. The major two

components were isolated by gas chromatography in sufficient quantity for identification. The n.m.r. and infrared spectra of the first component were identical with those of an authentic sample of dicyclopropylcarbinol. The second component was not identified. The infrared spectrum of component three had absorption bands at 3.28, 3.36, 9.9, 10.8, and 11.2 μ. These are considered by several authors to be indicative of the cyclopropane ring, but are by no means conclusive in themselves (56,57). There were no absorption bands in the alcohol (2.6-3.0 μ) or carbon-carbon double bond (6.0-6.3 μ) regions. The n.m.r. spectrum was quite revealing. It was characterized by three regions of absorbancy, two complex multiplets in the τ 9.0-10.0 region characteristic of the cyclopropane methinyl and methylene hydrogens and a triplet centered at τ 7.32 attributable to a tertiary hydrogen adjacent to oxygen. The area under the peaks showed the hydrogens in a ratio of 1:2:8 (lower to higher fields). No other bands were present. On this basis the compound was assigned the structure of bis-dicyclopropylcarbinyl ether.

Deamination of dicyclopropylcarbinylamine-α-d_1 by a similar procedure gave a similar product mixture. Of interest was the complete absence of methinyl hydrogen absorption at τ 7.53, conclusive evidence that there was no proton shift within the carbonium ion intermediate. An infrared spectrum was obtained for the unidentified product. The customary bands indicative of a cyclopropane ring were present. There was a carbon-deuterium band at 4.85 μ and a band at 6.13 μ indicative of a carbon-carbon double bond. Though there was a very weak band at 2.8 μ, 4-cyclopropyl-3-butene-1-ol was ruled out by comparison of

the retention time of this material with that of an authentic sample. There was not sufficient material available for an n.m.r. spectrum. Two possibilities which have not been excluded are bis-4-cyclopropyl-3-butene-1-yl ether and 4-cyclopropyl-3-butene-1-yl dicyclopropylcarbinyl ether.





The possibility was considered that the symmetrical ether and the unidentified product arose through a secondary reaction from dicyclopropylcarbinol. It was initially thought that the conditions of the reaction mixture could be approximated by steam distilling dicyclopropylcarbinol from dilute (0.3N) perchloric acid. The organic material recovered (85%) consisted of one major component (75-81%), 2-cyclopropyltetrahydrofuran, and several minor components whose composition varied in the course of several runs. Of these the major one was 4-cyclopropyl-3-butene-1-ol. The structure of 2-cyclopropyltetrahydrofuran was shown by its infrared (Figure 29) and n.m.r. (Figure 30) spectra. The structure assigned to the alcohol was consistent with the infrared (Figure 31) and n.m.r. (Figure 32) spectra. None of these corresponded to products obtained from the deamination reaction. They were analogous to those reported by Favorskaya (34) from dimethylcyclopropylcarbinol (cf. to page 15). Similar products were obtained by Hart and Law (58) when dicyclopropylcarbinol was heated with concentrated sulfuric acid. A mechanism for formation of these products is shown in Figure 2.

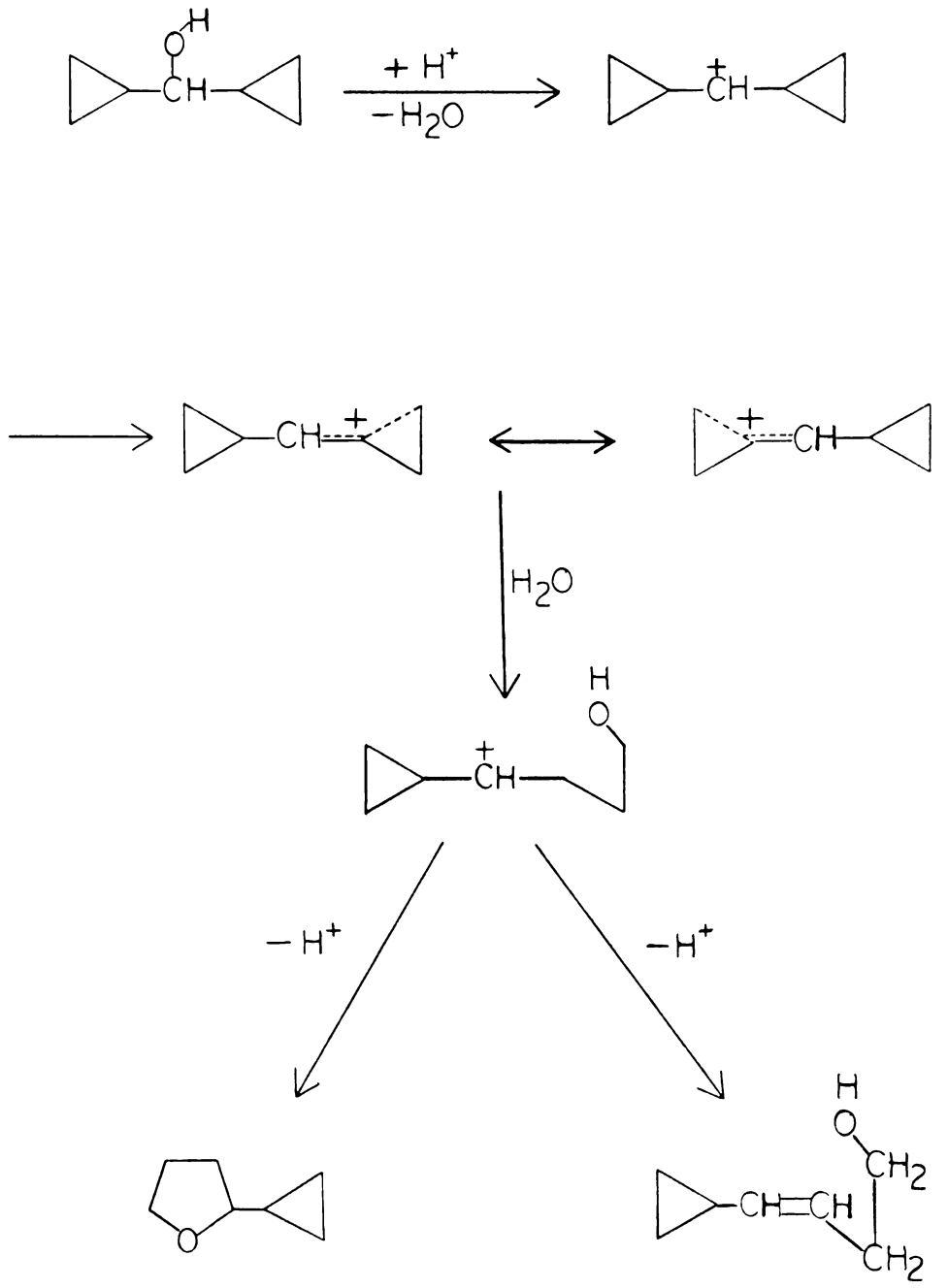
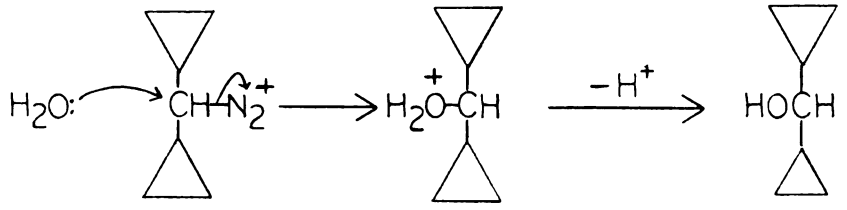


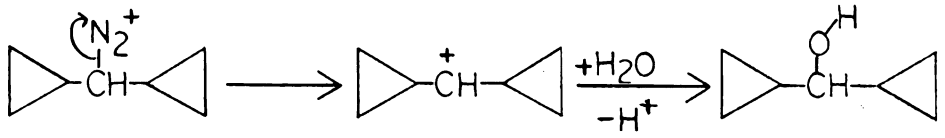
Figure 2. Mechanism for the Acid Catalyzed Rearrangement of Dicyclopropylcarbinol.

The previous experiment failed to simulate the deamination reaction mixture in that the effect of the amine was not taken into account. To rectify this ammonium hydroxide was used to simulate the amine in the aqueous perchloric acid. Crude organic material was recovered in 94% yield from the steam distillation. The identical components were obtained from this reaction as were obtained from the deamination experiment. This would suggest that dicyclopropylcarbinol was the only product obtained directly from the deamination of dicyclopropylcarbinylamine and that components two and three arose from the alcohol in the course of the work-up.

Several explanations could be offered for the fact that dicyclopropylcarbinol is the only product directly obtained from the deamination of dicyclopropylcarbinylamine. The simplest argument would be that proposed by Streitwieser. That in fact, no free carbonium is actually formed, but rather, the alcohol results from direct displacement on the alkyl diazonium ion by solvent.



Alternately, formation of the free carbonium ion could lead directly to the alcohol by attack of solvent at the carbinyl carbon.



As stated previously in the introduction, the distribution of charge in ions of this type is of great importance since carbonium ions tend to react most rapidly with solvent at the positions of greatest charge density. Whether or not the charge is delocalized on the two rings as is the case in solvolysis reactions of corresponding compounds is not known. If it is delocalized, principal charge distribution must involve resonance forms in which the positive charge is on the carbinyl carbon. It is not possible to decide from available facts whether the diazonium salt or the carbonium ion serves as the intermediate in this reaction. It is possible that both species are involved.

IV. An N.M.R. Study of Isopropyl Groups in Selected Compounds

This portion of the thesis was not intended originally to be a study of the n.m.r. of isopropyl groups in selected compounds. Rather, the sole purpose of using compounds containing isopropyl groups was to develop technique in carrying out certain reactions. When sufficient profiency was attained, corresponding dicyclopropyl compounds were to be prepared. As a matter of course, n.m.r. spectra were taken of these isopropyl compounds which proved to be of interest in themselves.

Diisopropylcarbinylamine was prepared by two procedures: a Leuckart reaction and a lithium aluminum hydride reduction of the corresponding ketoxime. The N-alkylformamide, prepared by refluxing diisopropyl ketone and ammonium formate, was hydrolyzed to give diisopropylcarbinylamine. The infrared spectrum (Figure 33) showed two bands at 2.96 μ and 3.02 μ characteristic of a primary amine and two bands at 7.23 μ and 7.31 μ characteristic of an isopropyl group (59). The n.m.r. spectrum (Figure 34) shows an interesting, and at first unexpected, pair of doublets for the methyl hydrogens centered at τ 9.13 and τ 9.16 units. These will be explained subsequently. The n.m.r. spectrum deteriorated with time due to the formation of an uncharacterized crystalline product. This occurred even in freshly purified carbon tetrachloride. An explanation for this may be found in the work of Foster (60) who reported the continuous formation of amine hydrochlorides from solutions of amines in carbon tetrachloride.

The other procedure for preparing diisopropylcarbinylamine began with diisopropyl ketone. Steric hindrance to formation of the oxime

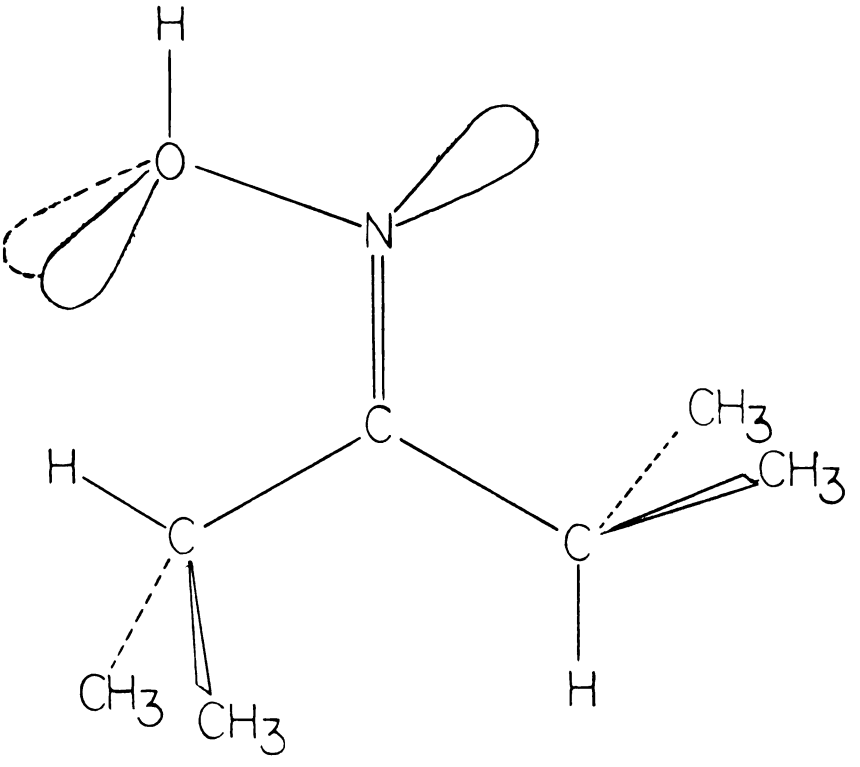
was apparent as 30% of unreacted ketone was recovered after six hours reflux. This is not too surprising as t-butyl ketones do not form the oxime at atmospheric pressure. Multiplets at τ 6.88 and τ 7.51 in the n.m.r. (Figure 36) spectrum of the oxime were assigned to the methinyl hydrogens, distinctly different because of their relationship to the oxime grouping. More unusual were the two doublets at τ 8.87 and τ 8.92 similar in appearance to those observed in the amine. At lower temperatures (Figure 38) this pair of doublets began to coalesce until at -50° it appeared as a single, though somewhat broader, doublet. These also will be discussed subsequently. Lithium aluminum hydride reduction of diisopropyl ketoxime afforded a sample of pure diisopropylcarbinylamine, identical in all respects with that obtained by the Leuckart reaction.

The amine was converted to the corresponding benzamide by the usual Schotten-Bauman procedure. The n.m.r. spectrum (Figure 40) again showed a pair of doublets at τ 9.03 and τ 9.09 for the methyl hydrogens.

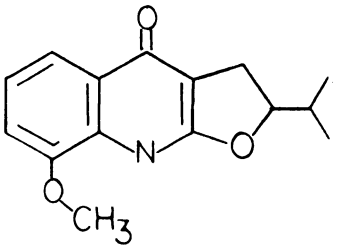
Samples of diisopropyl ketone and its lithium aluminum hydride reduction product, diisopropylcarbinol, were purified by gas chromatography for n.m.r. analysis. The n.m.r. spectrum of the ketone (Figure 41) was as expected, a heptet at τ 7.31 (methinyl hydrogen) and a doublet at τ 8.98 (methyl hydrogens). In view of the spectrum obtained for the amine, that of diisopropylcarbinol (Figure 42) unexpectedly showed a single doublet at τ 9.12.

The pairs of doublets which were observed in the n.m.r. spectra of the ketoxime, amine and benzamide, though similar in appearance

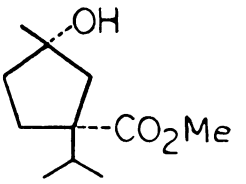
in all three cases, are due to two distinctly different phenomena. The n.m.r. spectrum of diisopropyl ketoxime was first reported by Lustig (61) in a study of syn-anti isomerism in ketoximes. He noted that "the case of diisopropyl ketoxime is exceptional, not only because two septets appear in CCl_4 solution also, but because two $(CH_3)_2CH$- doublets, 2.5 c.p.s. apart, are observed. Steric hindrance of some kind may be invoked to explain the non-equivalence of isopropyl groups or positions." It has been shown by Karabatsos and Taller (62) in a study of syn and anti isomers of ketoximes that α-hydrogens which are syn to the oxime grouping appear at lower fields than do those which are anti and that β-hydrogens syn to the oxime grouping appear at higher fields than do those which are anti. Because of the diamagnetic anisotropy of the oxime group those hydrogens, α or β, which are syn to the oxime group experience a different resultant magnetic field than do those which are anti. It was observed that the chemical shift of the methyl hydrogens was temperature dependent (Figure 38). Specifically, the doublet due to the methyls syn to the oxime shifted to lower fields as the temperature was lowered until at -50° it coalesced with the doublet of the anti methyl hydrogens. Groups syn to the oxime group should be more sterically hindered so that, as the temperature is lowered, they would encounter resistance to rotation. The most stable conformation of the molecule is probably that which has the syn methinyl hydrogen s-cis to the oxime and the anti methinyl hydrogen s-trans.



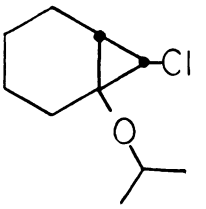
The magnetic nonequivalence observed in diisopropylcarbinylamine (doublets at τ 9.13 and τ 9.16) and N-diisopropylcarbinyl benzamide (doublets at τ 9.03 and τ 9.09) is probably due to an entirely different phenomenon. The case of the amine is probably identical to that of the amide though the change in chemical shift is twice as great in the latter. Whereas in the oxime case methyls on the same side of the oxime group were equivalent, in the amine and amide methyls of a given isopropyl group are nonequivalent. Such magnetic nonequivalence has been observed by a number of workers (63,64,65,66,67) in compounds shown below.



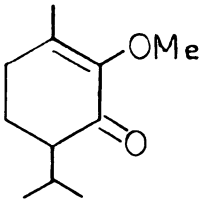
XLIII (63)



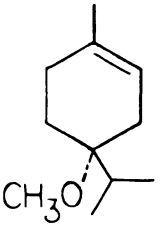
XLIV (64)



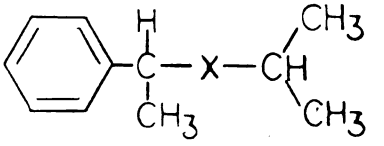
XLV (67)



XLVI (64)



XLVII (64)



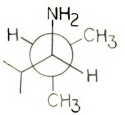
where X is from 0-3 atoms

XLVIII (66)

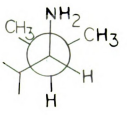
Two arguments have been proposed to explain this phenomenon. The one most usually invoked is that magnetic nonequivalence is due to differences in conformational populations (68,69). The other is that in certain molecules there is an intrinsic asymmetry such that, when the isomers are all accidentally of equal energy, or even if all rotational conformations had equal residence times, i.e., internal rotation is free, a chemical shift would be possible (65,70,71). House (64) ascribed the nonequivalence in XLIV to restricted rotation of the isopropyl group in the cis isomer, which restricted rotation was absent in the trans isomer. Goodwin (63) presented essentially the same argument. From examples cited in the literature the question seems to be not whether intrinsic asymmetry or conformational preference alone is responsible for magnetic nonequivalence, but rather how

much is due to intrinsic asymmetry. In general, conformational preference seems to make the major contribution to magnetic nonequivalence.

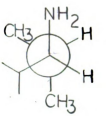
The three conformers of diisopropylcarbinylamine may be viewed as follows:



XLIX



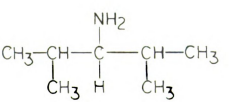
L



LI

If one considers the A-values (72) of the groups as indicative of their conformational requirements ($-CH(CH_3)_2$, 2.1; $-CH_3$, 1.7; NH_2, 1.2), XLIX is seen to be of lower energy than L and LI , which are almost of comparable energy. Hence, one would expect that the isopropyl group would spend an unequal time in the various conformations.

When the structure of diisopropylcarbinylamine is compared with other compounds which have shown a similar magnetic nonequivalence, it is noticed that the former is unique in that there is no asymmetric center in the molecule. An asymmetric molecule is evidently not a

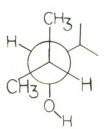


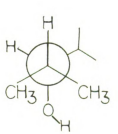
requirement for magnetic nonequivalence. However, when rotation of the isopropyl group about the C_2-C_3 bond is considered, it is noted

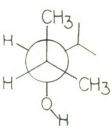
that there is still an intrinsic asymmetry in the environments of the two methyl groups.

The greater change in chemical shift observed in the amide could be ascribed to either argument. Surely, the steric requirement of the amide group is greater than that of an amino group, and hence, the molecule will experience a greater conformational preference. Similarly, one could argue that addition of a benzamide group increases the magnetic anisotropy about the C_2-C_3 bond and hence the increased change in chemical shift was due to an increased intrinsic asymmetry. The present state of knowledge is such that it is not possible to weight properly the effect of each argument.

In view of the magnetic nonequivalence of the methyl groups in diisopropylcarbinylamine, the absence of this phenomenon in the corresponding carbinol was somewhat unexpected. The various conformations for diisopropylcarbinol showing rotation about the C_2-C_3 bond are shown below. It would seem that whatever intrinsic asymmetry was present in







the amine should also be present in the alcohol. However, if conformational preference is a controlling factor, i.e., much more significant than intrinsic asymmetry, then the relative size of the amino and hydroxy groups should be important. It is a well-known fact that the atomic radius of elements decreases as one proceeds to the right in a given row in the periodic chart, i.e., oxygen is smaller than nitrogen.

The other difference between the two groups is that the hydroxyl group has two lone pairs and one hydrogen atom whereas the amino group has one lone pair and two hydrogens. Though it may not be exactly correct to assume that a lone pair on oxygen has the same steric requirements as a lone pair on nitrogen, the difference should not be great. Several workers (73,74,75,76) have recently shown both experimentally and theoretically that the hydrogen on nitrogen is larger than the lone pair on nitrogen. The A-value for hydrogen on the nitrogen of piperidine is 0.4. These arguments would suggest that the steric requirement of the hydroxyl group is significantly smaller. This is in agreement with the fact that the best A-value for the hydroxyl group is 0.7, about one half that for the amino group (1.2 in an aprotic solvent). The absence of magnetic non-equivalence in the carbinol would suggest then that conformational preference is of greater importance than is intrinsic asymmetry.

EXPERIMENTAL

I. Norbornene Experiments

A. Aluminum Chloride-Acetyl Chloride System

1. Acetylation of Norbornene

Into a 500-ml., three-necked flask equipped with dropping funnel, stirrer, thermometer, and a calcium chloride-phosphorus pentoxide drying train were introduced 53.4 g. (0.40 mole) of anhydrous aluminum chloride and 120 ml. of methylene chloride. A solution of 31.4 g. (0.40 mole) of acetyl chloride in 60 ml. of methylene chloride was added over 1.3 hours, keeping the temperature below 10° by means of a salt-ice bath. After stirring for 3.5 hours, the yellow, slightly cloudy solution was filtered through a scintered glass funnel into a similarly equipped flask. While maintaining the resulting clear solution below 10°, a solution of 35.3 g. (0.38 mole) of norbornene (commercial norbornene previously twice distilled from sodium) in 80 ml. of methylene chloride was added over a two hour period and then stirred for an additional 45 minutes. During the time of addition and stirring the solution took on a deep wine-red color. The reaction mixture was hydrolyzed by pouring with stirring onto a mixture of ice and 75 ml. of concentrated hydrochloric acid. The aqueous layer was separated and extracted with two 50-ml. portions of methylene chloride. The combined methylene chloride layers were washed successively with three 50-ml. portions of water, two 50-ml. portions of 10% sodium carbonate solution, and one 50-ml. portion of water, and dried over magnesium sulfate. After removal of the solvent, the residue was distilled under reduced pressure through a short Vigreux column to

yield two fractions of a colorless liquid: 1.) 23.6 g., b.p. 77-78.5° at 1.4 mm, n_D^{25} 1.4955 and 2.) 16.6 g., b.p. 83-7°0 at 1.2 mm., n_D^{25} 1.4962. Infrared spectra of the two fractions were nearly identical. There remained a residue, 12.7 g., which solidified into a glass. The product decomposed rather rapidly on standing at room temperature and even decomposed slowly in a refrigerator. Redistillation of chloroketone from several acetylation experiments gave a colorless liquid, b.p. 76-79° at 1.0 mm., n_D^{25} 1.4935-1.4940, literature value (77): b.p. 70-71° at 1.0 mm., n_D^{25} 1.4929-1.4943. Considerable chloroketone was lost through decomposition and polymerization during the distillation process. The infrared spectrum of the chloroketone is shown in Figure 3 and the gas chromatograph in Figure 4.

Two derivatives, the 2,4-dinitrophenylhydrazone and semicarbazone, of the chloroketone were prepared. The 2,4-dinitrophenylhydrazone after one recrystallization melted at 152-167°. After the fifth recrystallization from an alcohol-water mixture it melted at 179.8-180.5°.

Anal. Calc'd for $C_{15}H_{17}ClN_4O_4$: C, 51.07; H, 4.86; N, 15.88; Cl, 10.55.

Found: C, 51.20; H, 4.86; N, 16.08; Cl, 9.79, 9.54.

The semicarbazone, recrystallized from a methanol-water mixture, melted at 176-177°.

Anal. Calc'd for $C_{10}H_{16}ClN_3O$: C, 52.28; H, 7.02; N, 18.29; Cl, 15.44.

Found: C, 52.04, 52.28; H, 6.65, 6.74; N, 18.29; Cl, 14.77, 14.77.

Attempts to prepare the oxime were unsuccessful.

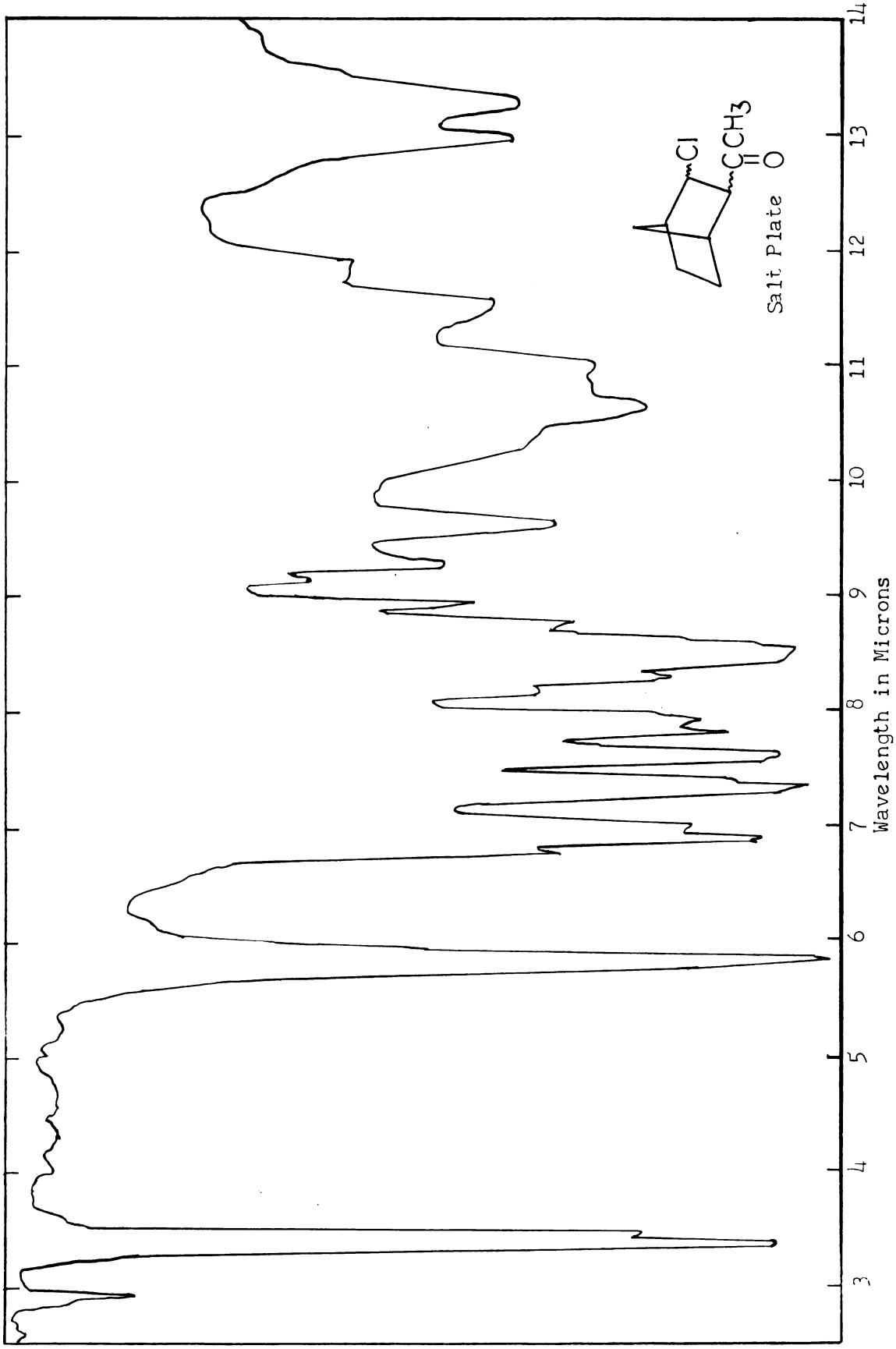


Figure 3. The Infrared Spectrum of the Chloroketone Obtained from the Acylation of Norbornene with Acetyl Chloride.

