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PART I. SYNTHESIS AND PROPERTIES OF SOME 5-SUBSTITUTED-5-AZABICYCLO[2.1.0]PENTANES. PART II. SOME SYNTHETIC APPROACHES TO THE 2-AZABICYCLO[1.1.0]BUTANE SYSTEM.

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PART I. SYNTHESIS AND PROPERTIES OF SOME 5-SUBSTITUTED-5-AZABICYCLO[2.1.0]PENTANES

PART II. SOME SYNTHETIC APPROACHES TO THE 2-AZABICYCLO[1.1.0]BUTANE SYSTEM

By

DAVID RICHARD FAGERBURG

A thesis submitted in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF WASHINGTON

1970

Approved by Arthur G. Anderson, Jr.
(Chairman of Supervisory Committee)

Department Chemistry
(Departmental Faculty sponsoring candidate)

Date August 19, 1970

UNIVERSITY OF WASHINGTON

Date: August 4, 1970

We have carefully read the dissertation entitled Part I. Synthesis and Properties of Some 5-Substituted-5-azabicyclo[2.1.0]pentanes. Part II. Some Synthetic Approaches to the 2-Azabicyclo[1.1.0]butane System. submitted by David Richard Fagerburg in partial fulfillment of the requirements of the degree of Doctor of Philosophy and recommend its acceptance. In support of this recommendation we present the following joint statement of evaluation to be filed with the dissertation.

Part I of this thesis describes the first synthesis (other than a perfluoro derivative) of the 5-azabicyclo[2.1.0]pentane ring system. This achievement required the formulation and study of a number of approaches and the ingenuity and resourcefulness of the investigator are clearly demonstrated in this work. The successful addition of suitable nitrenes to cyclobutene and 3,4-dichlorocyclobutene afforded several compounds for further work. It is established that the bicyclic ring undergoes thermal isomerization to the corresponding pyrrole and a mechanism for this rearrangement is advanced. A number of other reactions (e.g., halogenation, hydrogenation, hydrolysis, dehalogenation (of the vicinal dichloro compound), irradiation, and deuterium exchange) were studied and the course and products elucidated to the extent possible. The experimentation and interpretation of the results in this work is of high quality.

Part II concerns attempts to prepare the unknown 2-azabicyclo[1.1.0]butane system which is isomeric to the recently achieved 1-azabicyclo[1.1.0] structure. Although a number of plausible routes were devised and tried, none afforded the desired product. Indirect evidence of its possible existence as an intermediate was obtained, however. These results are attributed to an inherent instability of the structure under the conditions used and a reasonable theoretical explanation for this is advanced.

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ACKNOWLEDGMENT

The author would like to express appreciation to Dr. Arthur G. Anderson, Jr., for invaluable insight and encouragement during the course of this investigation. He is also indebted to the National Defense Education Act, Title IV, for support during his tenure. Most especially he would like to acknowledge the support of his wife, Maureen, and his children, Eric, Carla, and Brian, without which he would have been unable to carry out this research.

To my dear wife, Maureen, and our three lovely children, Eric, Carla, and Brian.

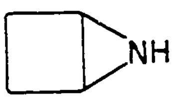
INTRODUCTION

To extend recent work in small ring bicyclic compounds, it was decided to synthesize the 5-azabicyclo[2.1.0]pentane system, 1, and study some of its properties.

Criegee and Rimmelin prepared the parent hydrocarbon, bicyclo-[2.1.0]pentane.[1] They and subsequent investigators found that it underwent several reactions at the 1,4 bond like those of an olefin.

The 5-oxaanalog parent system was prepared only recently by Ripoll and Conia,[2] the first example of the system having been made unknowingly when Reppe[3] epoxidized cyclooctatetraene. He was unable to differentiate between the structural isomers 2 and 3 and chose 2 as the structure. Later workers showed the epoxide to be the tricyclic one, 3, by chemical degradation.[4]

The 5-thia-analog, 4, has been made by a 2+2 photocycloaddition.[5] The parent episulfide is unknown. A derivative of the 5-azabicyclo[2.1.0]pentane system, 5, has been synthesized independently by a dipolar addition route.[6]



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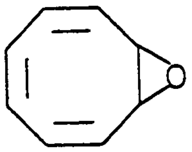

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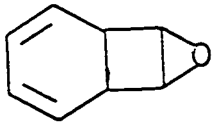

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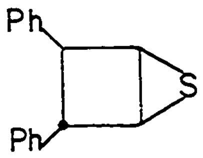

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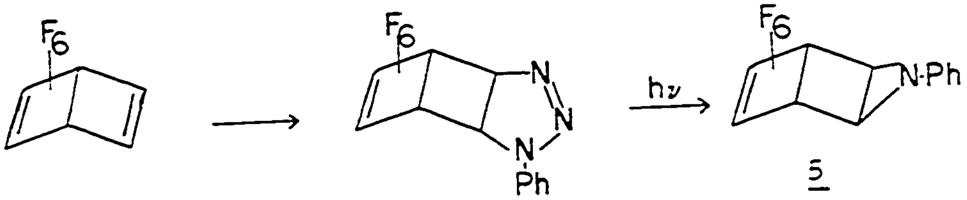
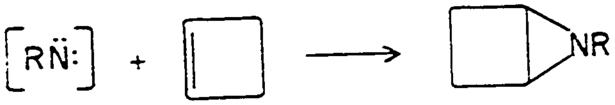


5

In the present study, several different methods of synthesis were attempted. The first category of these started with a cyclobutyl compound and sought to close the aziridine ring. Among these methods was a group of well known, and also some newer aziridine forming reactions using reagents which would add across a cyclobutene in a <u>trans</u> stereospecific sense. The intermediates produced could potentially further react to eventually form the aziridine ring by intramolecular nucleophilic displacement of the nitrogen function on a good leaving group. A more detailed discussion of these methods will be undertaken in the section "Parent System Synthesis." Included in this category is an attempted Gabriel aziridine synthesis, a displacement by an amine on a <u>cis</u>-<u>vicinal</u> dihalide. Finally, the formation of the aziridine ring was considered through use of 1,3-dipolar addition of an azide to a cyclobutene and then, if the intermediate triazoline were isolable, irradiation of it with UV light to form the aziridine.

The second possibility, also an aziridine forming path, could actually be considered part of the first category methods but differs sufficiently to merit special consideration. The general scheme is a one step reaction, involving the insertion of a nitrene, a neutral electron-deficient nitrogen species, into a double bond. This insertion may or may not be considered as a synchronous process depending on the state of the nitrene involved, whether singlet or triplet, in analogy to carbenes.



The last category attempted began with a five-membered nitrogen containing ring and sought to form the 1,4-bridging bond. These possibilities will be considered in more detail at the beginning of each section in which the particular route was used.

A route beginning with the appropriately substituted aziridine ring and closing the four-membered ring was rejected. From both rate and yield standpoints it is easier and better within a homocyclic series to form a three-membered ring as opposed to a four-membered ring.

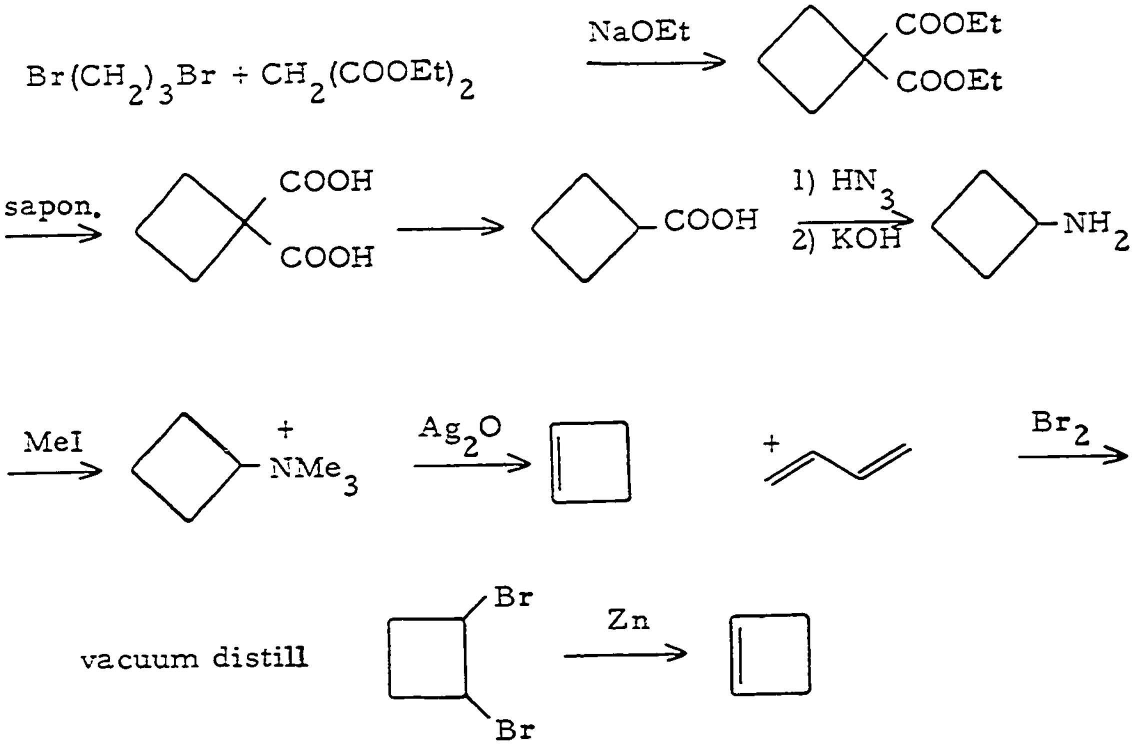
DISCUSSION OF RESULTS

Cyclobutene Synthesis

Having chosen synthetic approaches using aziridine forming reactions for the most part, it became necessary to synthesize various cyclobutenes. A thorough search of the literature revealed several methods of synthesis of the parent hydrocarbon, none of which were particularly convenient and suitable for large quantities of cyclobutene.

The simplest preparation of the hydrocarbon has been reported by Srinivasan.[7] He photolyzed 1,3-butadiene with 2537 Å light and obtained a 30% yield. The photolysis was carried out in dilute solution. Since butadiene and cyclobutene boil at -6° and 2° respectively, and since bicyclo[1.1.0]butane was also formed in 6% yield, separation was undertaken by distillation followed by preparative VPC separation. This tedious separation procedure and the small quantities involved make the method impractical for synthetic purposes.

The classical method of synthesis of the olefin involves a large number of steps, some of which proceed in very low yield.[8]

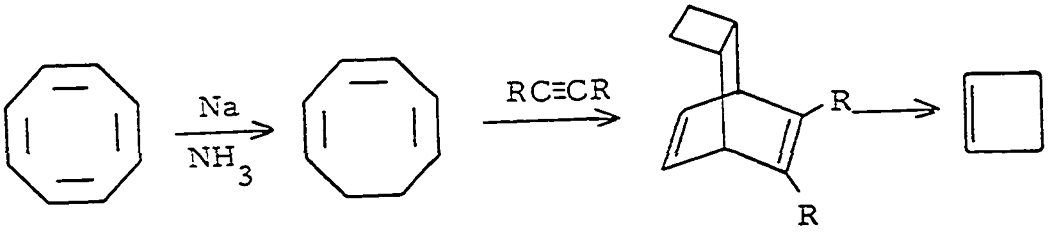


The last two steps, bromination and debromination, were necessary to separate 1,3-butadiene from the product. This of course may be done by preparative VPC as in the previous method, but would be quite tedious.

This contamination difficulty along with the large number of steps involved and the low overall yield (ca. 9%) preclude its practical use in spite of the large quantities obtainable.

A third method of cyclobutene synthesis involves the use of cyclobutanecarboxylic acid, obtaining cyclobutene by Pb^{IV} decarboxylation.[9] The original report in the literature indicated a 67% yield by VPC analysis. The reaction was done on a 13 mmol scale, i. e., yield of cyclobutene was 0.47 g. In attempting to scale the reaction up for preparative use, it was found that the yield dropped to 10% even on a 50 mmol reaction scale. This, therefore would seem impractical for the larger quantities of the material needed. In addition to this difficulty, a large excess of cyclobutanecarboxylic acid is required. Only half of it may be recovered giving an olefin yield of 3.8% based on the acid.

The last method was reported by A. C. Cope and coworkers.[10]

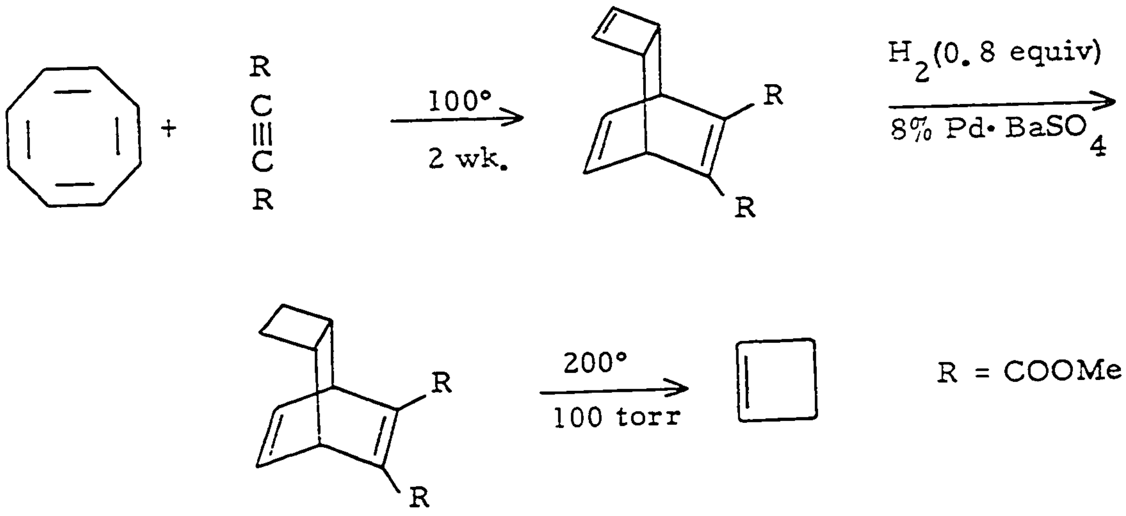


R=COOMe

The cyclobutene was free from 1,3-butadiene contamination. The major drawback here is the sodium-liquid ammonia reduction of cyclooctatetraene (COT) which is highly inconvenient and the product of which is a mixture that must either be separated by silver nitrate complex formation, which adds a 50% yield step in the sequence and was published as the preferred method, or isomerization with potassium t-butoxide, followed by distillation and silver nitrate complex formation. An attempt at reproducing the reduction step in these laboratories (see Experimental Section) failed to produce the reported 51% yield. It is believed that the disparity, 17% *vs.* 51%, is largely due to omission of some important experimental detail or details in the literature report rather than a lack of proper technique. Impurities in the sodium or their lack may also play an important role.

Thus all of the literature methods seemed to have at least one major drawback.

In attempting to develop a convenient cyclobutene synthesis, two routes were explored. The first made use of a Diels-Alder addition followed by a partial hydrogenation and pyrolysis of the partially hydrogenated material. Of the steps of the sequence, only the selective hydrogenation was unknown. After this route was developed, I. Fleming and E. Wildsmith reported the preparation of *cis*-3,4-dideuterocyclobutene by the same route giving little detail and no yields.[11]



R = COOMe

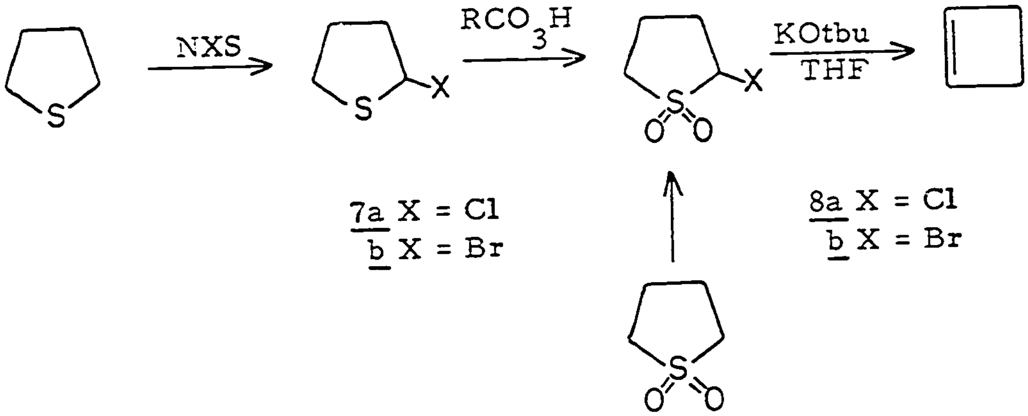
The Diels-Alder adduct,[10] 6, was decomposed partially during isolation by vacuum distillation to yield dimethyl phthalate and "cyclobutadiene". In addition to lowering the yield, 6 was thus contaminated with large amounts of dimethyl phthalate if distilled. It was found that distillation of unreacted COT from the crude pot mixture, removal of excess acetylene diester with vacuum, treatment with methanol, filtration of the precipitated solid, hydrogenation of the methanol solution, and pyrolysis of the neat, crude hydrogenation product gave yields of 34-39% cyclobutene based on COT. (59-67% based on unrecovered COT).

The white precipitate which was methanol insoluble was very difficult to dissolve in common solvents, even dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF). The compound was soluble in trifluoroacetic acid and the NMR in that solvent seemed to indicate a discrete compound, as opposed to a polymer, with NMR absorptions at (τ): 3.75 (m), 6.15 (m), 6.40 (s), and 8.5 (br s). The compound accounted for a maximum of 7% by weight of the reaction mixture. Its yield dropped to less than 1% if freshly distilled acetylene compound was used and hence suggested its formation from an impurity that accumulated in dimethyl acetylenedicarboxylate upon long standing. Further analysis of the material was not undertaken.

This method provided a new isolation procedure which may be used on a scale up to 0.1 mol without loss of yield and was found to be very convenient since actual experimental time involved was small. A table of the experiments conducted for the yield optimization is found in the

Experimental Section. The experiments indicated the best conditions to be those shown over the reaction arrows shown on the previous page.

The major drawback to the above method was the use of COT, an expensive reagent. Because of the expense, an alternative method was attempted. The Ramburg-Bäcklund rearrangement has been used in a series of recent papers by Paquette, et. al., to synthesize selected cyclobutenes.[12] They found potassium t-butoxide in tetrahydrofuran (THF) to be superior as the base for the elimination reaction over alkali hydroxide in water. By analogy to Paquette's work, one would expect the parent system to be produced from the following scheme:



7a X = Cl
b X = Br

8a X = Cl
b X = Br

Indeed, in a series of experiments employing crude products, cyclobutene was obtained and identified as its dibromide. The yields were, however, very poor, the intermediate materials were unstable, and the product dibromide contained an impurity not observed in the bromination of authentic pure cyclobutene.

Compound 7a is reported to undergo decomposition upon attempted vacuum distillation.[13] For this reason, crude 7a was oxidized by peracetic acid without purification. The product proved to be a tarry substance, insoluble in most all organic solvents. By contrast, crude 8b synthesized from sulfolane was easily soluble in several common solvents. Crude 7b from the reaction of N-bromosuccinimide (NBS) with tetrahydrothiophene decomposed rapidly from a yellow oil to a thick black tar and hence could not be further converted to 8b. An attempt to produce 8b by reaction of NBS with sulfolane gave only minute amounts of material, very impure, even after prolonged reaction times.

Compound 8b was successfully synthesized in an impure state by treating sulfolane with methyl lithium and adding the resulting carbanion to a benzene solution of bromine. The yield of crude product was low. When this crude material was treated with potassium t-butoxide in refluxing THF the trap material collected upon separation and bromination gave dibromocyclobutane (by comparison with an authentic sample) with three contaminating compounds, one of which was present in an amount about equal to that of the dibromocyclobutane. It was suspected that this contaminant might be from the bromination product of 1,3-butadiene but was not further investigated.

It would seem that refinements need to be made in this scheme before it can become of practical value. It does show promise and probably could merit further investigation.

Cis-3,4-dichlorocyclobutene Synthesis

Reppe and coworkers claimed to have made cis-3,4-dichlorocyclobutene by a thermolysis of the Diels-Alder adduct of dimethyl acetylenedicarboxylate and dichlorocyclooctatriene.[14] Later reinvestigation by Nenitzescu showed Reppe's "cyclobutene" to be 1,4-dichloro-1,3-butadiene. Nenitzescu improved upon the procedure of Reppe and made the cyclobutene.[15] His procedure was followed and moderate yields (28-29%) were obtained. (Nenitzescu did not publish a yield). The product was distilled under vacuum (60 torr) through a two-foot Podbielniak column with a heated jacket. Distillation at atmospheric pressure resulted in formation of a fuming, colorless liquid which displayed a large number of peaks in the NMR spectrum as opposed to the two narrow triplets of dichlorocyclobutene.

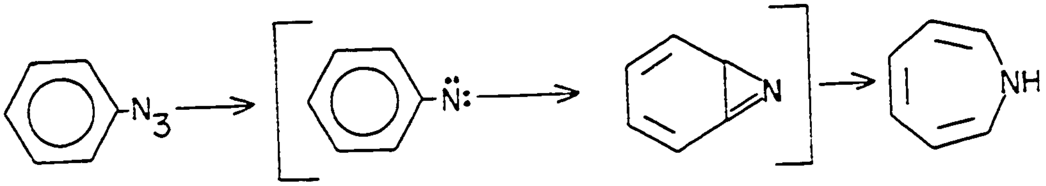
After samples of the olefin had stood in the refrigerator for a long time, they also began to fume slightly in air. An NMR spectrum of the fuming sample revealed no appearance of new peaks and so the fuming compound was indicated to be present only in small quantity. Further identification of the fuming material was not undertaken.

Nitrene Approach

Introduction

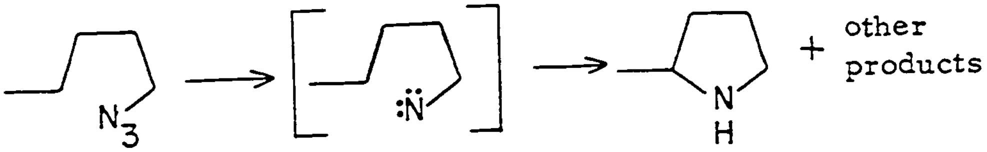
Nitrenes are neutral electron-deficient nitrogen species (the nitrogen possessing only six electrons). Several classes of nitrenes are known, and they are made generally through thermolysis or photolysis of azides.

Aryl nitrenes such as from phenyl azide undergo preferential intramolecular reactions.



Alkyl nitrenes undergo preferential α-hydrogen abstraction to give imines although one case has been reported where cyclization occurred. The cyclization was not reproducible.[16]

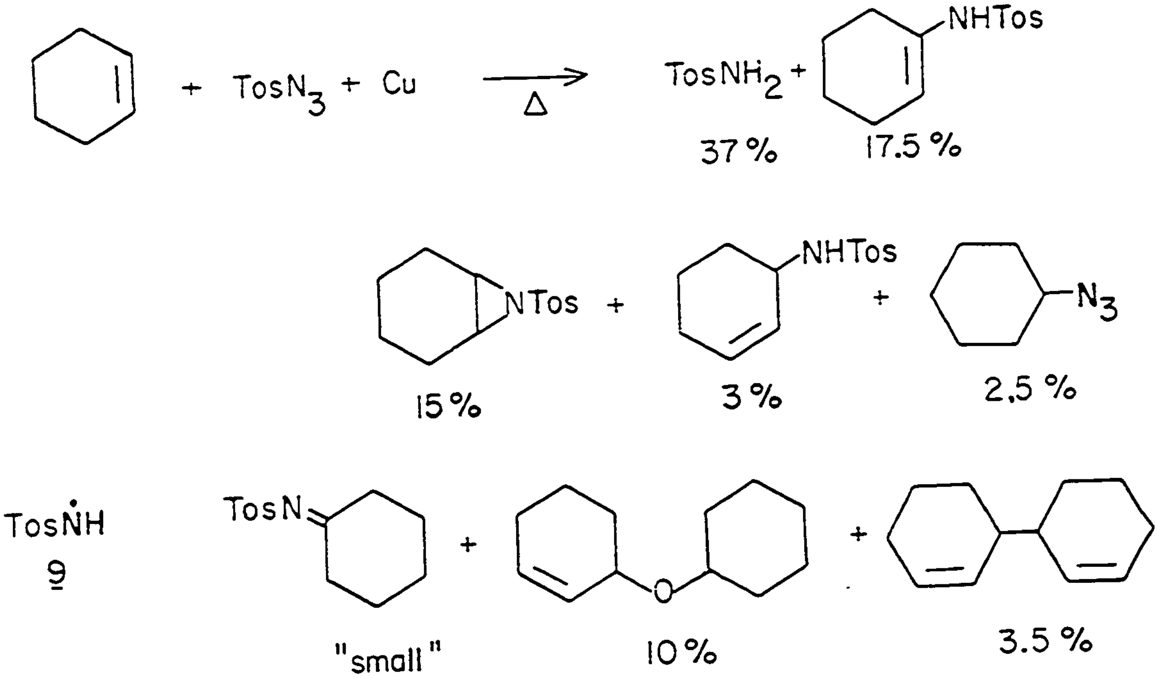
$$RCH_2N_3 \longrightarrow \left[\ RCH_2\ddot{N}\colon \longrightarrow R\dot{C}H\text{-}\dot{N}H \right] \longrightarrow RCH{=}NH$$



Sulfonyl nitrenes tend to undergo hydrogen abstraction from the solvent to give mainly sulfonamides along with a multitude of other products as illustrated on the following page.[17]

The radical products, 75% of the mixture, could arise from this hydrogen abstraction which forms the radical <u>9</u>. For the interested reader, a good review article on these nitrenes is available.[18]

Beginning in 1962, Lwowski and his coworkers published a series of papers on the generation and synthetic use of carboethoxynitrene.[19] They found that the nitrene underwent the same reactions as the analogous carbene, i.e. addition to double bonds, C-H insertion, and



TosṄH
9

hydrogen abstraction. Unlike alkyl and aryl nitrenes, however, it did not undergo group migration. The nitrene also showed a preference for intermolecular reaction. Insertion into a double bond was found to be 11 times faster than insertion into a 3° C-H bond, 36 times faster than insertion into a 2° C-H bond, and 360 times faster than insertion into a 1° C-H bond. This is a greater selectivity than that generally shown by carbenes.

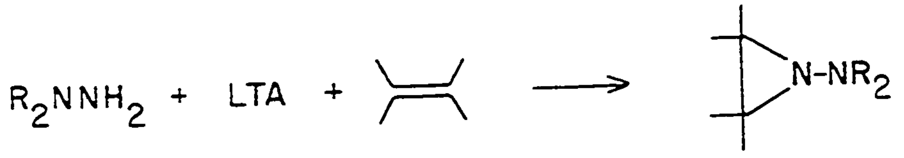
Two of the three methods of generation of the nitrene seemed to be particularly suited for synthetic purposes.

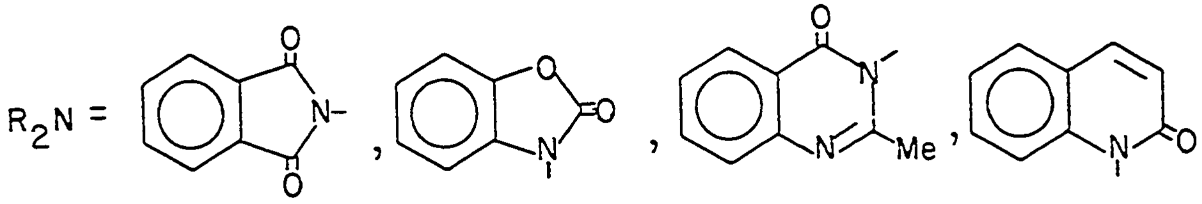
$$N_3COOEt \xrightarrow[h\nu]{} [:N\text{-}COOEt]$$

$$EtOOCNHOSO_2\phi NO_2\text{-}p + B: \longrightarrow [:N\text{-}COOEt] + B^{\oplus}H, \; pNO_2\phi O_2SO^{\ominus}$$

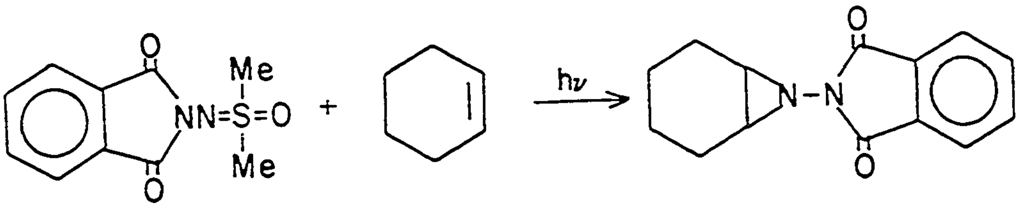
Thermolysis of the azide to produce the nitrene did not seem to be a practical route since cyclobutene and many of its substituted derivatives are very volatile.

Rees and coworkers have recently made synthetic use of N-amidyl and N-imidyl nitrenes generated from the corresponding N-amino compounds.[20]





They used a variety of olefins, with yields ranging from 40 to 96%. Rees also generated N-phthalimidyl nitrene by a photolytic route.



The yield was 20% as opposed to 40% by the direct oxidation process.

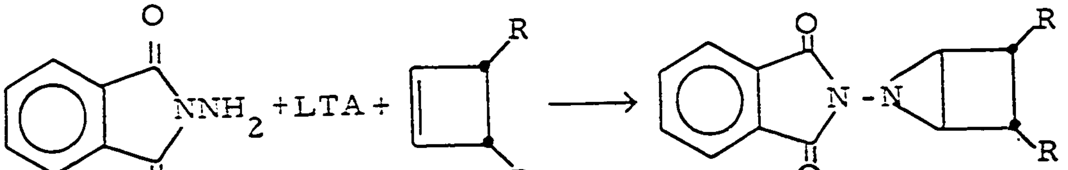
Hoesch recently published independent work with N-aminophthalimide and found that oxidation of N-aminophthalimide with one-half equivalent of lead tetraacetate (LTA) gave a good yield of phthalimide.[21]

Both sets of workers found stereospecific addition to cis- and trans-2-butene even at very low olefin concentration, indicating a singlet state nitrene to be involved in the reaction.

These last two nitrenes, carboethoxynitrene and N-phthalimidylnitrene, seemed well suited for synthetic purposes also since they do not undergo group migration, intramolecular reaction, or intramolecular hydrogen abstraction as with aryl and alkyl nitrenes.

Synthesis of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentanes.

To synthesize the ring system, variations were used on the method of Rees and coworkers to form aziridines from olefins.[20]



10

10a R=H
b R=Cl

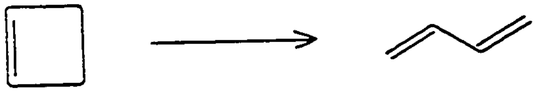
A study of the best reaction conditions and isolation techniques was carried out in the synthesis of compound 10b. A table summarizing the various experiments is found in the Experimental Section. It was found that the presence during the reaction of potassium carbonate in the amount to neutralize the acetic acid produced in the oxidation lowered the yield. Rapid addition of LTA to the reaction mixture lowered the yield as opposed to gradual addition over several minutes. Increase in the ratio of olefin to nitrene precursor predictably raised the yield. In the synthesis of 10b a 3.25 to 1 ratio gave a 12.2% yield (significantly lower ratios gave yields of 2.5-6.2%) and 64% of the original olefin could be recovered. Use of much higher ratios than this were not practical due to the availability of the olefin.

In the synthesis of 10a a smaller fraction of the excess cyclobutene could be recovered as a solution in dichloromethane. The yield of 10a with a ratio of olefin to nitrene precursor similar to that used for 10b synthesis was 18-22%. This would seem to contradict the postulate of Rees that N-phthalimidylnitrene is nucleophilic, i.e. it should give a better yield on electron poor olefins than on electron rich ones.[20]

It was also noted that a slight excess of N-aminophthalimide over the LTA increased the yield, probably since no unreacted LTA was present to further react with product. (Storage and handling precautions for LTA are found in the Experimental Section. Using them, samples of LTA have been observed to remain in good, usable condition for over a year even with frequent sample withdrawal.)

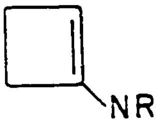
Both compounds 10a and 10b were purified by chromatography as recrystallization was impractical with the amounts of phthalimide present in the crude mixture. Compound 10a exhibited an impurity in large amount which showed a multiplet at 6.44τ.

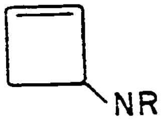
The possibility of this being from the aziridine formed in the reaction of the nitrene with 1,3-butadiene seemed remote but necessary to consider. The cyclobutene synthesis itself has been shown by A. C. Cope to give exclusively the cyclic olefin.[10] It is possible, however, to envision formation of the diene by too high a pyrolysis temperature during cyclobutene formation since at higher temperatures the following rearrangement does take place:



However an NMR spectrum of the crude material in acetone showed virtually no signals between the aromatic signal and the impurity peak at 6.44τ. This excludes the vinyl aziridine that would be formed from any 1,3-butadiene.

Also excluded is the possibility that a C-H insertion of the nitrene on cyclobutene has occurred giving the products 11a or 11b





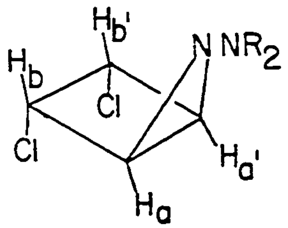
since both would show olefinic protons in the NMR spectrum.

Since in the crude material a singlet also appears at 7.8τ, the product contaminant could reasonably have been produced by LTA oxidation of the bridging bond. This being the case, the use of a bulkier oxidizing agent to hinder approach to the bond would be desirable. For this reason, lead tetrabenzoate[22] (LTBz) was used to generate the nitrene.

The crude yield of the bicyclic material is slightly higher with LTBz. The crude product, 10a, is free from the contaminant signals observed before, but it is contaminated with large amounts of benzoic acid and, if evaporated to complete dryness under vacuum with heating, chars very badly. The wet product must therefore be dried overnight in a desiccator under vacuum at room temperature. Because of these problems, and also because LTBz must be synthesized from LTA, the latter remains the oxidant of choice for synthesis by this route.

Upon storage, both 10a and 10b darken, although 10b does so more rapidly. If stored in base-washed vials under nitrogen, the decomposition is somewhat retarded.

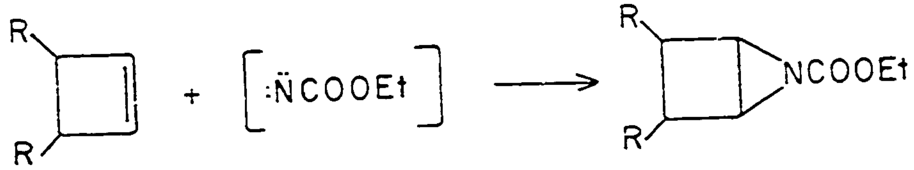
The spectra of the compounds were consistent with the proposed structures as were the analyses and mass spectra. The NMR spectrum of 10b was more complex than first expected. Each set of bicyclic ring protons consisted of six peaks and were mirror images of one another. The pattern (see Spectral Section) was that expected for an AA'BB' system where the cross-ring coupling *e. g.* H_A to $H_{B'}$, was near or equal to zero.



This arises from the fact that H_A and $H_{A'}$ (or H_B and $H_{B'}$) are distinguishable from one another in that their coupling constants to the same other-lettered proton are different, *i. e.* $J_{AB} \neq J_{A'B}$.

Synthesis of 5-Carboethoxy-5-azabicyclo[2.1.0]pentane.

The bicyclic system may also be synthesized through use of carboethoxynitrene. (see p. 12)



12a R = H
b R = Cl

When the nitrene was generated in situ by α-elimination in the presence of excess cyclobutene, a small yield of the bicyclic compound 12a was obtained as determined by NMR.

The compound, in addition to signals for the ethoxy group, showed absorptions at 6.93 (m, 2), 7.88 (m, 2), and 8.23 (m, 2). (see Spectral Section) The methylene protons are not as well separated as in the N-phthalimidyl compound. This was easily explained by considering that the carboethoxy group is a stronger electron withdrawing substituent than the phthalimidyl group by virtue of resonance. The decrease in availability of the nitrogen lone pair results in a decreased ring current and hence a decreased shielding for the endo protons.

An attempted micropreparative separation by VPC at 85° with a 220° injector temperature gave at least one compound in addition to the bicyclic material as indicated by absorptions appearing at 3.5 τ and 5.1 τ and additional absorptions for an ethoxy group giving a double quartet and a double triplet.

Attempted synthesis of 12b by the same route gave several products, none of which were identifiable as the bicyclic material. Since the yield of 12a was on the order of 1%, the expected yield of 12b would be less, thus making it very difficult to isolate in large enough quantity to identify.

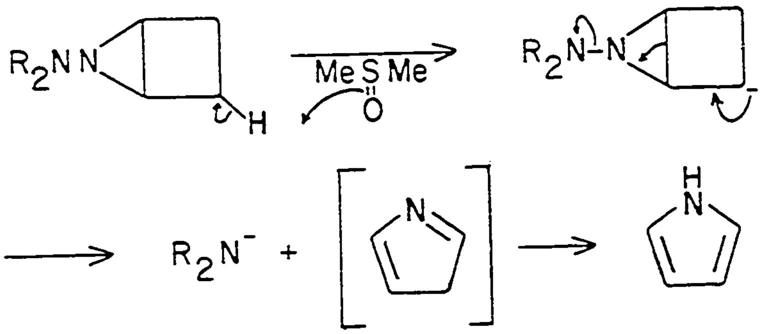
Since no large amounts of 12a or 12b were synthesizable, the hydrolysis to the parent compound was impractical.

Reactions of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane, (10a)

When compound 10a was heated in DMSO-d_6 for as short a time as five minutes at 115° or four hours at 57°, loss of the phthalimidyl group was observed giving phthalimide. The ring protons completely disappeared and two doublet of doublets appeared at 3.17 and 4.00τ. This did not correspond to N-phthalimidylpyrrole which exhibited peaks at (τ): 3.00 and 3.86 for the pyrrole protons. (Even after heating for several hours in DMSO or DMSO with added water, the NMR spectrum of N-phthalimidylpyrrole remained unchanged.)

A TLC of the reaction mixture showed phthalimide and two other components (after DMSO evaporation at 10^{-3} torr) both of which gave pyrrole tests. The minor one was pyrrole as shown by comparison to authentic material. An attempt to isolate the major pyrrole component by preparative TLC failed. (At this particular point the T-60 spectrometer was inoperative for a long period and accordingly the bands isolated were run on the HA-60 using the Computer of Average Transients. After 20 scans the spectrum showed no signals appearing. Since ca 3 mg of material was in the sample it was assumed that the sharp peaks observed prior to chromatography should have been visable had the compound survived the isolation technique.)

A mechanism for the aromatization may easily be written and is consistent with the results of deuterium exchange on the compound. (see below)



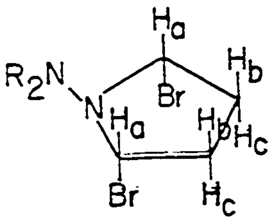
For this reason, formation of carbanions with organometallic reagents followed by alkylation, was not attempted.

Heating of <u>10a</u> in DMSO-d_6 with D_2O and sodium deuteroxide showed the disappearance of the ring protons before the appearance of the pyrrole signals observed in the case above. It was noted that the high field methylene signals, *i.e.*, the endo-protons, disappeared sooner than the low field protons or than the bridgehead protons, the multiplets of which both seemed to be simplifying. The *endo*-protons are thus exchanged faster, a result which is not expected.

Heating with an excess of D_2O, sodium deuteroxide gave mainly hydrolysis of the phthalimidyl group, the highfield ring protons moving downfield so as to make an almost continuous multiplet with the *exo*-protons, the bridgehead protons moving upfield. This is easily explained on basis of changing the substituent on the ring nitrogen by opening of the phthalimidyl group with deuteroxide ion.

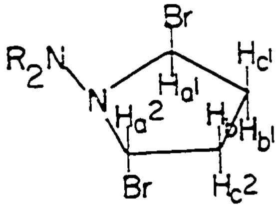
Compound 10a reacted with bromine in dichloromethane to give a dibromide, 13. In addition, phthalimide and at least one minor compound was produced. The NMR spectrum of the aliphatic protons of 13 consisted of two unresolved multiplets at 5.83 (width *ca.* 38 hz) and 7.87 τ (width *ca.* 56 hz).

If the addition to the bridging bond were *cis*, one would expect a spectrum in general similar to that observed for 10a.



The H_a protons are equivalent and would be split by two non-equivalent sets of two methylene protons each as in 10a. The predominant nitrogen invertomer present would be the one shown, due to steric considerations, and the product might even be expected to show only one invertomer. The H_b protons would remain equivalent to each other regardless of the nitrogen invertomer present, as would be the H_c protons to each other. H_b and H_c will always, however, be nonequivalent from each other and thus the expected pattern would be a narrow H_a multiplet and two separated methylene multiplets.

For *trans*-addition, due to the effect of the phthalimidyl group, all of the various protons should be nonequivalent.



13

Here both nitrogen invertomers would be present in equal amounts and, assuming a slow nitrogen inversion as observed with N-phthalimidyl-aziridines, would give two signals for the H_a1 and H_a2 protons. The same would hold true for the H_b and H_c protons. Inversion at the nitrogen would interchange the absorption positions of the same-lettered hydrogens.

Thus the spectrum expected would be considerably broader multiplets than for cis-addition, with the possibility of overlap of the methylene protons to produce one continuous multiplet rather than the two distinctly separated ones expected for cis-addition.

It is thus concluded from the NMR spectrum of 13, that trans-addition had most likely occurred.

An attempt to make a Diels-Alder adduct of 10a with tetraphenylcyclopentadienone gave only traces of a new compound even after long reaction time. Because of the minute quantity present and also the difficulty in removing remaining dienone, the product was not identified.

Reactions of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane (10b)

Compound 10b was found to be hydrolyzed rapidly by 5% aqueous potassium hydroxide with loss of the phthalimidyl group. The N-amino bicyclic system could not be isolated. Only a tarry material was obtained.

The material was rapidly oxidized by LTA, only 54% being recovered after twenty minutes at room temperature. Monomeric oxidation products were not isolated. Compound 10b was, however, surprisingly stable to hot glacial acetic acid. A total of 28% was recovered after twenty-four hours of heating on a steam cone. A similar observation was made with room temperature acetic acid on the *cis*-aziridine from N-phthalimidyl nitrene and *cis*-2-butene whereas the corresponding *trans* isomer was destroyed rapidly at room temperature.[20]

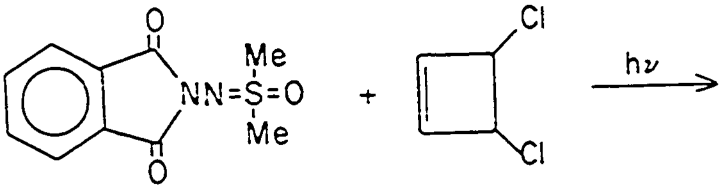
A dehalogenation attempt with lithium gave no isolable product soluble in common solvents. Dehalogenation with sodium iodide also failed to give a product. Reaction with lithium amalgam gave only a few milligrams of an air-sensitive compound having aromatic absorptions in the aromatic region of the NMR spectrum. They were not from a pyrrole compound. Reaction with potassium t-butoxide gave a polymeric material plus a precipitate which was identified as a carbanion of 10b by its reaction with water to give starting material back. Attempted alkylation of the carbanion gave mostly a water soluble material that tested positive for iodide ion, indicating the quaternization of, evidently, the ring nitrogen. The NMR spectrum in D_2O of the alkylated material showed two different N-Me singlets and no evidence of a bicyclic ring remaining. The other absorptions were a broad peak at 2.40 τ and a sharp singlet at 2.50 τ. Attempted dehalogenation with excess Cr(II) ethylenediamine complex[23] gave phthalimide as the major product. Most of the other material was no doubt lost in the work up, but a small quantity (milligrams) of material was isolated by preparative TLC which showed aromatic absorptions in the NMR spectrum. Again they did not correspond to a pyrrole compound. All of these results seemed to point to the instability of the expected azabicyclopentene.

The compound was inert to cleavage by sodium hydrosulfite. Reaction with hydrazine produced phthaloylhydrazide but no N-amino compound could be isolated. The only material obtainable was a very gooey intractable tar.

Hydrogenation over rhodium-on-alumina poisoned the catalyst at 17% uptake. A similar observation was made by Hortmann with 3-phenyl-1-azabicyclo[1.1.0]butane.[24]

Irradiation of 10b with a 450 watt high pressure lamp through a Vycor filter produced a polymer, the material being completely destroyed in four hours. The bridging bond was thought to undergo cleavage to a diradical followed by polymerization. The bond would not be expected to absorb in the UV above 220 mμ (Vycor cutoff) but instead would undergo intermolecular triplet-triplet sensitization by the carbonyl group of the molecule.

Not surprisingly, thus, 10b could not be produced in significant quantities by irradiation of the sulfoximine, 14, used by Rees for Aziridine syntheses.[20]



10b (trace)

The Vycor filter was chosen as the minimum energy route after examining the UV spectrum of 14 in comparison to those of 10a and 10b. A shoulder at 245 mμ was noted in the spectrum of 14 that was absent in 10a and 10b, the other bands corresponding closely. This shoulder was reasoned to be due to the difference between the two molecules and thus the N = S and/or S = O chromophores. Since it was desired to break the N = S by excitation, the required wavelength would be in that region of the spectrum. Since Pyrex and Corex filters cut off substantially before 245 mμ, Vycor was the next logical choice.

Attempted exchange with sodium deuteroxide and D_2O in DMSO-d_6 gave no apparent decrease in the ring proton signals even after sitting for several weeks at room temperature. The sample was then heated in a oil bath at 57°. NMR spectra over a period of minutes showed the slow appearance of a singlet at 2.43τ. After long heating the ring protons gave an integration less than that expected for the phthalimidyl ring protons where before it had shown the correct correspondence. After overnight heating the only peak present in the spectrum was the singlet at 2.43τ. Evaporation gave a solid from which was isolated a small amount of starting material (as confirmed by TLC). The majority of the material was in a spot near the origin. Its IR spectrum was similar in the carbonyl region to those of the hydroxyphthalimidines 35 and 36, (see p. 45), both of which exhibit singlets at 2.43 τ.

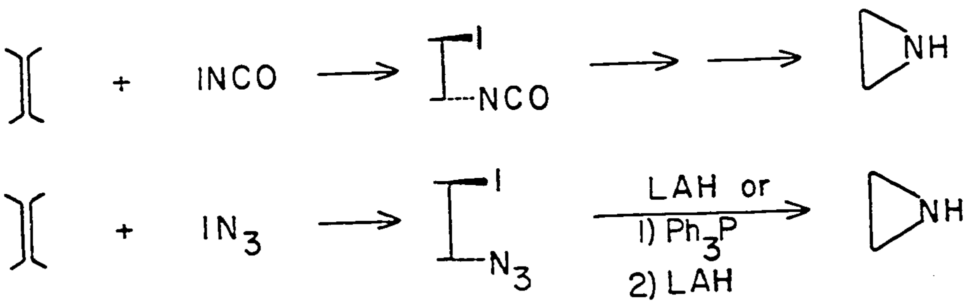
Exchange in 10b is thus slow and of about equal rates for both the bridgehead and methine protons. Accompanying the process is a reduction of the phthalimidyl group to a hydroxyphthalimidine (for which only spectral evidence exists).

In an attempted reaction with tetracycanoethylene at room temperature over a period of weeks, 89% of the starting material was recovered. No other products were isolable in quantities sufficient for identification.

Parent System Synthesis

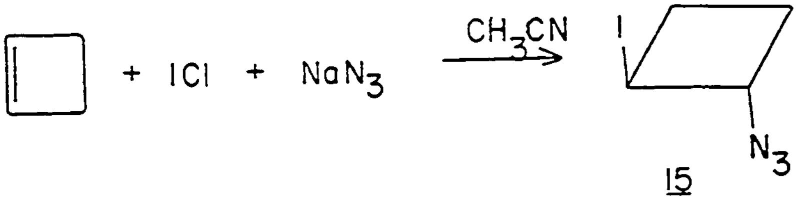
There are a large number of aziridine forming reactions in the chemical literature, most of which depend on the addition of a reagent containing a nitrogen function to a double bond.

Two of the more interesting and convenient methods which give good yields are the procedures developed by Hassner and coworkers using iodine isocyanate[25] and iodine azide.[26]



The interested reader is referred to Hassner's publications for a more detailed discussion of mechanism, scope of the reactions, side reactions, etc.

Using the method of Hassner for iodoazides, compound 15 was synthesized in good yield.

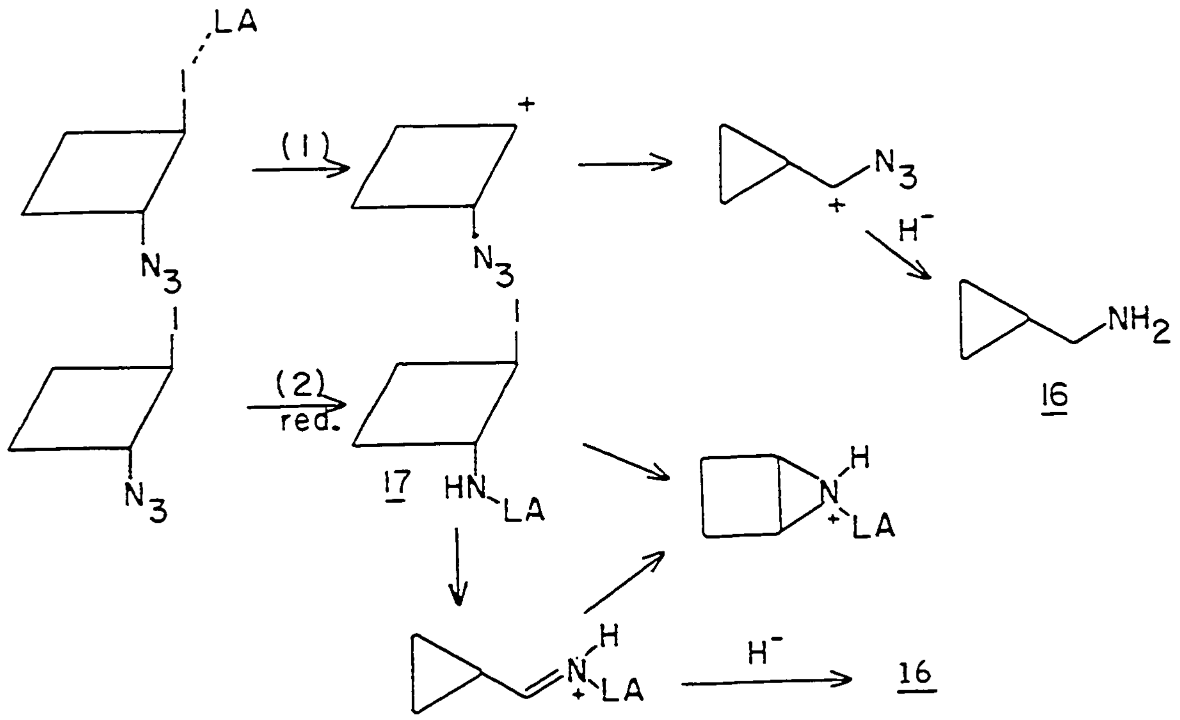


15

The NMR spectrum showed an unexpected shift of one of the four methylene protons to higher field than the rest. This was attributed to the azide functionality since upon reduction to the aminoiodide (see p. 29) this separation was not observed. This was also not observed with the addition product of cyclobutene and iodonium isocyanate. (see p. 30)

The iodoazide, 15, was treated with lithium aluminum hydride (LAH) in dry ether according to the literature procedure.[27] Upon workup, the only product isolated was cyclopropylcarbinylamine.[28] By TLC no cyclobutylamine was found to be present. There are two possible mechanisms of formation of this unexpected product, one of which proceeds through the bicyclic aziridine as an intermediate.

Path (1) is not likely to be operative since some of the initially formed cyclobutyl carbonium ion would likely be reduced with hydride ion to cyclobutyl azide which would then be reduced to cyclobutylamine.

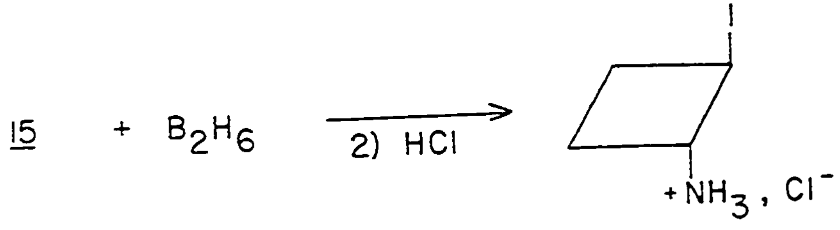


LA = Lewis Acid

Path (2) seems reasonable but as shown need not go through the bicyclic amine since the intermediate 17 may eliminate iodide without cyclization.

Since reductive cyclization of the iodoazide with LAH did not produce the desired results, the obvious next thing to try was to reduce the azide to an iodoamine and cyclize that under basic conditions. Attempted reduction of 15 with diborane in tetrahydrofuran (THF) gave very poor results.[27] About 50% of the azide was recovered and the amine hydrochloride obtained was very impure.

Attempted cyclization of 18 with potassium t-butoxide in THF gave such a large number of products in small quantity as to be impractical to separate and identify them all. Only one of them proved to be volatile at 0.1 torr and room temperature, certainly a necessary condition for the parent compound, but it gave a negative test for secondary amine.

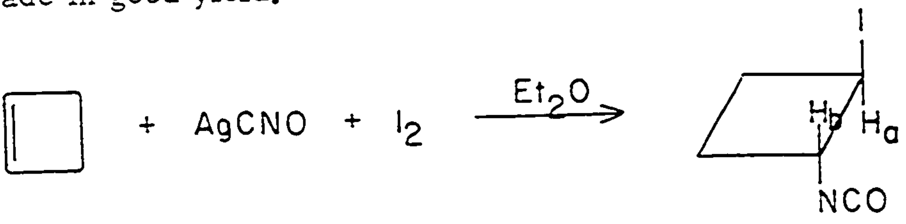


18

Reaction of iodoazides with triphenylphosphine has recently been reported to give good yields of N-triphenylphosphonium iodides. Cleavage of them with LAH gives the free amine.[29] This reaction has the advantage over the LAH reduction in that the cyclizing reagent is a Lewis base and hence should not cause rearrangement of the system if formed.