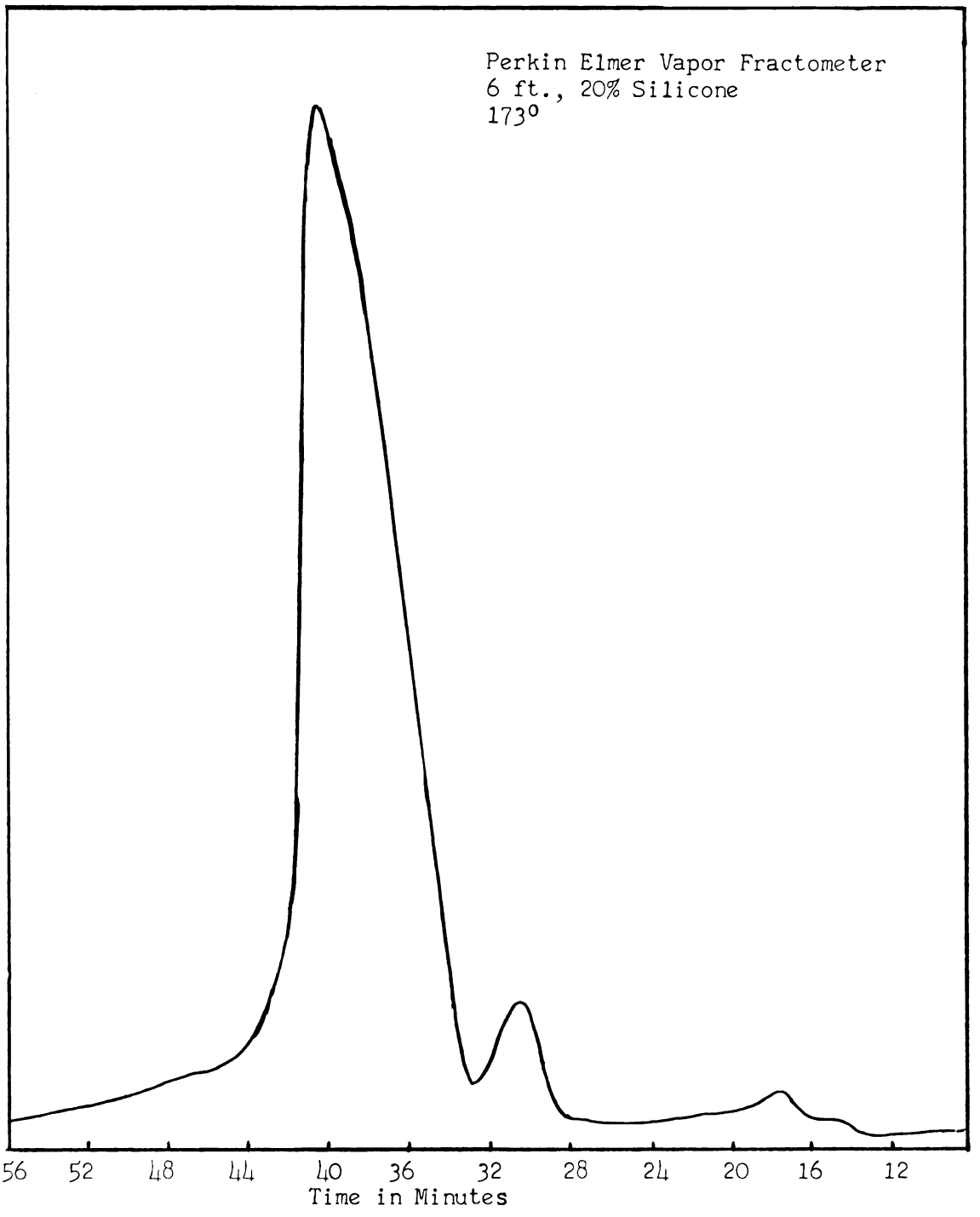


Figure 4. The Gas Chromatograph of the Chloroketone Obtained from the Acylation of Norbornene with Acetyl Chloride.

2. Haloform Oxidation of Acetylation Product

Sodium hypobromite was prepared by adding 139 g. (0.87 mole) of bromine to an ice-cold solution of 116 g. (2.9 mole) of sodium hydroxide in 750 ml. of water. The solution was added dropwise to 50 g. (0.29 mole) of chloroketone, obtained from acetylation of norbornene, contained in a two-liter flask. The flask was equipped with a condenser, stirrer, thermometer, and dropping funnel. During the one hour addition period the temperature was maintained below 10°. After stirring for 3.5 hours more, the opaque white solution was heated until the temperature reached 45°. As the reaction mixture began to darken, heating was discontinued. The solution was cooled and washed with ether. The aqueous layer was treated with sodium bisulfite, acidified to Congo red with concentrated hydrochloric acid, and extracted with ether. The preceding process was repeated, i.e., the ether solution was washed with several portions of 10% sodium hydroxide, the aqueous layer separated and acidified to Congo red with concentrated hydrochloric acid, and finally extracted with ether. The ether extracts were combined, dried over magnesium sulfate, and the ether evaporated. The product (30 g., 59%) was at first a viscous oil. Upon cooling and scratching the walls of the flask, it began to crystallize. At room temperature it had the appearance of a white slushy ice. The infrared spectrum is shown in Figure 5.

All other attempted haloform reactions gave only a very viscous oil. Attempts to crystallize this oily product from ligroin and from benzene were unsuccessful. Partial success was attained when water was used as a crystallization solvent. Though the vast majority of the

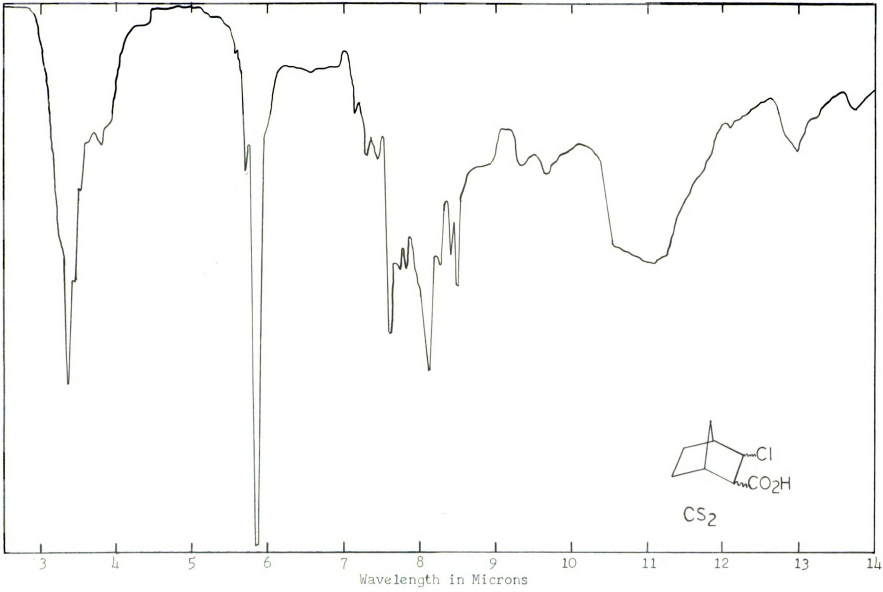


Figure 5. The Infrared Spectrum of the Chloroacids Obtained from the Haloform Oxidation of the Chloroketone.

acid came out again as an oil, a small amount (< 0.3 g.) of crystals was obtained. The melting point was observed through a microscope. A portion of the crystals melted at 147-149° while the larger amount melted at 160-163.5°.

The extent of the mixture was determined by analyzing the methyl esters by gas chromatography. Diazomethane prepared from N-methyl-N-nitrosourea according to the procedure in Organic Syntheses (78) was allowed to react with the haloform oxidation product. The gas chromatograph of the methyl esters is shown in Figure 6.

3. Removal of Halogen Atom

a. Attempted Dehydrohalogenation of Chloroketone. To 65 ml. of tert.-butyl alcohol in a 100-ml. round-bottomed flask was added 2.8 g. of potassium metal. The reaction mixture was refluxed until all potassium had reacted. Upon addition of 8.6 g. (0.05 mole) of chloroketone the solution became quite opaque and progressively dirty orange. The reaction mixture was refluxed for 10 hours and cooled. After adding water to the mixture, it was extracted with ether. The combined ether extracts were washed with water, dried over magnesium sulfate, and the solvent removed with a Rinco evaporator. Attempted distillation of the residue under reduced pressure yielded a small amount of unchanged starting material while the rest polymerized in the distilling flask.

A second attempt employing a slurry of potassium tert.-butoxide in ether was partially successful in that a small amount of chloride ion was detected. However the major portion of starting material was unchanged.

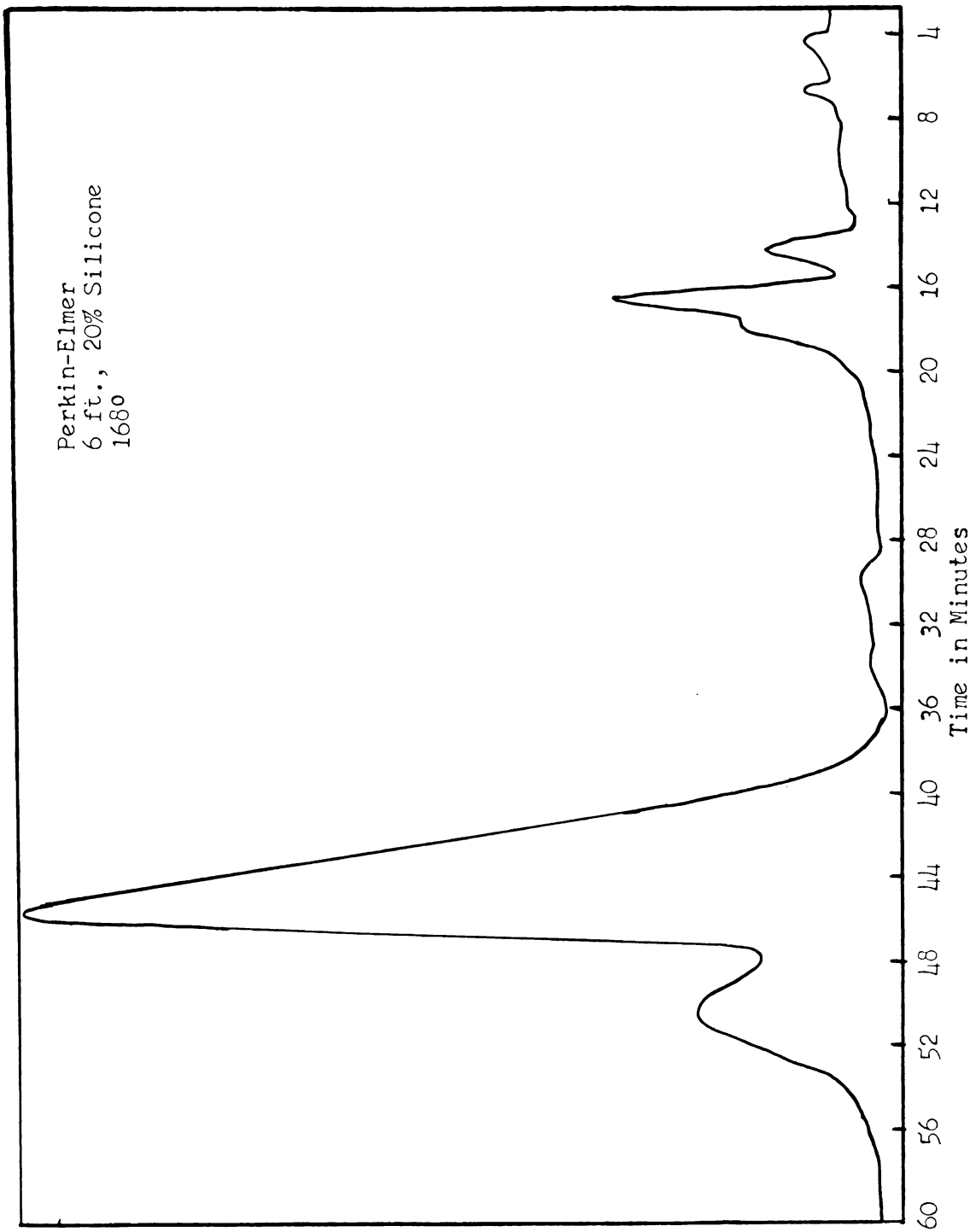


Figure 6. The Gas Chromatograph of the Methyl Esters of the Chloroacids Obtained from the Haloform Oxidation of the Chloroketone.

b. Attempted Reductive Dehalogenation of Chloroacids

1.) Phosphorus-Hydriodic Acid Method (79): To 25 ml. of hydriodic acid (sp. gr. 1.5) was added 0.8 g. of red phosphorus and 2.5 g. (0.015 mole) of oily chloroacid obtained from a haloform reaction on the chloroketone. After heating on a steam bath for 21 hours, the mixture was cooled, filtered through a scintered glass filter, and washed successively with water and ether. The ether layer was separated and extracted with several portions of 10% sodium hydroxide solution. Acidification of the aqueous layer produced an oily acid shown by sodium fusion to be still rich in chlorine.

2.) Zinc-Acetic Acid-Hydrogen Chloride Method (80): A 300-ml. three-necked flask was fitted with stirrer, condenser, and gas inlet tube. To a solution of 5.0 g. (0.029 mole) of chloroacid in 75 ml. of glacial acetic acid was added 10 g. of zinc dust. The solution was saturated with hydrogen chloride gas and a gentle reflux maintained for 24 hours. Periodically additional hydrogen chloride was bubbled through the system. The reaction mixture was filtered, 500 ml. of water was added to the filtrate, and the aqueous layer extracted with ether. After the combined ether extracts were washed with water and dried over magnesium sulfate, the solvent was evaporated on a steam bath to give 3.4 g. of oily acid, still containing chlorine.

c. Attempted Hydrogenolysis of Chloroketone. A solution of 10 g. (0.058 mole) of chloroketone in 100 ml. of 95% ethanol was placed in a Paar low pressure hydrogenation bottle with 0.222 g. of platinum oxide. The system was purged of oxygen, placed under an initial pressure of

30 p.s.i. and agitation begun. After three hours the pressure had dropped 4 p.s.i., equivalent to one mole of hydrogen per mole of chloroketone. Additional agitation for twelve hours caused no further pressure drop. The platinum black was removed by filtration and the solvent was distilled through a Vigreux column. Distillation of the residue under reduced pressure gave 9.0 g. of an alcohol containing chlorine, b.p. 84-99° at 0.6 mm., n_D^{25} 1.5018.

In a procedure identical to the previous one except that 1 ml. of concentrated hydrochloric acid (42) was added to the reaction mixture, similar results were obtained. Distillation of the residue gave a quantitative yield of a chloroalcohol, b.p. 80-94° at 0.8 mm., n_D^{25} 1.4996-1.5033. Analysis by gas chromatography indicated a similar multiplicity of peaks as was observed with the original chloroketone and the methyl esters of the acids derived from the chloroketone.

d. Raney Alloy (44) Reduction of Chloroalcohol. The product obtained from the attempted hydrogenolysis of chloroketone was used as starting material for this reaction. Similar results were obtained when chloroketone was used as starting material. In a three liter flask equipped with stirrer, dropping funnel, and condenser were placed 21.9 g. (0.125 mole) of chloroalcohol, 200 ml. of ethanol, and 130 g. of Raney alloy. Over a four hour period one liter of 10% sodium hydroxide solution was added. The initial reaction was so vigorous that cooling was required to prevent loss of reagents. After refluxing the reaction mixture for an additional four hours, it was cooled and filtered. When trituration of the Raney alloy seemed ineffective in removing the product completely, steam distillation was used. The

previous filtrates and steam distillate were extracted with pentane and the combined pentane extracts dried over magnesium sulfate. The solvent was evaporated into the hood through a glass-packed column and the residue was distilled under reduced pressure through a 25 cm. vacuum-jacketed Vigreux column. Gas chromatographic analysis of the fractions collected showed a 76% yield of methylnorbornylcarbinol, b.p. 70-5° at 2.8 mm., n_D^{25} 1.4837. The infrared spectrum is shown in Figure 7. Fifteen percent of the isomeric chloroalcohols was recovered unchanged.

Anal. Calc'd for $C_9H_{16}O$: C, 77.09; H, 11.50.

Found: C, 76.81, 76.77; H, 11.39, 11.42.

e.) Reduction of Chloroketone with Sodium and tert.-Butyl Alcohol (43). To 125 ml. of tert.-butyl alcohol were added 10 g. (0.058 mole) of chloroketone and 10 g. of finely sliced sodium. The mixture was refluxed for 24 hours. The alcohol solution was washed with an aqueous salt solution and the organic solution concentrated. The organic layer was taken up in pentane, washed with water, and dried over magnesium sulfate. After removal of the solvent by distillation, the residue was distilled under reduced pressure to give 4.3 g. (54%) of methylnorbornylcarbinol, b.p. 62-4° at 1 mm., n_D^{25} 1.4832-1.4840. There was recovered by distillation 0.8 g. of unchanged starting material and a residue of 2.29 g. remained.

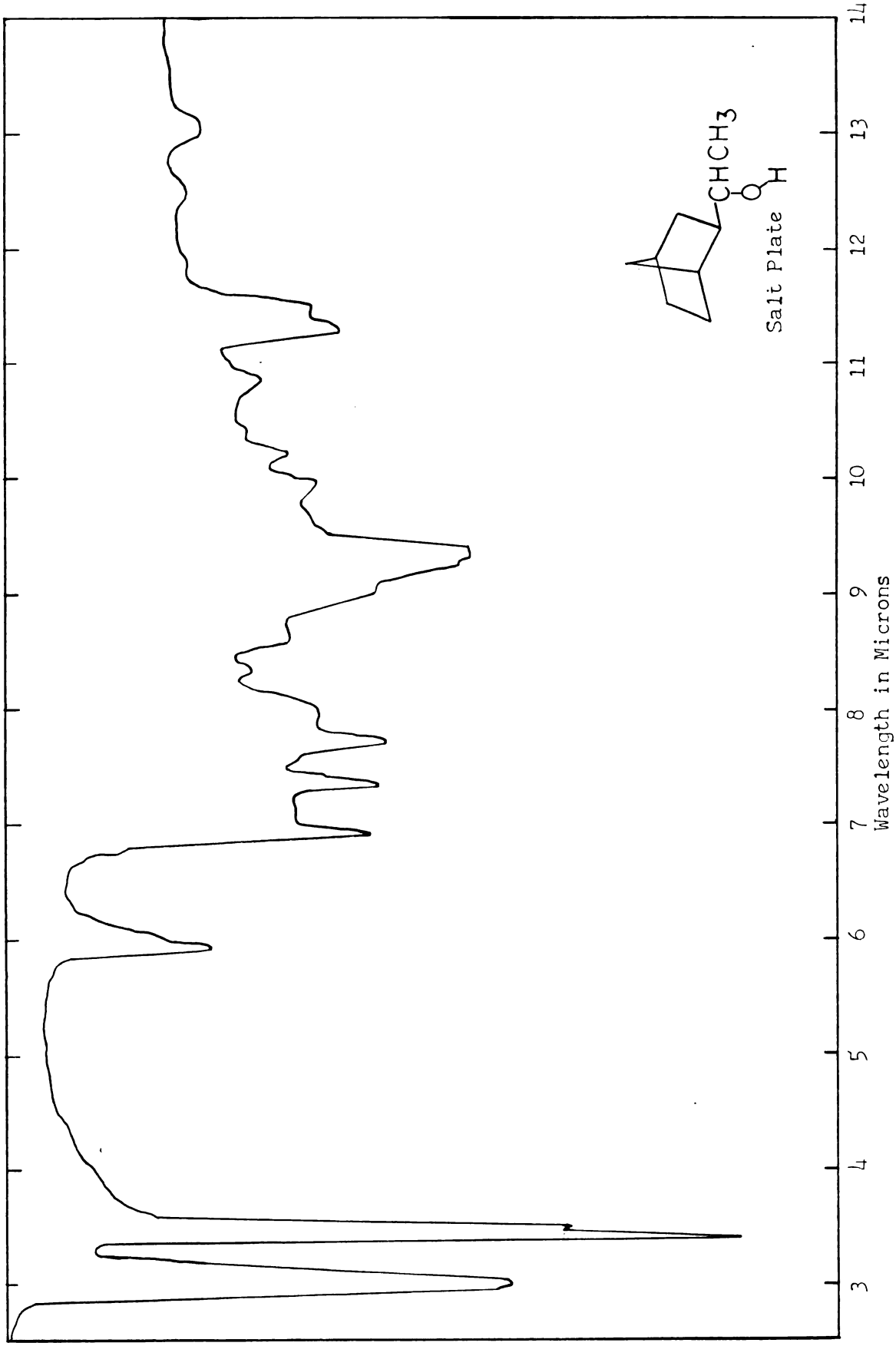


Figure 7. The Infrared Spectrum of Methylnorbornylcarbinol.

4. Chromic Acid Oxidation (81) of Methylnorbornylcarbinol

A solution of the Raney alloy reduction product, methylnorbornylcarbinol, 3.50 g. (0.025 mole) in 20 ml. of ether, was placed in a 100-ml. round-bottomed flask equipped with magnetic stirrer, reflux condenser, and addition funnel. A chromic acid solution, prepared by dissolving 2.7 g. of sodium dichromate dihydrate in 2.0 ml. of concentrated sulfuric acid diluted to 25 ml., was added to the stirred ether solution. An ice bath was used to maintain the temperature at 25°. After addition was complete, the reaction mixture was stirred for 2.5 hours. The upper ether layer was separated, the aqueous layer was extracted with two 10-ml. portions of ether, and the combined ether layers washed with a saturated sodium bicarbonate solution and several small portions of water. After drying over magnesium sulfate, the solvent was distilled through a glass-packed column. The residue was distilled under reduced pressure from a small Claisen-type flask to give three fractions: (1) 0.79 g. of ketone, b.p. 70° at 7.2 mm., n_D^{25} 1.4703; (2) 0.87 g., b.p. 70-72° at 7.2 mm., n_D^{25} 1.4710; and (3) 0.43 g., b.p. 72-3° at 7.2 mm., n_D^{25} 1.4710. The infrared and n.m.r. spectra shown in Figures 8 and 9 are identical with that of authentic 2-exo-acetonorbornane, literature values (45): b.p. 87° at 19 mm., n_D^{25} 1.4710.

Anal. Calc'd for $C_9H_{14}O$: C, 78.21; H, 10.21.

Found: C, 78.01; H, 10.28.

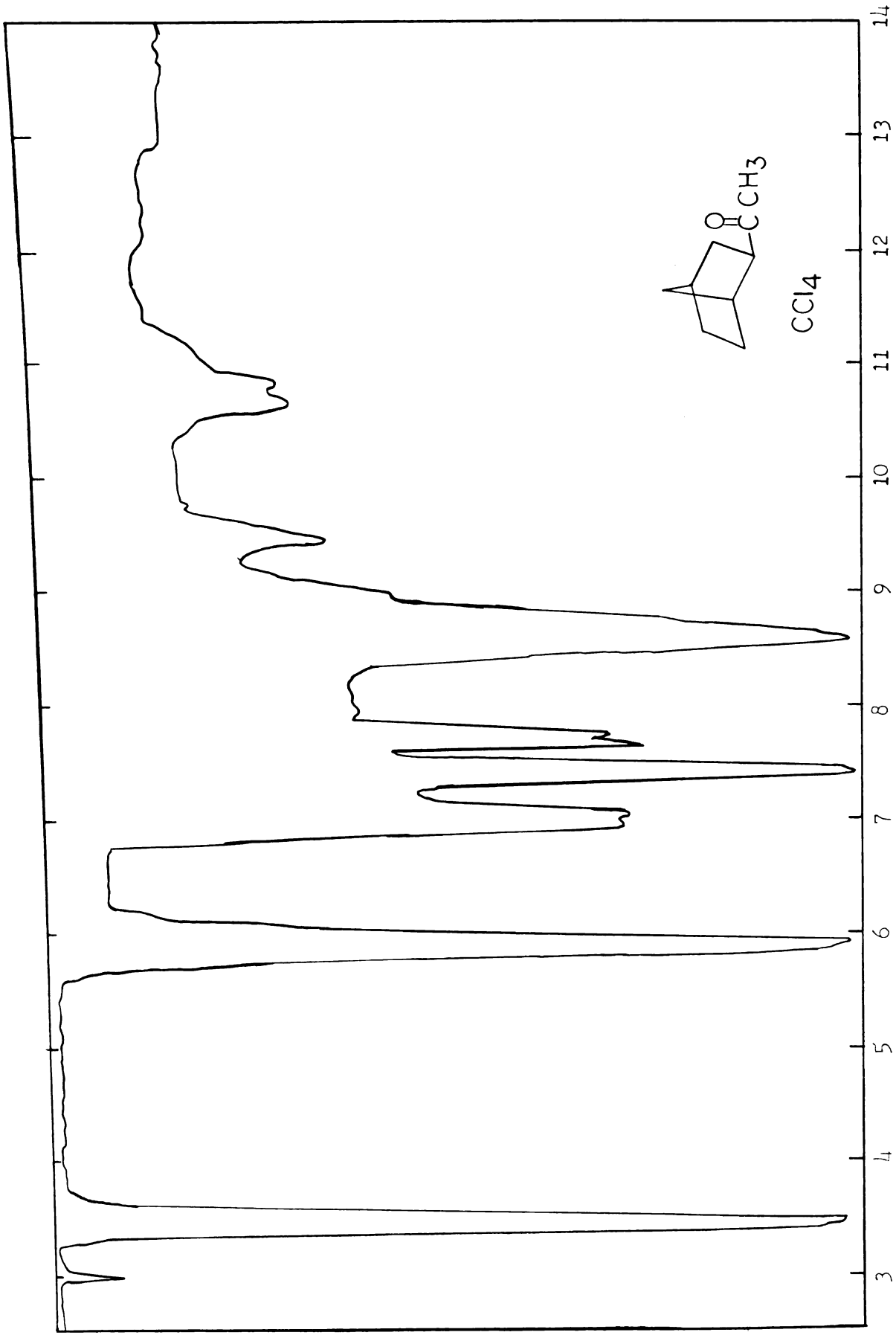


Figure 8. The Infrared Spectrum of the Chromic Acid Oxidation Product of Methylnorbornylcarbinol.