Reaction of 15 with triphenylphosphine gave a gooey product which could be solidified under vacuum with heating. The material showed no absorptions in the NMR spectrum above 7.5τ, but exhibited broad absorptions from 6.0 to 7.4τ in addition to the aromatic signals. The material could not be recrystallized from absolute ethanol, ethanol-benzene, or ethanol-petroleum ether. In light of these data the material was assumed to be a polymer, formed by intermolecular displacement of iodine by the iminophosphorane intermediate rather than the intramolecular displacement necessary to form the aziridine ring. This can be taken as an indication of a high free energy of formation of the ring due to strain and electronic destabilization. (see Part II, p. 144

The iodoazide path was not being very useful, another system was needed. Using the standard procedure the iodoisocyanate of cyclobutene can be made in good yield.[25]



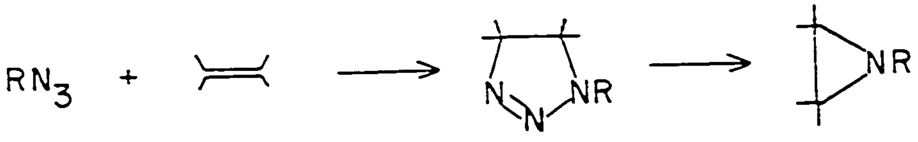
19

The NMR spectrum of the compound was interesting from the standpoint that H_a and H_b were distinctly separated multiplets whereas with the iodoazide they were somewhat overlapping. The methylene protons in the iodoazide were in two multiplets of 3:1 ratio. With the iodoisocyanate, however, the multiplet was continuous over 66 hz in width in a more or less even height indicating all four methylene protons to be nonequivalent. The H_a protons, i. e. α to the iodine were in nearly identical positions whereas the H_b proton in the iodoisocyanate was at 48 hz lower field than the proton α to the azide in the iodoazide. This served to confirm the proton assignments for both compounds and substantiate that the single upfield proton in the iodoazide must be in the shielding cone of the azide group.

The sodium bisulfite addition product of 19 was formed only incompletely and when heated with base in triethylene glycol gave no parent compound or other volatile amine.

1,3-Dipolar Addition Route

In the early 1950's, Huisgen and his coworkers began exploring 1,3-dipolar additions of various "dipolarophiles" with strained and unstrained olefins. Several reviews have been made of this work.[30] A particularly interesting dipolar addition was observed with azides.

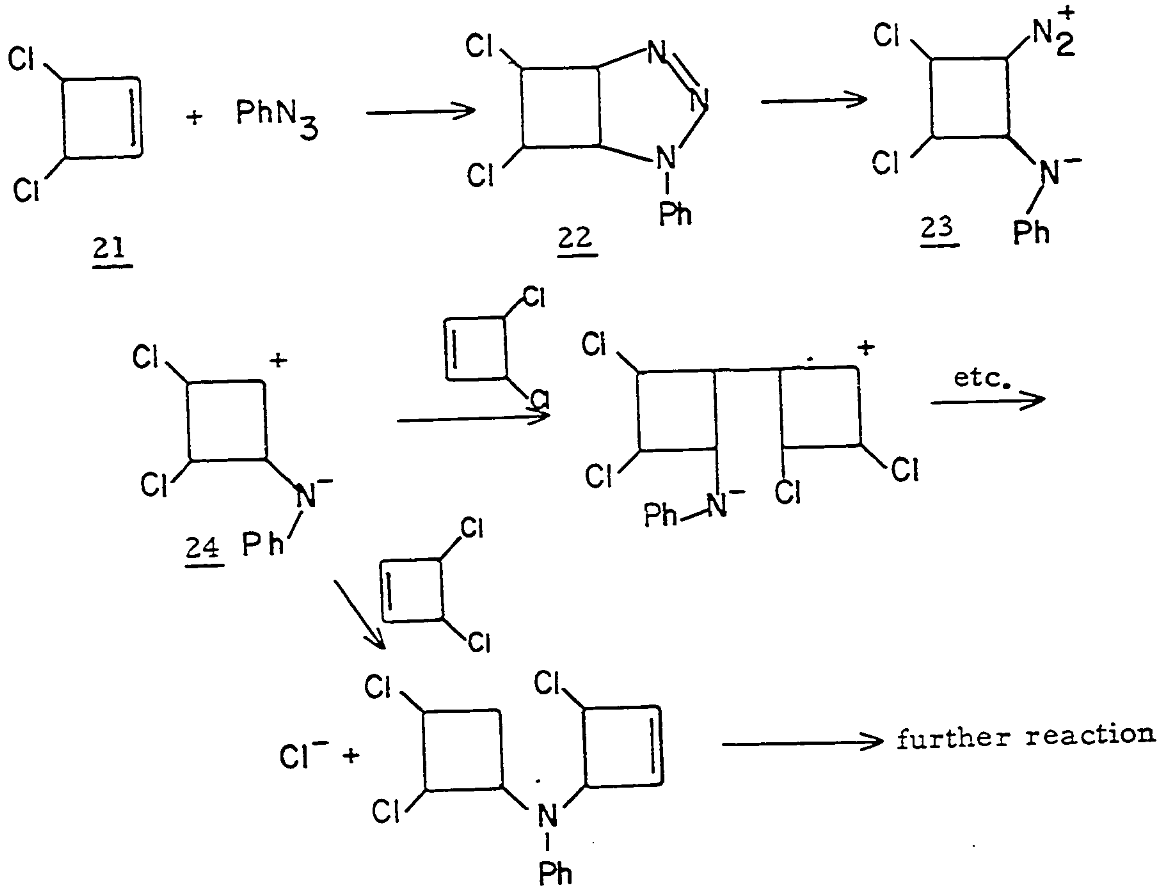


20

The reactions, for the most part were run at room temperature or below and the triazoline produced, 20, was capable of further transformation by photolysis, or sometimes pyrolysis, to give the aziridine in generally excellent yields. Some triazolines, particularly from azides with strong electron withdrawing groups were unstable at room temperature and spontaneously lost nitrogen to form the aziridine ring.[31]

It was hoped to use this particularly mild set of conditions to synthesize the azabicyclic system. 3,4-Dichlorocyclobutene, 21, was chosen for initial dipolar addition attempts since it has a boiling point of 70° at 60 torr and is hence much easier to work with than cyclobutene itself. When 21 was treated with tosyl azide, a very slow deposition of tar in the reaction flask was noted. The azide peak showed no apparent decrease. An NMR spectrum of the filtered, evaporated reaction mixture failed to reveal the presence of materials other than the reactants.

Phenyl azide[32] was treated with 21 in both carbon tetrachloride and dimethylformamide (DMF) (since rate accelerations of dipolar additions have recently been observed in that solvent[33]). The mixture turned dark with time, slowly with carbon tetrachloride and rapidly with DMF, a dark gooey precipitate being observed in the former case. In both cases, an aqueous extract of the tarry substance and an aqueous extract of the DMF solution showed the presence of chloride ion in large amounts. None of the reactants will react with silver nitrate. A possible explanation of these observations is represented in the scheme below:



The intermediate, 22, is proposed to be unstable at the temperature of formation and decomposes spontaneously to 23 and 24 which then may either polymerize the olefin by carbonium ion initiation or displace chloride from the cyclobutene, an allylic chloride.

To test this hypothesis of a diazonium intermediate in the path, the reaction was repeated in the presence of an equimolar amount of N,N-dimethyl-1-napthylamine with DMF as the solvent. In this manner, the intermediate 23 might couple with the amine to form an azo-compound.

A red compound was obtained after incomplete reaction which by IR spectral analysis contained a secondary N-H (from neutralization of the N^- in 23 or 24) in addition to ones for a phenyl ring. No colored compounds were observed in the absence of the napthylamine.

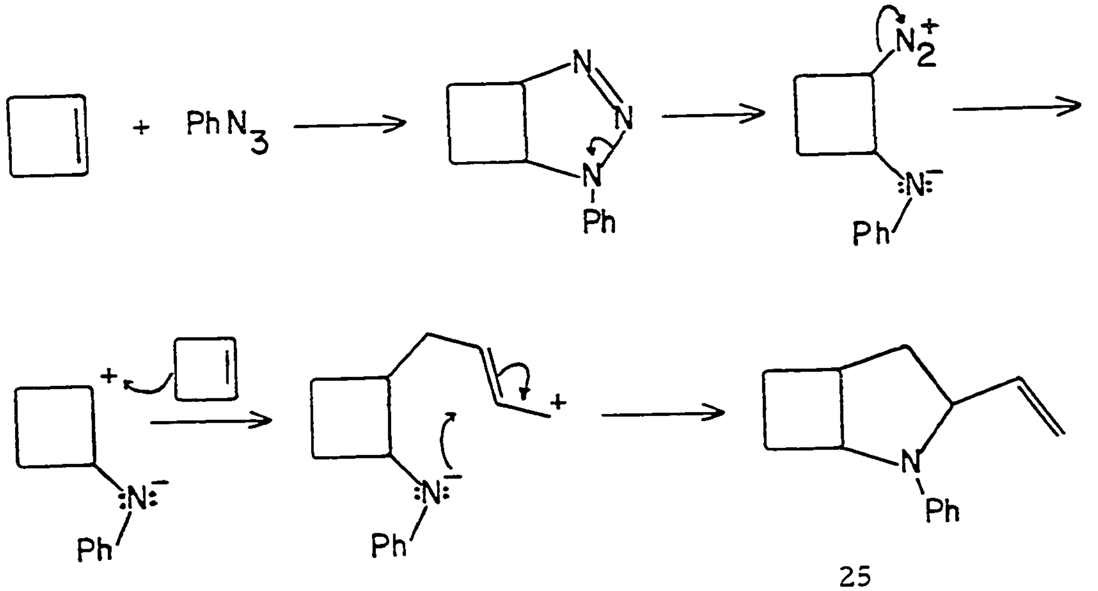
An NMR spectrum indicated a ratio of eleven aromatic protons to four aliphatic ones but the sample was impure by TLC. It could not be purified sufficiently by preparative TLC for better analysis. TLC detected the presence of some of the napthylamine. Because of this, oxidation by permanganate to phthalic acid to show the presence of a 1,4-disubstituted napthylene ring was not attempted since the napthylamine itself would also be expected to give phthalic acid upon oxidation. Instead a test for azo-compounds was carried out which showed a positive reaction. (see Experimental Section)

Production of a colored azo-compound in the presence of the napthylamine along with the occurrence of a secondary N-H proton in the IR spectrum would thus seem to substantiate this hypothesis.

The precipitated goo in the carbon tetrachloride reaction was dissolved in trifluoroacetic acid and NMR analysis showed the material to have broad absorptions in the areas (τ, rel. ratio): 2.6 (2), 6.15 (29), and 8.10 (28). This would indicate a polymer having mostly dichlorocyclobutane units in it.

The obvious way to circumvent some of these side reactions was to use the parent or alkyl substituted cyclobutenes. Because of the volatility of cyclobutene, it was decided to run the addition of it to phenyl azide at reduced temperature, -20° being conveniently available. After several weeks, no decrease in the azide peak was noted in the IR spectrum. The material was transferred to a vial, sealed, and allowed to sit for several weeks at room temperature.

A product was obtained in low yield that by mass spectral analysis had the composition $C_{14}H_{17}N$, indicating a 2:1 adduct of cyclobutene to phenyl azide. The data best support the structure <u>25</u>.

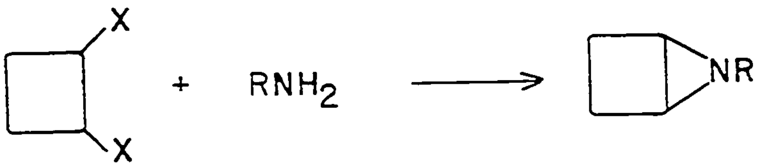


<u>25</u>

Thus the triazolines in both the reaction with dichlorocyclobutene and cyclobutene are unstable at room temperature but do not cyclize to give useful products. Quite obviously then, the use of dipolar addition as a synthetic entry into the 5-azabicyclo[2.1.0]pentane system did not prove to be satisfactory.

Nucleophilic Displacement Route

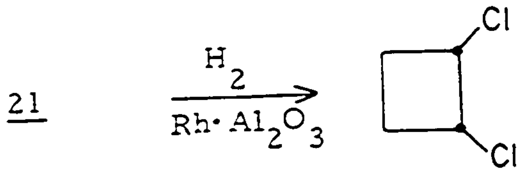
A very simple route that could be envisioned for the synthesis of the parent system and derivatives would be through a double displacement by an amine on a cis-vicinal dihalide.



Regular addition halogenation of a cyclobutene would produce a dihalide of the wrong stereochemistry for ring closure. Therefore, the logical route for synthesis of a cis dihalide such as 26 would be hydrogenation of the available cis cyclobutene, 21.

Hydrogenation over Pd• C gave only hydrogenolysis of the halides, the only isolated product less volatile than solvent being 3-chlorocyclobutene. Hydrogenation over rhodium-on-alumina gave the dichlorocyclobutane, 26, as confirmed by the NMR spectrum.

To test the feasibility of this route, t-butylamine was chosen as the primary amine in order to reduce double displacement which would give a



26

diamine. The solvent of choice for the reaction would seem to be dry DMSO since large rate accelerations of hydrogenolysis of cycloalkyl halides with sodium borohydride have been reported in DMSO and sulfolane.[34] Dry t-butylamine was dropped slowly over a period of several days into the stirred solution of 26 in dry DMSO in the dry box. Periodic checks were taken for chloride ion and showed no displacement over a period of weeks, so the reaction mixture was heated (80-85°) and after a week showed chloride displacement.

Chromatography of the material more volatile than DMSO gave 26 and t-butylpyrrole (by NMR) plus trace amounts of other compounds that did not show a methylene ring proton pattern in the general area expected by analogy to the other azabicyclic compounds isolated.

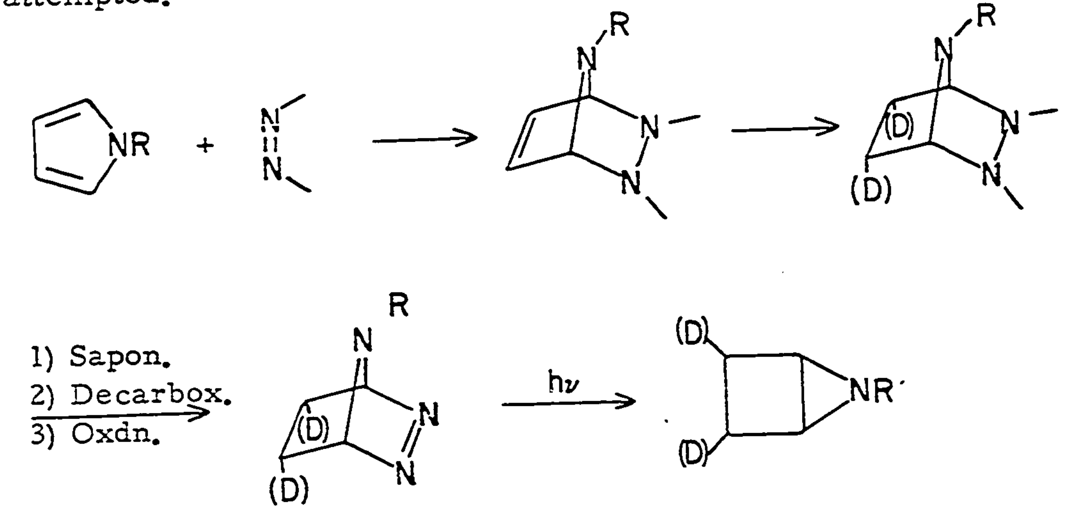
The ratio of cyclobutane to pyrrole was the same as the ratio of cyclobutane to unhydrogenated cyclobutene in the starting material. Since the cyclobutene would be expected to easily form the pyrrole with t-butylamine,[35] that was no doubt the source of the pyrrole. Thus the displacement on the dichlorocyclobutane did not proceed at a useful rate for bicyclic compound synthesis in this case.

The obvious better method would need a cis-dibromo- or, better yet, a cis-diiodocyclobutane or other good leaving group for more rapid displacement. No such compounds are easily available. It is well to note that Reppe reported the synthesis of <u>cis</u>-3, 4-dibromocyclobutene, the structure of which was assigned by analogy to the <u>cis</u>-dichloro compound.[14] Since his "dichlorocyclobutene" was later shown to be 1, 4-dichloro-1, 3-butadiene,[15] the identity of the dibromocyclobutene is in serious doubt.

Diels-Alder Route

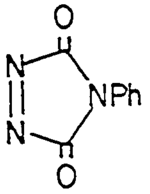
Introduction

For the synthesis of the bicyclic system from a five-membered ring starting material the following route based on a Diels-Alder reaction was attempted.



Specific deuteration by this route would allow assessment of the direction of addition of various reagents that might add to the bridging bond.

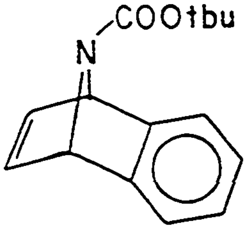
The dienophile, <u>27</u>, is conveniently generated by nitrogen tetroxide oxidation of the easily available N-phenylurazole.[36] The yield is good and the product easily purified by sublimation. This particular compound was chosen over others since it is known to be the most reactive in Diels-Alder addition of any "azo-dienophile."[37]


27

Reaction of Pyrroles with 4-Phenyl-1, 2, 4-triazoline-3, 5-dione.

When pyrrole was treated with 27 in THF or dioxane a black tarry material resulted. Several trace constituents were detected by TLC and separated by preparative TLC. Their amounts were not sufficient for spectral analysis. In the presence of hydroquinone, to cut down on polymerization reactions, essentially identical results were obtained.

It is known that N-carbo-t-butoxypyrrole reacts with benzyne in Diels-Alder addition fashion to produce 28.[38]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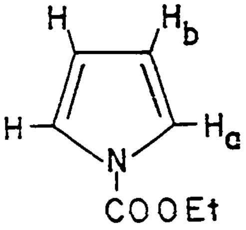

29

Diels-Alder additions of dienophiles have also been observed with other N-substituted pyrroles.[39] By analogy one might expect N-carboethoxypyrrole (29) to react in a similar manner towards 25.

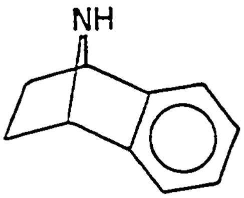
N-carboethoxypyrrole (29) was synthesized by the same method used for the N-carbo-t-butoxy compound except that ethyl instead of t-butyl azido formate was used.[38] (see Experimental Section) Previous workers used diethyl carbonate[40] or ethyl chloroformate[41] to synthesize the compound. The yield (58%) was moderate. An NMR spectrum showed the N-substitution clearly (τ, area): 2.8 (t, 2), H_a, 3.7 (t, 2) H_b, 5.7 (q, 2), and 8.6 (t, 3).

When <u>29</u> was reacted with the dienophile (<u>27</u>) in the presence of hydroquinone a dark red reaction mixture resulted with no evident tar formation. Unreacted <u>29</u> was found to be present by TLC; also 4-phenylurazole, the dienophile precursor was present. A yellow spot at R_f 0.3 was the other major product and isolation was attempted by column chromatography. Chromatography on silica gel (200-325 mesh), Florisil (60-100 mesh), and neutral alumina (Woelm) failed to give the products in quantities sufficient for identification even though several tenths of a gram of crude material were used with each column. The compounds adhered tightly to the column and perhaps even reacted with the support material.

The spots of interest when separated by analytical TLC, did not give a pyrrole color test. N-carboethoxypyrrole, pyrrole, and 2,5-dimethylpyrrole gave this test; N-phthalimidyl-2,5-dimethylpyrrole gave an orange colored dye.

Because of this isolation problem, the crude material was hydrogenated over Pd• C in a Parr apparatus. An uptake was observed but could be attributed to any N-carboethoxypyrrole that was present since it is rapidly reduced under the hydrogenation conditions (methanol, 46 psi, 5% Pd• C). Indeed in the NMR spectrum of the crude hydrogenated material, the multiplets for the ring hydrogens of N-carboethoxypyrrolidine were observed.

In hopes of obtaining compounds capable of isolation, the crude hydrogenated material was hydrolyzed with 5% potassium hydroxide. The amines found in the workup were aniline, and N-carboethoxypyrrolidine in one case, and aniline from one hydrolysis run without a condenser. In neither case did signals appear in an area of the NMR spectra that could reasonably be assigned to the desired bicyclic triamine, 30. It is, of course, possible that it was present in very small amounts and covered by other signals but this would indicate the route to be very poor. The model compound used to estimate the approximate absorption positions was 30.[38]



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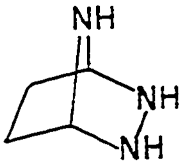
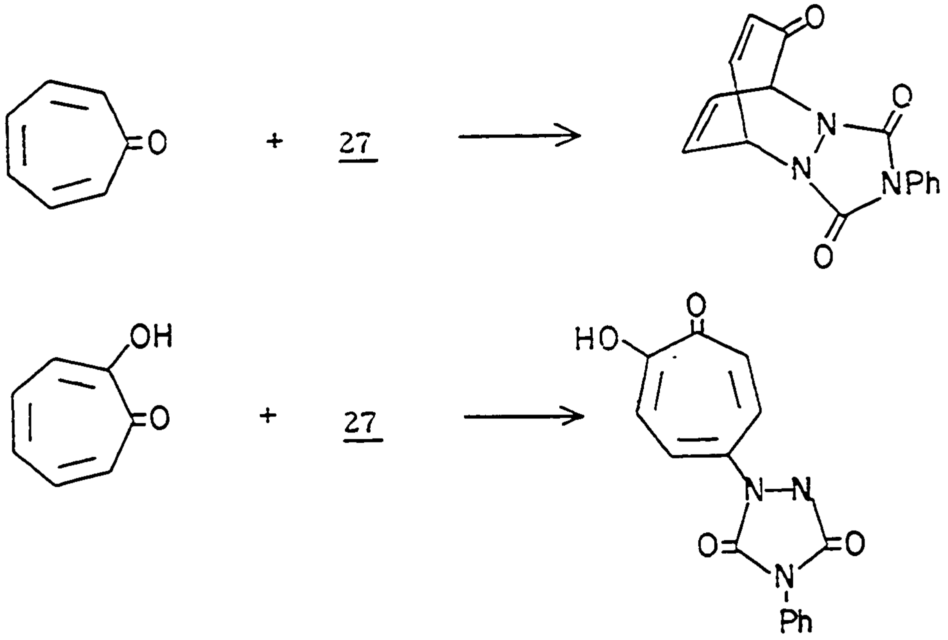


31

It was assumed that the methylene hydrogens would be little affected by the different ring system but that the bridgehead protons in 31 would be further downfield from compound 30's bridgehead absorptions.

	30	31 (expected)
methylene	7.02 and 8.81 τ	ca. 7 and ca. 8.5-9.0 τ
bridgehead	5.67 τ	ca. 5 τ

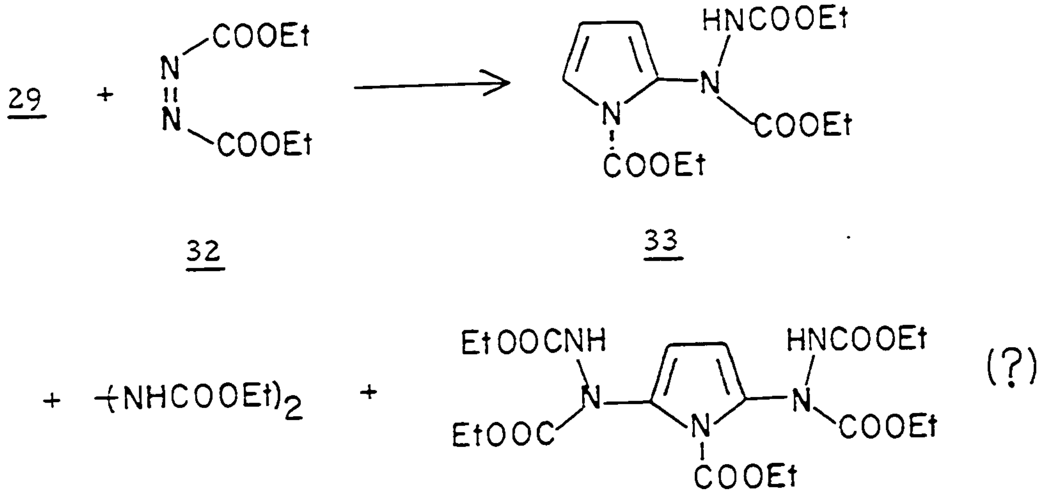
The azo-dienophile used, 27, is electrophilic[37] in character and has recently been found to substitute on an aromatic system rather than undergo Diels-Alder addition.[42]



Reaction of N-Carboethoxypyrrole with Ethyl Azodiformate.

Since pyrroles are very reactive toward electrophiles, one desires a dienophile of the lowest electrophilicity. Feeling that perhaps the Diels-Alder reactivity and electrophilicity of the dienophile might be directly proportional or at least related in the same way, a less reactive dienophile, 32, was used for reaction with N-carboethoxypyrrole. The reaction was not complete after one month while with 27 it was complete overnight. Three products slowly appeared as shown by TLC analysis, two of them giving an orange pyrrole color test, very similar to the test given by 1-phthalimidyl-2,5-dimethylpyrrole.

When the incomplete reaction was worked up by initial vacuum separation at 10^{-6} torr to remove most of the starting materials, followed by preparative TLC of the residue on HF_{254} silica gel plates, the major product isolated (66% by weight of the converted reactants) was 33.



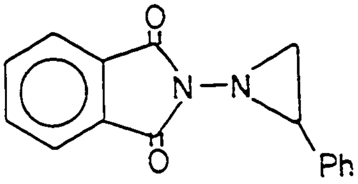
Its NMR spectrum clearly showed three nonequivalent pyrrole protons, an N-H proton, and three carboethoxy groups (see Spectral Section). Elemental analysis was satisfactory for the compound.

By analogy, the reaction of the pyrrole with 27 no doubt gave similar ring substitution products as in the case above. The predominance of tar in the first instance is understandable since the reaction of strong electrophiles with pyrroles leads to formation of tar-like materials.

Since this method will not give Diels-Alder addition, it has no potential for synthesis of the azabicyclic compounds desired.

Attempted N-N Bond Cleavage Reactions

For reactions leading to attempted cleavage of the N-N bond of compounds 10a and 10b, it was desirable from the economy standpoint to have large quantities of a model compound available to work out the necessary reaction conditions. Although not ideally suited, the N-phthalimidylaziridine from the reaction of styrene with N-phthalimidylnitrene, 34, is readily synthesized.[20]



34

Because of its ease of synthesis from readily available starting materials, and since large quantities had already been made to work out reaction conditions for compound 10b synthesis, it was decided to use this compound for cleavage attempts.

The classical hydrazine cleavage reactions can be considered in two categories: 1) cleavage with sodium dithionite,[43] and 2) cleavage using metal hydride reagents, lithium aluminum hydride being the only example used in the literature.[44]

Two major factors governing the selection of potentially good cleavage reactions must be considered: the stability of the initial compound to the reaction conditions, and the stability of the product to reaction conditions. Considering the rearrangement observed in the reaction of 1-azido-2-iodocyclobutane with lithium aluminum hydride to give cyclopropylcarbinylamine, one concludes that Lewis acids are undesirable as they would no doubt destroy the product expected from the cleavage of the azabicyclopentanes and possibly also rearrange the starting material.

This consideration rules out use of the lithium aluminum hydride method, although perhaps other hydride reagents such as metal borohydrides could be used on the basis of their lower Lewis acidity.

Sodium dithionite did not cleave compound <u>10b</u> itself. (see p. 24)

A possibly feasible route might be to use the reactive diimide for the N-N bond cleavage. Of the several methods for diimide generation, the mildest method reported is by Drückheimer.[45]

$$NH_2OSO_3H + NH_2OH \xrightarrow{KOH} H\text{-}N = N\text{-}H$$

When this reaction was attempted with compound <u>34</u>, no phthalimide was found to be present by TLC. It of course could have been hydrolyzed or partly hydrolyzed, and thus not have been detected, in the workup procedure used.