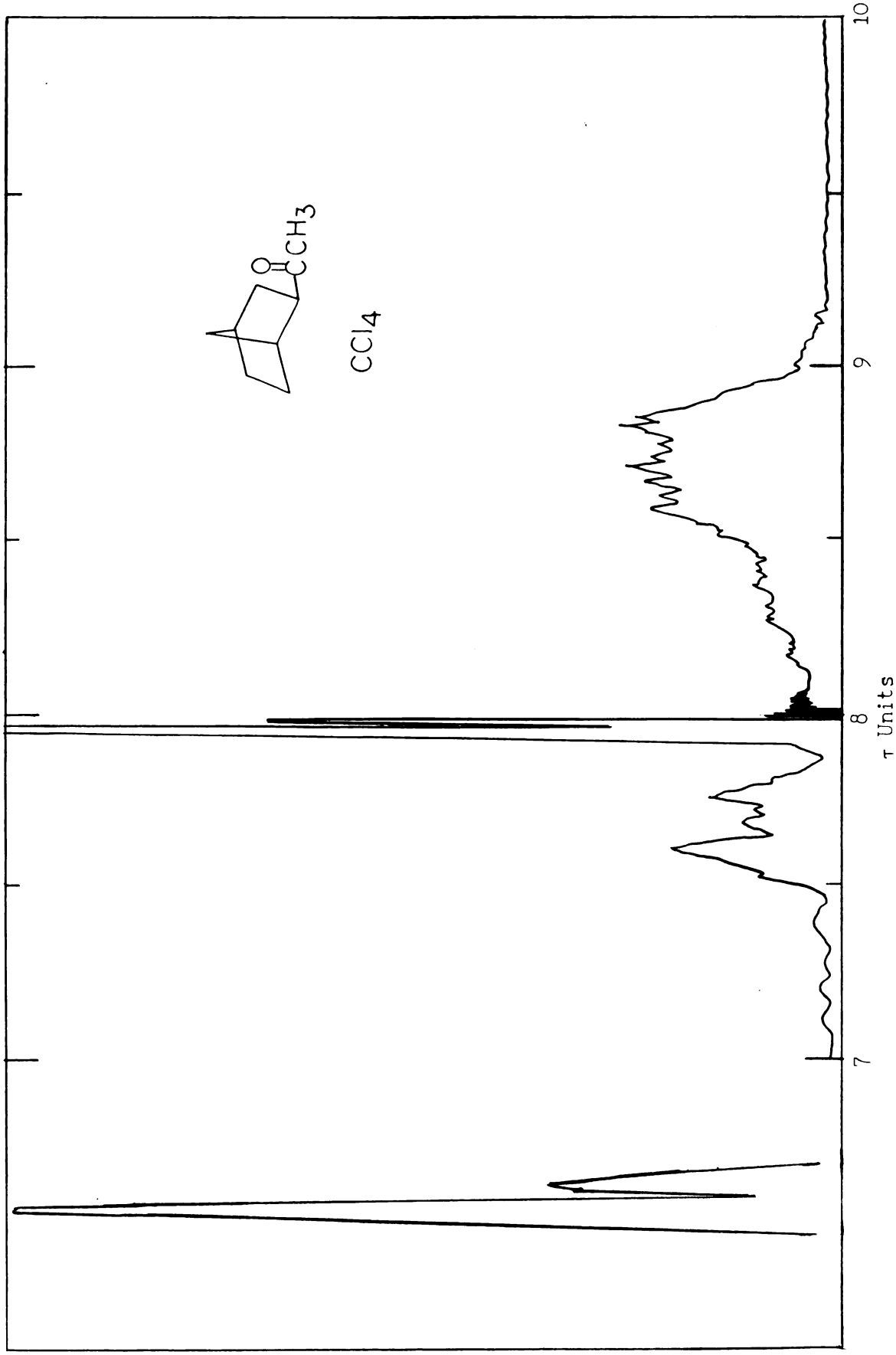


Figure 9. The N.M.R. Spectrum of the Chromic Acid Oxidation Product of Methylnorbornylcarbinol.

B. Preparation of Acetylnorbornanes

1. Preparation of Acids

a. Preparation of 5-Endo-norbornenecarboxylic Acid. The method of Alder (82) was employed in this preparation. To 40.0 g. (0.55 mole) of ice-cold acrylic acid in a 125-ml. Erlenmeyer flask was added 34.0 g. (0.51 mole) of freshly distilled cyclopentadiene (b.p. 40-45° at 743 mm.). The reaction mixture was cooled in an ice bath and a magnetic stirrer was employed so as to maintain a maximum temperature of 40°. The mixture was dissolved in 5% sodium carbonate solution and extracted with ether to remove neutral material. The aqueous layer was acidified to Congo Red with 6 M sulfuric acid and extracted with ether. After drying over magnesium sulfate and removal of solvent, the acid was distilled under reduced pressure through a Vigreux column to give 57.9 g. (82%) of crude 5-endo-norbornenecarboxylic acid, b.p. 84-85° at 0.7 mm., literature value: (82) 118.5-120.5° at 5.7 mm. This material could be further purified by recrystallization from pentane at dry ice temperature.

The method of Berson (83) employing the γ-3 lactone of 2-exo-iodo-3-endo-hydroxy-5-norbornanecarboxylic acid was also used to prepare 5-endo-norbornenecarboxylic acid. The iodolactone, 32.0 g. (0.12 mole) was dissolved in 55 ml. of glacial acetic acid, cooled to 15°, and 16.4 g. (0.25 g. atom) of zinc dust was added over a ten minute period with vigorous stirring. The stirring was continued as the flask was allowed to come to room temperature. After six hours, the bath was removed, and stirring was continued overnight. The acetic

acid solution was filtered, the grey solid washed alternately with acetic acid and water, and the combined filtrates were diluted with more water. The filtrate was extracted with ether, the extracts dried over magnesium sulfate, and the ether removed by distillation. Distillation under reduced pressure gave 13.0 g. (78%) of pure 5-endo-norbornenecarboxylic acid, b.p. 82-86° at 0.7 mm., m.p. 43-45°, literature value: (84) 45-46°.

b.) Preparation of Methyl 5-Endo-norbornenecarboxylate. This compound was prepared by the procedure of Roberts (10). A 300-ml. three-necked flask equipped with stirrer, reflux condenser, and dropping funnel was charged with 65 g. (0.75 mole) of methyl acrylate (b.p. 78.5° at 743 mm.), 0.5 g. of hydroquinone, and 50 ml. of anhydrous ether. The reaction mixture was cooled in an ice bath and 44 g. (0.67 mole) of freshly distilled cyclopentadiene was added dropwise with stirring over a one hour period. Stirring was continued for one hour at ice bath temperature and an additional ninety minutes after removal of the bath, during which time the mixture warmed up quite noticeably. The ether and unchanged methyl acrylate were distilled at atmospheric pressure through a 30 x 1 cm. glass helix-packed column. The residue was distilled under reduced pressure through the same column to give 89.6 g. (88%) of methyl 5-endo-norbornenecarboxylate, b.p. 60° at 3 mm., n_D^{25} 1.4715-1.4728, literature values: (10) 63.5° at 5.2 mm., 1.4719.

c. Preparation of 5-Exo-norbornenecarboxylic Acid. The method of Roberts (10) was employed. A mixture of 65 g. (0.45 mole) of methyl 5-endo-norbornenecarboxylate, 39 g. (0.72 mole) of sodium methoxide, and 91 g. of absolute methanol contained in a 500-ml. flask was refluxed on a steam bath for 48 hours. Most of the methanol was removed at water aspirator pressure. Water (50 ml.) was added and the mixture was refluxed for 20 hours. The methanol formed by the hydrolysis reaction was distilled at atmospheric pressure through an 8" Vigreux column and the aqueous residue was washed with ether. The aqueous layer was acidified to Congo Red with 6 M sulfuric acid and extracted with ether. After drying over magnesium sulfate and evaporating the solvent, the residue was distilled under reduced pressure to give 42.3 g. (71.5%) of acid, b.p. 64° at 0.07 mm., literature value (10): 103-105° at 2 mm.

The crude exo acid was purified according to a procedure described by Van Tamelen (85) and Ver Nooy (86). Crude acid (42.3 g., 0.30 mole) was neutralized with 10% sodium hydroxide solution in a one-liter separatory funnel. Sodium bicarbonate (9 g.) and excess iodine-potassium iodide solution (400 ml., 0.67 M iodine and 2.0 M potassium iodide) were added. The dark oil which formed was extracted with several portions of ether. The combined ether extracts were washed with 10% sodium thiosulfate and dried over calcium chloride. Removal of the solvent gave 42 g. (52%) of crude γ-3-lactone of 2-exo-iodo-3-endo-hydroxy-5-endo-norbornanecarboxylic acid. Recrystallization from ethyl acetate-ligroin (Norite treatment) gave 37 g. of iodolactone, m.p. 57-59°, literature value (86): 58-59°. The aqueous layer was

treated with 10% sodium thiosulfate solution, acidified to Congo Red with 6 M sulfuric acid, and extracted with ether. The extracts were washed successively with water, 1% sodium thiosulfate, and water, and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled under reduced pressure through an 8" Vigreux column to give 18.7 g. (44%) of white acid, b.p. 83-86° at 0.8 mm. Recrystallization from pentane by cooling in dry ice gave 15.2 g. of 5-exo-norbornanecarboxylic acid, m.p. 43-44°, literature values (86): b.p. 100-101.5° at 1.25 mm., m.p. 44-45°.

d. Preparation of 2-Exo-norbornanecarboxylic Acid. A solution of 14.7 g. (0.106 mole) of 5-exo-norbornenecarboxylic acid in 125 ml. of methanol was placed in a Paar bottle over platinum oxide under an initial hydrogen pressure of 50 pounds per square inch. No significant drop in the hydrogen pressure was noticed after 30 minutes. The odor of hydrogen sulfide indicated the presence of elemental sulfur which would poison the catalyst. The solution was filtered and desulfurized by refluxing for 24 hours over Raney-nickel. On the second attempt the theoretical uptake of hydrogen was complete in 20 minutes. The platinum black was removed by filtration, the methanol evaporated, and the residual oil triturated with pentane to yield 13.4 g. (90%) of 2-exo-norbornanecarboxylic acid, m.p. 55-57°, literature values (83-87): 58-58.5°, 56-57°.

e. Preparation of 2-Endo-norbornanecarboxylic Acid. A solution of 53.5 g. (0.39 mole) of 5-endo-norbornenecarboxylic acid in 200 ml. of ethyl acetate was placed in a Paar hydrogenation bottle with 0.4 g.

of 5% palladium on charcoal under an initial hydrogen pressure of 50 pounds per square inch. The theoretical uptake of hydrogen was complete in 25 minutes. The palladium on charcoal was removed by filtration and the solvent evaporated on a steam bath under a slow stream of air to give a crystalline acid. Two recrystallizations from pentane by cooling in dry ice gave 36 g. (68%) of 2-endo-norbornanecarboxylic acid, m.p. 61.5-63°, literature value (83): 64-66°.

2. Preparation of Acid Chlorides

a. Preparation of 2-Endo-norbornanecarbonyl Chloride. The acid chlorides were prepared essentially by the method of Boehme (84). A solution of 10 g. (0.071 mole) of 2-endo-norbornanecarboxylic acid and 12.0 g. (0.10 mole) of thionyl chloride in 25 ml. of chloroform was refluxed in a 100-ml. round-bottomed flask fitted with a reflux condenser. After six hours, chloroform and excess thionyl chloride were removed by fractional distillation through an 8" Vigreux column. Under the reduced pressure of a water aspirator the residue was distilled to give 11.0 g. (97%) of 2-endo-norbornanecarbonyl chloride, b.p. 85.7-87° at 14 mm., literature value (88): 84° at 12 mm. In a similar experiment an 86% yield of acid chloride was obtained, b.p. 80-81° at 10 mm.

b. Preparation of 2-Exo-norbornanecarbonyl Chloride. By a procedure similar to that used for the endo isomer, 10 g. (0.071 mole) of 2-exo-norbornanecarboxylic acid was converted into 10.9 g. (96%) of 2-exo-norbornanecarbonyl chloride, b.p. 86-87° at 13 mm., literature value (89): 83-84° at 12 mm.

3. Preparation of Acetylnorbornanes

a. Preparation of 2-exo-Acetylnorbornane. A procedure quite similar to that of Berson (45) was employed in the preparation of the acetylnorbornanes. A 500-ml. three-necked flask was equipped with mechanical stirrer, Friedrich condenser, dropping funnel, and gas inlet tube. The methyl Grignard reagent was prepared by bubbling methyl bromide, dried by passing it through a calcium chloride drying tower, through 300 ml. of ether until the magnesium (8.3 g., 0.34 g. atoms) had completely reacted. The reaction, moderated by cooling with an ice bath, was complete within one hour. Anhydrous cadmium chloride (46.0 g., 0.25 mole) was added in small portions over a ten minute period and the mixture was refluxed for three hours. Gilman's method (90) using Michler's ketone gave a negative test for the presence of Grignard reagent. Most of the ether was removed by distillation and replaced simultaneously by 100 ml. of anhydrous benzene. A solution of 10.0 g. (0.063 mole) of 2-exo-norbornanecarbonyl chloride in 100 ml. of benzene was added dropwise and the solution stirred at room temperature for eight hours. After refluxing for fifteen minutes, excess dimethylcadmium was decomposed by cautious addition of water. Cadmium salts were dissolved by the addition of 50 ml. of concentrated hydrochloric acid diluted to 150 ml. The layers were separated, the aqueous layer extracted with benzene, and the combined solutions washed with a sodium carbonate solution and dried over magnesium sulfate. Removal of the solvent by distillation and fractional distillation of the remainder through a silver-lined, vacuum jacketed Vigreux column gave 6.5 g. (75%) of 2-exo-acetylnorbornane, b.p. 78.5-82° at

11 mm., n_D^{25} 1.4712, literature values (45): b.p. 87° at 19 mm., n_D^{25} 1.4710. The infrared and n.m.r. spectra are shown in Figures 10 and 11.

The semicarbazone was obtained by the method of Shriner, Fuson, and Curtin (91), m.p. 181-182°, literature value (45), 182-183°.

b. Preparation of 2-endo-Acetylnorbornane. The preparation of the endo isomer was attempted by the same procedure as was employed for the exo isomer. A reaction involving 16.6 g. (0.68 g. atoms) of magnesium, 92.0 g. (0.50 mole) of cadmium chloride, and 21.4 g. (0.135 mole) of 2-endo-norbornanecarbonyl chloride gave 11.3 g. (60%) of acetylnorbornane, b.p. 81.5-85° at 15 mm., n_D^{25} 1.4708-1.4725, literature values (45) for the endo isomer: b.p. 87° at 18 mm., n_D^{25} 1.4721-23. There was an 8.0 g. residue after distillation.

This material was combined with that of a similar preparation and redistilled through a silver-lined, vacuum jacketed Vigreux column to give the following fractions: (1) 2.7 g., b.p. 66-74° at 11 mm., n_D^{25} 1.4740; (2) 4.0 g., b.p. 76-79.5° at 11 mm., n_D^{25} 1.4713; (3) 4.8 g., b.p. 79.5-81° at 11 mm., n_D^{25} 1.4709; (4) 0.6 g., b.p. 65° at 3 mm., n_D^{25} 1.4730. The n.m.r. spectrum of fraction 3 is practically identical with that of 2-exo-acetylnorbornane. The n.m.r. spectrum of an early fraction of a previous sample shows two methyl singlets at 7.94 and 7.96 τ units (2:3 ratio) for the exo and endo isomers respectively. The semicarbazone of fraction (3) melted at 179-180° and showed no appreciable depression when mixed with the semicarbazone of 2-exo-acetylnorbornane.

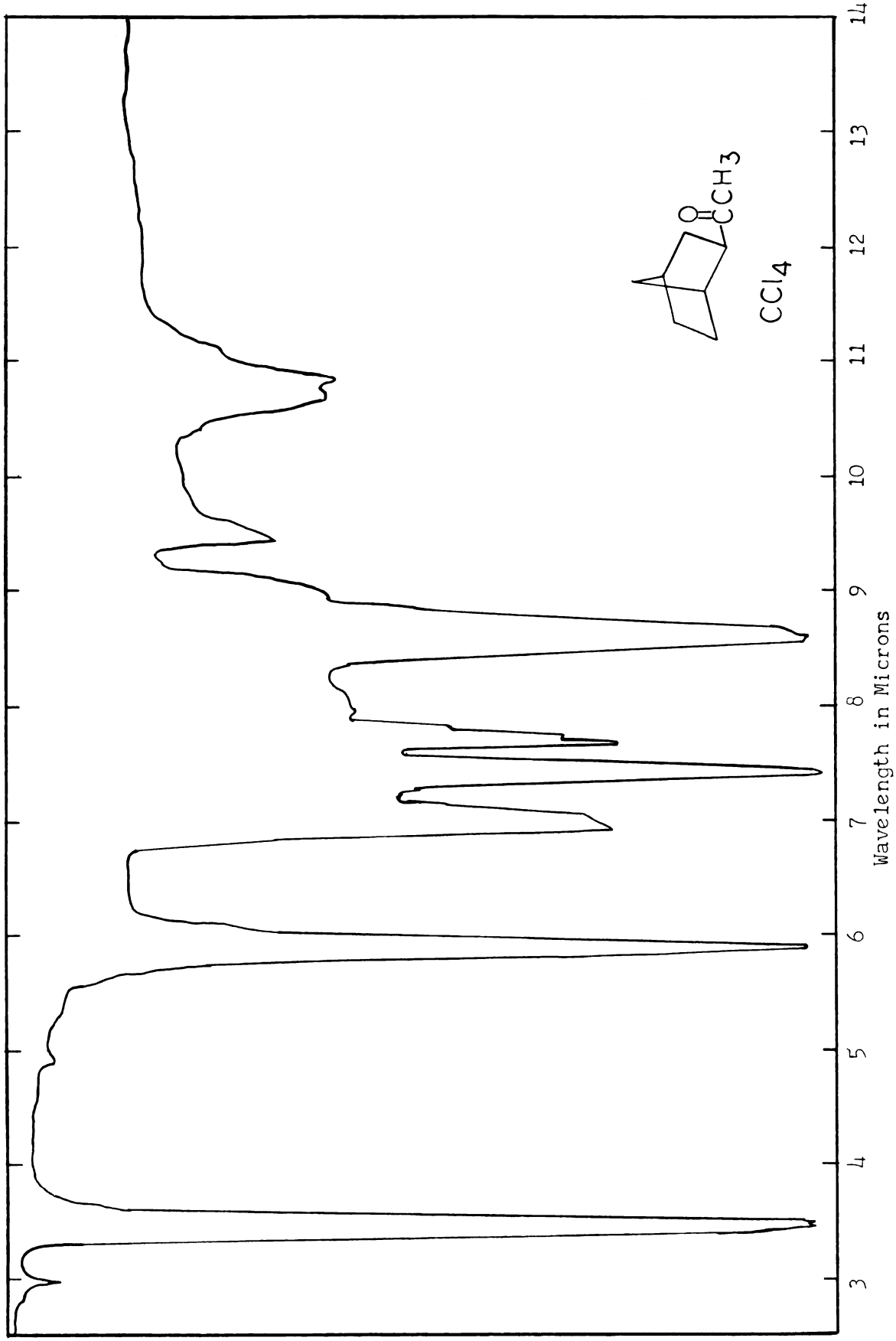


Figure 10. The Infrared Spectrum of 2-Exo-acetylnorbornane.

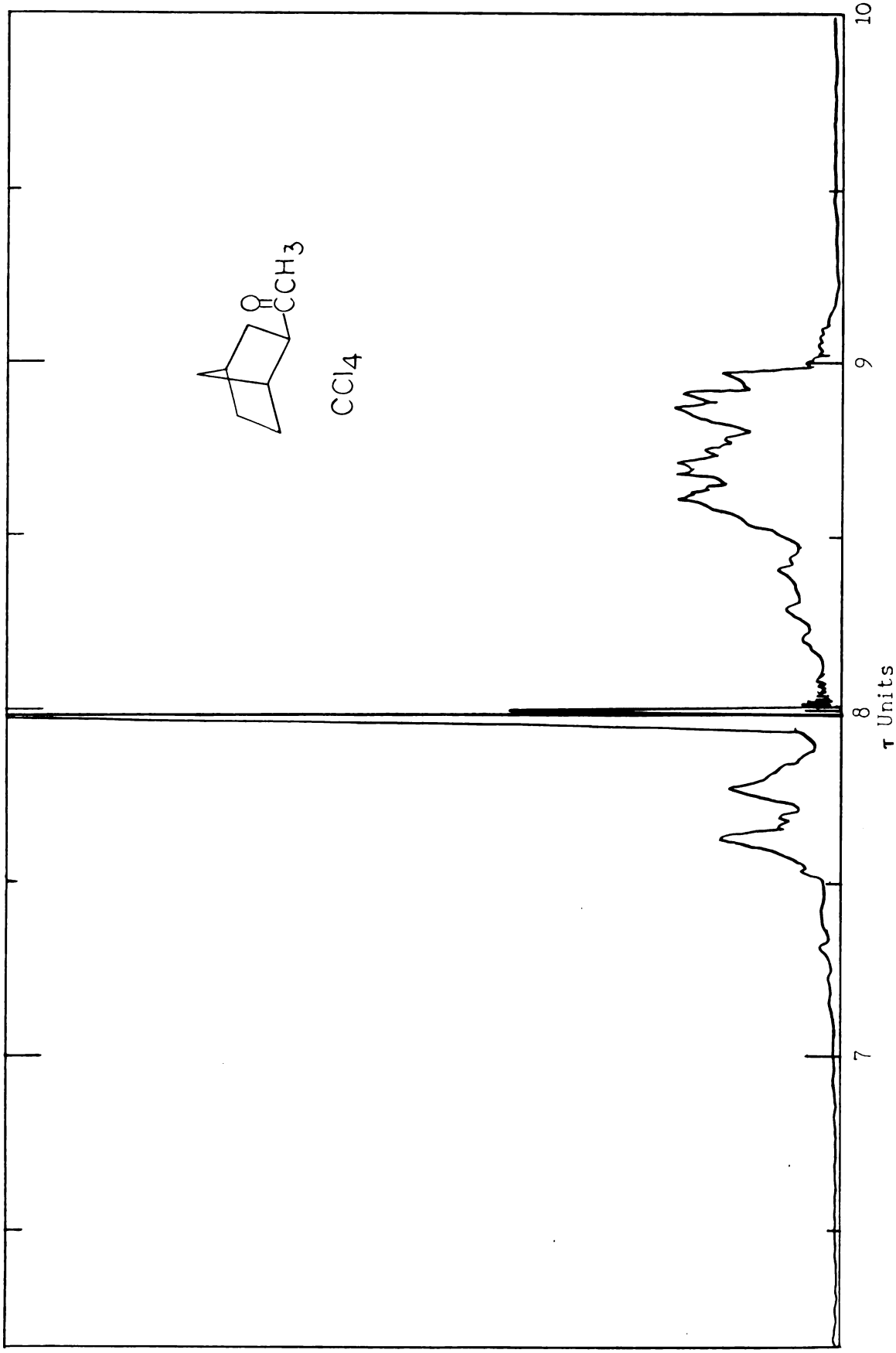


Figure 11. The N.M.R. Spectrum of 2-Exo-acetylnorbornane.

The 2,4-dinitrophenylhydrazone of the exo isomer and of fraction (3) had respective melting points of 122-123.5° and 121.5-122.5°. A mixed melting point showed no depression.

C. Stannic Chloride-Acetic Anhydride System

1. The Stannic Chloride Catalyzed Reaction between Norbornene and Acetic Anhydride

A set-up identical to the one employed for the aluminum chloride catalyzed acetylation was used. To 70.6 g. (0.75 mole) of norbornene in 100 ml. of methylene chloride was added 130.2 g. (0.50 mole) of stannic chloride. An ice bath was used to keep the temperature between 25-30°. With slow stirring 51 g. (0.50 mole) of acetic anhydride was added over a half hour period. The reaction was quite exothermic. After addition was complete, stirring was continued for 15 minutes. During the stannic chloride addition the reaction mixture became a pale yellow. When the acetic anhydride was added, it became a very dark red. The reaction mixture was hydrolyzed by pouring onto an ice-concentrated hydrochloric acid mixture. Emulsions which formed caused difficulty in separating the layers. The methylene chloride layer was washed successively with portions of water, 10% sodium carbonate solution (the deep red color became orange-red during this wash), and again with water. After drying over magnesium sulfate and removing the solvent by distillation, the residue was distilled under reduced pressure to yield 29.2 g. of a colorless liquid, b.p. 50-64° at 0.8 mm., n_D^{25} 1.4631-1.4670. A small amount of a higher boiling, more viscous liquid distilled over and there remained 61.7 g. of a viscous liquid which, upon cooling, became a glass-like solid.

Crude fractions from two such reactions (n_D^{25} 1.4631-1.4728) were fractionally distilled under reduced pressure through a glass-packed column. Data for the various fractions are recorded in Table I. The infrared spectrum (Figure 12) of fraction twelve shows strong absorption bands at 5.82 μ, indicative of a carbonyl grouping, and at 8.05-8.14 μ, probably indicative of C-O stretching frequencies. The n.m.r. spectrum (Figure 13) of fraction 11 integrated very sharply for an H_{14} compound. A single proton at τ 5.57 units suggested a tertiary hydrogen adjacent to an acetoxy group. This data indicated that the major product, b.p. 69-70° at 6 mm., n_D^{25} 1.4569, n_D^{20} 1.4585, was a norbornyl acetate. Literature values for norbornyl acetates are as follows: 2-exo-acetoxynorbornane (92), b.p. 89-90° at 20 mm., n_D^{20} 1.45864; 2-endo-acetoxynorbornane (93), b.p. 81-83° at 12 mm., n_D^{25} 1.4578.

Anal. Calc'd for $C_9H_{14}O_2$: C, 70.10; H, 9.15.

Found: C, 69.00, 70.46, 72.17; H, 8.79, 9.30, 9.13.

The above values are reported in the sequence in which the determinations were made. The analyst commented that "the ascending carbon values would indicate the possibility of changing composition" (94). The refractive index of fraction 12, n_D^{25} 1.4565, was virtually unchanged after five weeks.

2. Lithium Aluminum Hydride Reduction of 2-Exo-acetoxynorbornane

To a suspension of 1.35 g. (0.036 mole) of lithium aluminum hydride in 100 ml. of ether was added over 15 minutes a solution of 5.5 g. (0.036 mole) of 2-exo-acetoxynorbornane in 30 ml. of ether. After refluxing for four hours, the reaction mixture was hydrolyzed by the

Table I. Fractional distillation of products from stannic chloride catalyzed reaction between norbornene and acetic anhydride.