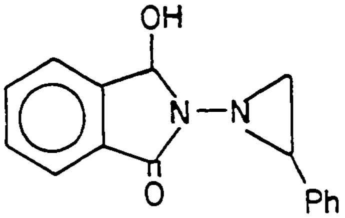
Although phthalimide loss and also compound <u>34</u> loss could reasonably be argued on this basis, the 2-phenylaziridine would be expected to be base stable and should have been isolated with the workup procedure used. (see Experimental Section) The crude material obtained in small quantity showed only a small amount of phenyl protons in the NMR spectrum and hence only a small portion could be the desired aziridine. Since the material was in small quantity, separation and purification of the components was not attempted. The important point is that the cleavage did not take place to any usable extent.

Lithium borohydride was the last reagent considered for N-N bond cleavage. Because of the reduced Lewis acidity, it is probable that rearrangement of the product would not be catalyzed by this material. Lithium borohydride is more soluble in THF than the sodium salt and can thus provide a homogenous reaction medium.

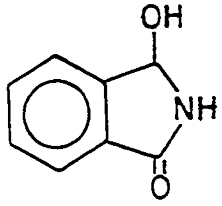
Reaction of lithium borohydride with compound 34 in THF gave interesting results. At no time during the reaction was the presence of phthalimide indicated by TLC. The major spot noticed in the reaction mixture was of considerably lower R_f value than the starting material.

A test reaction indicated that phthalimide does not survive the reaction conditions but is rapidly converted to another product of R_f value close to that of the major product of the attempted cleavage reaction. This material was isolated and purified by recrystallizing twice from water. The material showed a m.p. 175-6° (lit. 179°) corresponding to 36.[46] The NMR spectrum showed peaks at (τ, area): 1.25 (br s, 1), 2.43 (s, 4), 3.70 (d, J = 9, 1) and 4.15 (d, J = 9, 1). A similar spectrum was obtained for the reaction with 34.

The IR spectra of the phthalimidine, 36, and the reaction product of 34 with lithium borohydride were very similar, the carbonyl absorptions coming at exactly the same position. It can thus be concluded that the product is a phthalimidine, 35.



35



36

By TLC comparison a very small amount of 36 was present in the attempted cleavage reaction and no doubt came from reduction of the contaminant phthalimide in the starting material. The amide 35 is stable to further reduction by borohydride with no evidence of N-N bond cleavage.

CONCLUSIONS

Of the methods tried for bicyclic compound synthesis, only nitrene reaction with a cyclobutene produces the results desired. This was no doubt due to the high strain energy of the system which was reflected in a high transition state energy leading to the ring system. The N-phthalimidyl compounds are characterized by a higher acidity of the methylene hydrogens than the bridgehead hydrogens. The bridging bond of the system is indicated to add bromine trans. The bridging bond however is not reactive enough to give addition compounds with tetracyanoethylene or tetraphenylcyclopentadienone.

No satisfactory N-N bond cleavage reaction was found for the system.

EXPERIMENTAL SECTION

The following chemicals used in the experiments detailed in this section were obtained from their suppliers as listed. Sulfolane was a sample from Shell Development Co. Methyl lithium was obtained from Alfa Inorganics as a 2.15 M solution in ether. Cyclobutanecarboxylic acid was from Columbia Organic Chemicals. Lead tetraacetate was obtained from either Arapahoe Chemical Co. or Alfa Inorganics. Cyclooctatetraene was a generous gift by BASF Corporation to the late Dr. Hyp Dauben. All other chemicals were obtained from the supplies listed in the Experimental Section of Part II of this thesis or from common suppliers.

Lead tetraacetate (LTA) was recrystallized from hot glacial acetic acid after filtering off the suspended lead dioxide if the material was any darker than a medium brown. Material that was supplied by Alfa Inorganics was generally white and was used without recrystallization although the acetic acid present had to be removed under vacuum in a desiccator. The LTA was stored in taped bottles in a vacuum desiccator over phosphorus pentoxide. The recrystallized material should be washed with dry benzene to remove acetic acid and then while still damp with benzene, transferred to a taped bottle, placed in a desiccator, and the excess benzene removed with aspirator vacuum for several hours. The desiccator may then be repressurized if desired carefully with dry nitrogen.

Acetonitrile, ether, tetrahydrofuran (THF), 1,2-dimethoxyethane (glyme) were all dried as stated in the Experimental Section of Part II of this thesis. Benzene was kept dry over sodium wire. Dichloromethane was refluxed overnight over, distilled from phosphorus pentoxide, and stored over Drierite. Dimethylsulfoxide (DMSO) was dried over molecular sieves. Triethylamine and t-butylamine were both refluxed over and distilled from barium oxide pellets.

Silica gel for column chromatography was 200-325 mesh Davison desiccant grade; for TLC plates Silica Gel G or HF_{254} types were used. Molecular sieves were Linde 4 Å type, activated by heating at 200° under a flow of dry nitrogen for several hours. Deutero solvents were obtained from Stohler Isotope Chemicals.

NMR spectra were recorded on Varian HA-60, A-60, and T-60 spectrometers with TMS as internal reference unless otherwise noted. Spectra are given as in ppm followed by the relative area of the peak unless noted. UV spectra were recorded on a Cary Model 14 spectrophotometer with 1.0 cm path length quartz cells. IR spectra were taken on Perkin Elmer Models 137 and 225 spectrophotometers with 0.1 mm path length sodium chloride cells for solution spectra. Mass spectra were recorded on an AEI MS-9 mass spectrometer at 70 eV ionizing voltage.

Sodium-Liquid Ammonia Reduction of Cyclooctatetraene. - The method of A. C. Cope[10] was followed for 10.4 g (10 mmol) of cyclooctatetraene. The yield of faintly yellow trienes was 1.8 g (17%).

The silver nitrate complex was made, 2.4 g (51%) but could not be recrystallized as stated in the literature.

Decarboxylation of Cyclobutanecarboxylic Acid With Lead Tetraacetate. - This was an attempt to scale up the literature preparation.[9] Cyclobutanecarboxylic acid, 26 g (0.26 mmol), was heated in 250 ml of dry benzene together with 22.2 g (0.05 mol) of LTA and 0.5 g (2.5 mmol) of cupric acetate monohydrate. The top of the condenser was fitted for gas take off which lead to two successive traps in Dewar flasks containing salt-ice mixtures (-19°). The apparatus was swept by a very slow nitrogen flow and heated under gentle reflux. Carbon dioxide evolution (identified by passing the trap effluent through a saturated solution of barium hydroxide) began shortly before reflux was obtained and ceased about 3 hr. after reflux began.

The first trap contained all the liquid, the majority of which was benzene (NMR). Separation by the usual trap to trap distillation used for cyclobutene (see p. 53) gave 0.1 g of the olefin. The benzene remaining had 17 mole per cent cyclobutene content (NMR analysis) giving a total yield of 0.2 g (7%).

Evaporation of the cooled reaction mixture gave a syrupy blue liquid which was directly vacuum distilled to give 10.0 g (38%) of the recovered acid. The pot residue was a hard, dark cake.

Cyclobutene. - COT and dimethyl acetylenedicarboxylate (DMAD) were stirred in a heated oil bath under nitrogen as indicated in the table below:

TABLE 1

Reaction Conditions for 6

COT (mol)	DMAD (ml)	time	temp.	recov. COT (%)	yield
0.1	0.1[a]	5 hr.	158-60°	18	44.6[b]
0.5	0.5	16 hr.	140-50°	13	42.5[b]
0.5	0.5	13½ da.	94-102°	17.3	82.5[c]
0.5	0.5[a]	3 da. 3 mo.	130-40° RT	5.2	91.5[c]

[a] Freshly distilled material.

[b] Purified by vacuum distillation.

[c] Purified by dissolving the reaction mixture in 100-200 ml of methanol, filtering the precipitate off through medium porosity sintered glass with suction, followed by washing of the precipitate with two 50 ml portions of methanol used to rinse out the reaction flask. The filtrate is then evaporated with a Rotovac followed by overnight at 0.1 torr or less at room temperature with slow magnetic stirring.

The product purified by vacuum distillation contained a substantial amount of dimethyl phthalate and had an NMR spectrum corresponding to 7,8-dicarbomethoxytricyclo$[4.2.2.0^{2,5}]$decatriene.

The product was hydrogenated at atmospheric pressure according to the table given on the following pages. The crude hydrogenated product was obtained by filtering the hydrogenation mixture through medium porosity sintered glass covered with a 2 cm thick layer of Celite filter aid using

TABLE 2

Hydrogenation of 6 and Pyrolysis of the Crude Diene

Diels-Alder run	6, g	catalyst	Hydrogenation solvent	% hydrogenation	yield[a]	% cyclobutene
1	4.8	Pd• C, 5%	MeOH	109	94	40.5
	2.33	"	"	103	99.8	59
2	3.3	Pd• $BaSO_4$, 8%	"	94	97.5	44
	25.0	"	PhH	80	95.5	57
						50
	25.0	"	PhH:MeOH	81	100	64
			(3:2)			62
3	10.5	"	MeOH	62	100	44
	12.0	"	"	70	97	43
	12.0	"	"	80	99.4	46
	12.0	"	"	90	100	42
	24.0	"	"	85	99	43

TABLE 2 (continued)

Diels-Alder run	6, g	catalyst	Hydrogenation solvent	% hydrogenation[a]	yield	% cyclobutene
	24.0	"	PhH:MeOH (1:1)	80	99	48
	7.0	"	PhH:MeOH (4:1)	69	83	52
4	11.3	Rh· Al_2O_3, 5%	PhH:MeOH (2:1)	80	103	39
	50.0	Pd· $BaSO_4$, 8%	"	80	100	29

[a] Per cent of one equivalent.

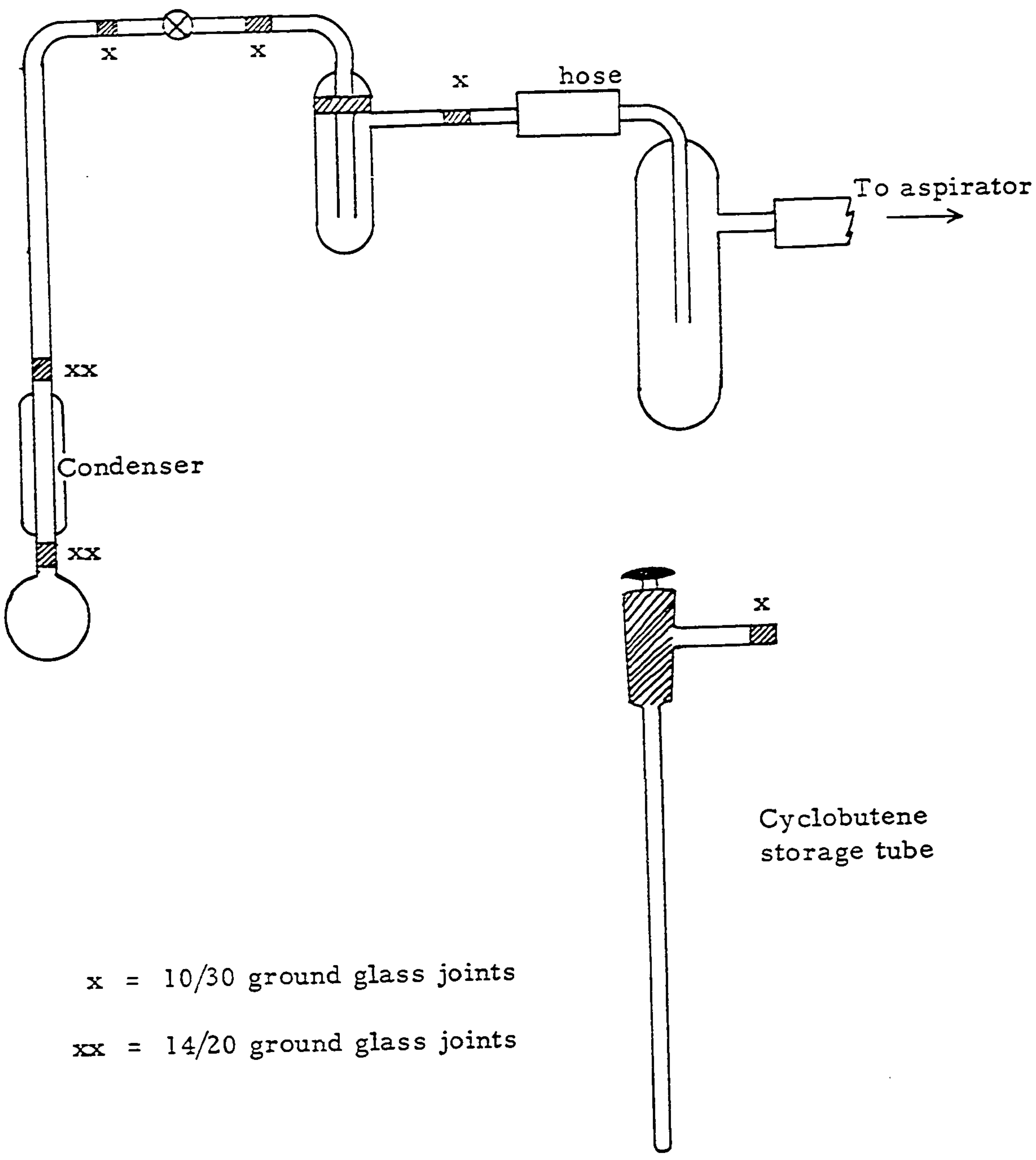
suction. The Celite was washed with two 25 ml portions of methanol used to rinse out the hydrogenation flask. The solution was evaporated on a Rotovac with a hot-water bath followed by several hours at 0.1 torr or less (preferably overnight) with magnetic stirring in the flask to remove excess solvent.

Cyclobutene was obtained by heating the crude hydrogenated product in the amounts given in the table at 190-200° in the system diagrammed on page 54 under a nominal 100 torr vacuum until cessation of gas evolution. The traps were cooled in liquid nitrogen. The first trap contained all the material and was attached by means of ground glass connections to a storage tube, evacuated under liquid nitrogen cooling of the trap contents, and distilled to the storage tube cooled in liquid nitrogen by allowing the trap to warm to room temperature. Trap residue was small and identified as dimethylphthalate (NMR). The cyclobutene may be stored indefinitely at liquid nitrogen temperature. For removal of the olefin from the storage tube, it is placed first in a Dry Ice-acetone bath while venting the stopcock, and then in a salt-ice bath. The material may then be poured out after stopcock removal or removed by long transfer pipet.

Attempted Preparation of 2-Chlorotetrahydrothiophene (7a). - Tetrahydrothiophene, 0.88 g (10 mmol), was refluxed together with 1.34 g (10 mmol) of recrystallized N-chlorosuccinimide in 50 ml of carbon tetrachloride for 18 hr. The gray solid was filtered off; 0.8 g (81%), m.p. 121-5° (literature for succinimide, 126-7°). The solution was evaporated to 0.45 g of a red-brown oil that exhibited a multiplet in the NMR

FIGURE 1

CYCLOBUTENE APPARATUS



x = 10/30 ground glass joints

xx = 14/20 ground glass joints

spectrum (CCl_4) from 5.8 to 8.4. Since previous reports indicated decomposition upon distillation, the product was used as was.[13] A peak in the IR spectrum at 1709 cm^{-1} showed some succinimide (or N-chlorosuccinimide) was still present.

Reaction of Crude 2-Chlorotetrahydrothiophene With Peracetic Acid. - Crude product from the above reaction, 0.45 g, and 1.5 ml of ca. 40% peracetic acid (7.25 M by titration, 10.9 mmol) were stirred together in 20 ml of dry ether. After 1.5 hr. an oil began to separate out. After stirring overnight, the oil was filtered off. It was a very tarry substance insoluble in most solvents and was thus assumed to be a polymer. Evaporation of the ether solution gave a residue of acetic acid only (NMR).

Reaction of Tetrahydrothiophene With N-bromosuccinimide (NBS). - Tetrahydrothiophene, 0.88 g (10 mmol), and 1.80 g (10 mmol) of recrystallized NBS were heated in 50 ml of refluxing carbon tetrachloride for 2 hr.

After cooling, the black crystalline material was removed by suction filtration and the solvent evaporated to a dark orange oil, 1.1 g, which on short standing in air turned brown-black and deposited a black tar on the vial walls. After sitting over the weekend, the material was almost completely converted to the black tarry substance.

Reaction of Sulfolane With NBS. - Sulfolane, 1.20 g (10 mmol), dried by azeotropic distillation with benzene followed by removal of excess benzene by distillation, was refluxed in 50 ml of carbon tetrachloride with 1.80 g (10 mmol) of recrystallized NBS. No bromine color developed for several hr. After two days, the reaction mixture was cooled, filtered, and washed with 20 ml of water followed by 10 ml of saturated sodium bisulfite solution. The colorless organic layer was separated and dried over magnesium sulfate. After filtering off the drying agent, the solution was evaporated to give 0.17 g of a light yellow oil which was a mixture of several products (TLC). Because of the mixture present and the small yield, no further workup was attempted.

Reaction of Sulfolane with Methyl Lithium and Bromine (8b). - A solution of 1.20 g (10 mmol) of dry sulfolane (see previous experiment) in 25 ml of dry ether was stirred in a flamed-out three-neck round bottom flask fitted with a gas outlet tube and a syringe cap. The outlet tube was attached to a rubber tube which was placed in a beaker containing some water to act as a bubble monitor. Methyl lithium, 5.5 ml (1.9 M, 10.4 mmol), was added dropwise with vigorous stirring through a syringe. A white precipitate formed simultaneously with gas evolution. After addition was completed, stirring was continued until gas evolution ceased (2 hr. from reaction initiation). The gas outlet was replaced by a 105° glass connection to a three-neck 100-ml round bottom flask previously flame dried containing 2.0 g (12.5 mmol) of bromine in 25 ml of dry benzene. The carbanion solution was tipped portionwise into the benzene-bromine solution which was stirred vigorously. It was necessary to have one of the necks of the flask attached to a U-tube bubbler with mineral oil in it to vent pressure built up in the reaction due to heating. After addition of the slurry, the solution was poured into a separatory funnel and 20 ml of sodium bisulfite solution was added. The organic layer after washing was clear and colorless. It was separated, dried over magnesium sulfate, filtered, and evaporated to yield an orange oil, 0.37 g (18%), which showed a positive sodium fusion test for sulfur and bromine.

In another run of this reaction in which the bromine was added to the carbanion suspension, a thick red oil (39%) showing four products (TLC) plus residual sulfolane was obtained. It was this material that was used for the elimination reaction below.

Reaction of Crude α-Bromosulfolane With Potassium t-Butoxide. - Crude bromosulfolane, 5.5 g, was dissolved in 80 ml of dry THF and placed in a three-neck flask connected to a nitrogen inlet and a condenser, which in turn was connected through a gas outlet tube and a rubber tube (no Tygon!) to a trap immersed in Dry Ice-acetone. Dry potassium t-butoxide, 2.8 g, was added and the mixture refluxed while passing a gentle nitrogen stream through the apparatus.

After 5 hr. reflux, several ml of trap liquid were obtained and the pot mixture allowed to cool. The trap liquid was purified by one trap-to-trap distillation. The collection tube was washed with 3 ml of dilute bromine in dichloromethane solution and evaporated to a small drop of liquid.

A TLC against authentic dibromocyclobutane on silica gel (2:1 petroleum ether pet. ether-acetone) showed spots at 0.9 (dibromocyclobutane), 0.8 (an impurity found in the authentic sample), 0.55 (equal in size to the 0.9 spot), and 0.4. Both the 0.8 and 0.4 spots were small.

5-Phthalimidyl-5-azabicyclo[2.1.0]pentane (10a). - The general method used was that of Rees and coworkers with some modifications.[20] Actual best conditions were worked out in the synthesis of 10b. The specified amount of N-aminophthalimide[47] was stirred in dry dichloromethane (usually 20 ml for each 6.25 mmol of N-aminophthalimide) with cyclobutene as indicated in the table below. The LTA was added portionwise with stirring over the time specified and stirred for an additional time as listed. The mixture was then filtered by suction, the salts being washed

TABLE 3

Reaction Conditions for 10a

mmol NAP[a]	ratio LTA/NAP	ratio olefin/LTA	addition/ stir, min.	yield
6.25	1.05	3.71	10/10	21.7
12.5	1.05	3.12	13/10	18.4
3.06	1.01	7.25	15/15	b
18.0	1.05	3.19	20/10[c]	22.4[d]

[a] N-aminophthalimide.

[b] Lead tetrabenzoate[22] used as the oxidant. Crude yield, 55%, with at least an equimolar quantity of benzoic acid present.

[c] Ice cooling used.

[d] 29% cyclobutane recovered.

with additional solvent and the solution evaporated with a Rotovac. The product was reevaporated with two small portions of benzene to remove acetic acid.

The product was purified by column chromatography (6.7 x 13 cm using 5:1 pet. ether-acetone elutant) followed by continuous elution on silica gel preparative TLC plates with 6:1 pet. ether-acetone, the yellow band being allowed to travel one-half to two-thirds the length of the plate. The major impurity travels with the leading edge of the band and may easily be removed by marking the band under UV blacklight and discarding the colorless leading ca. 0.5 cm. The yellow crystals were recrystallized from methanol or carbon tetrachloride for the analytical sample, m.p. 114-6°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.11; H, 4.72; N, 12.99.

An NMR spectrum was recorded (DMSO-d_6): 2.25 (s, 4), 6.66 (m, 2), 7.82 (m, 2), and 8.60 (m, 2). An IR spectrum showed characteristic peaks as 1770 and 1710 cm^{-1}. UV absorptions were recorded (ethanol) λ_{max} ($\log \epsilon$): 234 (4.57), 295 (3.08), 304 (3.04), and 330 shoulder (2.57) mμ.

A mass spectrum showed a parent peak at 214.0747 (calcd. for $C_{12}H_{10}N_2O_2$: 214.0741) Other major peaks of interest were at 212 (10 times parent amplitude, $C_{12}H_8N_2O_2^+$), 146 ($C_8H_4NO_2^+$), 91 ($C_6H_5N^+$), and 66 (base peak, $C_4H_4N^+$).

The material darkened slowly when stored in base washed sample vials in a desiccator. Its rate of darkening was slower than 10b under the same conditions.

Reaction of 100 mg of 10a with *ca.* 100 mg of bromine in 1 ml of dry dichloromethane gave 16.3 mg of phthalimide and 64.8 mg (38%) of a thick, pale yellow oil, a dibromide, $C_{12}H_{10}Br_2N_2O_2$. NMR spectrum ($CDCl_3$): 2.27 (m, 4), 5.83 (br m, 2), 7.87 (br m, 4). The width of the multiplets was: 5.83, *ca.* 38 hz; 7.87, *ca.* 56 hz. A mass spectrum showed an extremely weak parent peak at 371.8890 (calcd. for $C_{12}H_{10}Br_2N_2O_2$: 371.9115) with no peaks above the parent set of peaks up to m/e 800. The material discolored quite rapidly even when stored in a desiccator in purified state.

2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane (10b). - The compound was synthesized by the method for 10a but substituting *cis*-3,4-dichlorocyclobutene for cyclobutene. A table of the experiments conducted for yield optimization is on the following page.

The material after purification by one of the methods listed was sublimed at 0.01 torr at 50°. The white crystals which collected rapidly were discarded.

In the first three reactions in the table, potassium carbonate was present in an amount to neutralize acetic acid produced in the oxidation process. In the next three it was added after the reaction had been carried out and before filtration. The last three experiments were done without

TABLE 4

Reaction Conditions for <u>10b</u>

mmol NAP[a]	ratio LTA/NAP	ratio olefin/LTA	addition/ stir, min.	purification[b]	yield
6.25	1.0[c]	1.6	6/5	A	2.5
6.25	1.0[c]	1.55	8/10	B	3.2
6.25	1.0	1.7	8/10	B	5.1
6.25	1.0	2.0	8/14	B	6.2
6.25	1.0	2.5	1/1[d]	B	3.6
6.25	1.0	2.0	8/5	B,C[e]	3.9, 0.6
6.25	1.0	2.5	45/30	C	trace[f]
30.9	1.05	2.58[g]	35/30	D	9.9
13.0	1.05	3.25[h]	20/10	D	12.2

[a] N-aminophthalimide.

[b] Methods of purification: A. Elution on a silica gel column with 2:1 pet. ether-acetone followed by separation on silica gel preparative TLC plates using 3:1 pet. ether-acetone. B. Separation on silica gel preparative TLC plates using 3 or 4:1 pet. ether-acetone. C. Separation on alumina preparative TLC plates with 5:1 pet. ether-acetone. D. Elution on a silica gel column (6.7 x 13.5 cm) with 5:1 pet. ether-acetone, the compound being followed down the column with a UV blacklight.

[c] Crude LTA used.

[d] Temperature maintained at 8 to 12° with ice cooling.

[e] The crude product was divided in half and one-half purified by method B, the other by method C.

[f] Pyridine solvent.

[g] 64% olefin recovered.

[h] 63% olefine recovered.

any potassium carbonate.

The compound was obtained as pale yellow crystals, m.p. 165-70° (decomp). Recrystallization was unsuccessful from several solvents.

Anal. Calcd. for $C_{12}H_8Cl_2N_2O_2$: C, 50.91; H, 2.85; N, 9.90. Found: C, 51.08; H, 3.01; N, 9.60.

NMR absorptions (acetone-d_6, ratios based on 4 aromatic protons): 2.08 (s, 4), 5.50 (m, 0.2), 5.58 (m, 0.8), 5.85 (m, 0.2), 6.26 (m, 0.8). Spin decoupling at 6.26 produced a singlet at 5.58 leaving the other two peaks unaffected. The UV spectrum (CH_3CN) showed λ_{max} ($\log \epsilon$): 231 (3.4), 295 (2.15), 305 (2.11) mμ. A Beer-Lambert law check gave a straight line for absorbance _vs._ concentration for the 231 mμ peak. An IR spectrum showed characteristic absorption at 1770 and 1710 cm^{-1} (see Spectral Section).

A mass spectrum showed a weak parent peak (P) at 281.99440 (calcd. 281.99622) with a P+2 peak of over 0.5 times the intensity of P. Other strong peaks of interest were at 247 (P-Cl), 212 ($P-Cl_2$), 184 ($P-C_2H_4Cl_2$), 147, 91, and 76. The appropriate sized P+2 peaks were found for these fragments.

Examination of the several fractions from column chromatography indicated a ratio from 2:1 to 6:1 for the peaks 5.85:5.50 and 6.25:5.85. The material is best stored in vials rinsed in 5% potassium hydroxide followed by several distilled water rinses and drying in the steam cabinet.

N-Phthalimidyldimethylsulfoximine (14). - The material was prepared according to the literature procedure[20] in 34% yield. The product was white crystals, m.p. 205-7° (lit. 208°). A UV spectrum was recorded (CH_3CN) with λ_{max}: 303, 293, 245 (shoulder), 228 mμ.

Photolysis of N-Phthalimidyldimethylsulfoximine in the Presence of 3,4-Dichlorocyclobutene. - The sulfoximine, 0.83 g (3.5 mmol), and 1.0 g (8.1 mmol) of 3,4-dichlorocyclobutene was dissolved in 100 ml of dry acetonitrile and irradiated with a 450 Watt Hi-pressure Hanovia type 679-1 lamp through a Vycor filter with nitrogen bubbling through the solution.

Periodic TLC checks of the reaction mixture with silica gel plates showed only a very tiny spot for 10b but an increasing spot at the origin that fluoresced orange under a UV blacklight. After 72 hr., the irradiation was stopped and the red-brown solution evaporated to a semi-solid mass. Preparative separation of the mass gave a band containing all the bicyclic material but consisting mostly of phthalimide. The weight of the band was 2.5 mg. Several other products were observed but not isolated and characterized.