Fraction	b.p. °/mm.	n_D^{25}	wt., g.	VPC Analysis, %			
1	51/12	1.4784	1.3	5	95		
2	50-52/11	1.4797	2.2	Trace	95	5	
3	50-42/11	1.4785	0.8	Trace	80	20	
4	67/6	1.4678	2.1		25	35	40
5	67-68/6	1.4578	2.3			10	90
6	68/6	1.4570	3.0				100
7	69/6	1.4571	2.5				100
8	69/6	1.4571	3.0				100
9	69/6	1.4572	2.7				100
10	69/6	1.4569	2.7				100
11	70/6	1.4569	2.1				100
12	71/7	1.4569	2.0				100
13	72/6	1.4569	2.7				100
14	70/6	1.4571	1.2				100
15	69-70/6	1.4572	2.2				100
16	68.5/6	1.4576	2.8				100
17	69/6	1.4577	2.5				100
18	69-65/6	1.4573	2.3				100
19	63.5/6	1.4588	3.2				100
20	Forced over.	1.4678	1.1	Considerable tailing on main peak.			
21		1.4879	1.9				
22	50-95/1	1.4958	3.2				

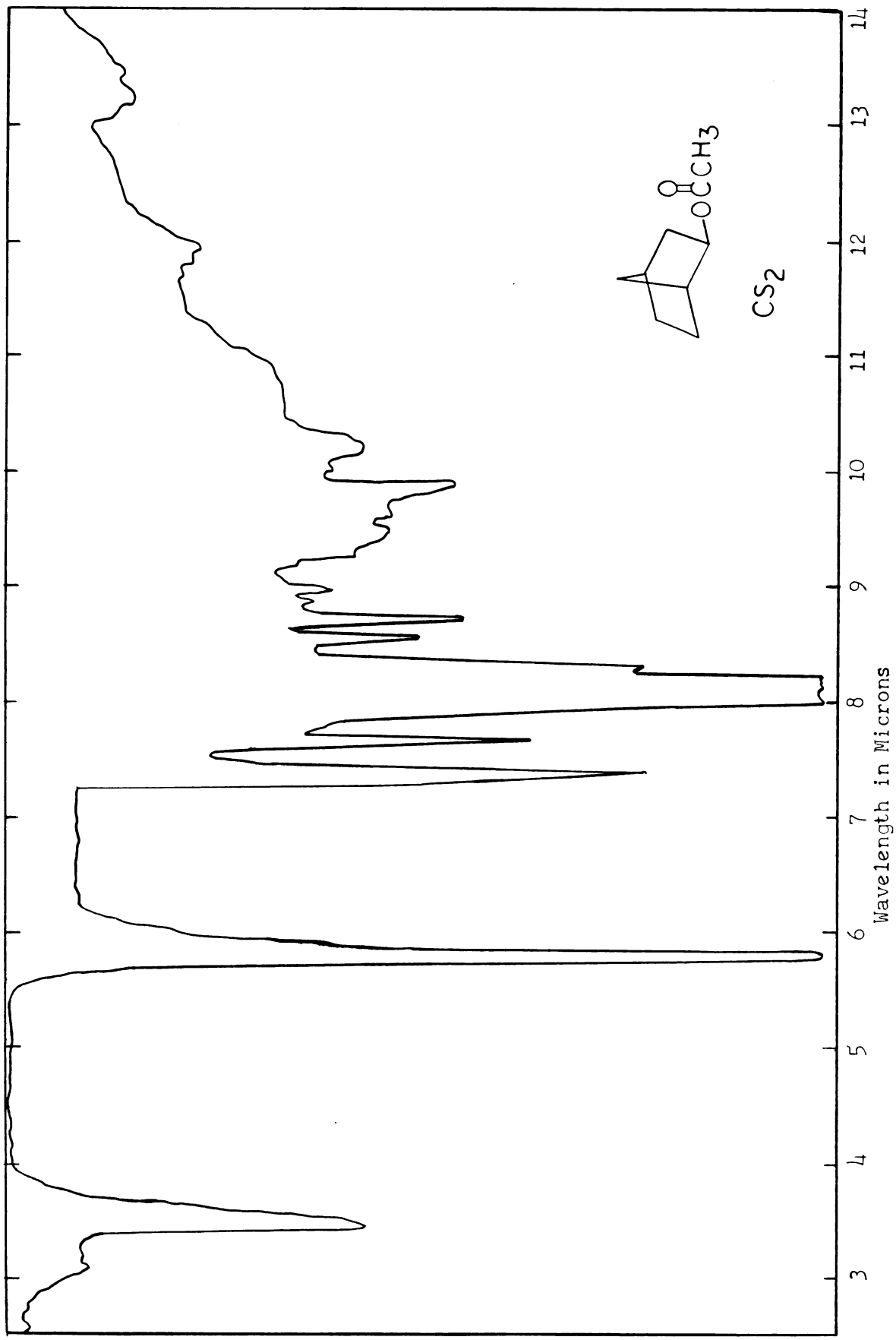


Figure 12. The Infrared Spectrum of 2-Exo-acetoxynorbornane.

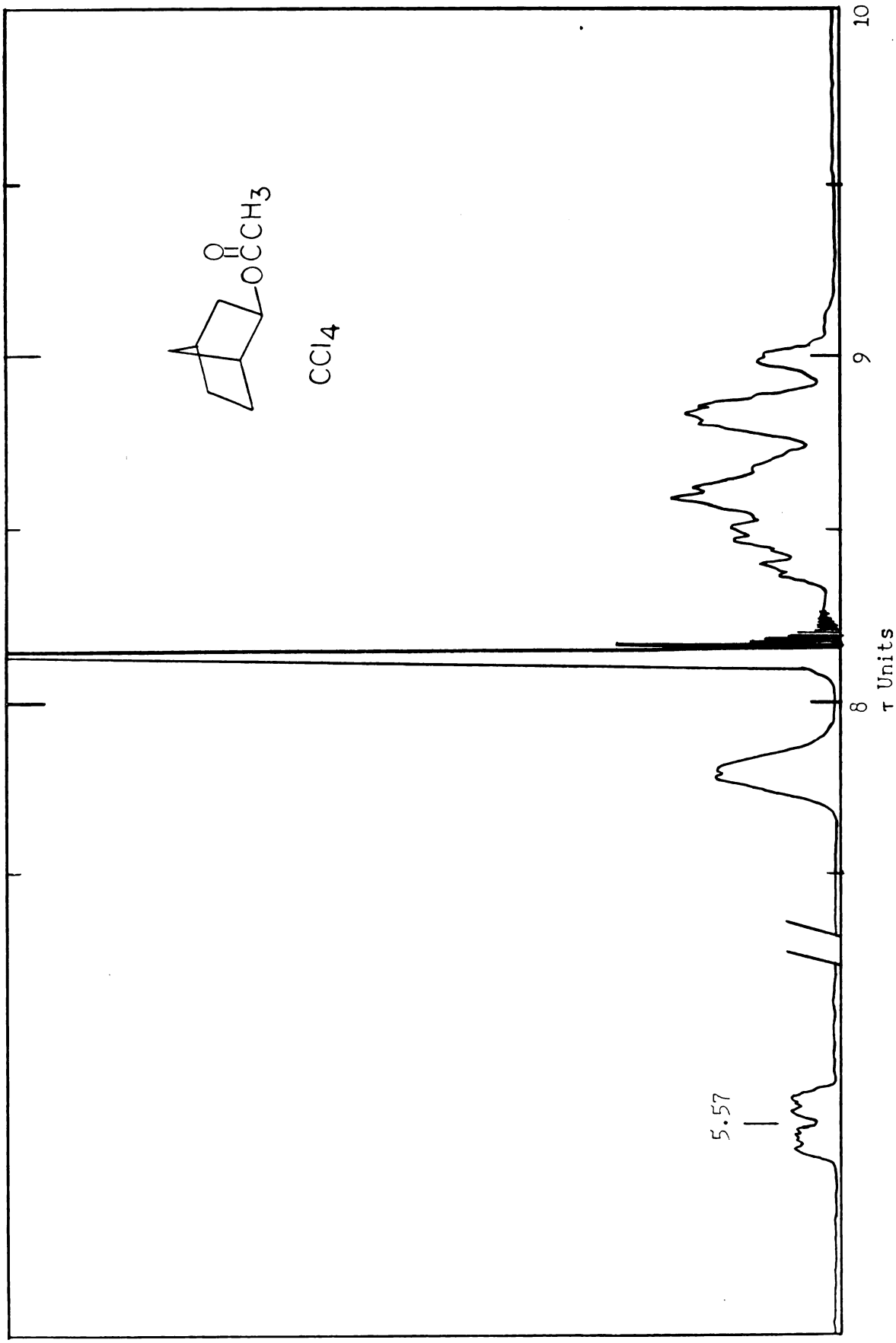


Figure 13. The N.M.R. Spectrum of 2-Exo-acetoxynorbornane.

cautious addition of a saturated sodium sulfate solution. The ether suspension was dried by stirring with an excess of magnesium sulfate. Filtration and evaporation of the solvent yielded 4.05 g. (quantitative yield) of crude material which solidified upon cooling. Sublimation at atmospheric pressure produced 2.70 g. (68%) of 2-exo-hydroxynorbornane, m.p. 125-126.5° (sealed tube), literature value (95); m.p. 127.8-128.5°, reported (5) for 2-endo-hydroxynorbornane, m.p. 152-153°.

The 3,5-dinitrobenzoate (96) was an oil which solidified upon standing. Recrystallization from ligroin (b.p. 65-110°) gave pale yellow crystals, m.p. 101.5-102°, literature value (92): 105°, reported for endo isomer (93), 123°.

II. Dicyclopropylcarbinyl System

A. Synthesis of Dicyclopropylcarbinylamine

1. Preparation of Dicyclopropyl Ketone

Using the procedure of Hart (97) a solution of 117 g. of commercial sodium methoxide in 520 ml. of absolute methanol was placed in a three liter, three-necked flask equipped with a sealed stirrer, dropping funnel, and a condenser set downward for distillation. To the stirred solution was added in one batch 344 g. (4.0 mole) of freshly distilled γ-butyrolactone, and the flask was heated until methanol distilled at a rapid rate. After 475 ml. of methanol had been collected, a vacuum take-off system was added and the vacuum applied intermittently to control excess frothing. Stirring of the residual dibutyrolactone was continued as long as possible while an additional 75 ml. of a mixture of methanol and γ-butyrolactone was obtained.

With the condenser set for reflux and heating with a direct flame 800 ml. of concentrated hydrochloric acid was added cautiously with stirring over a fifteen minute period. The mixture was refluxed for twenty minutes and then cooled in an ice bath. A solution of 480 g. of sodium hydroxide in 600 ml. of water was added to the stirred mixture, maintaining the temperature below 50°. The mixture was refluxed for thirty minutes.

The condenser was again set downward and the ketone-water mixture was distilled until no odor of ketone was present in the distillate. The water layer was saturated with potassium carbonate and the organic

layer separated. The aqueous layer was washed with three 100-ml. portions of ether and the combined ether-ketone layer dried over magnesium sulfate. After removal of ether by distillation through a 30 cm. Vigreux column, the ketone was distilled through a 30 cm. glass-packed column. The yield of dicyclopropyl ketone, b.p. 73-4° at 29 mm., n_D^{25} 1.4647, literature value (97): 72-4° at 33 mm., n_D^{25} 1.4654, was 88 g. (40%).

2. Preparation of Dicyclopropyl Ketoxime

A mixture of 21 g. (0.19 mole) of dicyclopropyl ketone, 20 g. (0.28 mole) of hydroxylamine hydrochloride, 17 g. (0.20 mole) of sodium bicarbonate and 60 ml. of water was refluxed on a steam bath with stirring for six hours. Upon cooling the upper layer of oxime solidified. The oxime was dissolved in ether and the separated aqueous layer extracted with two 100-ml portions of ether. After the combined ether solutions were dried over potassium carbonate and filtered, evaporation of solvent provided crude ketoxime in 95% yield. The crude product was recrystallized from petroleum ether to yield 15 g., m.p. 75.3-76°. Further evaporation of the mother liquor gave an additional 2.9 g. of dicyclopropyl ketoxime, m.p. 75.1-76°. The total yield was 17.9 g. (75%).

The infrared and n.m.r. spectra are shown in Figures 14 and 15 respectively.

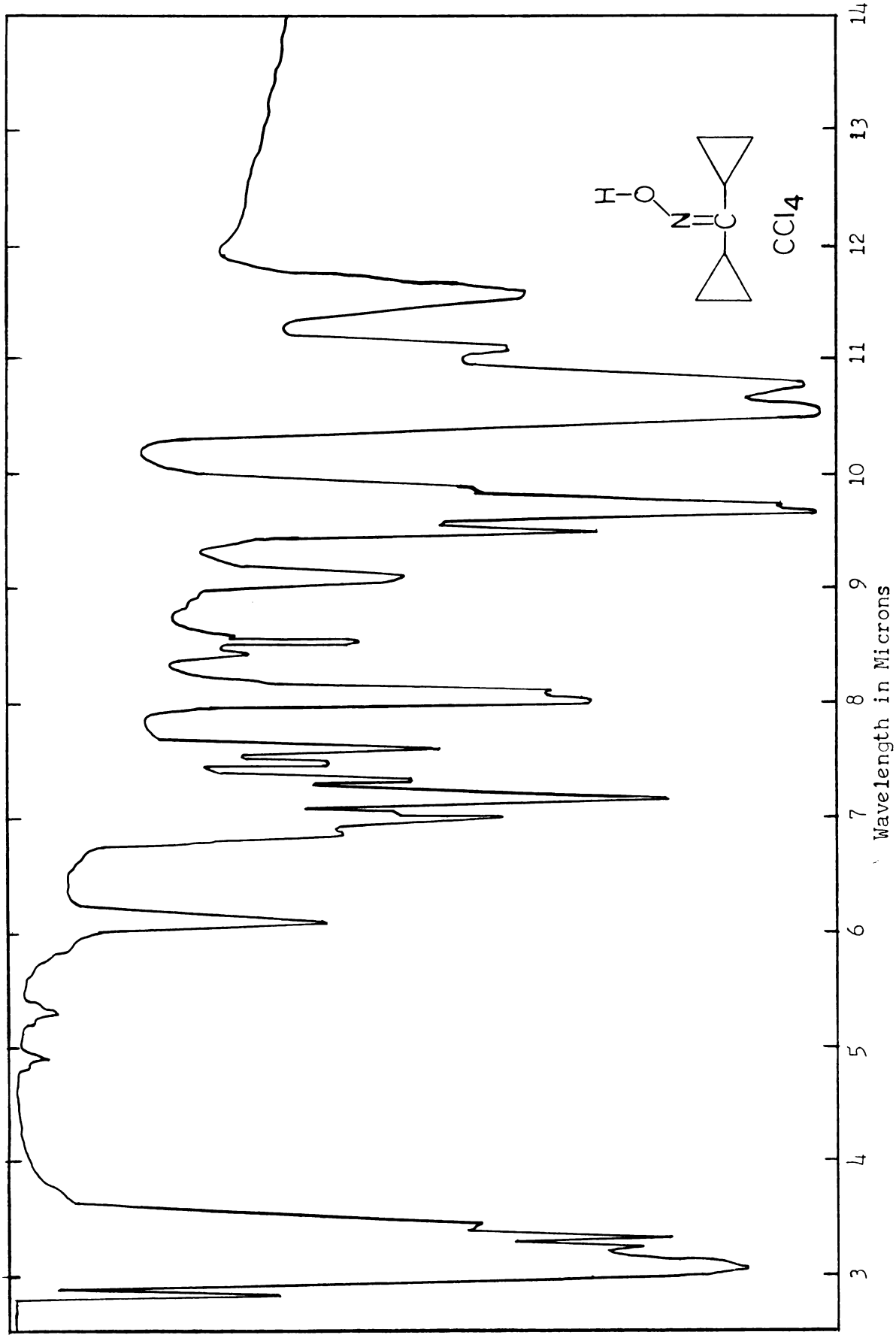


Figure 14. The Infrared Spectrum of Dicyclopropyl Ketoxime.

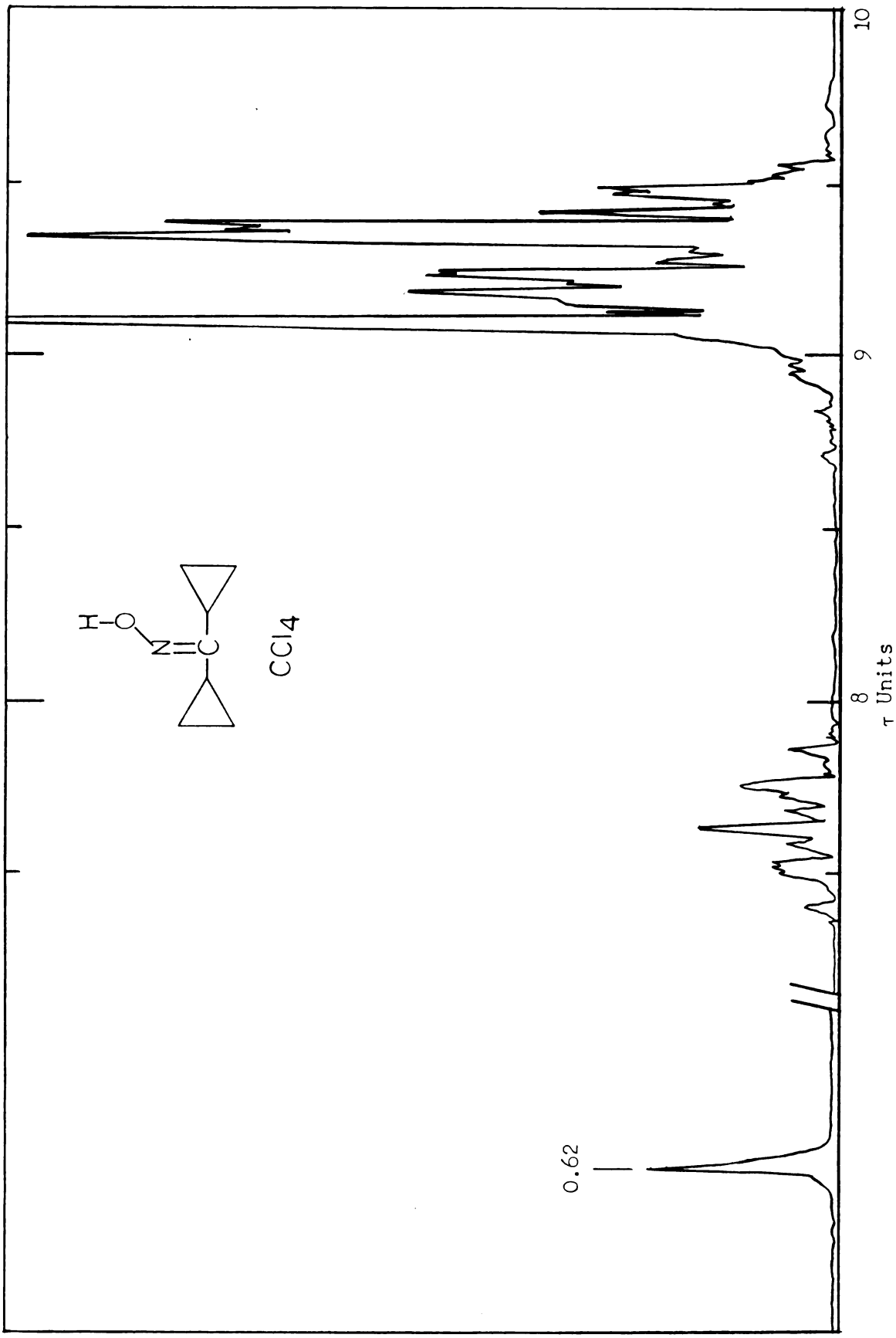


Figure 15. The N.M.R. Spectrum of Dicyclopropyl Ketoxime.

3. Lithium Aluminum Hydride Reduction of Dicyclopropyl Ketoxime

In a 500-ml. three-necked round-bottomed flask equipped with dropping funnel, stirrer, and Friedrich condenser were placed 3 g. (0.079 mole) of lithium aluminum hydride and 150 ml. of tetrahydrofuran. To this heated slurry was added 6.3 g. (0.05 mole) of dicyclopropyl ketoxime in 50 ml. of tetrahydrofuran over a one half hour period. The mixture was refluxed with stirring for twenty hours and cooled in an ice bath. The contents of the reaction flask were worked up in two manners.

Procedure A: Water was added dropwise to destroy the excess hydride. The reaction mixture was added to 500 ml. of a 20% potassium sodium tartrate solution. The organic material was extracted with several portions of ether and from this the amine was extracted with several portions of dilute hydrochloric acid (10 ml. of conc. hydrochloric acid diluted to 150 ml.). The amine was regenerated from the amine hydrochloride by the addition of sodium hydroxide pellets and the basic solution extracted with ether. After treatment with Norite and drying over a magnesium sulfate-potassium carbonate mixture, the solvent was distilled through a 60 cm. tantalum spiral column. The product was distilled through a 20 cm. Vigreux column under reduced pressure to give 4.38 g. (77% yield) of dicyclopropylcarbinylamine, b.p. 89-91° at 102 mm.

Procedure B: After cooling, the excess hydride was decomposed by dropwise addition to the reaction mixture of a saturated aqueous sodium sulfate solution until the solid material had taken on a

distinctive granular appearance. Excess magnesium sulfate was added and the stirring was continued for thirty minutes. The solid residue was collected on a fritted-glass funnel and washed with several portions of ether. After removal of the solvent by distillation through a glass-packed column, the product was distilled through a 20 cm. Vigreux column under reduced pressure to give 4.40 g. (77% yield) of dicyclopropylcarbinylamine, b.p. 89-91° at 100 mm.

Upon exposure of the amine to the atmosphere a white solid was formed. A similar solid was produced in copious amounts when a piece of solid carbon dioxide was introduced into a test tube containing several drops of the amine. Upon standing the solid would very gradually disappear. The solid was soluble in water and insoluble in ether and carbon tetrachloride.

Analysis by gas chromatography (Figure 16) showed one major peak with a fore-shoulder which was about 10% of the product mixture. A small portion of the amine was treated with acetic anhydride to give a precipitate which, after recrystallization from ligroin, melted at 123-124°. Its infrared spectrum was identical with that of N-dicyclopropylcarbinylacetamide. A mixed melting point showed no depression.

All attempts to purify the dicyclopropylcarbinylamine by fractional distillation through glass-packed, tantalum spiral, or various Vigreux columns were unsuccessful. Attempted purification by gas chromatography was also unsuccessful. The Perkin-Elmer Vapor Fractometer caused minor decomposition and the Beckman Megachrom caused extensive decomposition. Purification was achieved finally by fractional distillation through a Nester spinning-band column (98) at

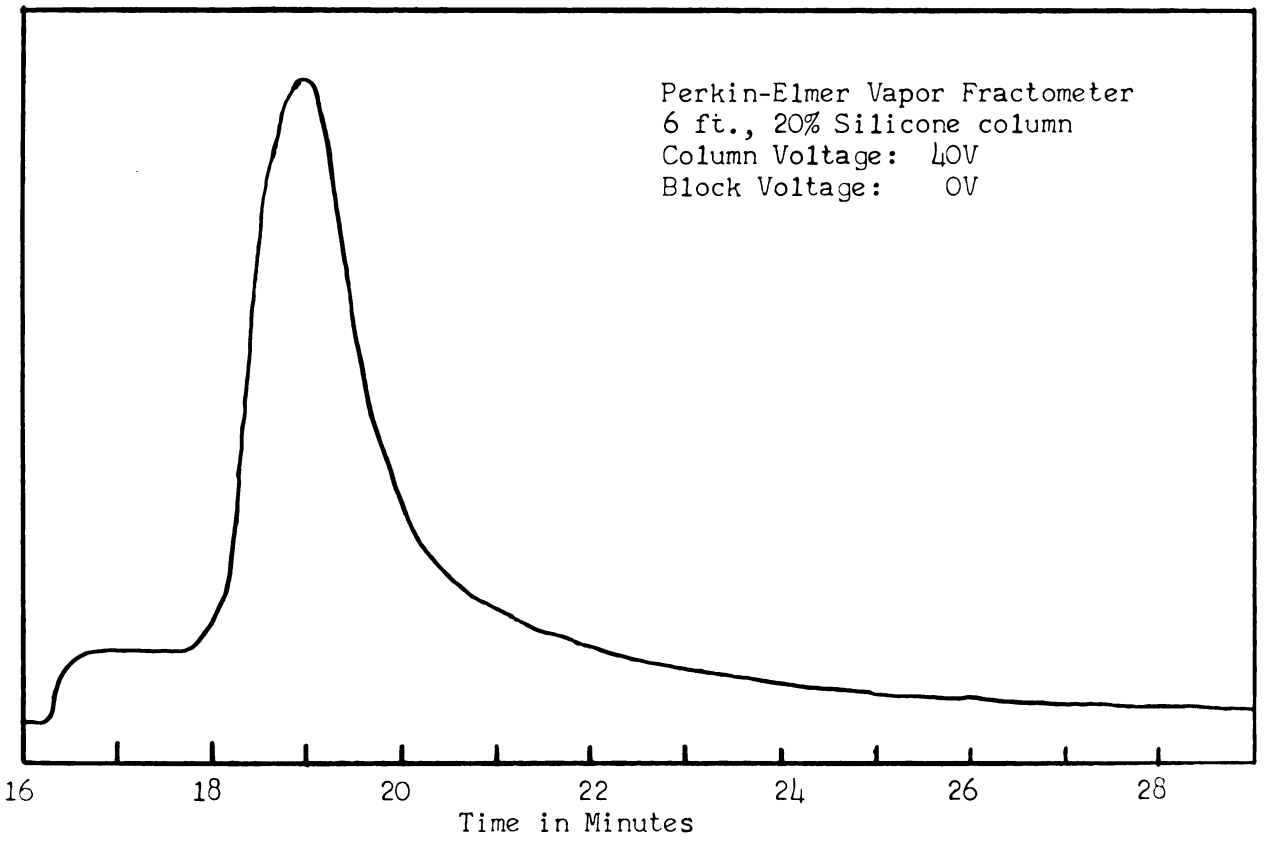


Figure 16. The Gas Chromatograph of Impure Dicyclopropylcarbinylamine.

atmospheric pressure. All of the previously prepared amine was combined and fractions one to twelve were collected in two dram vials. Fractions one and two contained at least 30% of the impurity; fraction three was considerably more pure though the impurity was still present in significant amounts. The gas chromatograph of fraction four showed only a slight inflection in the slope of the peak of the pure amine. Fractions five through twelve were pure dicyclopropylcarbinylamine, b.p. 150-151°, n_D^{25} 1.4577. The infrared and n.m.r. spectra are shown in Figures 17 and 18.

4. Preparation of N-Dicyclopropylcarbinylacetamide

A solution of 12.5 g. (0.1 mole) of dicyclopropyl ketoxime in 30 ml. of acetic anhydride was placed in a Paar low pressure hydrogenation bottle with 0.100 g. of platinum oxide. The system was purged of oxygen, placed under an initial pressure of 45 p.s.i. and shaking begun. The pressure drop was quite rapid at first but after two hours had dropped only 3.5 p.s.i. An additional 0.100 g. of platinum oxide in 10 ml. of acetic anhydride was placed in the reaction bottle and the hydrogen pressure raised to 46 p.s.i. After five hours the hydrogen pressure had dropped an additional 7 p.s.i. Addition of a third portion of catalyst resulted in no further pressure drop other than that associated with the original reduction of platinum oxide. The platinum black was removed by filtration and the vessel rinsed with several small portions of ether and water. A solution of 30 g. of sodium hydroxide in 60 ml. of water was added with efficient cooling and agitation. The basic solution was extracted with several portions of ether, and the combined extracts treated with

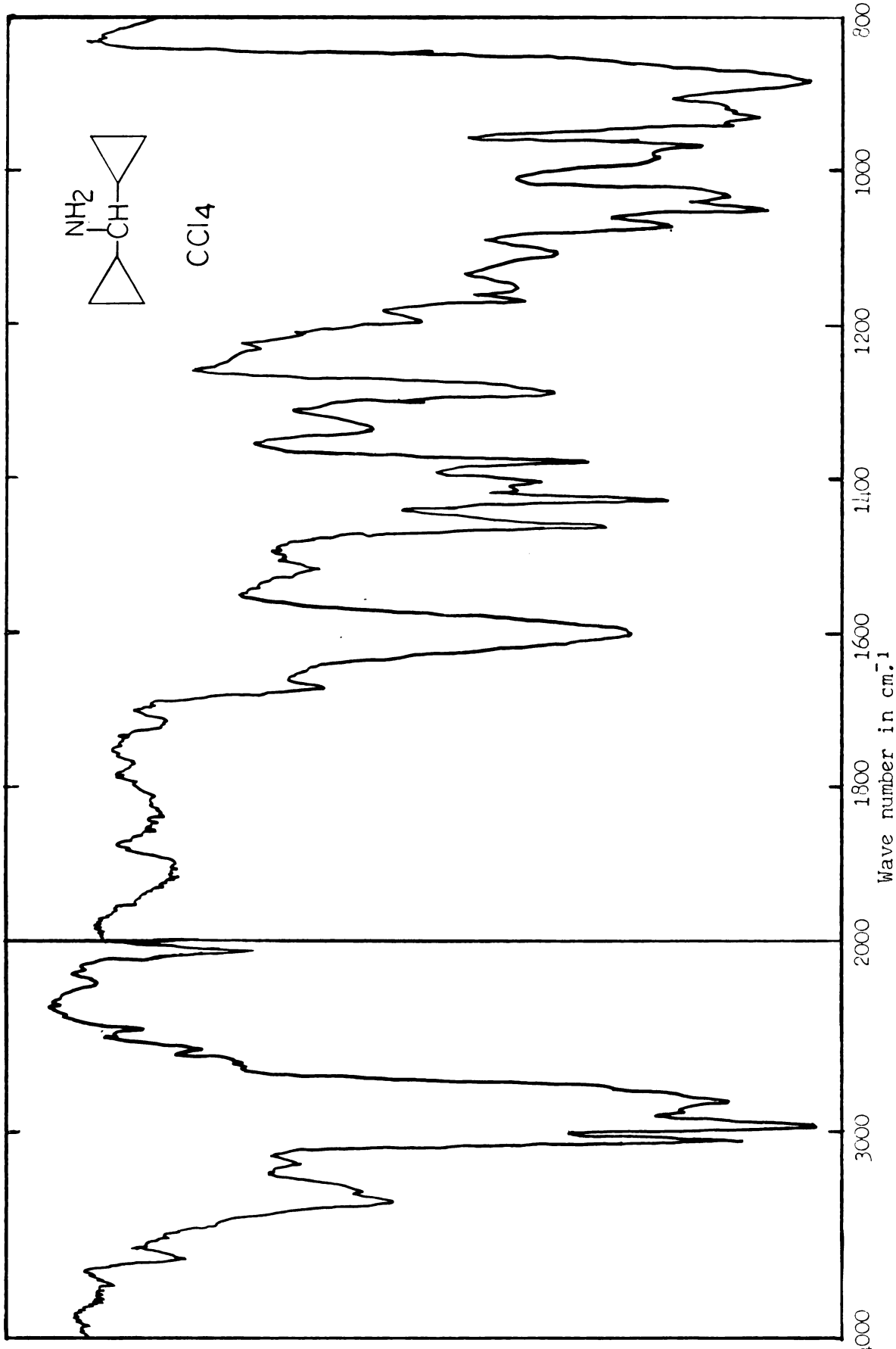


Figure 17. The Infrared Spectrum of Dicyclopropylcarbinylamine.

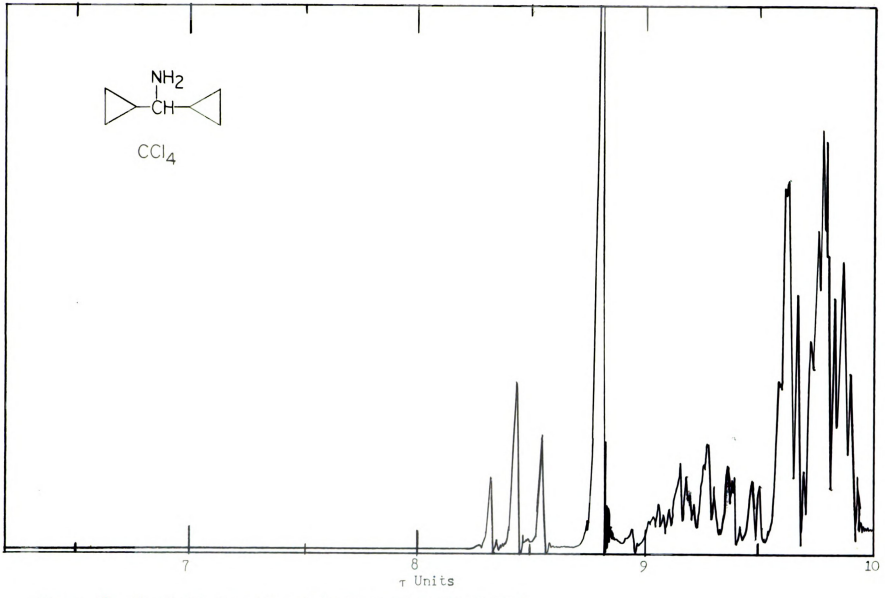


Figure 18. The N.M.R. Spectrum of Dicyclopropylcarbinylamine.

Norite and dried over magnesium sulfate. After filtration the ether was evaporated on a steam bath leaving 17.5 g. of an oil which solidified on cooling. Trituration with several portions of pentane removed most of the unchanged oxime. Recrystallization from ligroin (b.p. 90-120°) gave 7.0 g. (46%) of N-dicyclopropylcarbinylacetamide, m.p. 124-124.5°. The infrared and n.m.r. spectra are shown in Figures 19 and 20 respectively.

Anal. Calc'd. for $C_9H_{15}NO$: C, 70.50; H, 9.87; N, 9.14.

Found: C, 70.34; H, 9.67; N, 9.40.

A similar reaction was attempted using a commercial bottle heater. While maintaining the temperature at 45-55°, two separate portions of platinum oxide were employed. Each time the pressure dropped slightly as the platinum oxide was reduced and then remained constant as if something were poisoning the catalyst. The ketoxime was recovered after normal workup as an oil contaminated with some ketone.

5. Attempted Hydrolysis of N-dicyclopropylcarbinylacetamide

A suspension of 10 g. (0.065 mole) of N-dicyclopropylcarbinylacetamide in about 80 ml. of a 28% aqueous sodium hydroxide solution was placed in a round-bottom flask equipped with stirrer and Friedrichs condenser. At reflux temperature the suspension of the melted amide was stirred briskly for 68 hours. A faint odor of amine was detected and a small portion of a solid was noted in the condenser. Cooling in an ice bath caused the oily layer to solidify. Filtration and recrystallization from pentane gave unchanged amide, m.p. 120-122°. Sixty eight percent of the starting material was recovered after the recrystallization.

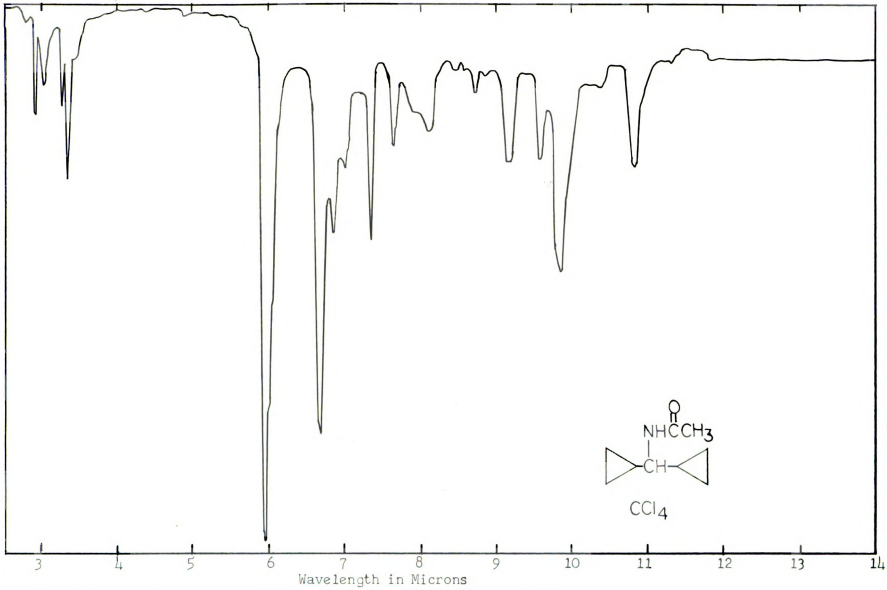


Figure 19. The Infrared Spectrum of N-Dicyclopropylcarbinylacetamide.

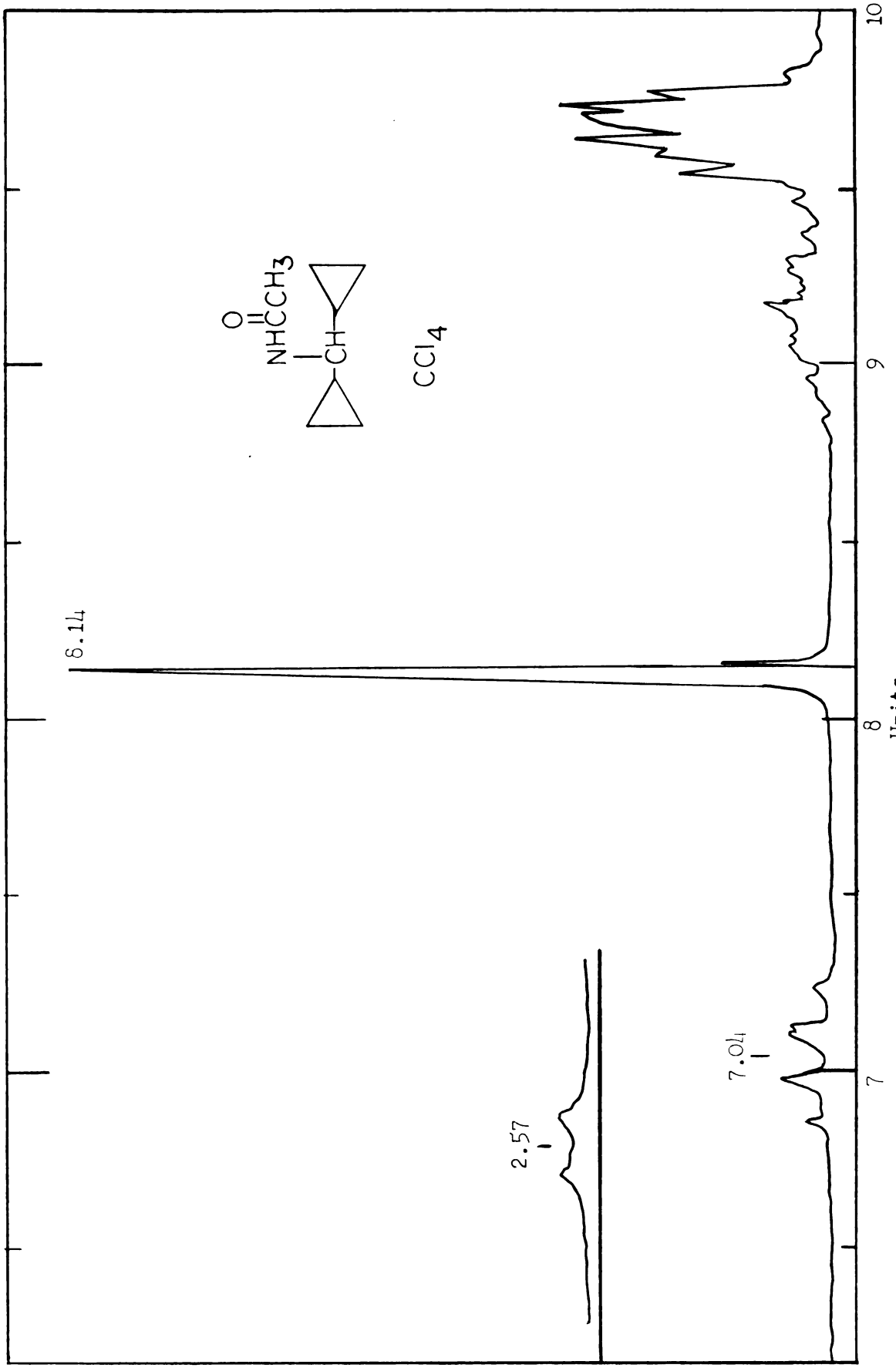


Figure 20. The N.M.R. Spectrum of N-Dicyclopropylcarbinylacetamide.

In a similar experiment the amide was refluxed in methanolic sodium hydroxide for 50 hours. It also was unsuccessful.

6. Preparation of Dicyclopropylcarbinylamine by the Leuckart Reaction with Dicyclopropyl Ketone (52,99)

To a 100-ml. round-bottomed flask equipped with a Barrett water separator and a reflux condenser were added 20.0 g. (0.18 mole) of dicyclopropyl ketone and 45.0 g. (0.72 mole) of ammonium formate. The flask was heated on a sand bath whose temperature was maintained between 180-240°. After the reaction mixture had become homogeneous, it was refluxed for an additional six hours during which time it became quite dark. After cooling, the formyl derivative and any unreacted ketone were extracted from formamide with benzene. A portion of the benzene was removed by evaporation. To the benzene solution of N-dicyclopropylcarbinylformamide was added 15 g. of sodium hydroxide in 160 ml. of 89% ethanol and the mixture was refluxed for twenty hours. A major portion of the solvent was removed by distillation, about 200 ml. of water was added, and hydrochloric acid was added until a pH of 3 was obtained. This acidic solution of the amine hydrochloride was extracted with ether, and the amine liberated from the aqueous solution by addition of sodium hydroxide pellets. The amine was extracted with ether, the ether solution dried over magnesium sulfate, treated with Norite, and the solids removed by filtration. The solvent, including some ethanol which remained, was distilled. Distillation under reduced pressure through a vacuum-jacketed Vigreux column gave 8.83 g. (43.7%) of dicyclopropylcarbinylamine, b.p. 60-60.5° at 27 mm.

The infrared spectrum of this product was similar to that of the amine obtained by the lithium aluminum hydride reduction of the ket-oxime. Analysis by gas chromatography indicated a similar minor impurity on the fore-side of the main peak. Several grams of higher boiling amine, probably secondary amines, remained in the distillation flask and were discarded.

In a similar Leuckart reaction (52) employing formamide and sufficient formic acid (added periodically) to maintain a slightly acidic medium, there was obtained a 32.5% yield of dicyclopropyl-carbinylamine. Gas chromatography showed no fore-shoulder as with other preparations of this amine, but both fractions contained a higher boiling material, indicating the formation of a greater amount of secondary amine.

7. Preparation of Dicyclopropylcarbinylamine-α-d_1

Tetrahydrofuran was scrupulously dried by distillation from sodium and then again from a mixture of lithium aluminum hydride and sodium hydride. To a suspension of 2.0 g. (0.048 mole) of lithium aluminum deuteride in 100 ml. of tetrahydrofuran was added a solution of 6.3 g. (0.050 mole) of dicyclopropyl ketoxime in 25 ml. of tetra-hydrofuran over a one hour period. The reaction mixture was refluxed for an additional 3 1/2 hours. The work up procedure B (with a saturated sodium sulfate solution) was used. The liquid product was fractionally distilled under reduced pressure through a small Vigreux column to give 1.90 g. (34% yield) of dicyclopropylcarbinylamine-α-d_1, b.p. 63° at 23 mm. There was recovered 3.74 g. of unchanged oxime. Based on recovered oxime the yield was 82%.

The deutero amine also reacts with carbon dioxide in the atmosphere to give a white precipitate. The infrared (Figure 21) and n.m.r. (Figure 22) spectra are consistent with the assigned structure.

B. Deamination of Dicyclopropylcarbinylamine and Identification of Products

1. Deamination of Dicyclopropylcarbinylamine in an Acetic Acid-Acetic Anhydride Mixture

To a stirred solution (magnetic stirrer) of 1.95 g. (0.018 mole) of dicyclopropylcarbinylamine in 30 ml. of acetic acid and 2 ml. of acetic anhydride was added over a one hour period 2.0 g. of sodium nitrite. After addition, the mixture was stirred for one hour, another 2.0 g. of sodium nitrite was added over a period of one hour, and the reaction mixture was stirred for an additional hour. The solution was neutralized by the addition of a saturated sodium bicarbonate solution. Copious evolution of carbon dioxide probably resulted in physical loss of some product. The aqueous solution was extracted with several portions of pentane. The combined pentane extracts were washed successively with water, dilute sodium bicarbonate, water, dilute hydrochloric acid, and again with water. After drying over magnesium sulfate, the pentane was removed by distillation through a Vigreux column with no attempt made to fractionate or record boiling ranges. Gas chromatographic analysis (Figure 23A) indicated the presence of twelve constituents in varying amounts. The solvent, pentane, gave a single peak in the gas chromatograph. No further attempt was made to identify the twelve components.

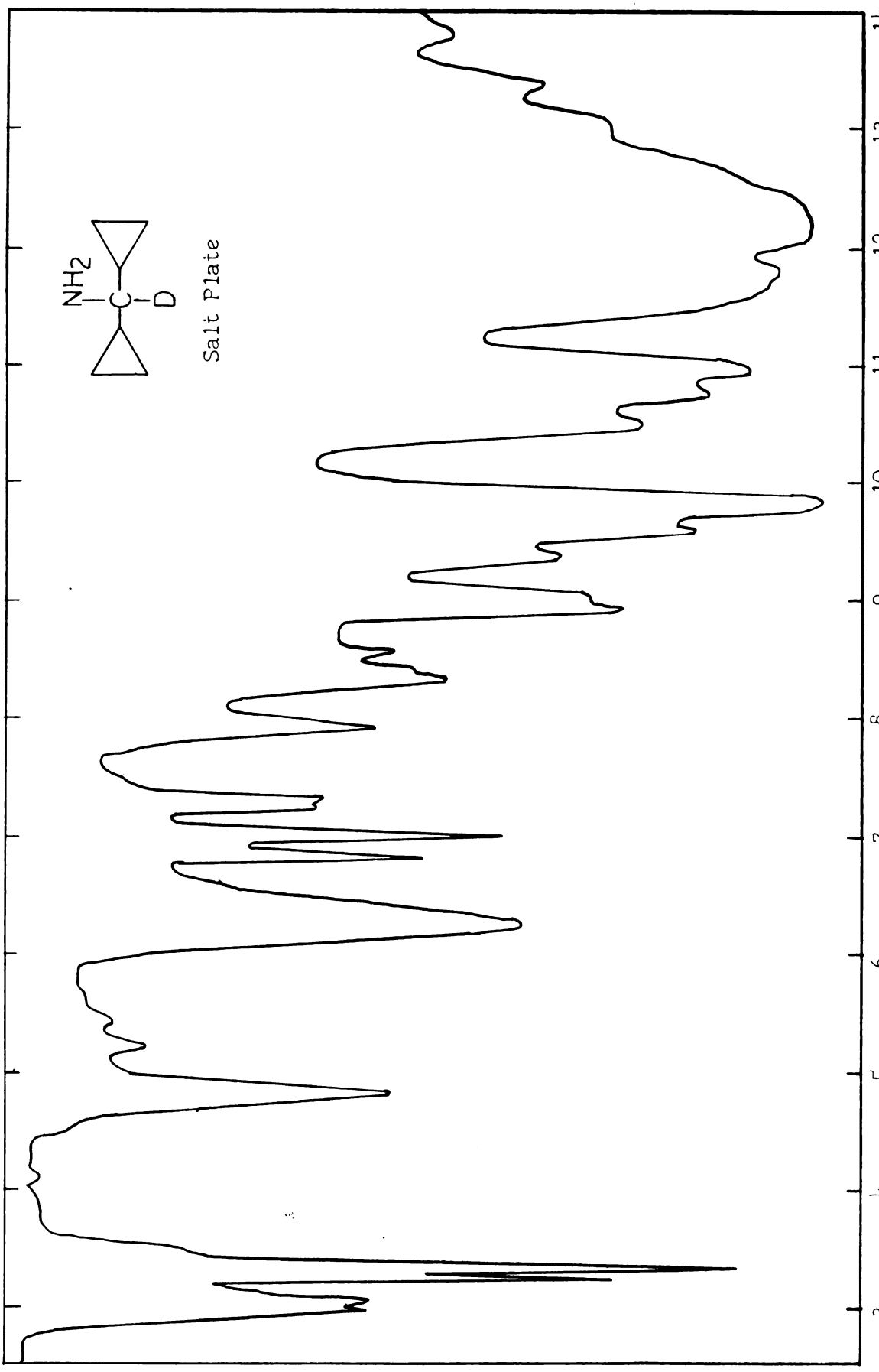


Figure 21. The Infrared Spectrum of Dicyclopropylcarbinylamine-α-d_1.

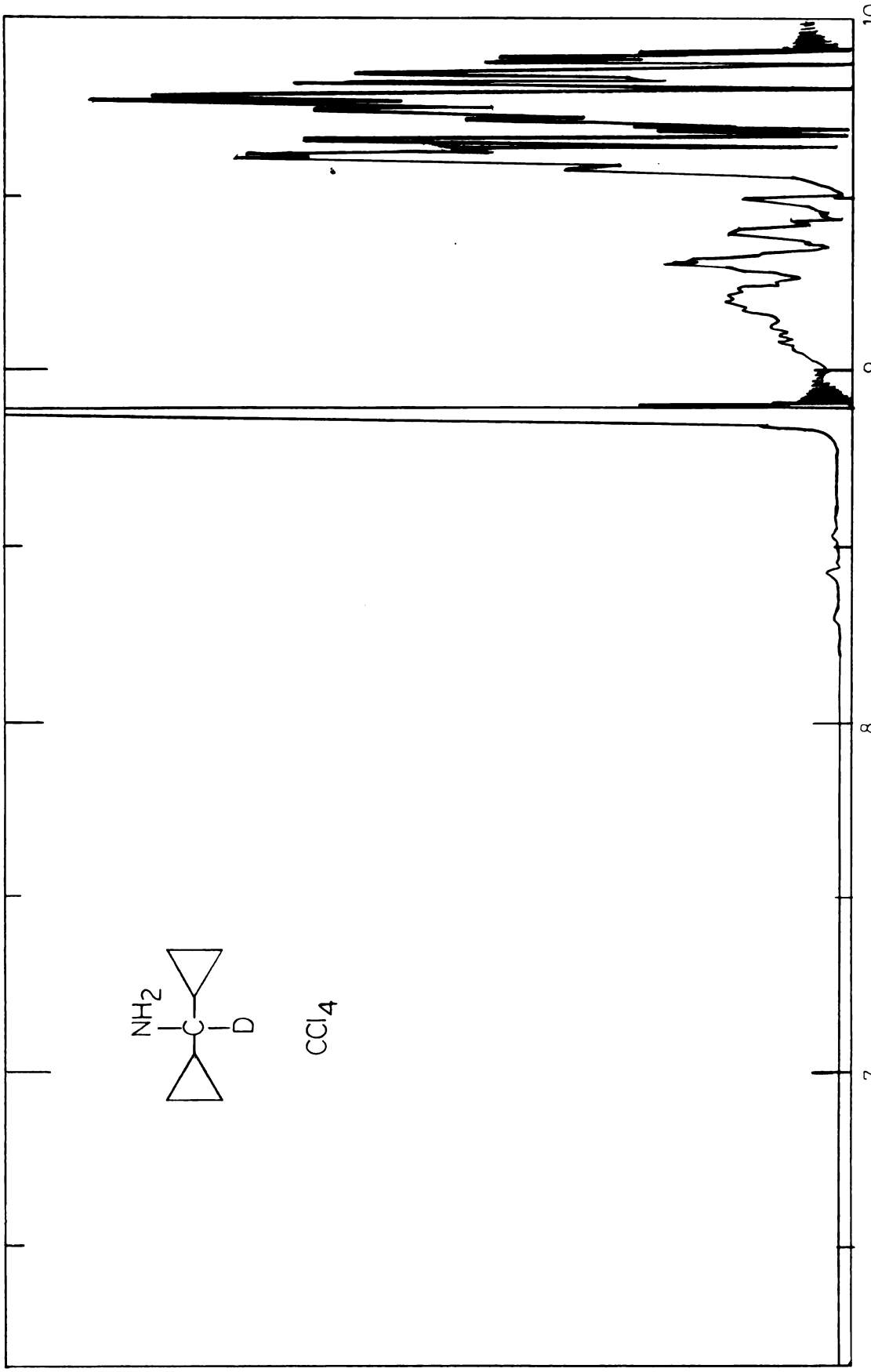


Figure 22. The N.M.R. Spectrum of Dicyclopropylcarbinylamine-a-d_1.

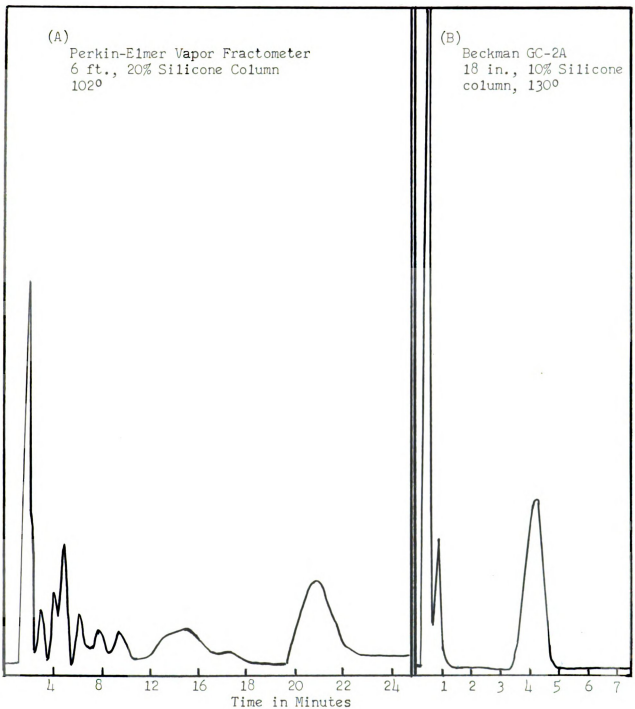


Figure 23. The Gas Chromatograph of the Products of Deamination of Dicyclopropylcarbinylamine.