5-Carboethoxy-5-azabicyclo[2.1.0]pentane (12a). - Cyclobutene, 2.3 g (42 mmol), in 3 ml of dry dichloromethane was placed in a 25-ml pear flask precooled in a salt-ice bath. Dry triethylamine, 1.4 ml (1.1 g, 10 mmol), was added and the flask equipped with a dropping funnel connected on the top to a mineral oil U-tube bubbler. N-benzenesulfonoxyurethane, 2.45 g (10 mmol), was dissolved in 7 ml of dry dichloromethane and added with stirring over 0.5 hr. The salt-ice bath was maintained for 1.5 hr. and then allowed to warm to room temperature while the mixture was stirred overnight.

The next day the solution was clear. Pet. ether, 5 ml, was added and a precipitate formed within a few seconds. The solution was filtered through sintered glass. The collected precipitate was air dried and weighed 2.25 g (87%).

The filtrate was evaporated to a yellow oil. TLC (2.5:1 pet. ether-acetone, silica gel) showed a major spot at 0.6; plus spots at 0.55, urethane; 0.4, ethyl hydrazodicarboxylate; 0.05; and 0.0. The starting urethane was 0.3 on the same plate.

The oil was separated by vacuum at 5×10^{-2} torr and 40°, the material collected in the liquid nitrogen cooled trap, 0.104 g, showing three spots of about equal size on TLC (2.5:1 pet. ether-acetone, silica gel) at 0.9, 0.75, and 0.5. The material was applied to two small HF_{254} preparative TLC plates and eluted with 4:1 pet. ether-acetone. The band from 1.0 to 0.9 was desorbed and evaporated to give 25 mg of yellow oil. An NMR spectrum showed signals at 5.83, 6.93, 7.88, 8.23 and 8.87 indicating the presence of the title compound with some impurities. Yield 21 mg (1.5%) by NMR. Attempted purification by micropreparative VPC on SE 30 at 85° with an injector temperature of 220° gave material of poorer purity (NMR) than was started with.

The other two bands at 0.85-0.75 and 0.7-0.6 gave 5.5 mg and 6.7 mg of yellow oils respectively also showing ethoxy signals. Band 2, in addition showed signals at 6.93 and 7.93 (both narrow multiplets). Band three showed signals at 4.23, 6.0, 7.33, and 8.9. (No integrations were taken on bands 2 and 3 due to the high amplitude necessary to record the spectra.) These bands showed no signals for the title compound and were not investigated further.

Thermolysis of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane in DMSO. - Run 1. - Compound 10a, 30 mg, was dissolved in enough DMSO-d_6 for a microtube NMR spectrum. An initial spectrum indicated impurity peaks at 7.93 and 8.89. The NMR tube was heated at 114-5° with the entire sample below oil level. The tube was removed from the bath after 30 min., wiped clean with a paper towel and cooled in cold running water for 2 min.

An NMR spectrum revealed no bicyclic material remaining, as only the 7.93 and 8.89 impurity singlets were visable above 6.5. Two new signals appeared at 3.17 (d of d, J = 2, 4), 4.00 (d of d, J = 2,4) both distorted. (see Spectral Section) The ratios were: 2.2 (5), 3.17 (2), 4.00 (2).

The material, smelling of dimethyl sulfide, was applied directly to a preparative TLC plate and eluted with 7:3 pet. ether-acetone. The wide absorbing band (UV) was desorbed and gave 10 mg of dry yellow crystals which gave a purple pyrrole test. Desorbing the plate back to the

DMSO front gave an additional 8 mg of material.

After storage over the weekend in a desiccator under nitrogen, the crystals were black and an NMR spectrum showed no pyrrole protons.

Run 2. - A solution of 100 mg (0.47 mmol), of 10a in 1 ml of dry DMSO was heated at 118° for 12 min. The solution was evaporated at 10^{-2} torr and room temperature, redissolved in acetone, and evaporated with a Rotovac followed by 2 hr. at 10^{-3} torr. Weight of crystals: 90.5 mg. A TLC (2:1 pet. ether-acetone, silica gel) showed spots at (R_f): 0.75 (pyrrole), 0.6 (major, phthalimide), and 0.45. The 0.45 spot gave a positive pyrrole test.[48] Treatment with 5 ml of carbon tetrachloride and filtration gave a pale yellow solid, 55.5 mg, identified as phthalimide by comparison with authentic material.

The carbon tetrachloride filtrate was evaporated to 35 mg of yellow oil which was indicated by TLC to still contain phthalimide. Chromatography on silica gel (6:1 pet. ether-acetone, HF_{254}) gave three bands under UV light. Band 1, 4.8 mg gave no pyrrole test and appeared to be mostly phthalimide (TLC). Band 2, 3.0 mg, and band 3, 7.8 mg, both gave positive pyrrole tests and were indicated by TLC to mixtures of phthalimide and the 0.45 spot. Their NMR spectra (CCl_4), however, were not obtainable even using the Computer of Average Transients on the HA-60 (20 scans).

Hydrogenation of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane. - 10a, 70 mg (0.33 mmol), was dissolved in 30 ml of methanol and 5 mg of 5% Pd·C catalyst was placed in the atmospheric hydrogenation apparatus.

There was no uptake within 1 hr. so the compound was reisolated by filtration through Celite on sintered glass and evaporation. It was redissolved in 35 ml abs. methanol and 10 mg of 18% $Pd(OH)_2 \cdot C$ was added. The uptake at atmospheric pressure was initially 1.5 ml/min. but rapidly slowed to 0.1 ml/min. and stopped at 2.5 ml (31% of 1 equiv.). The material was isolated as before and gave 50 mg of impure 10a (TLC).

Deuteration of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane. - Ca. 20 mg of 10a were dissolved in enough DMSO-d_6 with an added drop of sodium deuteroxide in D_2O for an NMR spectrum in a microtube. Allowing the sample to stand overnight did not produce an appreciable change in the spectrum. Heating at 57° produced pyrrole signals as in the thermolysis of 10a in DMSO, with the upfield methylene protons disappearing faster than the other two multiplets which seemed to be simplifying. (see Spectral Section)

Reaction of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane With Tetraphenylcyclopentadienone. - Compound 10a, 21 mg (0.1 mmol), and 38 mg (0.1 mmol) of tetraphenylcyclopentadienone were refluxed in 10 ml of dry benzene for 48 hr. in an apparatus fitted with a drying tube. After this time very little 10a was indicated to be present (TLC). The solution was evaporated to give dark purple crystals, the TLC of which showed spots at 0.85 (dienone), 0.75 (yellow) and 0.65 (10a) both very light, 0.5, 0.3, and 0.0. (2:1 pet. ether-acetone, silica gel). Sublimation at 0.1 torr and 50° did not separate the product from the dienone but gave less than a milligram of phthalimide as identified by TLC. Preparative TLC with 5:1 pet. ether-acetone (silica gel) gave mixtures of the products with the dienone, the dienone predominating. (The plate was streaked its whole length due to the low solubility of the dienone in the elution solvent).

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane With Acetic Acid. - Compound 10b, 42.5 mg (0.15 mmol), was heated in 5 ml of glacial acetic acid on a steam cone for 24 hr. The pot solution was poured into 20 ml of water and extracted with ether. The ether layer was separated and washed with 5% sodium bicarbonate solution until no more carbon dioxide evolution was observed. The layers were separated and the organic layer dried over magnesium sulfate and evaporated to dryness after filtering off the drying agent.

The residue was chromatographed on silica gel with 3:1 pet. ether-acetone. The material was indicated by the NMR spectrum to be pure 10b, 11.7 mg (28%).

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane With Lead Tetraacetate. - Bicyclic material, 28.1 mg (0.1 mmol), was dissolved in dichloromethane, then LTA, 46 mg (0.1 mmol), was added, and the whole was stirred for 20 min. at room temperature and then heated on a steam cone for 1 min. Evaporation of the mixture gave a solid residue which was treated with wet acetone to hydrolyze all excess lead IV compound. The precipitated material was filtered off by suction and the acetone evaporated. The material was purified by preparative TLC as in the experiment above.

The recovered 10b weighed 15 mg (54%). The rest of the material was present mostly in an orange fluorescent band (UV) at the origin on the plate but it was not isolated.

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane With Lithium. - Compound 10b, 89.5 mg (0.32 mmol), in 12 ml of dry THF was dropped gradually into 4 ml of dry THF containing 57 mg (8.2 mmol) of lithium wire in small chunks with stirring. After stirring overnight, the solution was full of fine precipitate.

Evaporation of the solution after filtering gave a small amount of solid, the NMR spectrum of which showed little or no phthalimidyl protons. An NMR check found them to be present in the water soluble salts filtered off. In neither case were protons for the starting material or a dehalogenated product observed.

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane With Sodium Iodide. - Sodium iodide, 96.0 mg (0.64 mmol), was dissolved in 5 ml of acetone and 28.3 mg (0.1 mmol) of compound 10b was added. After refluxing for 48 hr., a TLC check showed no apparent decrease in 10b relative to the small amount of phthalimide originally present as a contaminant in the bicyclic material. (Phthalimide was used as a standard of comparison since it should be unaffected by the reaction conditions.)

The flask was removed from heating and allowed to sit an additional two weeks. No precipitate was observed in the solution. Preparative TLC separation by the standard method after this time resulted in isolation of 8.0 mg of 10b and 3.5 mg of phthalimide (NMR). No other material could be isolated with and $R_f > 0.1$.

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane With Lithium Amalgam. - Compound 10b, 222 mg (7.8 mmol), was partly dissolved in 150 ml of dry ether and 41.8 g (20.0 mmol) of 0.5% lithium amalgam added. The flask was covered with foil and the solution stirred magnetically. After 2 days, 10b seemed to be present in only small quantity (TLC). The solution was filtered and evaporated to a dark dry mass. A TLC showed (2:1 pet. ether-acetone, silica gel) a major spot at 0.9 with small spots at 1.0, 0.8, 0.7 (10b), and 0.3. The crystals were placed on a silica gel column and eluted with 3:1 pet. ether-acetone. The first 150 ml of eluant contained all the material, 30 mg, which showed NMR absorptions at: 3.0 (s), 3.3 (s, very small), 4.3 (m) in addition to a small amount of 10b. A TLC showed the major component to be the 0.9 spot but also traces of the 0.8 and 0.7 spots.

The precipitated salts from the reaction gave only a very weak test for halide.

The oil was separated by preparative TLC using pet. ether and gave two components, the first a colorless oil, ca. 5 mg, and the second a yellow oil, less than 1 mg. After sitting overnight in a vacuum desiccator, the colorless oil showed three spots on TLC (pet. ether). It had darkened to yellow while standing overnight. Due to the unstable nature of the material, further identification was not undertaken.

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane With Hydrazine. - To a stirred solution of 0.11 g (2.2 mmol) of hydrazine hydrate in 30 ml of ethanol was added 0.14 g (0.5 mmol) of the compound 10b. The flask was stoppered. After several hours of stirring all the compound had dissolved, and after several days a precipitate formed. It was filtered off and shown by TLC to be phthaloylhydrazide, 62 mg (76.5%) by comparison with authentic material. The filtered solution turned dark red-brown rapidly. The solution was evaporated to a red-brown oil.

The oil was treated with phenyl isothiocyanate in chloroform. A small amount of phthalimide precipitated out. The oil was washed several times with excess pet. ether to remove unreacted isothiocyanate. The residual oil was found to contain mostly one component and was put through a silica gel column (2:1 pet. ether-acetone). A yellow band came through with the solvent front and gave a yellow semi-crystalline substance. It was dried in a desiccator under vacuum and then an IR spectrum was taken. It showed a band at 1710 cm^{-1} and characteristic absorptions for a phenyl ring. A mass spectrum showed a parent peak at 261.3 m/e. No peaks were found in the entire spectrum which contained chlorine, *i.e.* none where the P+2 peak was stronger than the P+1 peak.

A dark brown band remained at the start of the column during the separation and resisted further elution.

Photostability of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane. - Compound 10b, 81 mg (0.29 mmol), was dissolved in 100 ml dry acetonitrile. The solution was placed in a photochemical reactor and irradiated through a Vycor jacket with a Hanovia type 679-1 hi-pressure 450 watt lamp. After 3 hr. irradiation time, a TLC check (2:1 pet. ether-acetone, silica gel) showed very little 10b left. Irradiation was terminated at 4 hr. and the dark orange solution was evaporated to a black-brown mass (81 mg).

A TLC of the material (same conditions) showed four small spots in addition to a large orange fluorescing spot at the origin (one of the spots was starting material).

An NMR spectrum (DMSO-d_6) showed peaks at 2.0-2.6 (m, 85), 3.6-4.7 (br m, 22), 5.9-6.9 (br m, 37), 7.3-8.4 (m, 52), and 7.50 (m, 12). Further identification was not attempted.

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane With Chromous Ion. - The method of dehalogenation used was generally that of Kochi, Singelton, and Andrews.[23] A solution of chromous ion was prepared by weighing out the salt from an Inorganic Syntheses[49] preparation in the dry box and dissolving in distilled water. The salt turned a bit green during the weighing procedure indicating some oxidation to chromic ion but the solution was deep blue. Because of the oxidation, the solution normality was only approximate.

Dimethylformamide (DMF), 40 ml, was placed in a round bottom, 100-ml, three-neck flask fitted with a septum cap, a stopper, and a nitrogen inlet-outlet tube with sintered glass on the inlet tube. The sintered glass dipped well below the solution level but did not extend downward far enough to interfere with magnetic stirring. The outlet of the adapter was attached to a U-tube bubbler with mineral oil in it. The solution was stirred and bubbled with oxygen-free nitrogen to degas the solution. Ethylenediamine, 0.5 ml (7.5 mmol), was added by syringe and the nitrogen flow stopped. Five ml (ca. 4.0 mmol) of the approximately 0.8 N chromous chloride solution was added by syringe. The resulting solution was a deep purple. Compound 10b, 140 mg (0.5 mmol), was dissolved in 2 ml of DMF and added slowly to the solution through the syringe cap. The solution changed color almost instantly from purple to red-blue and then to a deep burgundy color. After stirring an additional 30 min., 5 ml of the solution was withdrawn and added to 10 ml of water. Extraction two times with 15-ml portions of ether and evaporation of the combined ether extracts gave a small volume of liquid shown by NMR to be DMF. The only other absorptions were for phthalimidyl protons at 2.1 (s), and water plus a trace of ether.

This entire DMF solution was applied to two large preparative TLC plates (2.5:1 pet. ether-acetone, silica gel) and eluted. The plates were cut into three bands: 1.0-0.8, band 1; 0.8-0.6, band 2; and 0.5-0.2, band 3.

They were desorbed with acetone. Almost no material was present in band 1. The NMR spectrum showed band 3 to be DMF, plus phthalimide, 2.0 (s, 4), 6.0 (br s, 1), plus trace peaks from 2.4 to 3.3. The band 2 NMR spectrum, due to the small amount of sample present, was difficult to interpret (high amplitude was necessary). Peaks were located at: 2.0 (s), 2.4-2.9 (m), 3.1 (s), 3.2 (m) and also perhaps a broad multiplet at 6.2. No integration was possible due to the high amplitude.

A TLC of band 2 indicated spots at 0.72, 0.6, and 0.4. The bicyclic starting material was 0.65 on the same plate. The NMR sample was spotted on an analytical plate to make a band and eluted with 7:3 pet. ether-acetone. Under UV light there were three well separated bands. They were desorbed with ethanol, filtered with sintered glass, and UV spectra taken directly on these solutions.

TABLE 5

UV Spectra

R_f	Band	λ_{max} (absorbance) mμ
0.72	1	218 (1.12), 273 (0.35)
0.6	2	270 broad shoulder (0.17) plus end absorption
0.4	3	264 (0.59), 273 (0.59), 280 (0.56), 300 shoulder (0.39)
	diluted	220 (0.3), 300 (0.03)

In an effort to isolate more of band 3 as it was the only one to show any promise, the rest of the solution was worked up using appropriately scaled up amounts according to the test procedure. Chromatography on preparative TLC (2.5:1 pet. ether-acetone) gave several impure bands (TLC) that produced only very small amounts of materials, not over a few milligrams. Because of small amounts, the bands were discarded. The UV spectrum of band 3 above did not correspond to that for N-phthalimidylpyrrole: 217 (1.96), 235 shoulder (0.5), 295 (0.09), 303 shoulder (0.08) mμ.

Reaction of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane With Potassium t-Butoxide. - Potassium t-butoxide, 0.1 g, was weighed out in a dry box into a 25-ml pear flask with a magnetic stirring bar and fitted with a septum cap before removal. After removal from the dry box, 5 ml of dry THF was injected by syringe and magnetic stirring was begun. Compound 10b, 141 mg (0.5 mmol), was dissolved in 5 ml of dry THF and added to the reaction mixture. A TLC 10 min. later on an aliquot withdrawn by syringe showed no new spots.

Just prior to 2 hr. stirring time, the solution which had been cloudy became clear and then clouded up again. A tarry looking material began to deposit on the flask walls shortly thereafter. A TLC showed only a small amount of 10b left and a large spot at the origin (UV).

After stirring overnight, the solution was a fairly clear orange-brown with a lot of tarry looking material on the flask walls. The solution was evaporated to dryness and part of the material was separated by preparative TLC with acetone on silica gel. The yellow band at 1.0 was desorbed with acetone. Evaporation gave a gooey orange material which showed peaks in the NMR spectrum at: 6.6 (br s), 8.82 (s). No peaks for phthalimidyl protons were present. The band at the origin of the plate was desorbed with water and evaporated to a yellow solid which was identical to 10b (NMR).

One-half of the total solid obtained upon evaporation of the original solution was placed in an oven-dried flask with a stirring bar, capped with a septum cap, and 10 ml of dry THF was added by syringe. After stirring was begun, 0.4 ml of methyl iodide was added. After stirring 6 hr. the septum cap was removed, several drops of water were added, and stirring continued for a few minutes, followed by evaporation on a Rotovac. A wet dark solid was obtained which was stored under reduced nitrogen pressure in a desiccator. Only a small part was soluble in THF. The THF soluble material was too small in quantity (*ca.* 1 mg) to be analyzed further. The non-THF soluble residue was soluble in water, a solution of which tested positive for iodide ion. The NMR spectrum of the water soluble material indicated no aliphatic ring protons. It showed peaks at: 2.05 (s, 4), 2.4 (m, 30), 2.50 (s, 20), 6.85 (m), 6.9 (s, total for both 12), 7.1 (s, 7).

Deuteration of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane. - An NMR sample of 10b dissolved in DMSO-d_6 was treated with

50 µl of D_2O which had reacted with a small chunk of sodium metal. The initial NMR spectrum showed no change in any signals for the compound. After sitting several days, the only change observed was the appearance of a small singlet at 2.43. Even after sitting several months, no other apparent change was observed. Unfortunately, the water peak present, which did not seem to grow with time, obscured the upfield exo-isomer protons.

After standing 5 months, little change was observed so the sample was placed in an oil bath maintained at 112-15°. NMR spectra were recorded at 35 min., 155 min., and 21.5 hr. A singlet at 2.43 appeared with time. The integration of the ring protons at 35 min. corresponded only to the phthalimidyl group, while at 155 min. it had dropped to 41% of the phthalimidyl protons and 26% of the total aromatic protons. At 21.5 hr. the only signal present was a singlet at 2.43. As the singlet appeared throughout the experiment, the water peak shifted gradually downfield. The ratio of the bridgehead to methine ring protons seemed to remain constant at 1:1.

The sample after cooling was evaporated at 0.1 torr for 6 hr. after which it was applied to a small preparative plate (HF_{254}) and eluted with 3:1 pet. ether-acetone. Four poorly separated bands were noted under UV light and desorbed with acetone. Band 1, 1.8 mg, was mostly 10b plus a spot at 0.25 (2:1 pet. ether-acetone, silica gel). Band 2, 4.3 mg, contained spots for 10b, phthalimide, and the 0.25 spot. An IR spectrum ($CHCl_3$) showed absorptions at (cm^{-1}): 3300 br, 1710, and 1605. Band 3, 0.9 mg, was entirely the 0.25 spot whereas band 4, 7.0 mg, was a mixture of the spot and DMSO. An IR spectrum of band 4 ($CHCl_3$) showed peaks at (cm^{-1}): 3300 br, 2400, 2300, and 1710.

Hydrogenation of 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]-pentane. - Compound 10b, 100 mg (0.35 mmol), was dissolved in 39 ml of methanol and 12 mg of 5% Rh·Al_2O_3 catalyst added. Uptake was initially 1.2 ml/min. at atmospheric pressure but dropped rapidly to 0.2 ml/min. and stopped at 1.5 ml uptake (17%). No further uptake was registered after 2 hr. The material isolated by filtration and evaporation was only slightly impure (TLC).

Reaction of Tetracyanoethylene With 2,3-Dichloro-5-phthalimidyl-5-azabicyclo[2.1.0]pentane. - Tetracyanoethylene (TCNE), 11.8 mg (0.1 mmol), was dissolved in 0.5 ml of dry THF and 27 mg (0.1 mmol) of 10b was added. The stoppered test tube was allowed to sit for 1 month. TLC checks run during that time (2:1 pet. ether-acetone) showed a constant decrease in the amount of TCNE. After 1 month, the mixture was applied directly to a small preparative TLC plate (HF_{254}) and eluted with 5:1 pet. ether-acetone. Two bands were visable, the higher one giving 24.1 mg of 10b of good purity (NMR). The second band, 5.1 mg, had too weak an NMR spectrum to interpret but appeared to be mostly aromatic protons.

1-Azido-2-iodocyclobutane (15). - A solution of iodonium azide, 27 mmol in 50 ml of dry acetonitrile, was prepared.[26] To the cooled solution (ice-salt bath) was added 1.5 g (27.7 mmol) of cyclobutene in 10 ml of dichloromethane. The cooling bath was allowed to warm to room temperature and the mixture was worked up as in the literature procedure.[26] The organic layer was dried over magnesium sulfate for a short time (too long a drying time causes a deepening of the coloration of the solution), filtered, and evaporated to an orange-red oil, 4.0-4.8 g (65-83%). Due to the inherent instability of iodoazides, no further purification was attempted. A TLC check (6.5:3 pet. ether-acetone, silica gel) showed four contaminants in very small quantity.

A sodium fusion was positive for nitrogen and iodine. The IR spectrum was similar to that for the iodoazide of methylcyclopropene. (see Spectral Section)

NMR (CCl_4): 5.9 (m), 6.2 (m, together 2), 7.8 (m, 3), 8.8 (m, 1). Spin decoupling of any of the peaks simplified the others but not sufficiently to permit a coupling analysis.

Reduction of 1-Azido-2-iodocyclobutane With Lithium Aluminum Hydride. - To a stirred suspension of 1.25 g (33 mmol) of lithium aluminum hydride in 50 ml of dry ether cooled in an ice bath was added dropwise a solution of 3.8 g (17 mmol) of crude iodoazide in 5 ml of dry ether over 15 min. An additional 3 ml of dry ether was used to wash through traces of the iodoazide in the dropping funnel. A small amount of frothing was observed and the solution took on a greenish cast. The mixture was allowed to warm slowly to room temperature and the green color gradually faded.

After stirring 6 hr., the mixture was stoppered and allowed to stand for five days. The solution was hydrolyzed carefully with 5 ml of 40% potassium hydroxide. The resulting salts were white and gave a positive test for iodide ion. The ether filtrate was dried over magnesium sulfate and then concentrated to a small volume on a steam cone by slowly distilling through a 22 cm glass helices-packed column with a total reflux head take off. The distillate came over at 34.2-35.0°. The concentrate, ca. 2 ml, 2.0 g, analyzed by TLC showed three small contaminants besides the major product, two of which seemed to correspond to starting material contaminants. No cyclobutylamine was detected. The NMR spectrum showed a 1:1 ratio of ether to amine.

Preparative VPC separation of 150 µl of the concentrate gave enough pure amine for NMR analysis. Peaks appeared at (CCl_4): 7.2 (br s, 2), 7.42 (d, J 6, 2), 9.1 (m, 1), 9.5 (m, 4). Irradiation of the 7.42 peak simplified the 9.1 multiplet but not the one at 9.5.

An N-benzamide was prepared from the concentrate but had a poor melting range even after sublimation. TLC showed it to be contaminated with a fair amount of benzoic anhydride.

Reduction of 1-Azido-2-iodocyclobutane With Diborane. - Sodium borohydride, 0.61 g (21.4 mmol), was dissolved in 50 ml of dry diglyme and placed in the dropping funnel of the reaction train indicated in the literature.[27] The apparatus was flushed with dry nitrogen and 3.1 g (22.3 mmol) of boron trifluoride etherate dissolved in 35 ml of dry diglyme was placed in the generation flask. The cyclobutane, 4.8 g (21.5 mmol), was dissolved in 50 ml of THF and placed in the reaction flask. Under a slow stream of nitrogen and with rapid stirring in both flasks, the borohydride solution was added dropwise to the etherate solution which turned from dark brown quickly to green, yellow, and then colorless. Addition took place over 1.5 hr. During this time the solution in the reaction flask lightened considerably. It was then stirred eight days under no nitrogen flow. Several ml of acetone were added to the reaction flask solution, the solution was evaporated to minimum volume, taken back up in 50 ml of ether and washed with 50 ml of water. The water wash was extracted with another 50 ml of ether and the combined ether layers were dried over magnesium sulfate.

The solution was saturated with hydrogen chloride gas and a pink-orange oil appeared which was extracted into 25 ml of distilled water. The ether layer was neutralized over potassium hydroxide pellets and dried over calcium chloride overnight. Evaporation of the ether layer produced 2.3 g of recovered iodoazide, the IR spectrum of which indicated it to be of good purity.

Evaporation of the water layer gave a black oil, 0.3 g, NMR 7.6 (m, 1), 8.05 (m, 4), 6.2 (m, 3-4).

Reaction of Crude 2-Iodocyclobutylammonium Chloride With Potassium t-Butoxide. - Potassium t-butoxide, 0.4 g, was weighed out in a dry box directly into a flask and capped with a syringe cap before removal from the dry box. The crude ammonium salt, 0.3 g, was dissolved in 8 ml of dry THF and added by syringe to the syringe-capped 25-ml round-bottom flask containing the base in 4 ml of dry THF.

After several hours stirring, a TLC check showed spots (2:1 pet. ether-acetone, silica gel) at 0.9, 0.8, 0.55, 0.45, 0.2, 0.1, and 0.0. Some were from the iodoazide precursor of the ammonium salt. After stirring overnight, the flask was connected to the vacuum line, with a trap immersed in liquid nitrogen in between. Transfer of the liquid under vacuum (0.1 torr) gave THF (NMR) and the 0.1 spot in the trap liquid. A VPC on SE 30 ($\frac{1}{4}$" x 6') at 57° showed a large peak for THF and a small one for another compound of shorter retention time than THF. A test for secondary amine was negative.

Reaction of 1-Azido-2-iodocyclobutane With Triphenylphosphine. - Triphenylphosphine, 2.5 g (9.5 mmol), was dissolved in 30 ml of dry benzene and stirred in a 100-ml flask fitted with a dropping funnel. The top of the funnel was equipped with a gas outlet tube leading to a mineral oil U-tube bubbler. A solution of 2.3 g (10.3 mmol) of the crude iodoazide in 5 ml of dry benzene was added over 2 hr. with stirring. The solution became cloudy 20 min. after addition was begun. After stirring 2 days, the solution was decanted and the precipitated oil was washed with benzene and pet. ether and evaporated under heating on a Rotovac to a dry yellow solid. An NMR spectrum (DMSO-d_6) showed peaks: 1.95-2.50 (m, 80), 6.0-7.4 (br m, *ca.* 14), 6.68 (s, 8). The solid had m.p. 94-103° (decomp) and showed no triphenylphosphine by TLC. The material could not be recrystallized from ethanol, ethanol-benzene, ethanol-pet. ether as an oil precipitated out in each case.