2. Deamination of Dicyclopropylcarbinylamine (22)

A 300-ml. round-bottomed flask was equipped with a stirrer and condenser set downward for distillation. A dry ice trap was placed in series after the receiver to collect any low boiling product. To the cooled flask was added 2.6 g. (0.023 mole) of dicyclopropylcarbinylamine in 30 ml. of water, 28 ml. of 1 N perchloric acid previously cooled, and a cooled solution of 4.85 g. of sodium nitrite in 25 ml. of water. The ice bath was removed, stirring begun, and the reaction mixture heated with a mantle until 75 ml. of an aqueous-organic mixture had distilled over. The dry-ice trap contained only a small amount of an acidic aqueous solution (probably oxides of nitrogen in water). The aqueous-organic mixture was saturated with potassium carbonate and extracted with several portions of ether. After drying over a potassium carbonate-magnesium sulfate mixture, the solvent was removed by distillation through a tantalum spiral column to give 2.44 g. of organic product. Gas chromatographic analysis (Figure 23B) indicated the presence of three products in the ratio of approximately 11:1:4. Fractional distillation through a small Vigreux column only served to concentrate the various components in a given fraction. The first component, purified by gas chromatography, was shown to be dicyclopropylcarbinol. The infrared and n.m.r. spectra were identical with those of an authentic sample. Its retention times on a 20% and a 30% silicone column were identical with those of an authentic sample. The second component is as yet unidentified. Component three, also purified by gas chromatography, was assigned the structure of bisdicyclopropylcarbinyl ether, b.p. 54° at 0.09 mm., n_D^{25} 1.4709. The

infrared and n.m.r. spectra are shown in Figures 24 and 25 respectively.

Anal. Calc'd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75.

Found: C, 80.89, 80.81; H, 10.82, 10.68.

Deamination of impure dicyclopropylcarbinylamine, i.e., amine not purified by distillation through the spinning band column, and analysis by gas chromatography of the products indicated that it would be feasible to deaminate a similarly impure deuterated amine.

3. Deamination of Dicyclopropylcarbinylamine-α-d_1

Using the same procedure as for the non-deuterated amine, 1.8 g. (0.016 mole) of dicyclopropylcarbinylamine-α-d_1 was deaminated to give a product mixture similar to that obtained from impure dicyclopropylcarbinylamine. The infrared and n.m.r. spectra of the major (> 80%) product, dicyclopropylcarbinol-α-d_1, are shown in Figures 26 and 27 respectively. The infrared spectrum of the unidentified deamination product (Figure 28) shows cyclopropane C-H stretching, 3.26 μ, C-D stretching at 4.85 μ, a very weak band at 2.80 μ, and a band at 6.13 μ which may be due to carbon-carbon double bond stretching. The presence of the symmetrical ether was indicated by a peak of identical retention time on the gas chromatograph.

4. Attempted Reaction of N-dicyclopropylcarbinylacetamide with Nitrous Acid (Sodium Nitrite and Acetic Acid) (100,101)

A solution of 3.0 g. (0.02 mole) of N-dicyclopropylcarbinylacetamide in 30 ml. of acetic acid and 3 ml. of acetic anhydride was placed in a round-bottomed flask equipped with Allihn condenser and magnetic stirrer and cooled with an ice bath. To the stirred solution

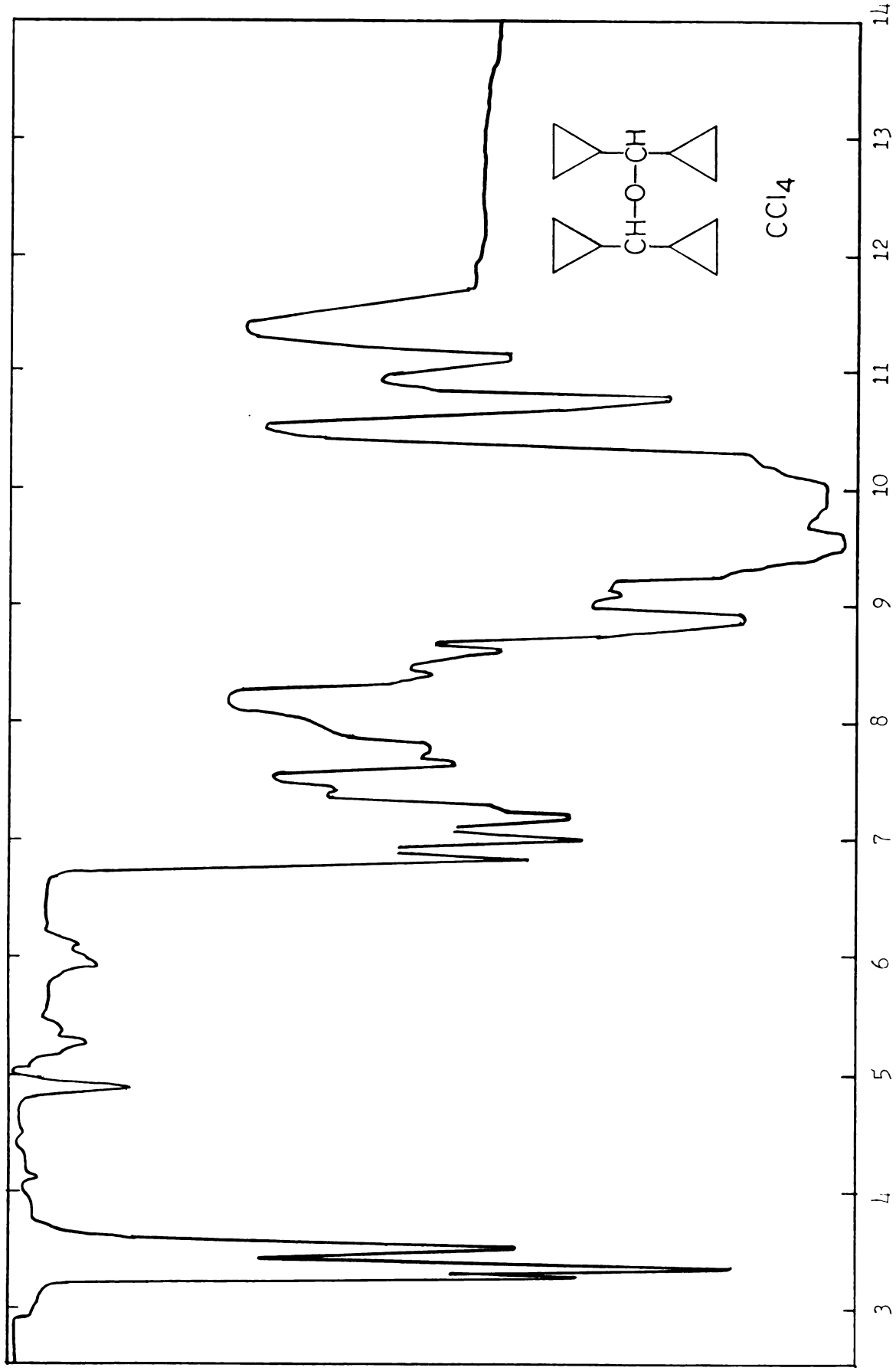


Figure 24. The Infrared Spectrum of Bis-dicyclopropylcarbinyl ether.

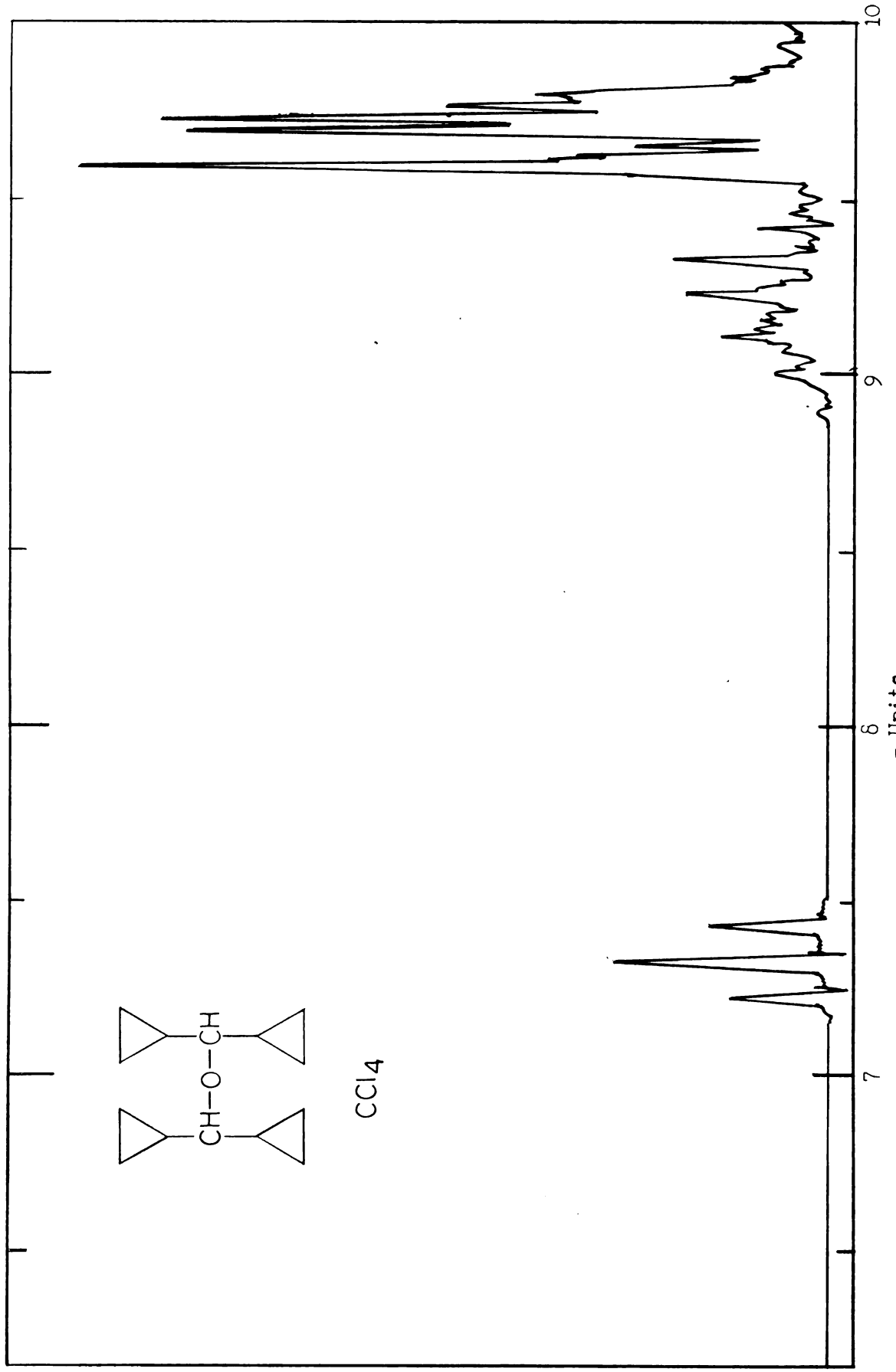


Figure 25. The N.M.R. Spectrum of Bis-dicyclopropylcarbinyl ether.

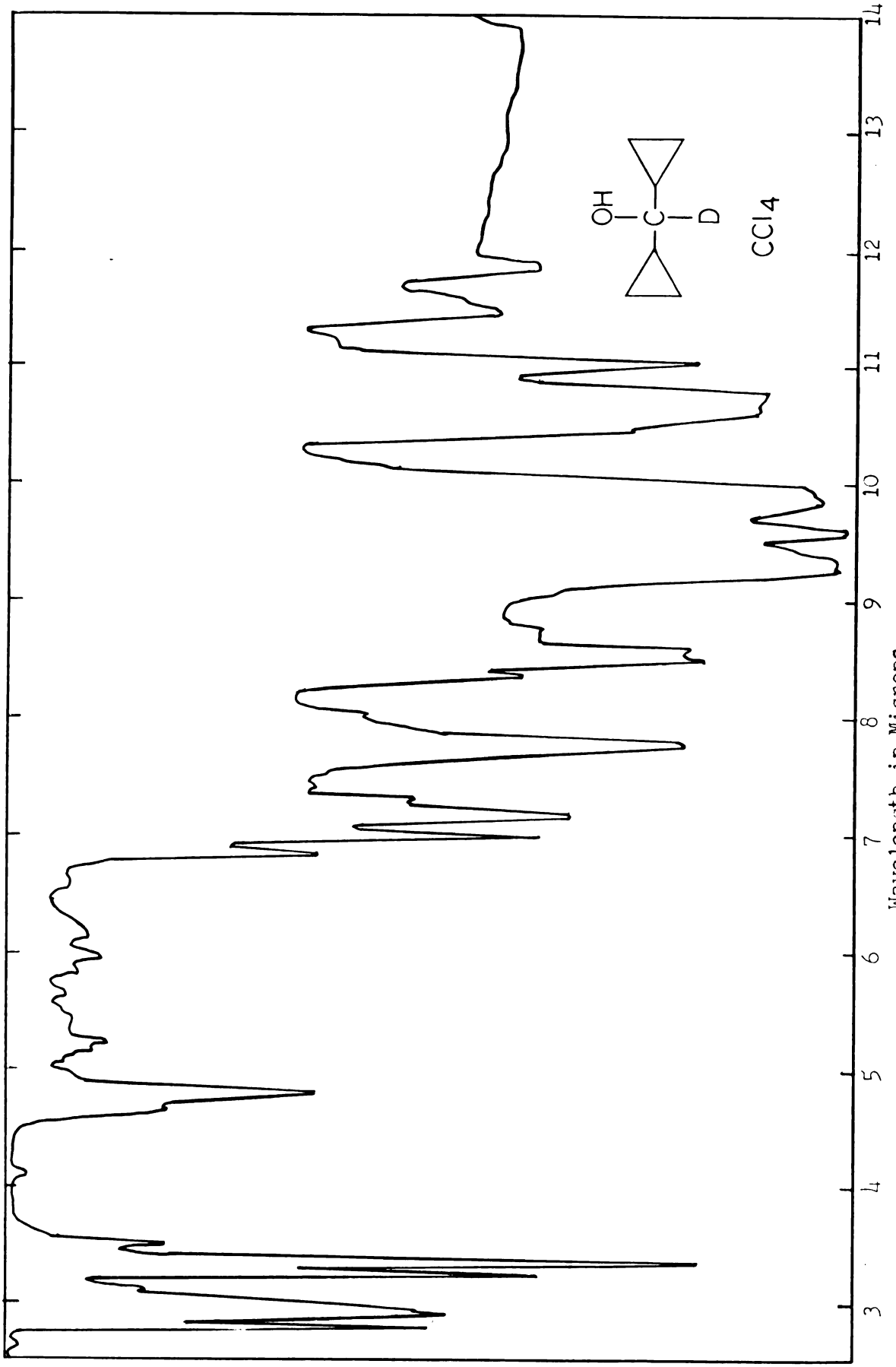


Figure 26. The Infrared Spectrum of Dicyclopropylcarbinol-α-d_1.

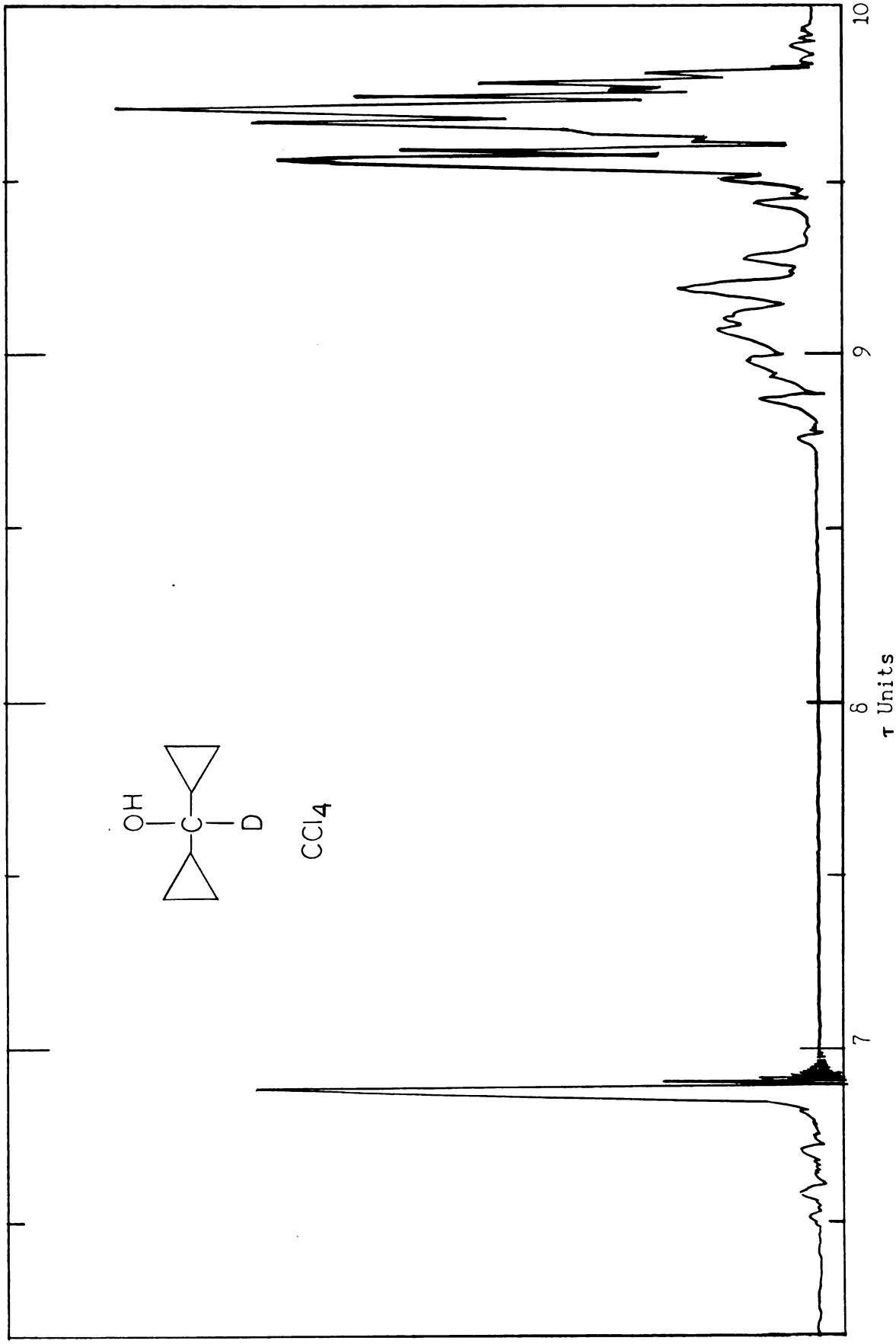


Figure 27. The N.M.R. Spectrum of Dicyclopropylcarbinol-α-d_1.

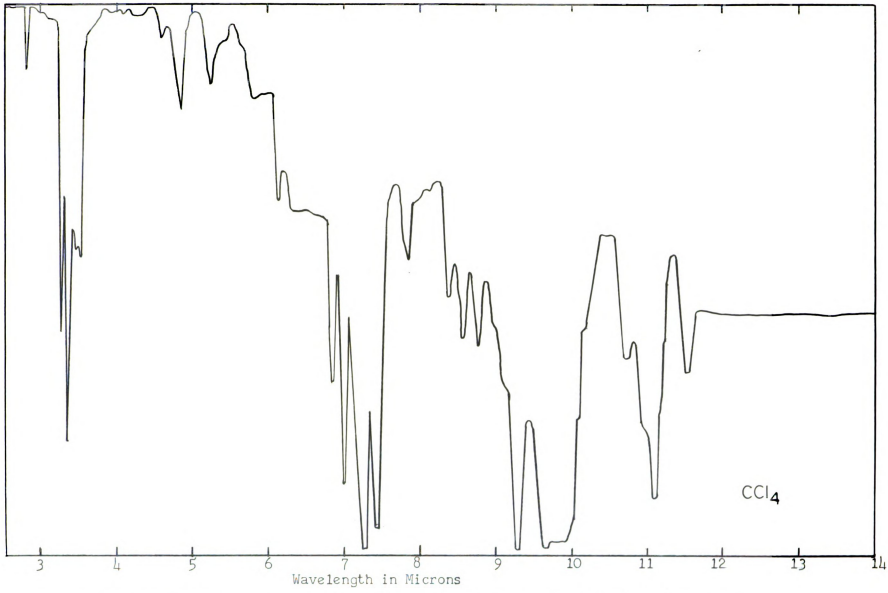


Figure 28. The Infrared Spectrum of the Unidentified Product of Deamination of Dicyclopropyl-carbinylamine-α-d_1.

was added 2.0 g. of sodium nitrite over a forty-minute period, and the mixture was stirred for an additional six hours at ice bath temperature. An additional 2 g. of sodium nitrite and 10 ml. of acetic acid were added, the mixture was stirred for one hour at ice bath temperature, and then allowed to come to room temperature over the weekend. (Several N-nitroso-N-alkylamides are known to decompose with violence at or above room temperature.) While the orange-red solution was heated on a steam bath for twenty-six hours, it became progressively darker, and a white solid suspended in the liquid disappeared. It appeared as if bubbles were slowly being evolved during this heating period. After cooling, the acidic reaction mixture was neutralized by the addition of ice-cold 10% sodium hydroxide. The basic medium was extracted with several portions of pentane, the extracts dried over magnesium sulfate, and the solvent removed by distillation through a Vigreux column to give 2.2 g. of a crude whitish precipitate. A melting point determination and mixed melting point showed the material to be unchanged amide.

5. Preparation of Dicyclopropylcarbinol

The procedure of O. E. Curtis was employed (102). To a slurry of 1.5 g. (0.04 mole) of lithium aluminum hydride in 100 ml. of ether was added dropwise a solution of 11 g. (0.10 mole) of dicyclopropyl ketone in 25 ml. of ether. After the fifteen-minute addition period, the reaction mixture was refluxed for one hour, cooled in an ice bath, and the excess hydride decomposed by dropwise addition of a saturated sodium sulfate solution. The solution was dried by the addition of

magnesium sulfate and stirring for 30 minutes. After filtration the solvent was removed by distillation on a steam bath and the liquid was distilled under reduced pressure to give 9.34 g. (83.5% yield) of dicyclopropylcarbinol, b.p. 55° at 3 mm., literature value: (102) 48° at 3 mm.

Whereas gas chromatography gave a single peak for the starting ketone, the reduction products gave small shoulders before and after the main peak. Total impurity was less than 5%. The 2,4-dinitrobenzoate was prepared by the method of Applequist (96), yellow needles, m.p. 83.5-84.5°, literature value: (102) 84-85°.

6. Reaction of Dicyclopropylcarbinol with Dilute Perchloric Acid

To an ice-cold suspension of five grams of dicyclopropylcarbinol in 140 ml. of water in a flask equipped with stirrer and condenser set downward for distillation was added 55 ml. of 1 N perchloric acid. The mixture was stirred at ice-bath temperature for five minutes. The ice-bath was replaced by a heating mantle and the organic product was steam distilled at a rapid rate into a vessel containing solid potassium carbonate. The distillate was saturated with potassium carbonate, extracted with ether, and the ether solution dried over a mixture of potassium carbonate and magnesium sulfate. Removal of the solvent by distillation through a Vigreux column gave 4.25 g. (85% recovery) of crude product. Analysis by gas chromatography indicated one major component in 75-81% yield and several minor components whose composition varied in the course of several runs. The contents of the reaction flask were extracted with ether. Removal of the solvent

after drying gave 0.35 g. of a viscous material (probably polymeric) which was discarded. The crude mixture was fractionally distilled to give 2.1 g. of 2-cyclopropyltetrahydrofuran, b.p. 38.5-39° at 13 mm., n_D^{25} 1.4655. The assigned structure is consistent with the infrared (Figure 29) and n.m.r. (Figure 30) spectra.

Anal. Calc'd. for $C_7H_{12}O$: C, 74.95; H, 10.79.

Found: C, 74.09; H, 10.49

Further distillation at lower pressures gave 0.60 g. of a mixture of products. The major one, 4-cyclopropyl-3-butene-1-ol, was isolated by gas chromatography. The infrared (Figure 31) and n.m.r. (Figure 32) spectra are consistent with this structure.

Anal. Calc'd. for $C_7H_{12}O$: C, 74.95; H, 10.79.

Found: C, 74.73; H, 11.07.

7. Reaction between Dicyclopropylcarbinol, Ammonia, Perchloric Acid and Sodium Nitrite

It was the intent of this experiment to simulate the experimental conditions obtained in the work up of the deamination products of dicyclopropylcarbinylamine. To an ice-cold 500-ml. round-bottomed flask equipped with stirrer and condenser set downward for distillation was added 2 g. (0.0178 mole) of dicyclopropylcarbinol, 2.4 ml. of concentrated ammonium hydroxide (28%, specific gravity 0.9) diluted with 35 ml. of water, 42.6 ml. of 1 N perchloric acid and a solution of 7.4 g. (0.107 mole) of sodium nitrite in 40 ml. of water. After stirring for five minutes, the ice bath was replaced with a heating mantle and the products were steam distilled into a flask which contained

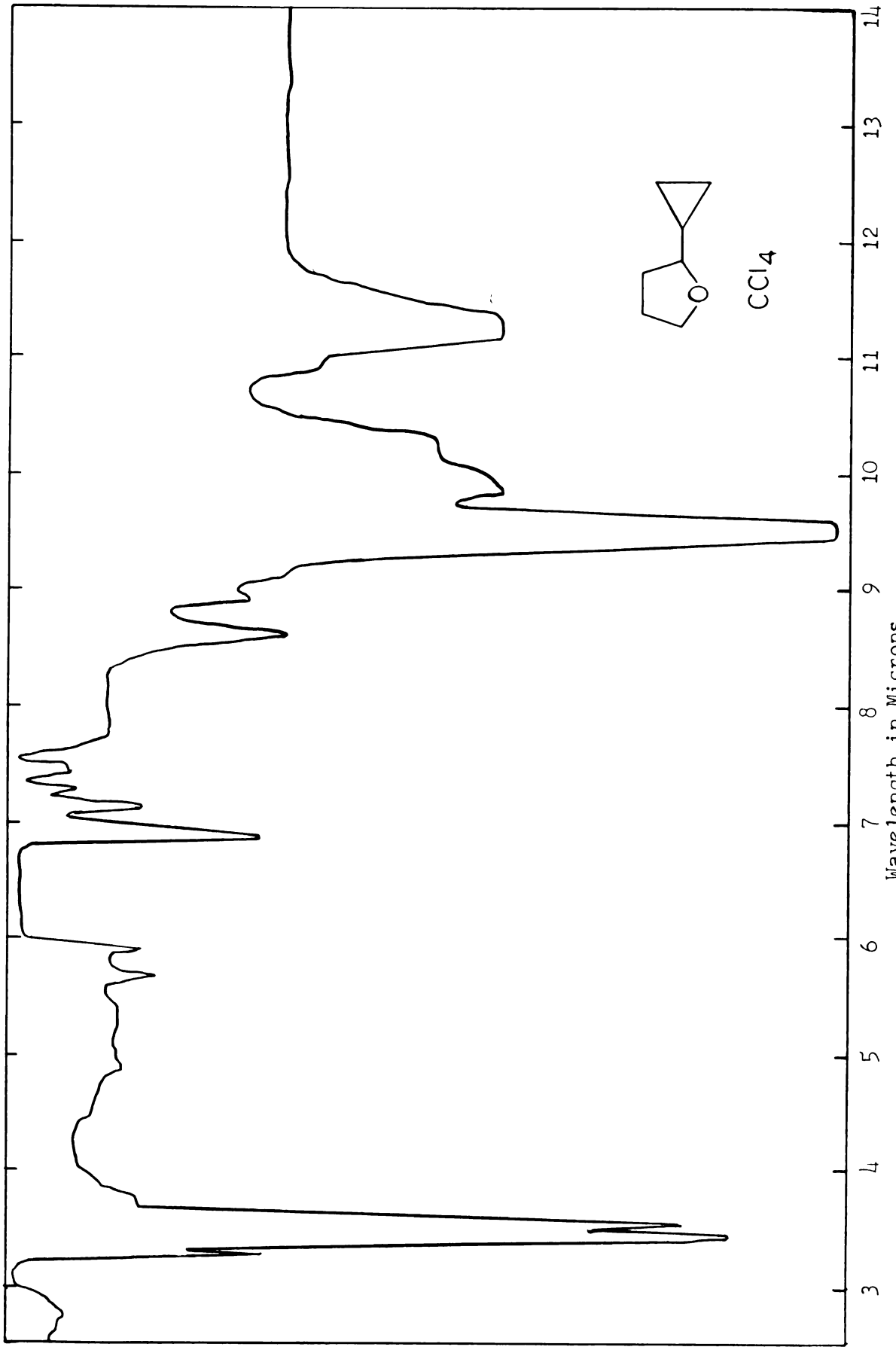


Figure 29. The Infrared Spectrum of 2-Cyclopropyltetrahydrofuran.

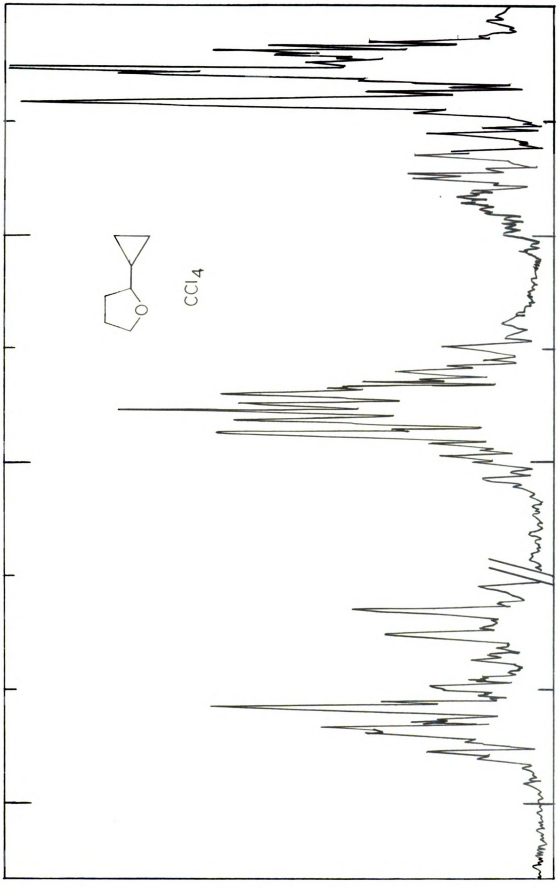


Figure 30. The N.M.R. Spectrum of 2-Cyclopropyltetrahydrofuran.

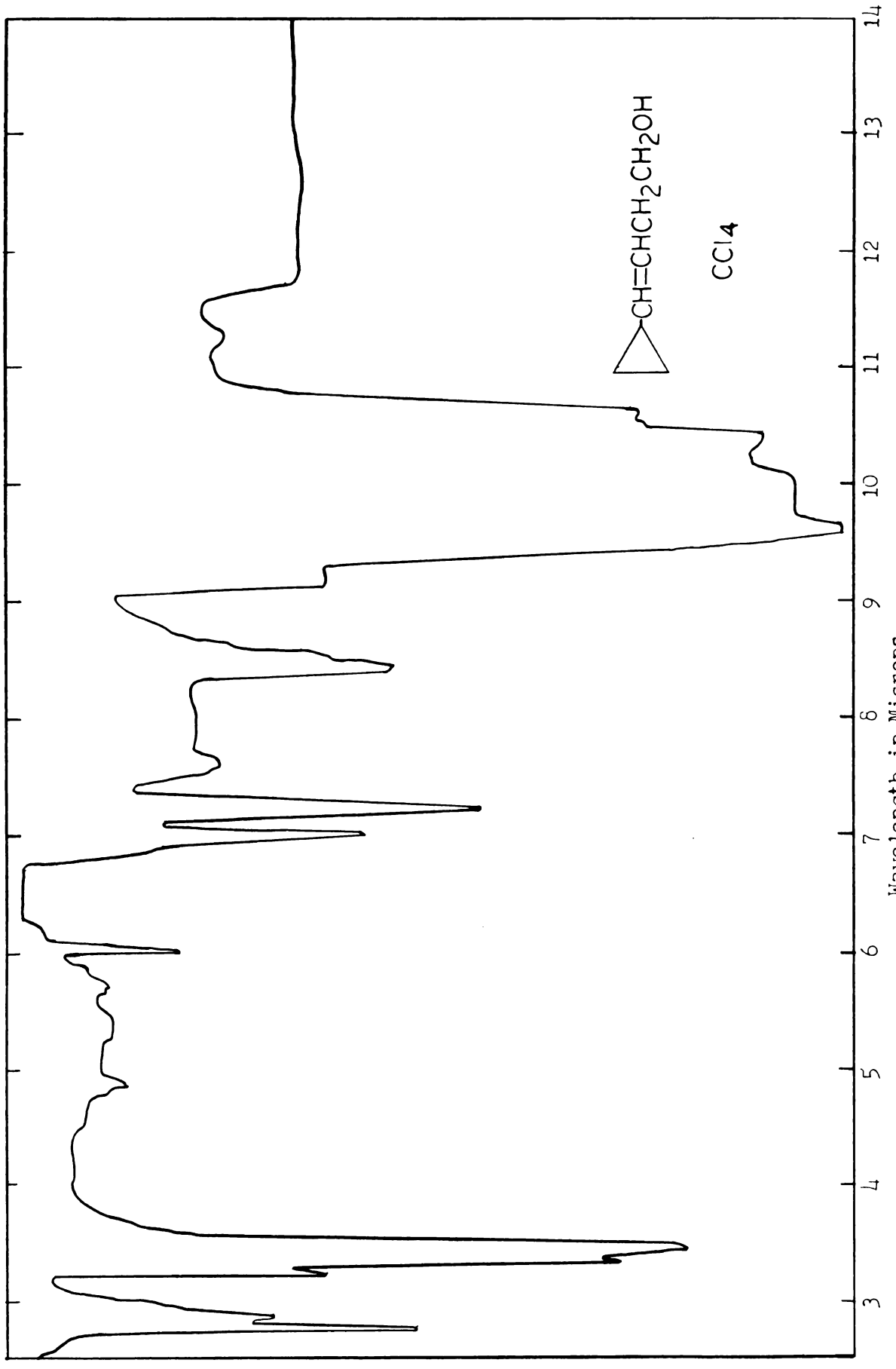


Figure 31. The Infrared Spectrum of 4-Cyclopropyl-3-butene-1-ol.

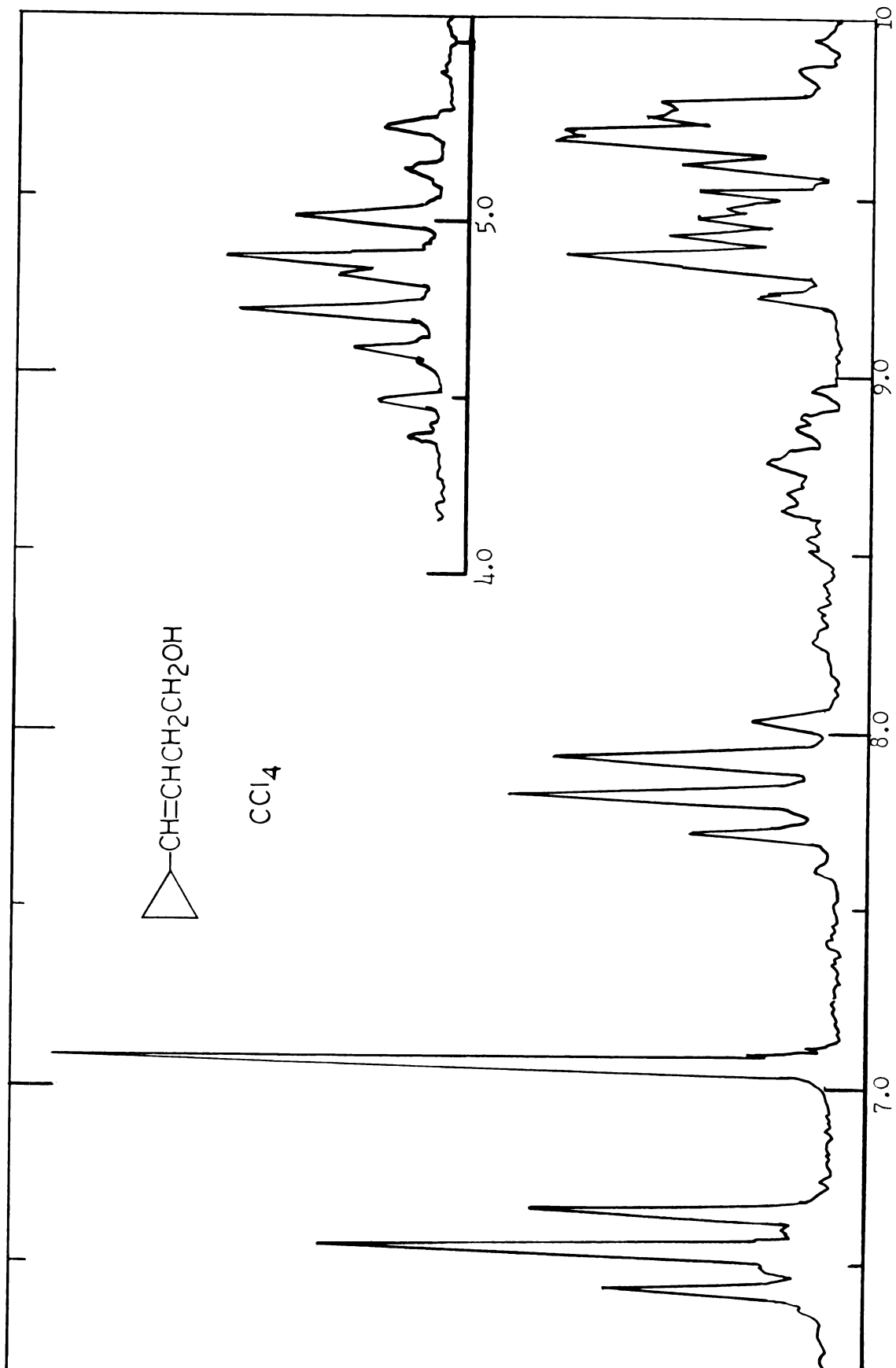


Figure 32. The N.M.R. Spectrum of 4-Cyclopropyl-3-butene-1-ol.

15 g. of potassium carbonate. The distillate was saturated with potassium carbonate, extracted with several portions of ether and the ether extracts dried over anhydrous potassium carbonate. Evaporation of the ether on a steam bath gave 1.88 g. of crude material (94% recovery). Analysis by gas chromatography (18 inch column, 10% silicone and 6 foot column, 30% silicone) indicated the presence of the same constituents as those obtained in the deamination of dicyclopropylcarbinylamine, one of which had not been previously located until the 18 inch column was used. Unreacted dicyclopropylcarbinol was present in over 80%. Bis-dicyclopropylcarbinyl ether was obtained in about 3% yield and an as yet unidentified third product, A, in about 15% yield. Retention times at 130° for the three compounds are as follows: 18 inch column, 10% silicone, alcohol, 20 sec.; product A, 40 sec.; the ether, 3 min. 20 sec. Six foot column, 30% silicone, alcohol, 11 2/3 min.; product A, 36 min., the ether, over two hours.

III. Miscellaneous Experiments

A. Synthesis of Diisopropylcarbinylamine

1. Preparation of Diisopropylcarbinylamine by the Leuckart Reaction (52, 99) with Diisopropyl ketone

To a 100-ml. round-bottomed flask equipped with a Barrett water separator and reflux condenser was added 20 g. (0.175 mole) of diisopropyl ketone and 45 g. (0.725 mole) of ammonium formate. The reaction mixture was heated at reflux for twenty hours on a sand bath. After cooling, 100 ml. of water was added to cause the formamide to separate. The formyl derivative of the amine was extracted with several portions of benzene. After removal of most of the benzene by distillation, the formyl derivative was hydrolyzed by refluxing for twenty hours with 200 ml. of a 1:1 mixture of concentrated hydrochloric acid and water. The solution was extracted with ether and the aqueous layer was treated with sodium hydroxide pellets to liberate the free amine. The amine layer was extracted with ether, the combined extracts dried over magnesium sulfate, the drying agent removed by filtration, and the solvent removed by distillation through a Vigreux column. Distillation at atmospheric pressure through a 45 cm. tantalum spiral column gave diisopropylcarbinylamine, fraction one, 1.66 g., b.p. 125-128.5°, n_D^{25} 1.4215 and fraction two, 3.57 g., b.p. 128°, n_D^{25} 1.4220, literature value: (103) 129°. The total yield, 5.23 g. was 25.5% of theory.

The infrared spectrum (Figure 33) is consistent with that of a primary aliphatic amine. The n.m.r. spectrum (Figure 34) is very

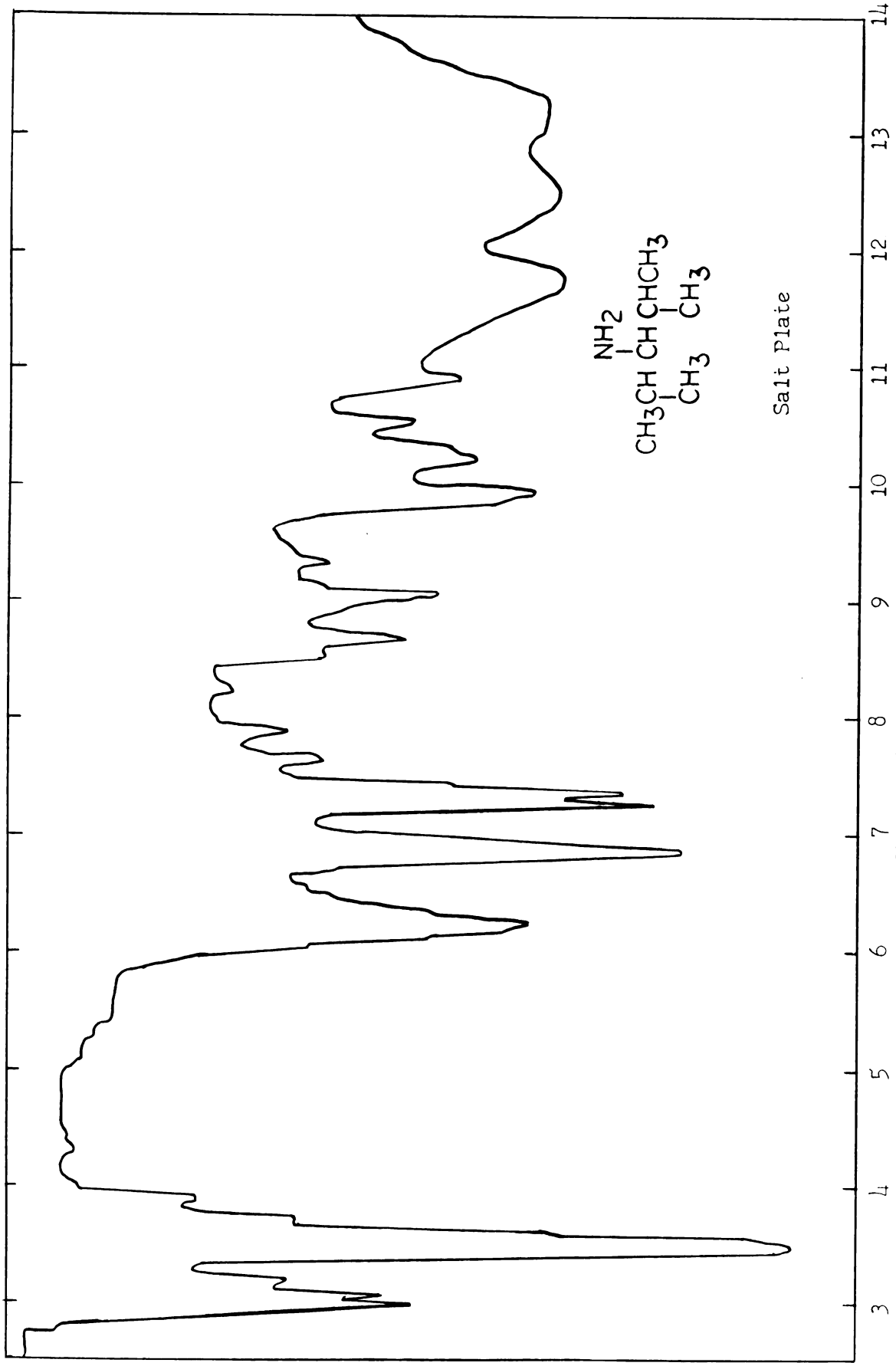


Figure 33. The Infrared Spectrum of Diisopropylcarbinylamine.

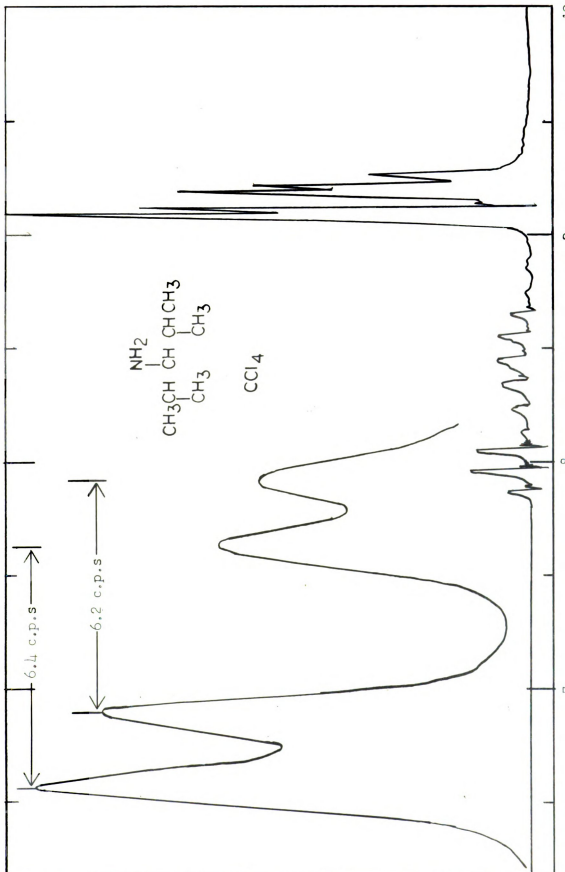


Figure 34. The N.M.R. Spectrum of Diisopropylcarbinylamine.

interesting in that there is a pair of doublets for the methyl hydrogens. A precipitate gradually formed in the n.m.r. tube until, after several days, it seemed to fill the tube. As it increased, the quality of the spectrum deteriorated.

A solution of 0.30 g. of diisopropylcarbinylamine in 10 ml. of ether was saturated with hydrogen chloride gas, generated by dropwise addition of concentrated hydrochloric acid into concentrated sulfuric acid. The precipitate which formed immediately was collected on a filter and washed with ether to give 0.34 g. of diisopropylcarbinylamine hydrochloride, m.p. 195-6°, literature value: (103) 196°.

2. Preparation of Diisopropyl Ketoxime

Diisopropyl ketone (57.0 g., 0.50 mole) and hydroxylamine hydrochloride (41.7 g., 0.60 mole) were placed in a one-liter three-necked round-bottomed flask equipped with stirrer, dropping funnel and Friedrichs condenser. To this was added with stirring 47.9 g. (0.57 mole) of sodium bicarbonate in 180 ml. of water. Evolution of carbon dioxide caused considerable frothing. After six hours reflux, the solution was cooled, separated, and the aqueous layer was extracted with ether. The combined organic portions were dried over magnesium sulfate, filtered, and the solvent removed by distillation through a 20-cm. Vigreux column. The fact that the residue failed to solidify upon cooling indicated that it was impure. Fractional distillation at reduced pressure produced two major fractions. Fraction one contained 17.0 g. of unchanged starting material, b.p. 72-83° at 100 mm., literature value: (104) 70.58° at 123.76 mm. There was an intermediate fraction

of 2.5 g. The second major fraction contained 32.4 g. (76% yield based on recovered ketone) of diisopropyl ketoxime, b.p. 98-103° at 25 mm., m.p. 27-33°, literature value: (105) b.p. 91.5° at 21 mm., m.p. 34°. The infrared spectrum is shown in Figure 35. The n.m.r. spectrum at room temperature (Figure 36) though consistent with assigned structure shows an unusual two doublets for the methyl hydrogens (61). At 0° and -25° this pair of doublets begins to coalesce until at -50° it appears as a single, though somewhat broader, doublet. These three spectra are shown in Figure 37.

3. Lithium Aluminum Hydride Reduction of Diisopropyl Ketoxime

Since a previous reduction with lithium aluminum hydride had resulted in a multiplicity of products, a sample of diisopropyl ketoxime was redistilled. The material boiling from 80.5-83° at 9 mm. was used in this preparation. To a stirred suspension of 3.8 g. of lithium aluminum hydride in 150 ml. of anhydrous tetrahydrofuran was added a solution of 10 g. (0.077 mole) of diisopropyl ketoxime in 40 ml. of tetrahydrofuran over a ten-minute period. The suspension was stirred at reflux for twelve hours. Excess lithium aluminum hydride was decomposed by dropwise addition of a saturated sodium sulfate solution. The solution was dried by continued stirring with a large excess of magnesium sulfate. Inorganic salts were collected on a coarse scintered glass funnel and washed repeatedly with small portions of ether. The solvent was removed by distillation through a 50-cm. glass-packed column. Distillation of the residue at atmospheric pressure gave fraction one, 2.55 g., b.p. 117-126° and fraction

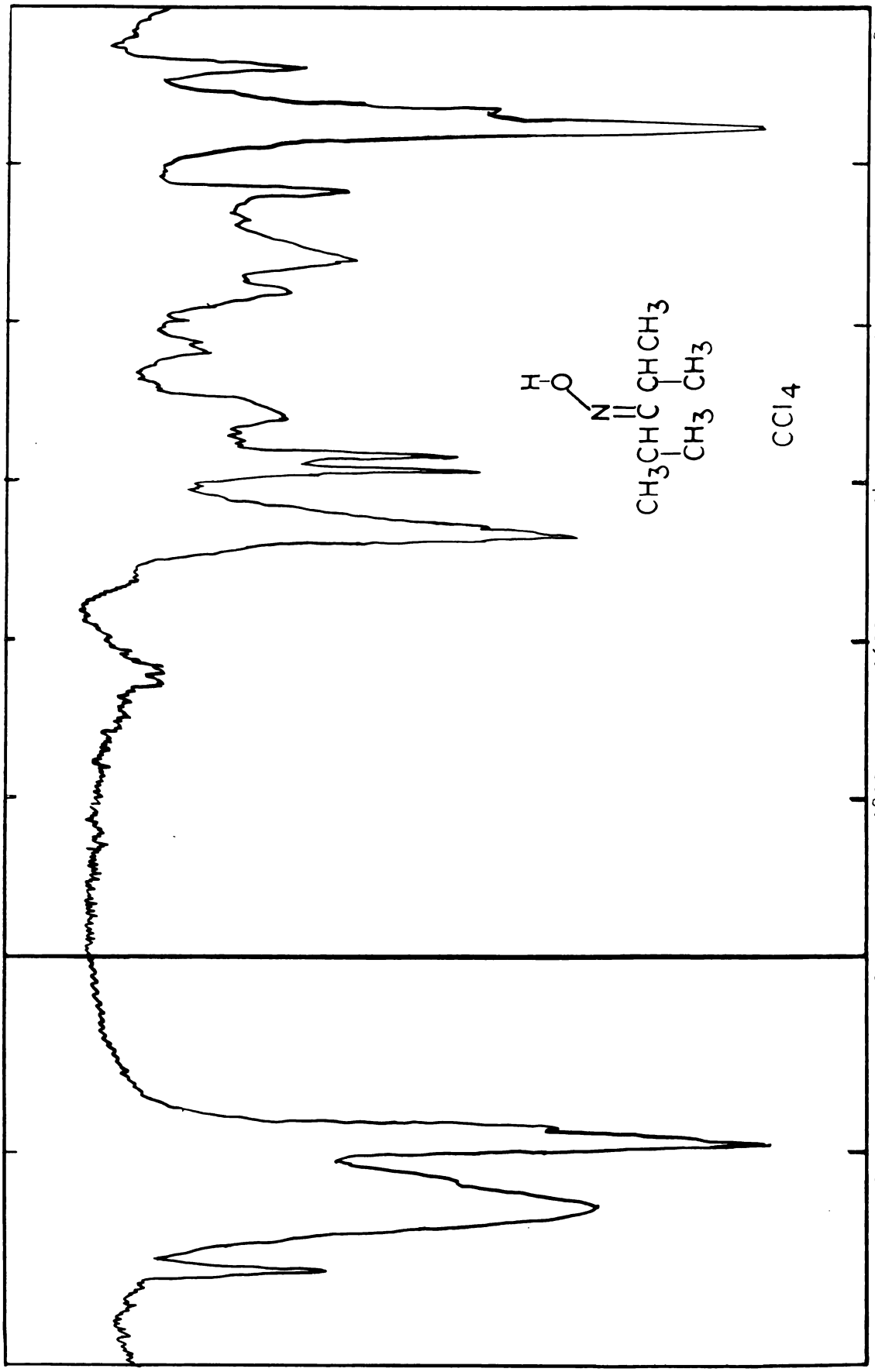


Figure 35. The Infrared Spectrum of Diisopropyl Ketoxime.