2-Iodocyclobutyl Isocyanate (19). - Hassner's procedure[25] was used on a 39 mmol scale. The yield of crude red oil was 6.7 g (78%). A TLC (2.5:1 pet. ether-acetone, silica gel) showed the material to be one major component. An IR spectrum (thin film) showed a peak at 2270 cm^{-1}. An NMR spectrum showed absorptions (CCl_4): 5.40 (m, 1), 5.85 (m, 1), 7.05-8.10 (m, 4).

Bisulfite Addition Product of 2-Iodocyclobutyl Isocyanate. - Crude 2-iodocyclobutyl isocyanate, 5.1 g (*ca.* 23 mmol) was stirred together with 20 ml of 40% aqueous sodium bisulfite, 11 ml of dioxane, and 10 ml of ether. After stirring an additional hour after precipitation began, the solution was filtered and the crystals dried in a vacuum desiccator overnight. The material was yellow and pungent smelling, weight 1.08 g.

After sitting overnight in a refrigerator, a precipitate had formed in the filtrate. After filtration and drying it weighed 3.55 and no doubt contained some sodium bisulfite since the crystal form was very much different than that of the previous batch. Total weight of crystals isolated was 4.63 g. Further analysis was not undertaken due to the rapid discoloration of the material.

A small amount of oil was noted in the filtrate which did not crystallize.

Reaction of the Bisulfite Addition Product of 2-Iodocyclobutyl Isocyanate With Base. - The crude product from the previous experiment was dissolved in 25 ml of triethylene glycol, and 3.2 g of potassium hydroxide was added. The flask was attached to a trap by the apparatus used for cyclobutene production (see p. 54). The pressure in the system was held by a manostat at 70 torr, the trap cooled in liquid nitrogen, and the flask immersed in a 100° oil bath. Vigorous bubbling was observed. After 3 hr. the bath was lowered and the trap isolated and repressurized with dry nitrogen.

On warming to room temperature the small amount of solid in the trap did not melt. No amine smell was evident in the trap. The solid was insoluble in carbon tetrachloride and only slightly soluble in acetone. It was not investigated further.

No amine smell was evident over the pot mixture after cooling.

Reaction of Phenyl Azide With 3,4-Dichlorocyclobutene in Carbon Tetrachloride. - Phenyl azide,[32] 1.20 g (10 mmol), and 3,4-dichlorocyclobutene,[15] 1.235 g (10 mmol), were stirred together in dry carbon tetrachloride at room temperature in a flask fitted with a drying tube. Monitoring of the azide peak in the IR spectrum showed no apparent decrease over several months even though the solution became very dark and slowly deposited a black material on the flask walls.

After several months reaction, some of the solution with suspended solid was filtered and the solid dried in a desiccator under vacuum overnight. The solid was partly soluble in water and gave a positive chloride ion test. The solid was dissolved in trifluoroacetic acid and an NMR taken which showed peaks at: 2.6 (br s, 2), 6.15 (m, 29), 8.10 (m, 28).

An NMR spectrum of the filtered carbon tetrachloride solution showed only a few small stray peaks other than that for the azide or the olefin.

Reaction of 3,4-Dichlorocyclobutene With Phenyl Azide in DMF. - 3,4-Dichlorocyclobutene, 1.79 g (14.5 mmol), and phenyl azide, 1.71 g (14.4 mmol), were stirred together in 15 ml of DMF in a stoppered, foil-covered flask. The mixture quickly turned dark over the period of a week but showed no apparent decrease in the azide peak in the IR spectrum. A TLC after 60 days showed the DMF spot from the mixture to be orange fluorescing under UV blacklight while DMF itself did not fluoresce under the same conditions.

An aqueous, filtered solution of 0.5 ml of the reaction mixture showed a positive test for chloride ion. Neither DMF, phenyl azide, the cyclobutene, nor an aqueous extract or aqueous-DMF extract of the super-cell filter aid gave a positive test for halide.

Reaction of 3,4-Dichlorocyclobutene With Phenyl Azide and N,N-Dimethyl-1-napthylamine. - 3,4-Dichlorocyclobutene, 1.1 g (9 mmol), and N,N-dimethyl-1-napthylamine, 1.5 g (9 mmol) were stirred together in 15 ml of DMF. IR spectra showed no apparent decrease in the azide peak over several months. After four months the mixture was evaporated on a Rotovac using a hot water bath (80°). A TLC of the dark residue (3:1 pet. ether-acetone, silica gel) showed in addition to the napthylamine, spots at 0.8 (yellow) and 0.65 (red) with a large amount of heavy streaking on the plate. Preparative TLC separation (7:1 pet. ether-acetone) of the red band gave 29 mg of material which still showed a fair amount of napthylamine present (TLC) so it was repurified under the same conditions. The red solid, 10.3 mg, showed only a small amount of napthylamine present but still showed streaking on the plate. A test for an azo-compound was positive (green color).[50] An NMR spectrum (CCl_4) showed peaks at: 1.9 (m, 10), 2.95 (br m, 83), 7.1 (m, 34), 8.8 (m, 10).

Reaction of Phenyl Azide With Cyclobutene. - Cyclobutene, 1.8 g (33 mmol), and phenyl azide, 1.0 g (8.4 mmol), were dissolved in 15 ml of dichloromethane and let sit in a stoppered flask at -20° for four months. During this time IR spectra showed no apparent decrease in the azide peak. The material was then transfered to a vial and sealed with a flame. The tube was then allowed to stand for 5 weeks at room temperature before opening. A large amount of pressure had built up in the tube. An IR spectrum showed a large amount of azide still present. The solution was placed in a flask, attached to the vacuum line with a liquid nitrogen-cooled trap in between, and separated at 0.01 torr. The trap material contained only phenyl azide and solvent. (Some cyclobutene was detected by bromine decolorization of the solution but it boiled off quickly at room temperature.) The non-volatile material was separated on a preparative TLC plate (6:1 pet. ether-acetone, HF_{254}) to give four bands: band 1, 106 mg; band 2, 26 mg; band 3, 40 mg; and band 4, 27 mg. Band 1 showed a weak azide peak in the IR spectrum and was repurified under the same conditions. The first band was one pure component, 0.95 (4:1 pet. ether-acetone, silica gel), and band two which was found in equal amount was a mixture of the 0.95 component and one at 0.85. The 0.95 and 0.85 spots were of about equal size. An IR spectrum was recorded (see Spectral Section). An NMR spectrum (CCl_4) showed peaks at: 3.10 (m, 5), 4.13 (m, 1), 5.13 (m, 2), 5.97 (m, 2), 7.70 (m, almost a quartet but finer splitting present, 1), 8.50 (m, 6). A UV spectrum (methanol) showed λ_{max} (log ϵ): 246 (4.82), 285 (3.87).

A mass spectrum of the material showed a strong parent peak at 199.1376 (matching to the 219 perfluorotributylamine peak, calcd. for $C_{14}H_{17}N$: 199.1360). Major fragments were noted at: 188, 170, 158, 145 ($P-C_4H_6$), 144 ($P-C_4H_7$ for which a metastable peak at 104.4 was found), 130, 117 ($145-C_2H_4$), 104 ($C_7H_6N^+$), 91 (C_6H_5N), 77, and 63 ($117-C_4H_6$ for which a metastable peak at 34 was found). The 188 peak had an exact mass (matched to the perfluorotributylamine 188 peak) of 188.0574 and corresponded to a very strong peak in the compound run prior to it. Other strong peaks were not from that source.

<u>Hydrogenation of 3,4-Dichlorocyclobutene.</u> <u>Run 1.</u> - The cyclobutene, 1.0 g (8.1 mmol) was dissolved in 40 ml of methanol and 0.1 g of 5% Pd· C added. It was hydrogenated at atmospheric pressure. The

uptake was rapid and stopped at 210 ml.

Evaporation of the methanol gave a yellow oil, 0.5 g, which on a TLC showed (3:1 pet. ether-acetone, silica gel) one major spot. An NMR spectrum revealed peaks at: 4.1 (br s, 2), 5.43 (br m, 1), 7.6 (m, 2) which corresponded to 3-chlorocyclobutene.

Run 2. - The cyclobutene, 1.5 g (12.2 mmol), was hydrogenated at atmospheric pressure in 50 ml of methanol over 0.2 g of 5% Rh$\cdot$Al$_2$O$_3$ catalyst. An initial pressure increase was observed followed by a rapid uptake. The uptake was stopped at 362 ml (11.4 mmol, 93%).

Filtration through Celite and evaporation with a Rotovac gave 0.6 g (39%) of a yellow-orange oil which showed NMR absorptions (CCl$_4$) at: 7.43 (m, 68), 5.30 (m, 33), 4.77 (m, 3), 3.63 (m, 3). This corresponds to 92% 1,2-dichlorocyclobutane and 8% of the starting material. A small amount of sticky green solid was observed but not analyzed.

Reaction of Crude 1,2-Dichlorocyclobutane With t-Butylamine. - Crude cyclobutane, 0.6 g (ca. 4.5 mmol), was dissolved in 5 ml of dry DMSO in a dry box and while stirring, 1.1 g (15.1 mmol) of dry t-butylamine in 5 ml of DMSO was added over several days. Aliquots of the mixture were removed periodically and tested for halide ion outside the dry box. After nineteen days, only a very small amount of halide could be detected. The reaction flask was stoppered, removed from the dry box, and placed in a heated oil bath at 80-85° with magnetic stirring of the mixture, fitted with a reflux condenser and a nitrogen line. A small positive pressure of nitrogen was maintained by a mineral oil bubbler. After six days an aliquot showed a much larger amount of halide present. The material was separated by distillation at 10^{-2} torr and the material caught in the liquid nitrogen trap examined by NMR. A large amount of t-butylamine was present.

The material was run through a silica gel column (2:1 pet. ether-acetone, 2 x 8 cm). The first two 15-ml fractions each gave 50 mg of material, the third and fourth fractions giving only minute amounts of material. Both fractions one and two showed peaks for t-butylpyrrole and the starting halide in ratios of 1:6 for fraction one and 1:15 for fraction two. The NMR spectrum showed no methylene ring multiplets in the area of 7.8 or 8.0-8.4.

An attempt to precipitate an amine hydrochloride from the pot residue by solution in ether followed by treatment with hydrogen chloride gas precipitated DMSO.

Reaction of Pyrrole With 4-Phenyl-1,2,4-triazoline-3,5-dione.

Run 1. - The dione was the crude product from oxidation of 1 g of 4-phenylurazole in 50 ml of dichloromethane.[36] The crimson-red needles were dissolved in 15 ml of dry THF and the solution stirred in a 25-ml pear-flask fitted with a septum cap. Freshly distilled pyrrole, 0.4 ml, was added by syringe. The first drop produced a purple coloration, the second turning the solution black. After stirring overnight, the solution was evaporated to give black, dry crystals. TLC (2:1 pet. ether-acetone, silica gel) showed small amounts of starting materials. In addition, three small spots appeared at 0.3, 0.1, and 0.05.

Attempted preparative separation (2:1 pet. ether-acetone) gave bands which gave only minute amounts of material. The 0.1 spot corresponds to 4-phenylurazole as shown by comparison with authentic material. The large majority of the material was a flakey solid (black) at the origin.

Run 2. - A repeat experiment using a few grams of added hydroquinone gave the same results. In this experiment, 0.2 g of 4-phenylurazole was isolated. Again the major product was the black tar.

N-Carboethoxypyrrole (29). - A literature method[38] for N-carbo-t-butoxypyrrole was used except the appropriate molar amount of ethyl azidoformate was substituted for t-butyl azidoformate. After a forerun of 2.2 g, b.p. 36-42°/9 torr, was obtained, the pyrrole compound, 8.1 g (58%), was collected as a clear colorless liquid at 67-68°/9 torr. NMR (CCl_4) gave peaks: 8.60 (t, J = 7, 3), 5.66 (q, J = 7, 2), 3.90 (t, J = 2, 2), 2.83 (t, J = 2, 2).

Reaction of N-Carboethoxypyrrole With 4-Phenyl-1,2,4-triazoline-3,5-dione. - Of several runs the following has been selected as a representative experiment since the results varied so little among the various runs. The triazolinedione, 1.2 g (6.85 mmol), purified by sublimation was dissolved in 12 ml of dry THF and 0.95 g (6.85 mmol) of

N-carboethoxypyrrole in 11 ml of dry THF was added dropwise with stirring. After stirring overnight, 1 ml of solution was withdrawn and separated by preparative TLC (3:1 pet. ether-acetone, silica gel). In runs using crude dione, diisooctyl phthalate was isolated that was no doubt dissolved from the Tygon tubing connecting the nitrogen tetroxide cylinder with the reaction flask in the dienophile synthesis.

A yellow band at 0.5 was desorbed with methanol but gave an insufficient amount of material for a micro NMR spectrum. The silica gel remained quite yellow.

After standing over the weekend, the reaction mixture was evaporated to semi-dry orange crystals, 1.91 g, which were stored in a desiccator. A sample (0.3 g) of the crude crystals were applied to a silica gel column (3:1 pet. ether-acetone, 1 x 5 cm) and eluted. After several 20-ml fractions the elutant was changed to 1:1 pet. ether-acetone and several yellow 50-ml fractions were collected. Evaporation of the fractions produced progressively smaller amounts of yellow oils that showed the presence of 4-phenylurazole (TLC) in small quantity. The major spot was 0.4 (1:1 pet. ether-acetone, silica gel), with a heavy streak back to the origin. The sample could not be concentrated enough for a good NMR spectrum due to the small amount but did show absorptions at: 2.5, 5.7, and 6.0-6.8, all unresolved multiplets.

A portion (0.3 g) of the crude crystals were placed on a Fluorisil column (60-100 mesh) and eluted with 1:1 pet. ether-acetone. The sample resisted elution from the column but did travel its full length staining the entire column yellow.

A sample (0.8 g) of the crude crystals was hydrogenated at 50 psig over 0.08 g of 5% Pd·C in methanol. A rapid uptake of 1.5 lb. was observed. A TLC of the hydrogenated material showed three spots: 0.4, 0.25, and 0.15 (original material: 0.3, 0.15, 0.1, 1:1 pet. ether-acetone, silica gel) that were somewhat concentration dependent. An NMR spectrum showed peaks at 2.53 (m, 70), 5.8 (m, ca. 20), 6.67 (m, 13), 8.17 (m, 12). 8.77 (m, 32). In the original material a spot was visable for the pyrrole starting material.

Hydrogenation of N-Carboethoxypyrrole. - N-carboethoxypyrrole, 0.25 g, was hydrogenated at 46 psig in methanol over 5% Pd·C. A rapid uptake (2.0 lb) was observed which slowed and stopped at 4.0 lb. (A slight leak was in the system; 3.4 lb. theoretical). After filtration and evaporation, the NMR spectrum of the crude product showed absorptions: 6.0 (q, J = 7, 2), 6.67 (m, 4), 8.13 (m, 4), 8.87 (m, J = 7, 3).

Hydrolysis of the Crude Reaction Product of N-Carboethoxypyrrole With 4-Phenyl-1,2,4-triazoline,3,5-dione After Hydrogenation. Run 1. - The crude reaction product, 0.25 g, in 10 ml of 5% potassium hydroxide was heated in a flask fitted with a reflux condenser in a 70° oil bath for 21 hr. The solution was poured into 10 ml of saturated ammonium chloride solution, 10 ml of water was added, and the solution was extracted three times with 30-ml portions of ether. The combined, dried ether layers were evaporated to a small amount of a yellow liquid which had an amine smell.

An NMR spectrum shows the presence of aniline which was also confirmed by TLC. Two other smaller spots were observed on either side of the aniline (2:1 pet. ether-acetone, silica gel).

Run 2. - One gram of the crude product was stirred with 10 ml of 5% potassium hydroxide for four days at room temperature. Acidification of a small aliquot of solution produces violent gas evolution (carbon dioxide). The solution was extracted with ether and the ether layer dried over magnesium sulfate. Evaporation to a small volume gave a liquid which, by comparison of VPC retention times (5% SE 30, 35°), contained ethanol and aniline. Pyrrolidine was not present. There were three components in addition to the ethanol and aniline present in small quantities.

An NMR of the liquid showed peaks superimposable with the spectra of N-carboethoxypyrrolidine (see p. 92) and aniline, with trace peaks for unidentified material. No peaks were found in the following areas: 3.5-5.6 and 6.9-8.0 (excluding two very small peaks at 3.85 and 4.53).

Reaction of N-Carboethoxypyrrole With Ethyl Azodiformate. - N-Carboethoxypyrrole, 1.39 g (10 mmol), and 1.74 g (10 mmol) of ethyl azodiformate were stirred together in 15 ml of dry THF in a flask fitted with a drying tube. Periodic TLC checks (2:1 pet. ether-acetone, silica gel) revealed the formation of product spots at 0.7, 0.5, and 0.35, the starting materials appearing at 0.95 (pyrrole compound) and 0.8 (azo compound).

After 38 days the reaction was still incomplete. The mixture was separated by distillation at 10^{-6} torr (mercury diffusion pump), the volatile material being collected in a trap immersed in liquid nitrogen. The material in the trap consisted only of the starting materials (TLC).

The residue, 2.2 g, was a thick orange oil. A portion (0.6 g) of the oil was separated on two preparative TLC plates (4:1 pet. ether-acetone, HF_{254}). Two bands were visable under UV light at 0.7 (wide) and 0.4. Starting materials (0.1 g) were isolated at 1.0. The band at 0.7 was desorbed with acetone to give 0.33 g of a faintly yellow, thick oil with NMR absorptions (CCl_4) at: 2.46 (br s, 1), 2.88 (d of d, J = 2, 4, 1), 3.68 (d of d, J = 2, 4, 1), 3.92 (t, J = 4, 1), 5.76 (sextuplet, J = 7, 6), 8.78 (m, 9). This corresponds to diethyl N-2-(1-carboethoxy)pyrrolyl-hydrazodicarboxylate. An analytical sample was obtained from 0.16 g of the material eluted on an HF_{254} silica gel plate with dry dichloromethane, taking a center cut of the band. In the analytical sample the 2.46 peak had shifted to 2.86, the other peaks remaining the same in τ and ratio values.

Anal. Calcd. for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.11; N, 13.41. Found: C, 49.97; H, 6.22; N, 13.53.

The second band, 0.16 g, was a 50:50 mixture by TLC of the 0.5 and 0.35 spots. It was rechromatographed (2:1 pet. ether-acetone, HF_{254}) to give two bands of equal weight, the first corresponding to the 0.5 spot, was identified (NMR and TLC) as ethyl hydrazodiformate. The second band, a yellow oil, corresponded to the 0.35 spot and showed NMR signals (CCl_4) at: 4.03 (m or br s, 6), 5.83 (m, 57), 8.78 (m, 92).

Reaction of 1-Phthalimidyl-2-phenylaziridine With Diimide.[45] - The impure aziridine[20] (phthalimide was the major impurity), 0.26 g (1 mmol) was dissolved in 45 ml of methanol-acetone-water (1:1:1) and 0.23 g (2 mmol) of hydroxylamine-O-sulfonic acid and 0.17 g (2 mmol) of hydroxylamine sulfate were added. To the stirred suspension at room temperature was added 0.6 ml of 40% potassium hydroxide. Vigorous bubbling was noted. After 20 min. of additional stirring, the solution was poured into water and extracted with ether. The ether layer was separated and extracted with 6 N hydrochloric acid. The acid layer was made basic with 40% potassium hydroxide (pH10) and extracted again with ether. The ether was separated, dried over magnesium sulfate, and after filtration was evaporated to a few milligrams of semi-solid material. An NMR spectrum of it revealed very few phenyl protons and hence not much aziridine.

The original ether layer was evaporated and seemed (NMR) to be mostly impure starting material.

Reduction of 1-Phthalimidyl-2-phenylaziridine With Lithium Borohydride. - The aziridine, 264 mg (1 mmol), was dissolved in 10 ml of dry THF and added slowly over 5 min. with stirring to a solution of 32 mg (1.5 mmol) of lithium borohydride in 5 ml of dry THF. TLC samples (2:1 pet. ether-acetone) taken daily showed a spot at 0.25 appearing.

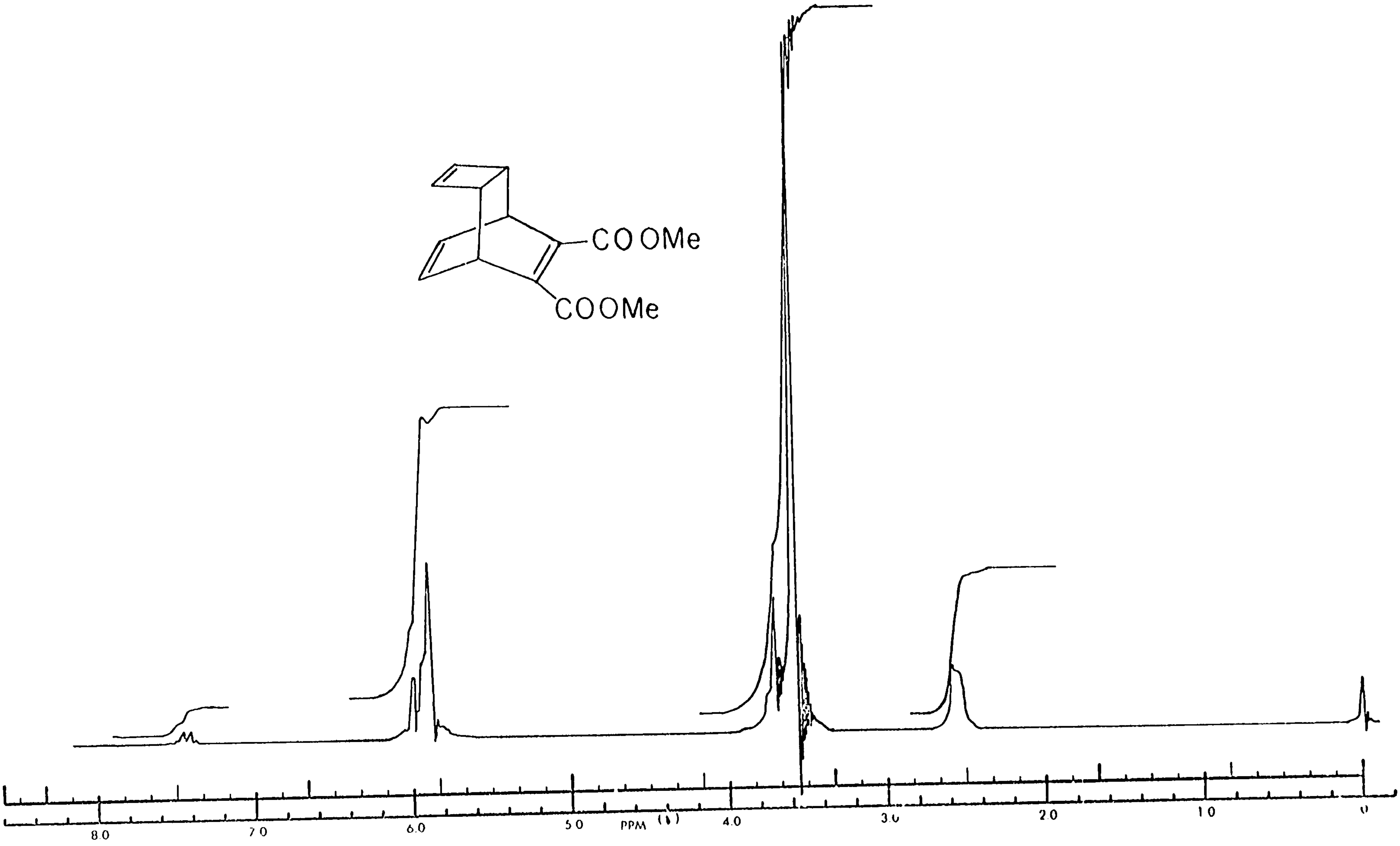
After stirring for nine days, the solution was hydrolyzed by pouring into 10 ml of water. The solution was extracted two times with 10-ml portions of dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated to give a total of 217 mg of white solid.

The solid was separated on a silica gel HF_{254} plate (3:1 pet. ether-acetone). The majority of the material was in a band centered around 0.3. A TLC of the white crystals (2:1 pet. ether-acetone) showed them to be the 0.25 spot contaminated with small amounts of the 0.75, 0.35, and 0.15 spots. The 0.15 spot corresponded to the product of the reaction of phthalimide with lithium borohydride (see below). An NMR spectrum (DMSO-d_6) of the material as separated showed peaks at: 2.43 (s, 37), 2.63 (br, s, 62), 3.6 (m, 3), 4.07 (m, 5), 4.70 (m, 8), 5.33 (m, 15), 6.53 (s, 18), 6.8 (m, 7). An IR spectrum (CH_2Cl_2) showed peaks (cm^{-1}): 3350, 1710, 1650.

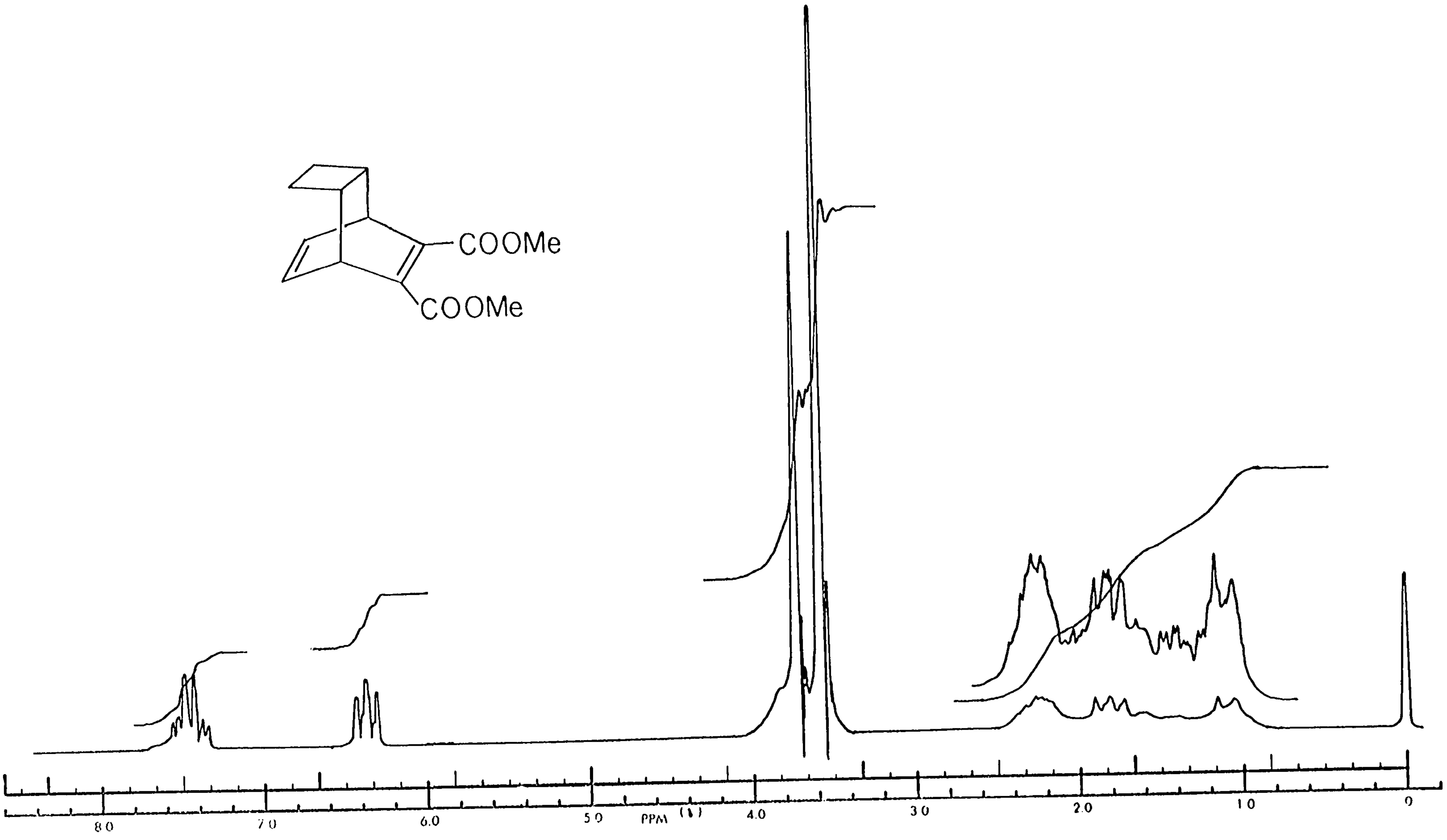
Reduction of Phthalimide With Lithium Borohydride. - Phthalimide, 2.94 g (20 mmol), was stirred with 0.64 g (30 mmol) of lithium borohydride in 170 ml of dry THF for three days. The solution was poured into 100 ml of water, salt was added to saturate the aqueous layer, the organic layer was separated, and the water layer extracted with two 100-ml portions of ether. Evaporation of the organic layers dried over magnesium sulfate, after filtration, gave 2.3 g of a pale yellow solid that showed one spot on TLC (1:1 pet. ether-acetone, silica gel).