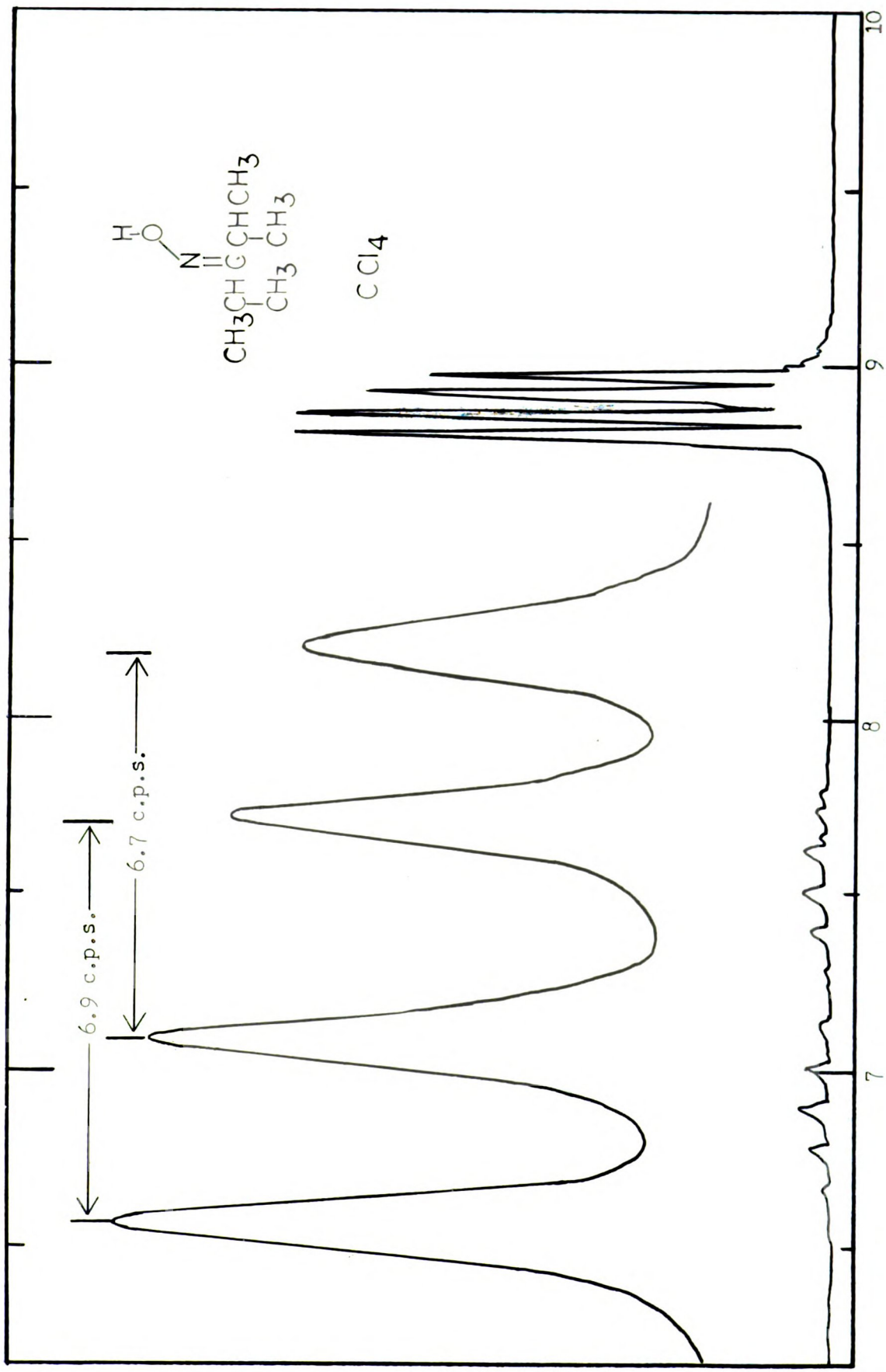


Figure 36. The N.M.R. Spectrum of Diisopropyl Ketoxime.

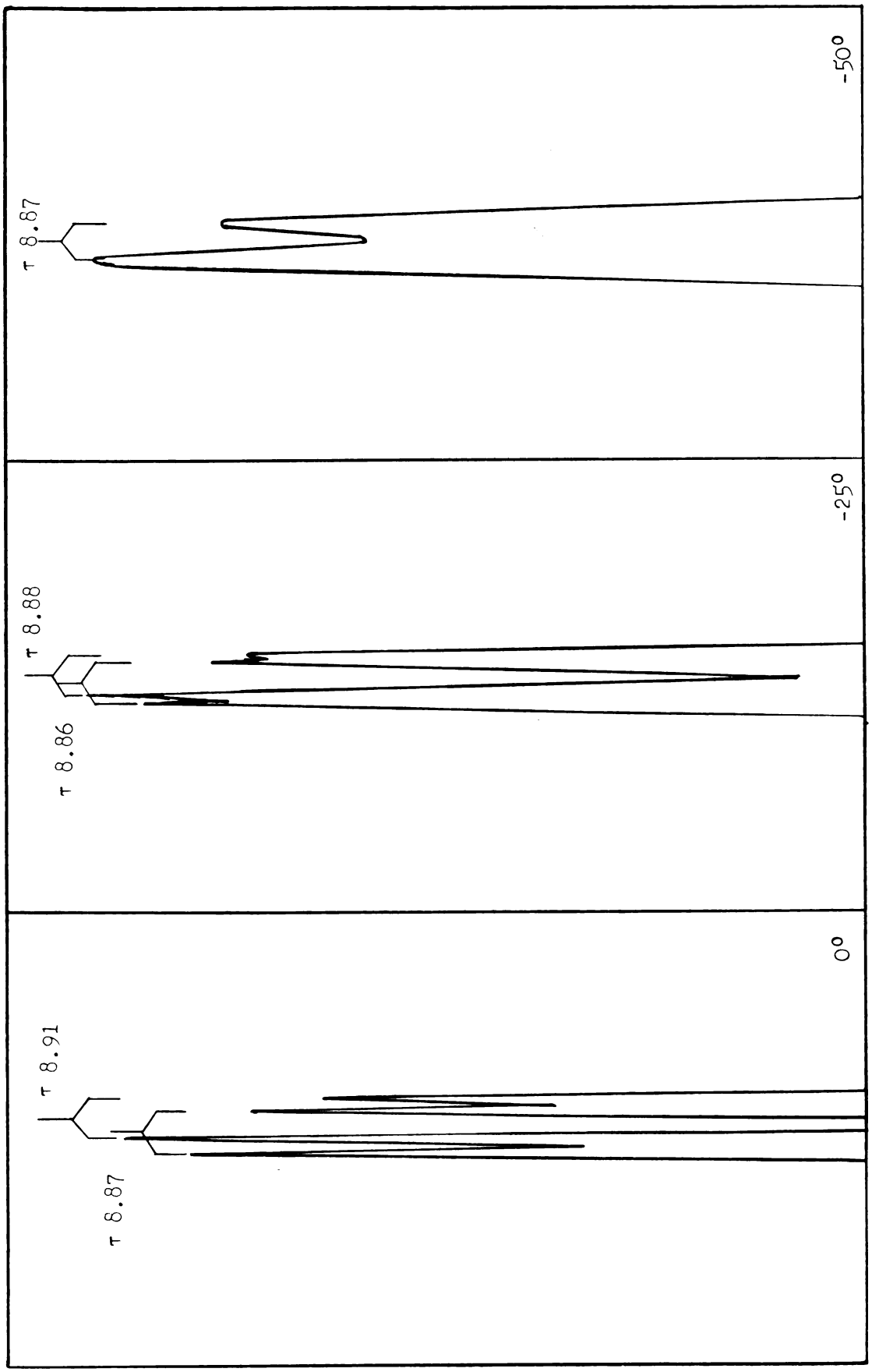


Figure 37. The N.M.R. Spectrum of Diisopropyl Ketoxime at Reduced Temperatures.

two, 1.73 g., b.p. 126.5-127.5°. There remained 2.71 g. of unreacted oxime. Analysis by gas chromatography showed a fore shoulder (about 20%) on fraction one. Fraction two is better than 95% pure diisopropylcarbinylamine.

B. Preparation of N-diisopropylcarbinylbenzamide

The Schotten-Bauman procedure was employed (106). To a glass-stoppered flask were added 0.50 g. of diisopropylcarbinylamine, 10 ml. of water, 2 ml. of benzoyl chloride and 10 ml. of 20% sodium hydroxide. The flask was shaken until all excess benzoyl chloride was hydrolyzed. The precipitate was collected on a filter and washed successively with water, dilute hydrochloric acid, and again with water to give 0.88 g. (93%) of N-diisopropylcarbinylbenzamide, m.p. 131-2°, literature value: (107) 129-30°.

The infrared and n.m.r. spectra are shown in Figures 38 and 39 respectively. The methyl hydrogens again give a pair of doublets in the n.m.r. spectrum.

C. Preparation of Diisopropylcarbinol

To a suspension of 1.66 g. (0.044 mole) of lithium aluminum hydride in 80 ml. of ether was added dropwise 10 g. (0.088 mole) of diisopropyl ketone in 20 ml. of ether. After addition the mixture was refluxed for four hours. The excess hydride was decomposed by dropwise addition of aqueous hydrochloric acid with cooling. Sufficient hydrochloric acid was added to dissolve all aluminum salts. The aqueous layer was extracted with several portions of ether, and the combined

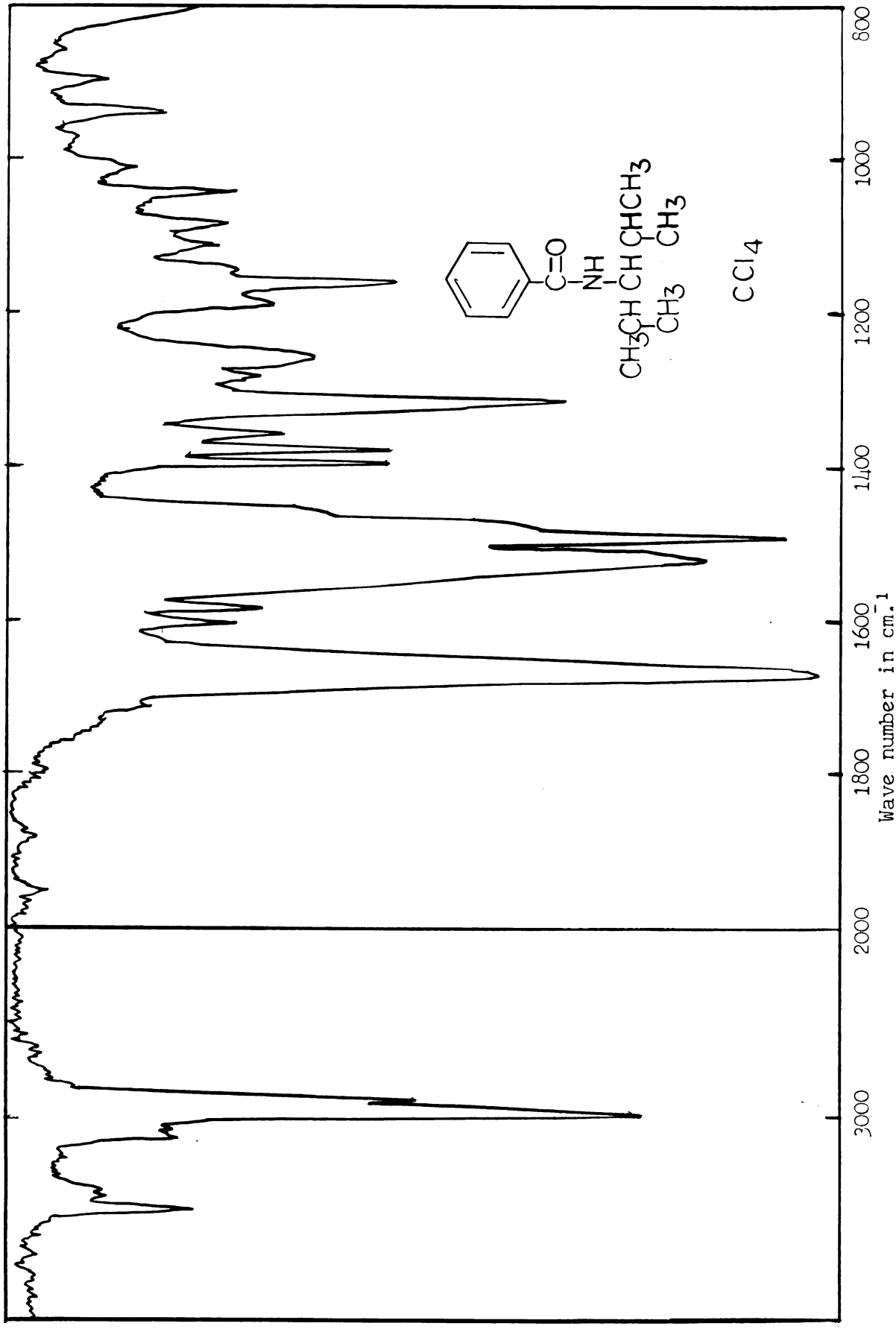


Figure 38. The Infrared Spectrum of N-Diisopropylcarbinylbenzamide.

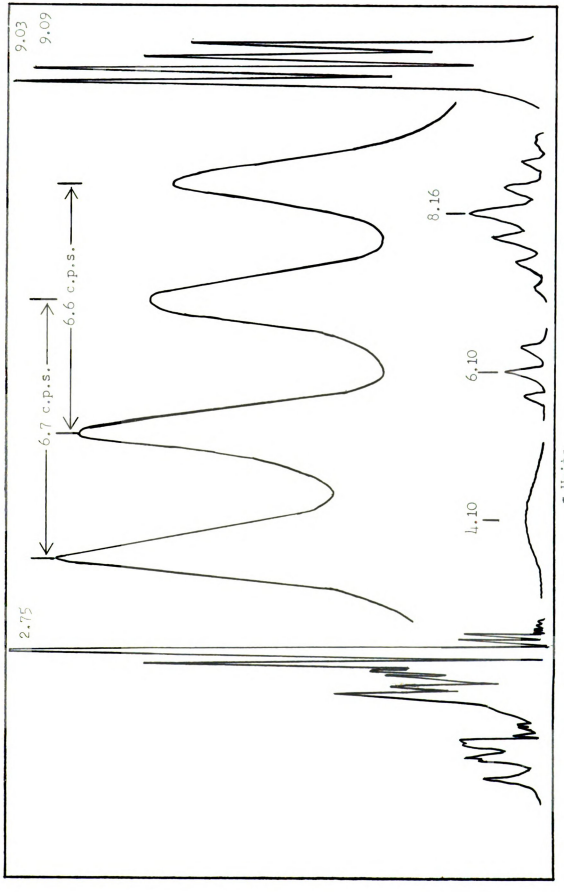


Figure 39. The N.M.R. Spectrum of N-Diisopropylcarbinylbenzamide.

ether extracts washed with water and dilute sodium bicarbonate. After drying over magnesium sulfate and filtering, the solvent was removed by distillation through a Vigreux column. Fractional distillation of the residue at atmospheric pressure gave two fractions of diisopropylcarbinol: 2.34 g. (95% pure by gas chromatographic analysis), b.p. 128.5-137°, and 4.64 g. (98% pure), b.p. 137-138°. Total yield of alcohol was 69% of theory. Analysis by gas chromatography showed that the starting material, diisopropyl ketone, was 97% pure.

Samples of the ketone and alcohol were purified by gas chromatography for n.m.r. analysis. The methyl hydrogens in both the ketone (Figure 40) and the alcohol (Figure 41) appear as doublets.

D. Preliminary Deamination of Diisopropylcarbinylamine

To an ice cold suspension of 1.9 g. (0.017 mole) of diisopropylcarbinylamine in 30 ml. of water was added 20 ml. of 1 N perchloric acid and a solution of 3.42 g. (0.05 mole) of sodium nitrite in 20 ml. of water. The solution was stirred continually and gradually heated to its boiling point. The product which steam distilled was collected in a flask containing 10 g. of potassium carbonate. The aqueous distillate was saturated with potassium carbonate and extracted twice with ether. The solution was dried over potassium carbonate, filtered, and the solvent removed by distillation. The residue was distilled at atmospheric pressure from a 5 ml. Claisen assembly with no attempt made to fractionate the product to give 0.83 g., b.p. 39-93°. The gas chromatogram is shown in Figure 42. The small peak immediately after the main peak is identified as diisopropylcarbinol by identical retention time with an authentic sample.

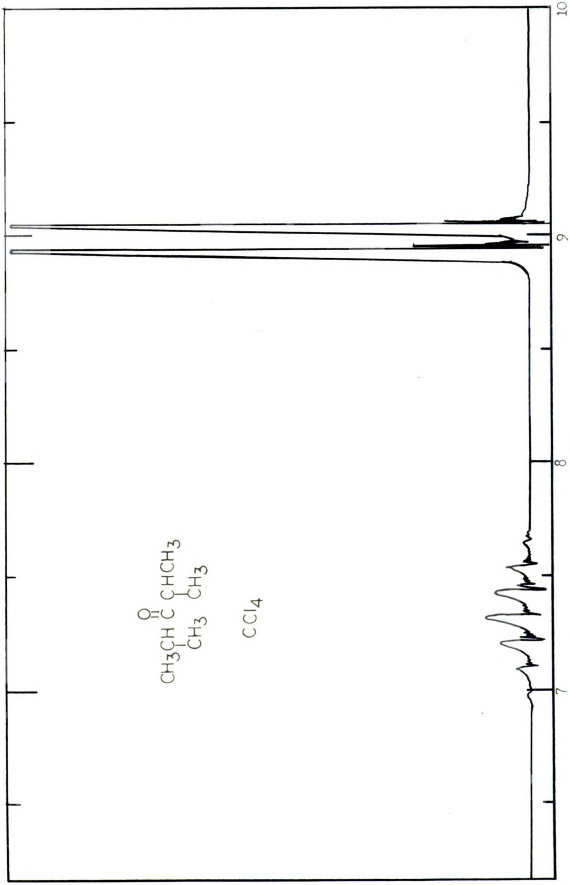


Figure 10. The N.M.R. Spectrum of Diisopropyl Ketone.

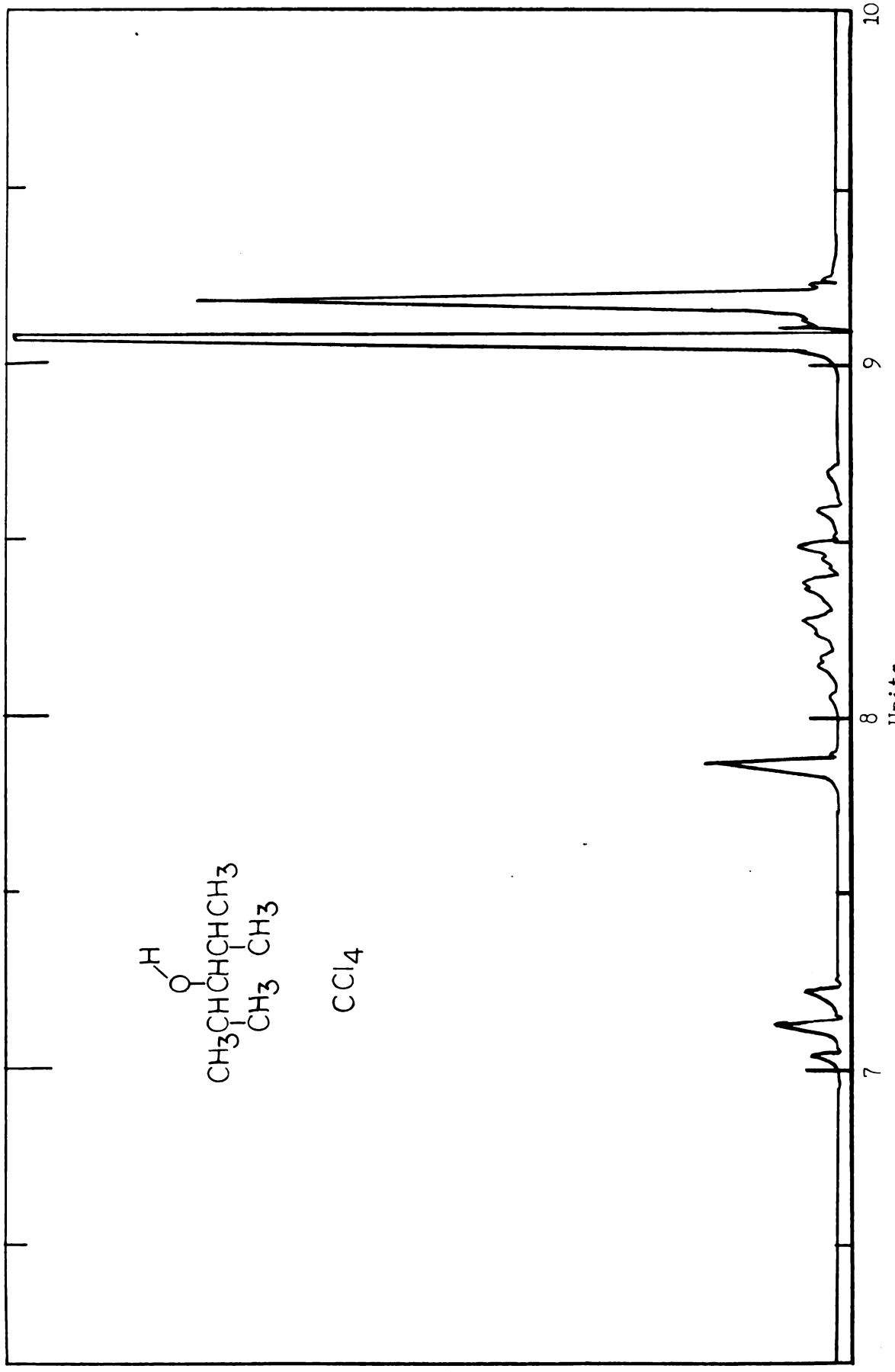


Figure 41. The N.M.R. Spectrum of Diisopropylcarbinol.

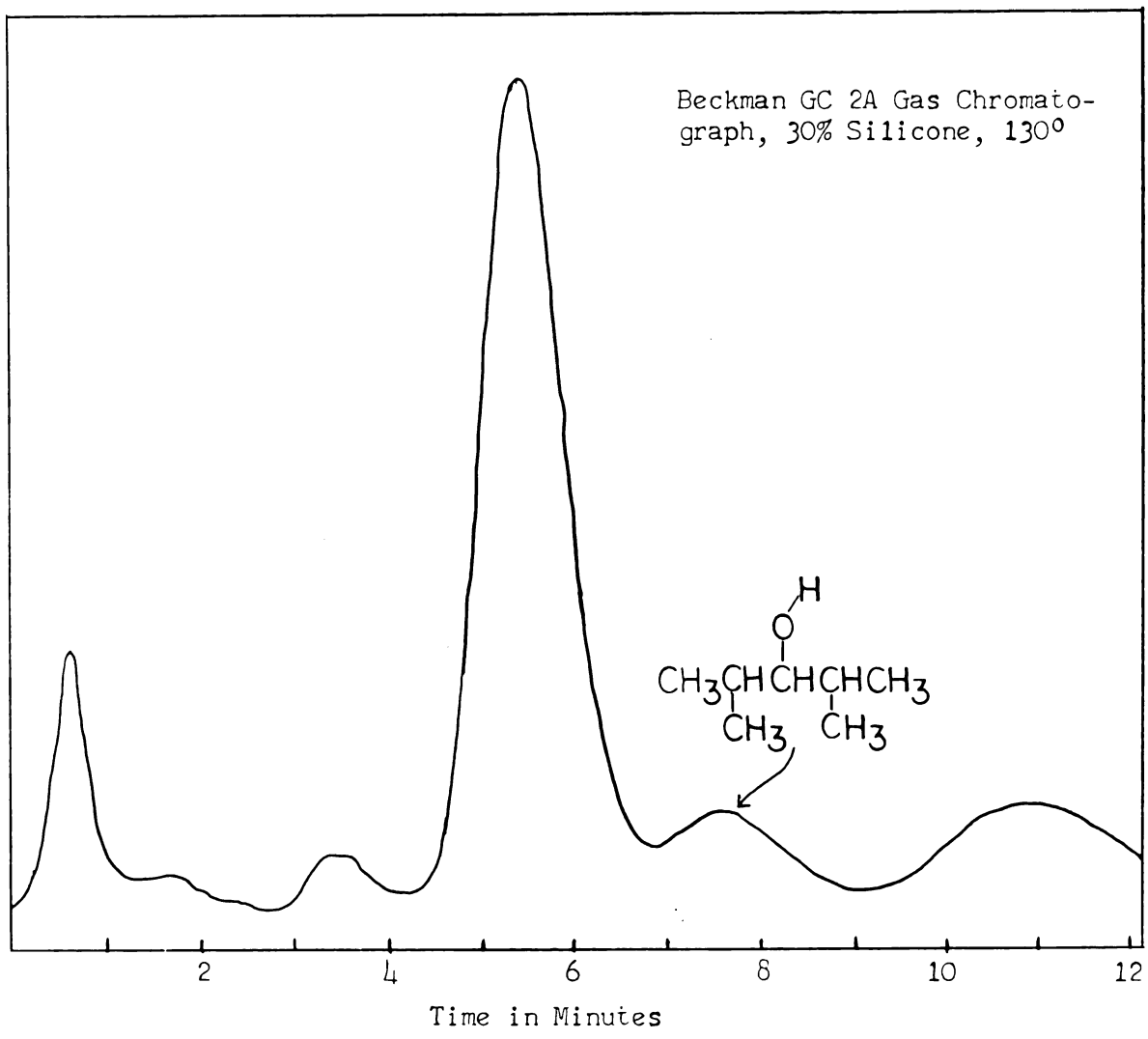


Figure 42. The Gas Chromatogram of the Products of Deamination of Diisopropylcarbinylamine.

SUMMARY

1. Norbornene was shown to react with a 1:1 complex of acetyl chloride-aluminum chloride to give 60% of a mixture of 2-chloro-3-acetylnorbornanes. Removal of halogen gave 2-exo-acetylnorbornane as the major product. The predominant product of acetylation is probably 2-exo-chloro-3-exo-acetylnorbornane. There was no evidence to support rearrangement during the course of the acetylation.

2. The configuration of 2-acetylnorbornane was shown to be exo by comparison with an authentic sample prepared from 2-exo-norbornanecarbonyl chloride. The reaction between dimethylcadmium and 2-endo-norbornanecarbonyl chloride proceeds with epimerization to give 2-exo-acetylnorbornane as the major product.

3. The addition of acetic anhydride to a methylene chloride solution of norbornene and stannic chloride unexpectedly produced 2-exo-acetoxynorbornane.

4. Dicyclopropylcarbinylamine and dicyclopropylcarbinylamine-α-d_1 were prepared from the oxime by reduction with lithium aluminum hydride and deuteride, respectively. The unlabeled amine was also prepared from dicyclopropyl ketone by a Leuckart reaction.

5. Deamination of dicyclopropylcarbinylamine in dilute perchloric acid gave dicyclopropylcarbinol as the major product. Bis-dicyclopropylcarbinyl ether and an unidentified third product were probably produced during the work-up of the reaction mixture. The three products, alcohol, ether and unidentified product, were formed in a ratio of 11:4:1.

6. When dicyclopropylcarbinol was heated with dilute perchloric acid, rearrangement occurred. The products obtained were

2-cyclopropyltetrahydrofuran and 4-cyclopropyl-3-butene-1-ol. When dicyclopropylcarbinol was heated in an aqueous solution of ammonium hydroxide, perchloric acid and sodium nitrite the major product was unchanged alcohol. In addition bis-dicyclopropylcarbinyl ether and the unidentified third product of the deamination reaction were obtained.

7. The n.m.r. spectra of diisopropyl ketoxime, diisopropylcarbinylamine and N-diisopropylcarbinyl benzamide show non-equivalent methyl groups. The case of the ketoxime is due to the syn and anti relationships of the methyl groups to the oxime group. Magnetic non-equivalence in the latter two cases is probably due principally to conformational preference.

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