A sample was recrystallized twice from water; m.p. 175-6° (lit.,[46] 179°). An NMR spectrum (DMSO-d_6) showed peaks at: 1.25 (br s, 1), 2.43 (s, 4), 3.70 (d, J = 9, 1), 4.15 (d, J = 9, 1), with a peak at 6.66 (s, 0.8) for water. This corresponds to 3-hydroxyphthalimidine.

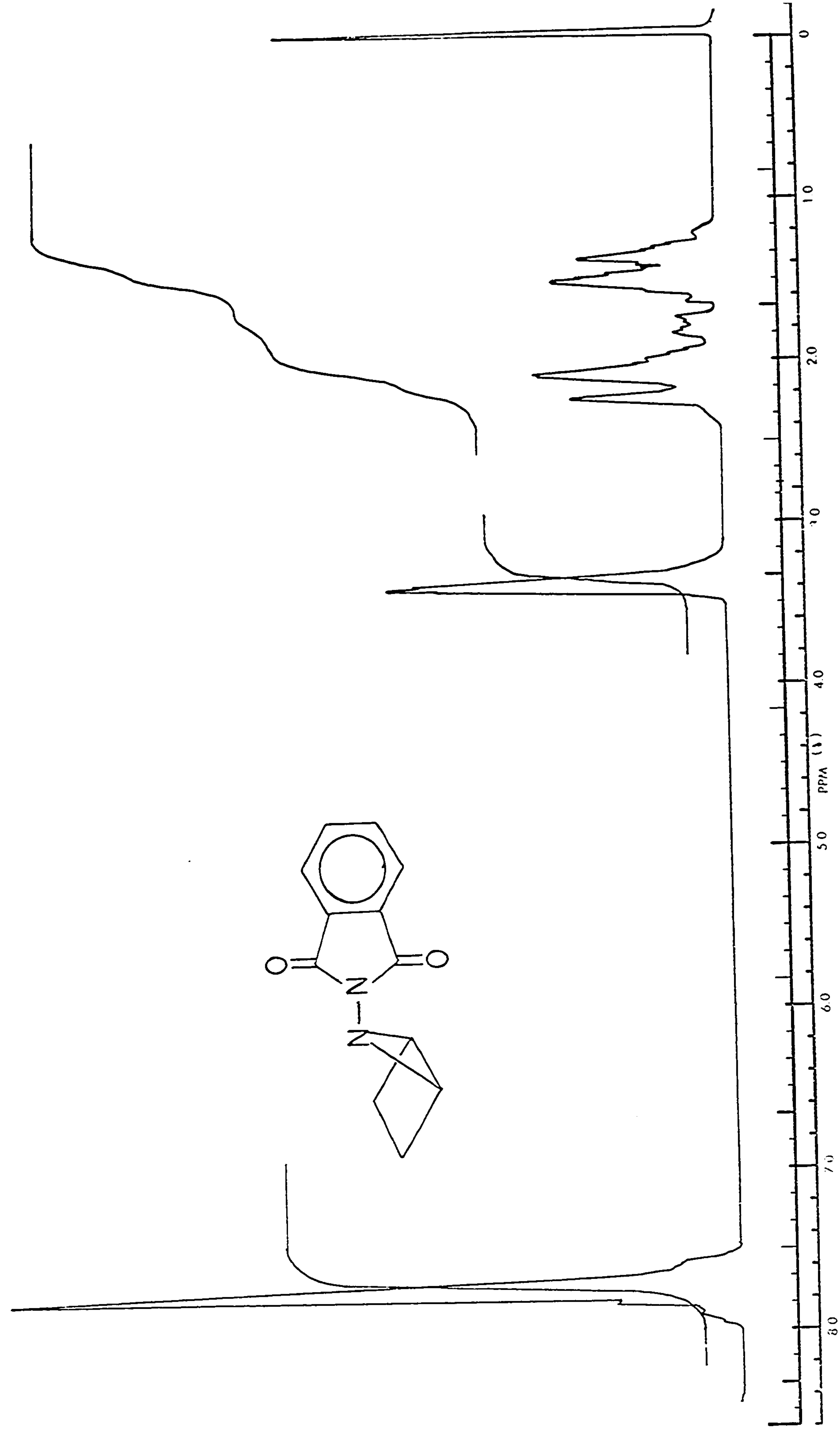
NMR Spectrum of 7,8-Dicarbomethoxytricyclo[4.2.2.$0^{2,5}$]decatriene (6) in Carbon Tetrachloride.


COOMe
COOMe
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

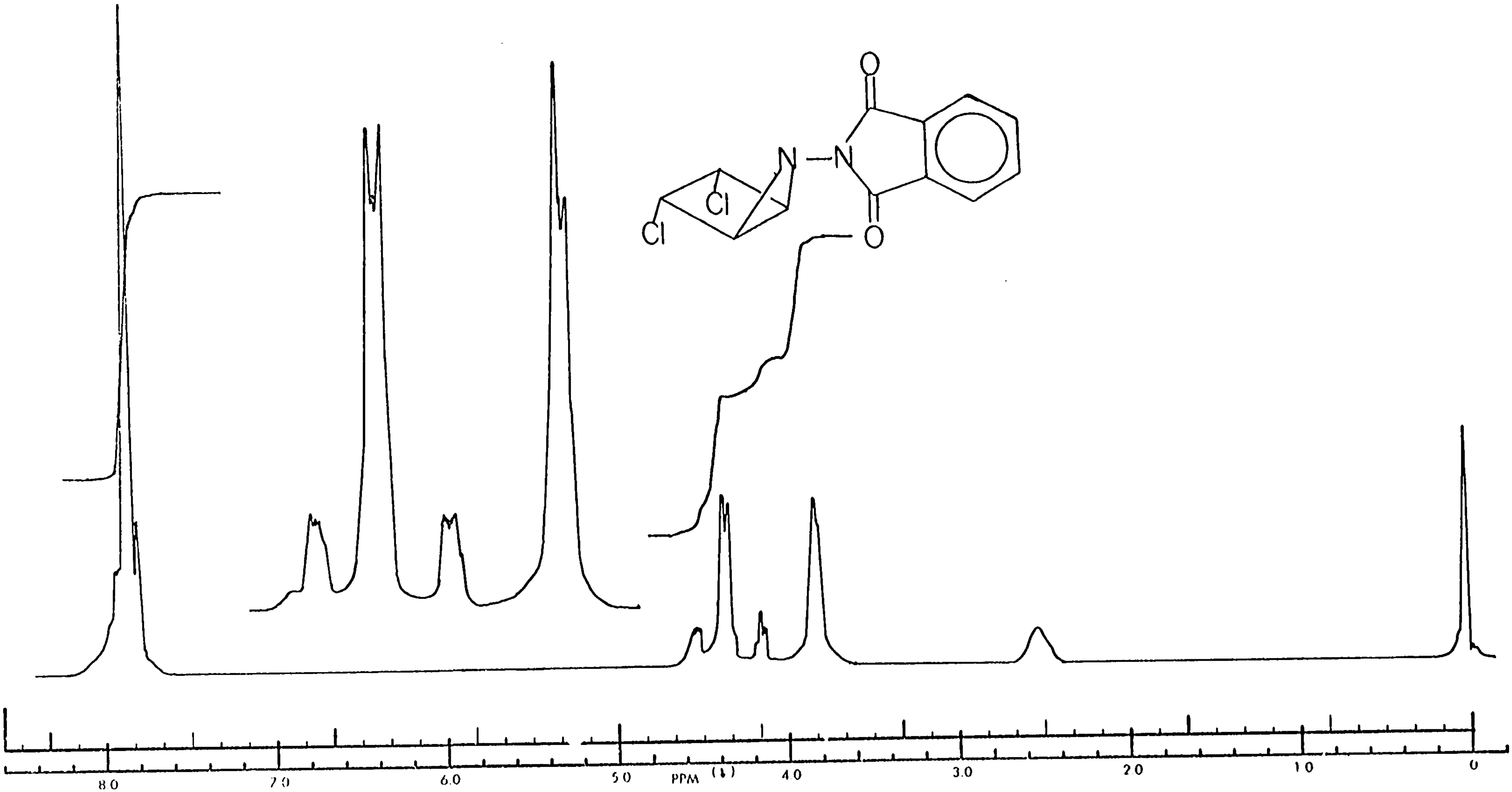
NMR Spectrum of Crude 7, 8-Dicarbomethoxy-7, 9-tricyclo[4. 2. 2. $0^{2,5}$]decadiene in Carbon Tetrachloride.


COOMe
COOMe
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

NMR Spectrum of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane (10a) in Deuterochloroform.


0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
PPM (δ)
O
N
N
O

NMR Spectrum of 2, 3-Dichloro-5-phthalimidyl-5-azabicyclo[2. 1. 0]pentane (10b) in Hexadeuterodimethylsulfoxide.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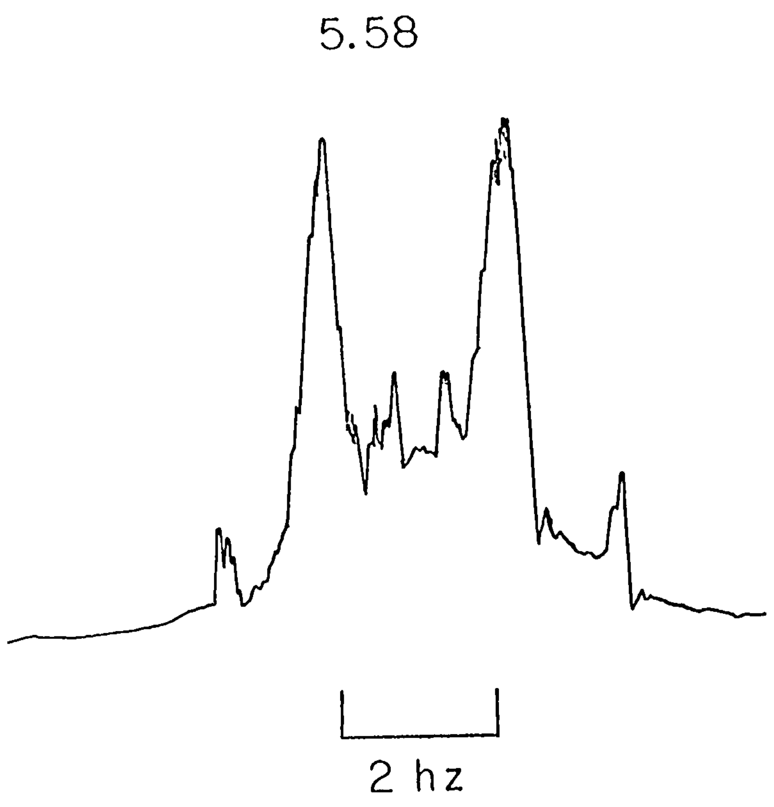
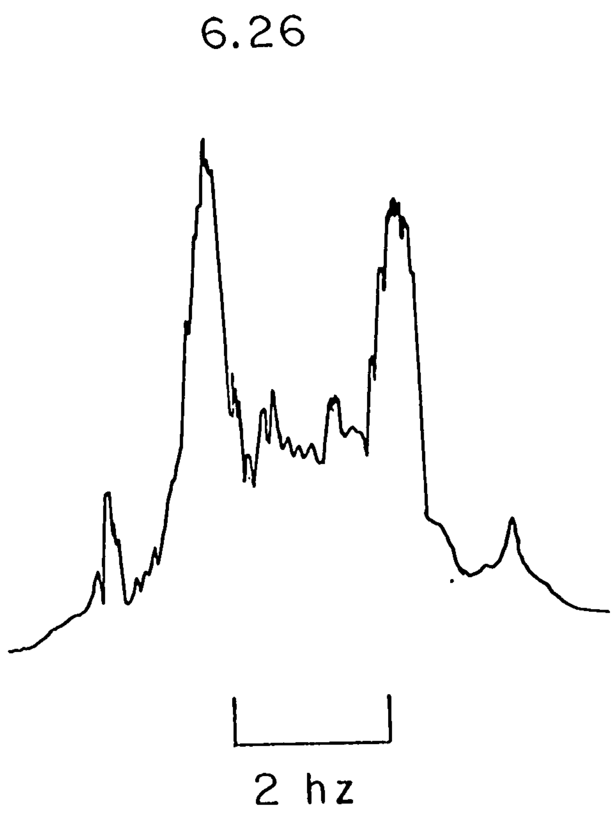
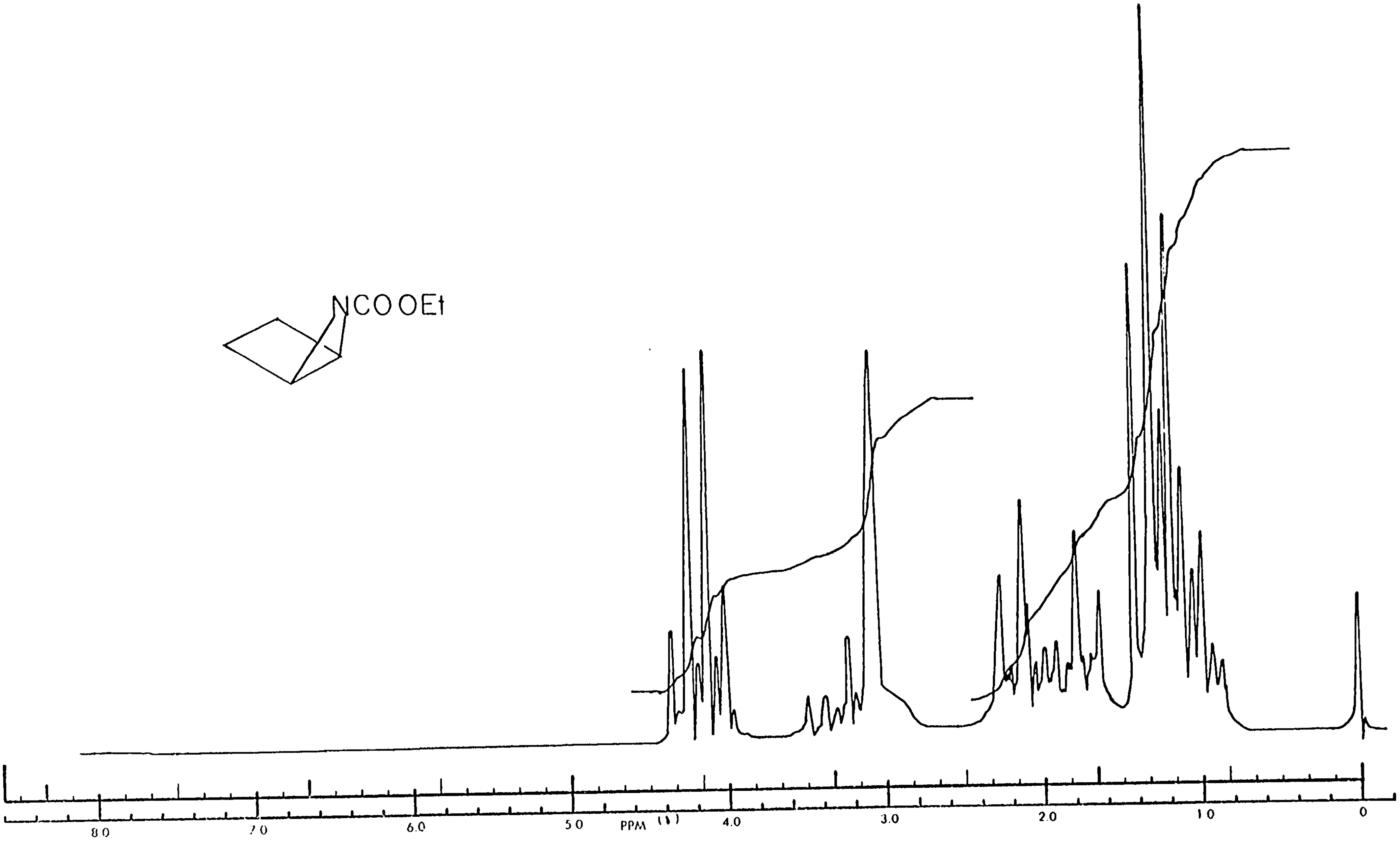
N
N
O
Cl
Cl
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

NMR Spectrum of the Bicyclic Ring Protons of 2, 3-Dichloro-5-phthalimidyl-5-azabicyclo[2. 1. 0]pentane (10b) in Hexadeuterodimethylsulfoxide.

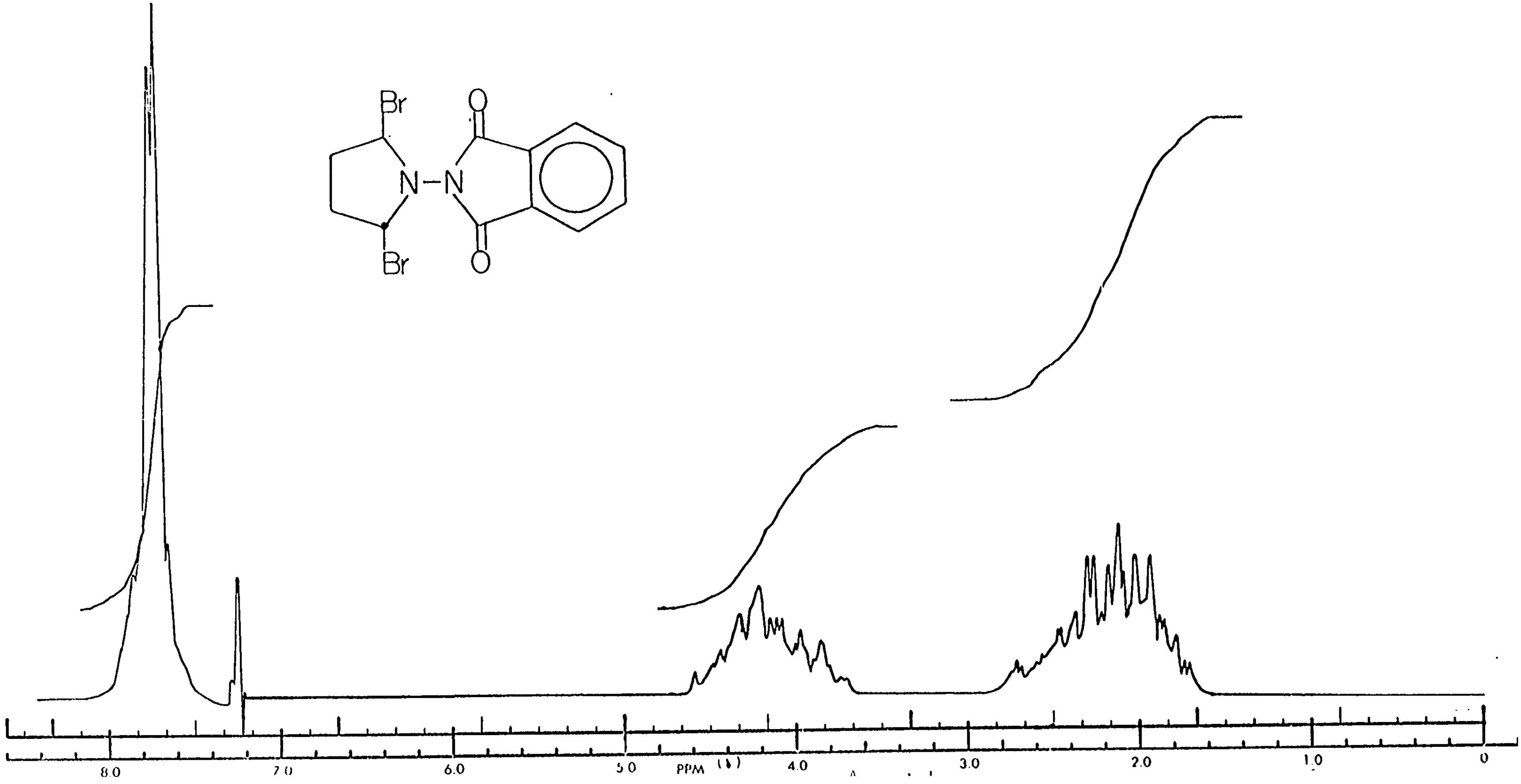

5.58
2 hz


6.26
2 hz

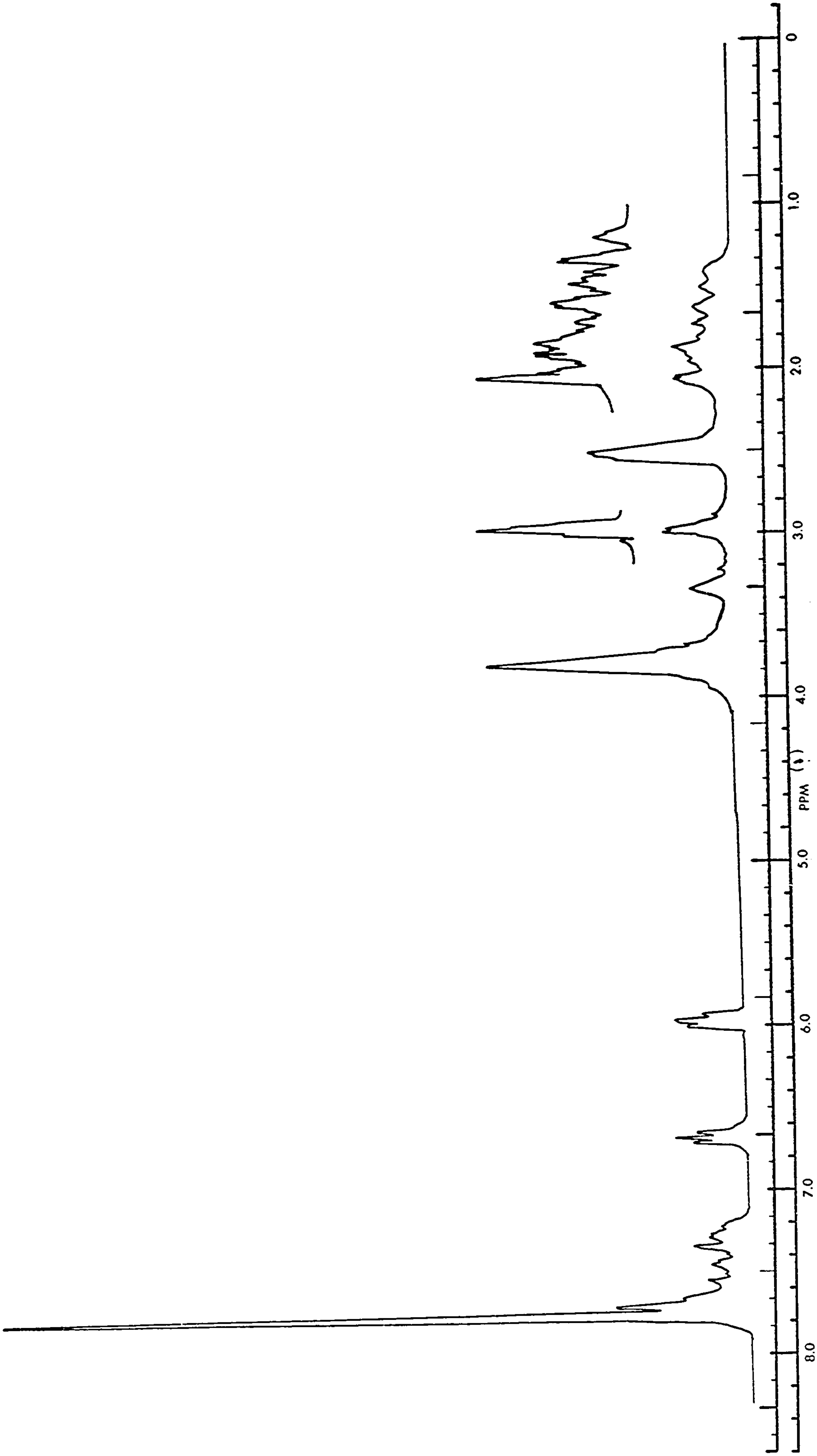
NMR Spectrum of 5-Carboethoxy-5-azabicyclo[2.1.0]pentane (12a) in Carbon Tetrachloride.


NCOOEt
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

NMR Spectrum of 2, 5-Dibromo-1-phthalimidylpyrrolidine (13) in Deuterochloroform.

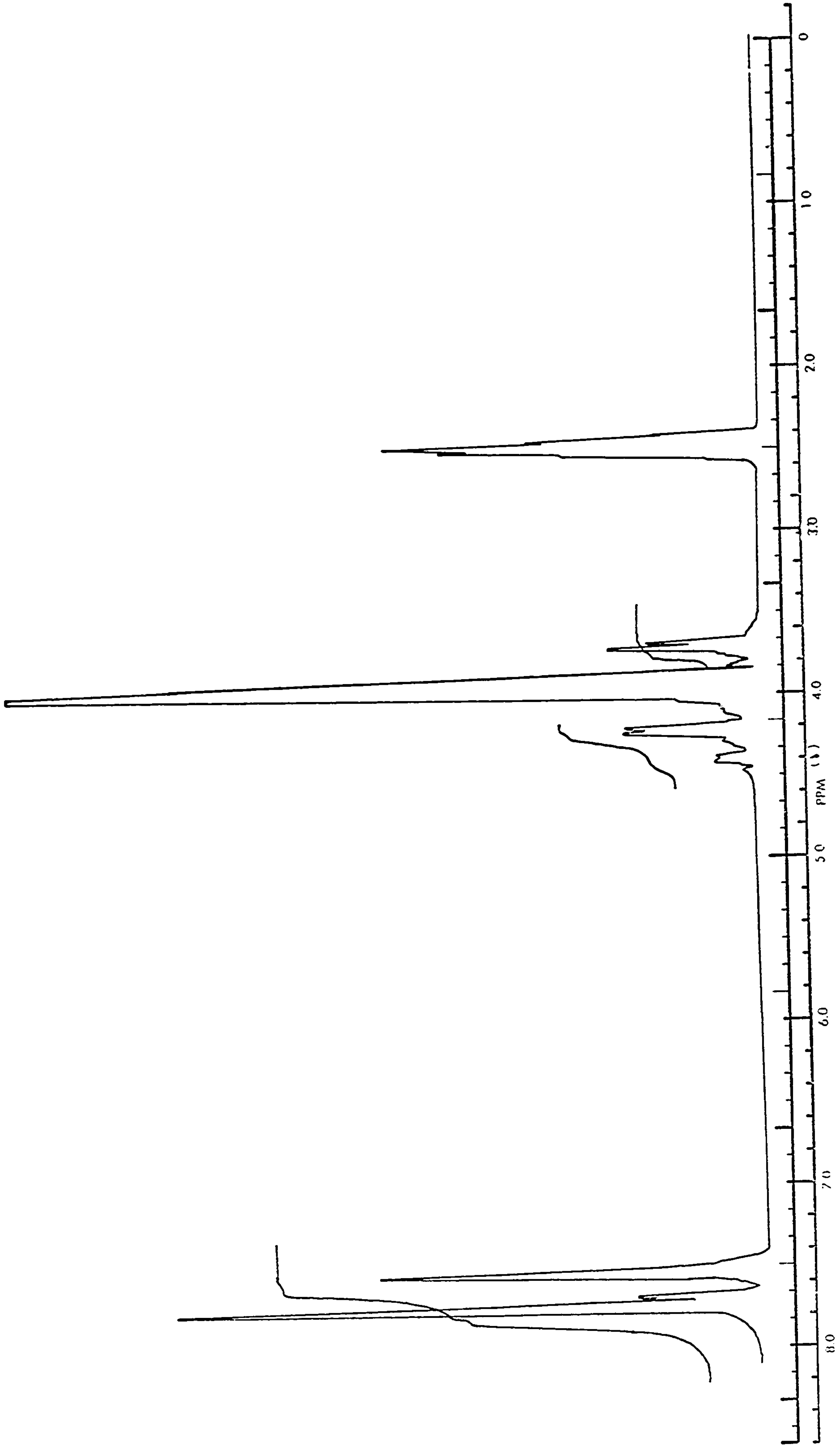

Br
Br
O
O
N–N
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

NMR Spectrum of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane, After Heating 3 Hr. With D_2O, Sodium Deuteroxide, in Hexadeuterodimethylsulfoxide.



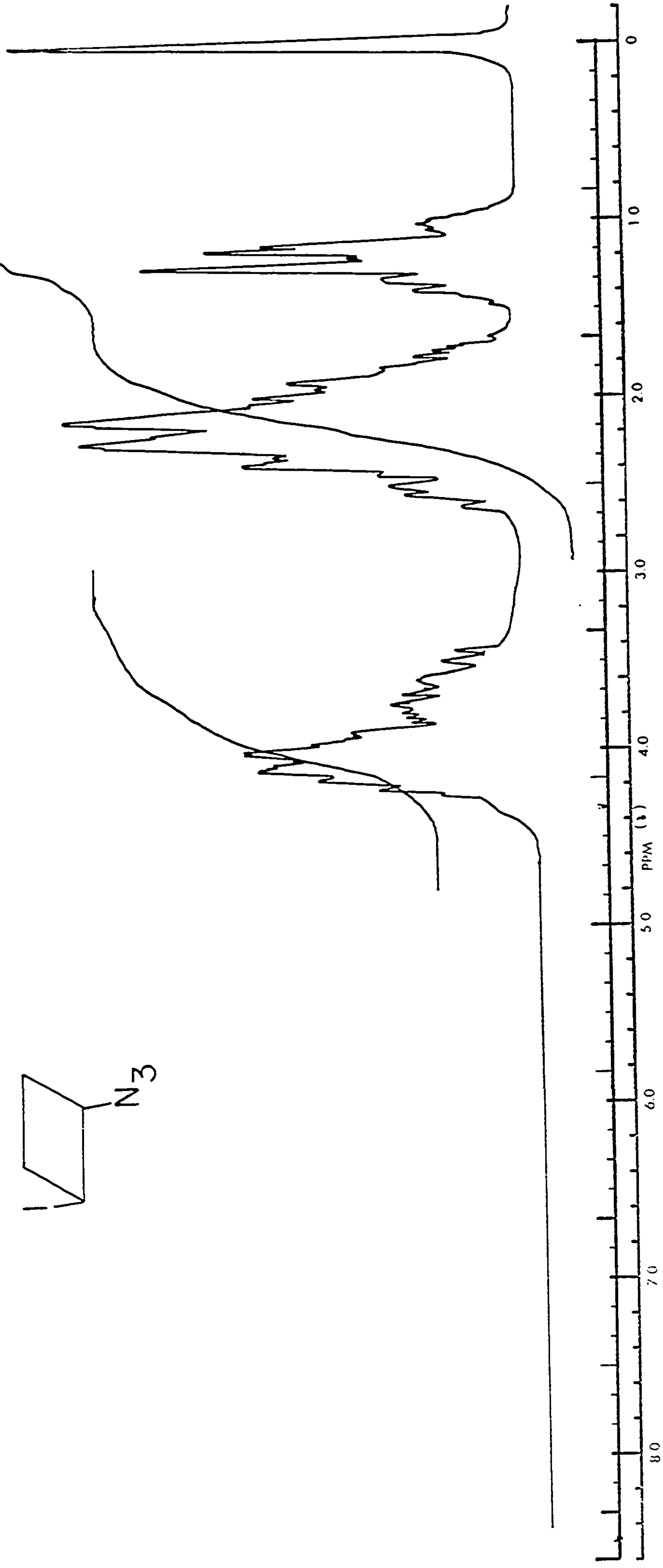
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

NMR Spectrum of 2, 3-Dichloro-5-phthalimidyl-5-azabicyclo[2. 1. 0]pentane, After Heating 155 Min. With D_2O, Sodium Deuteroxide, in Hexadeuterodimethylsulfoxide.

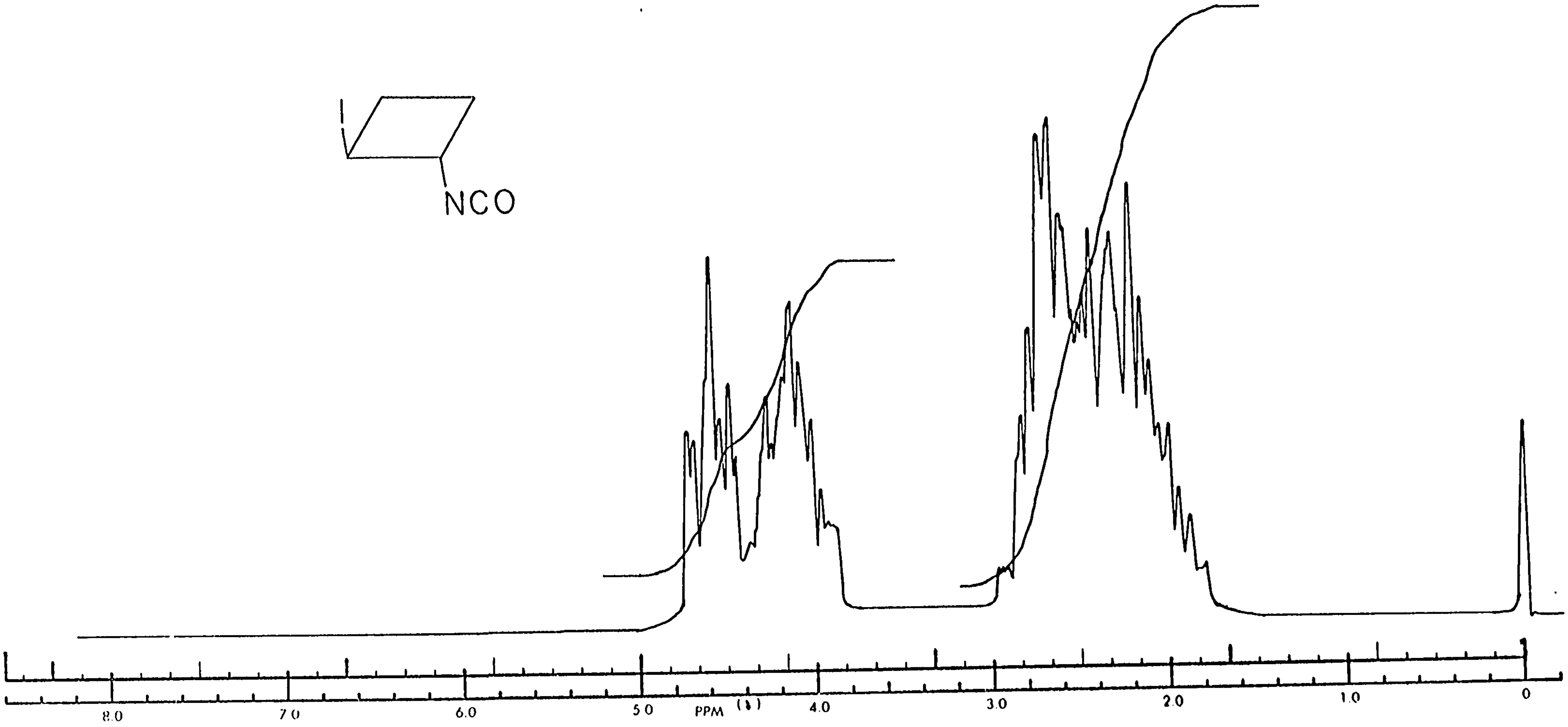


0
1.0
2.0
3.0
4.0
PPM (δ)
5.0
6.0
7.0
8.0

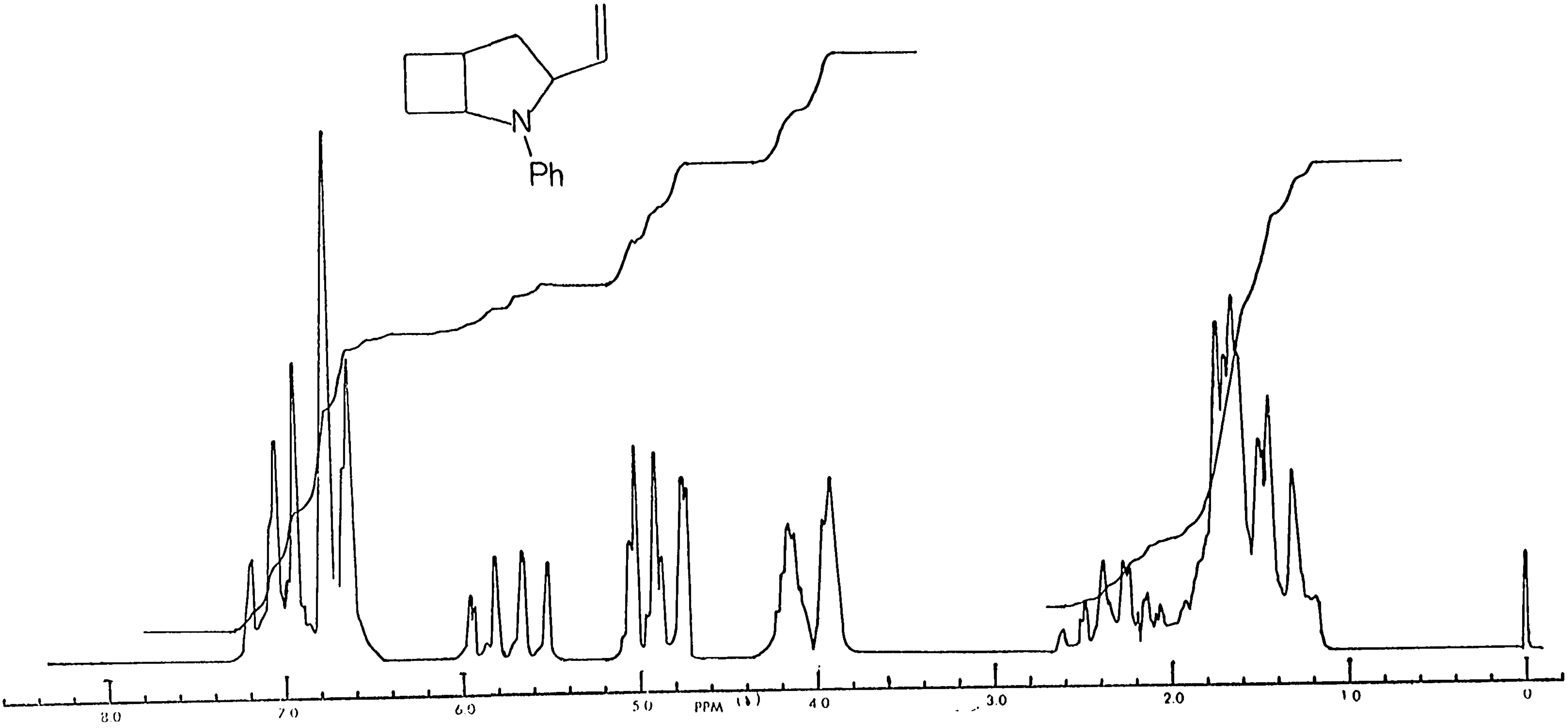
NMR Spectrum of 1-Azido-2-iodocyclobutane (<u>15</u>) in Carbon Tetrachloride.


N3
0
1.0
2.0
3.0
4.0
PPM (δ)
5.0
6.0
7.0
8.0

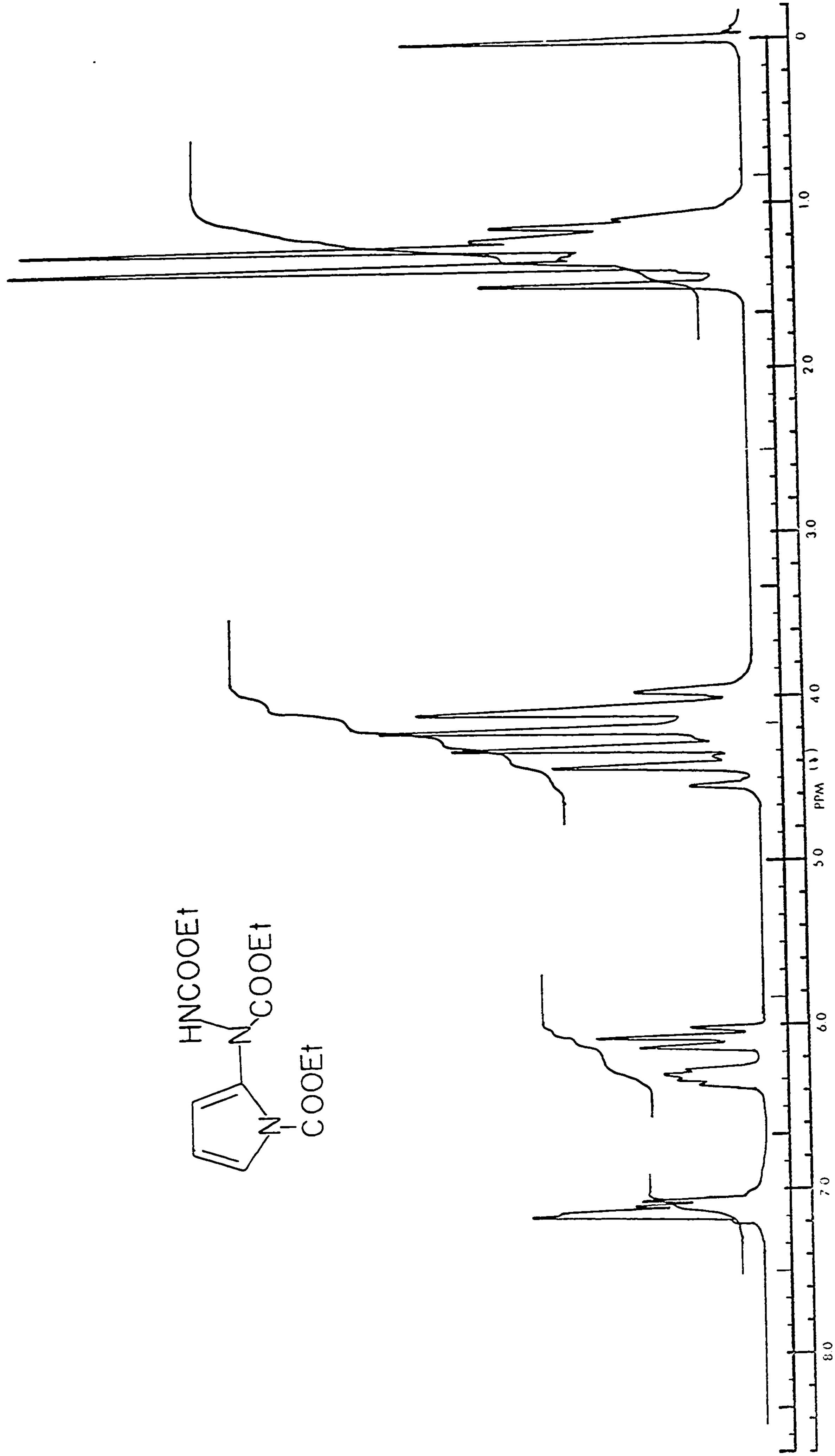
NMR Spectrum of 2-Iodocyclobutyl Isocyanate (19) in Carbon Tetrachloride.


NCO
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

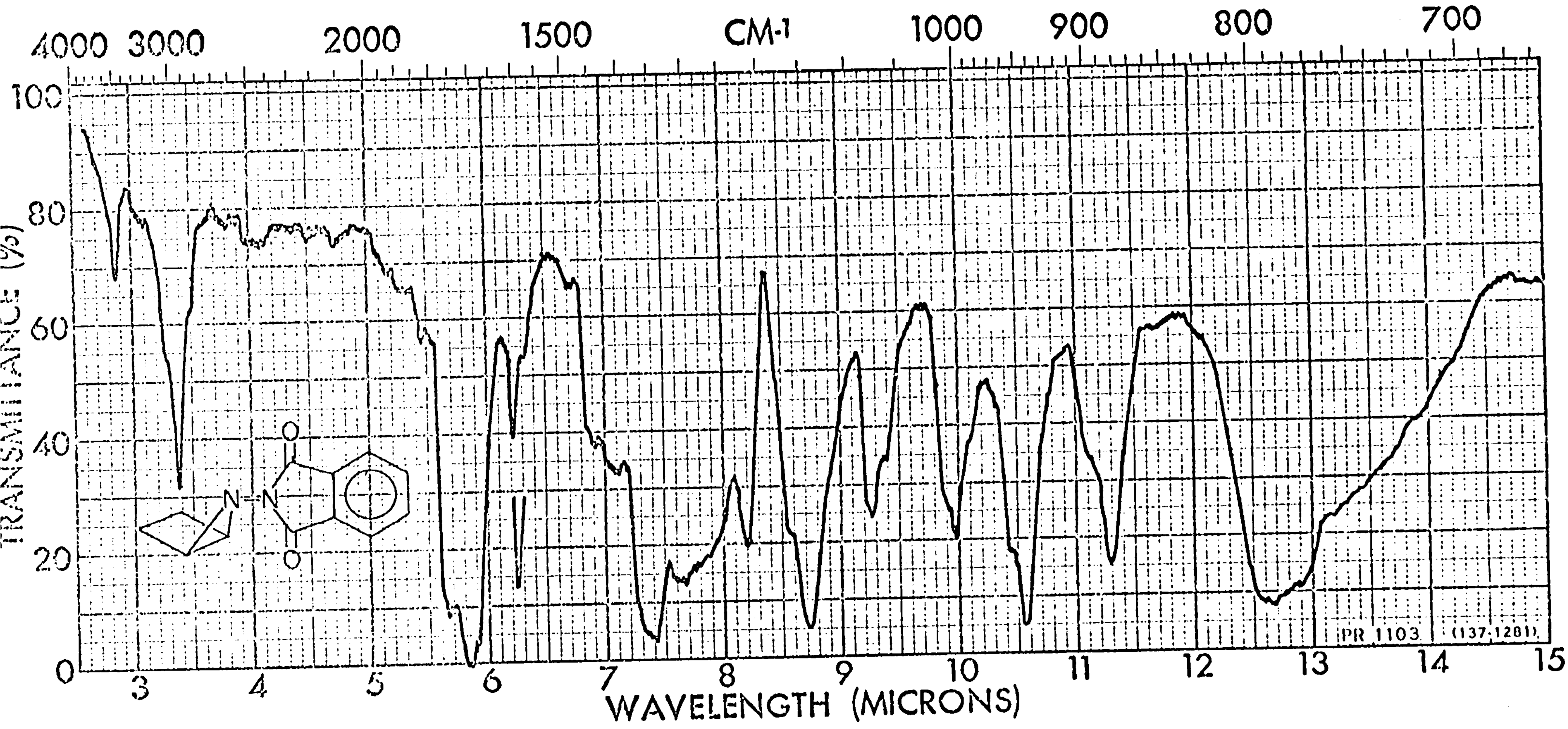
NMR Spectrum of 2-Phenyl-3-vinyl-2-azabicyclo[3. 2. 0]heptane (25) in Carbon Tetrachloride.


N
Ph
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

NMR Spectrum of Diethyl N- 2-(1-carboethoxy)pyrrolyl hydrazodicarboxylate (33).

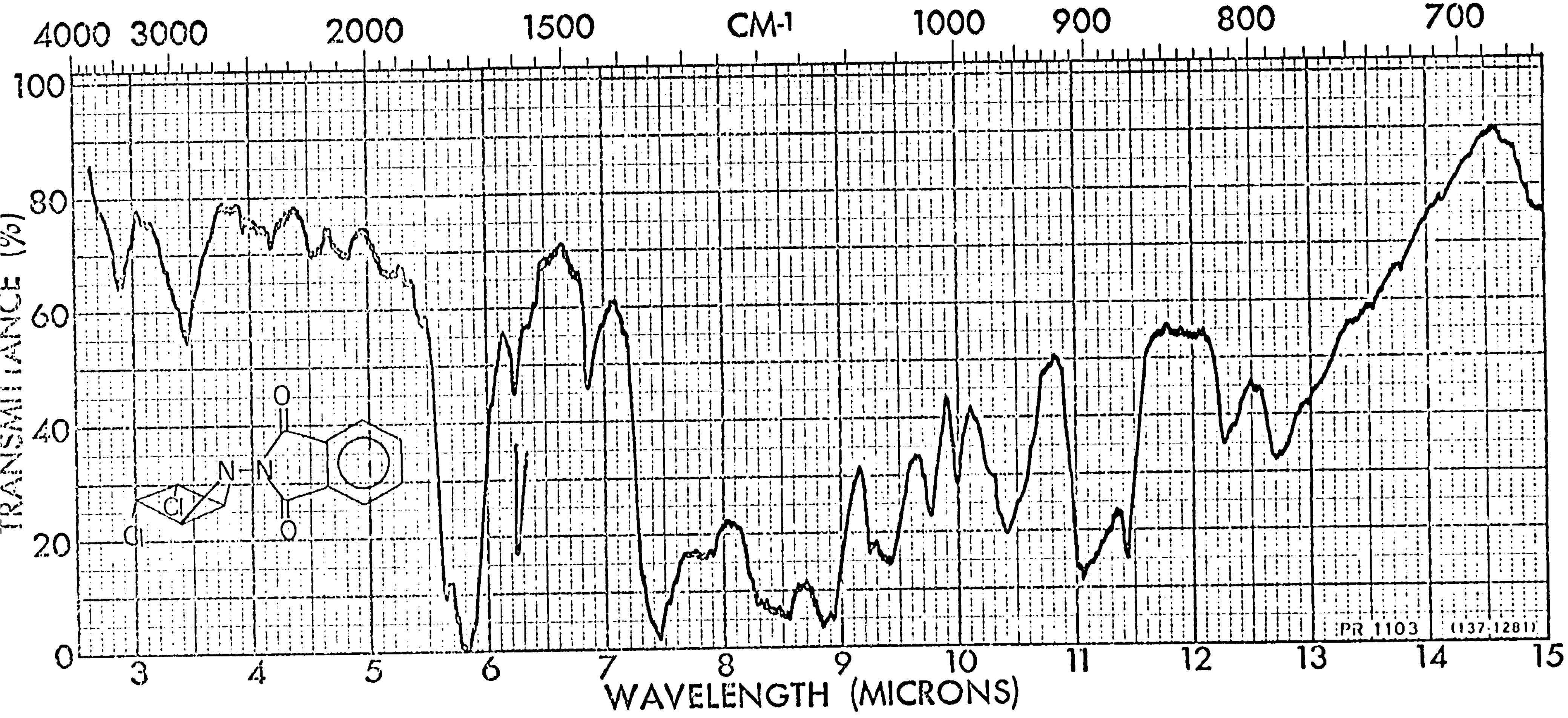

HNCOOEt
N
COOEt
N
COOEt
PPM (δ)
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0

IR Spectrum of 5-Phthalimidyl-5-azabicyclo[2.1.0]pentane (10a) in Dichloromethane.

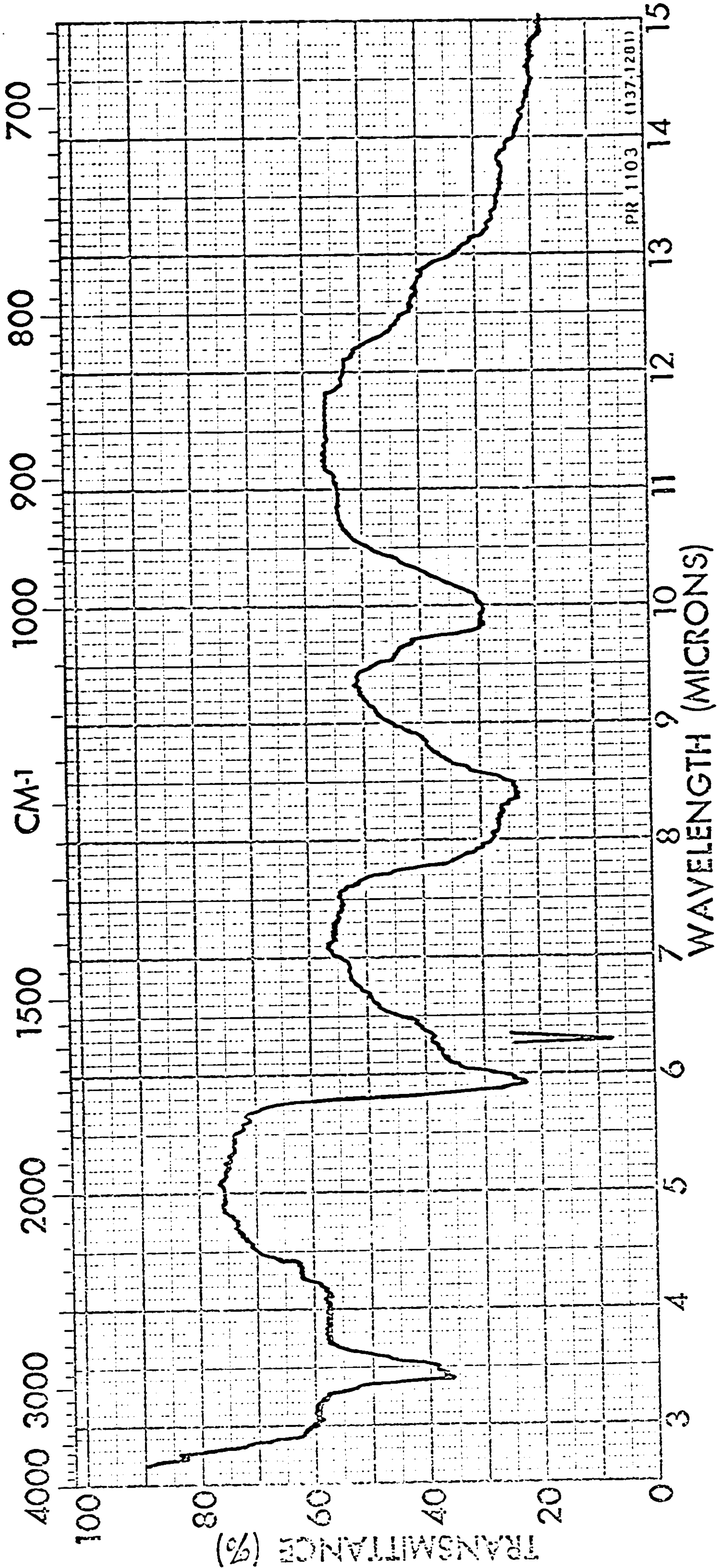


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
N
N
O
O
PR 1103
(137-1281)

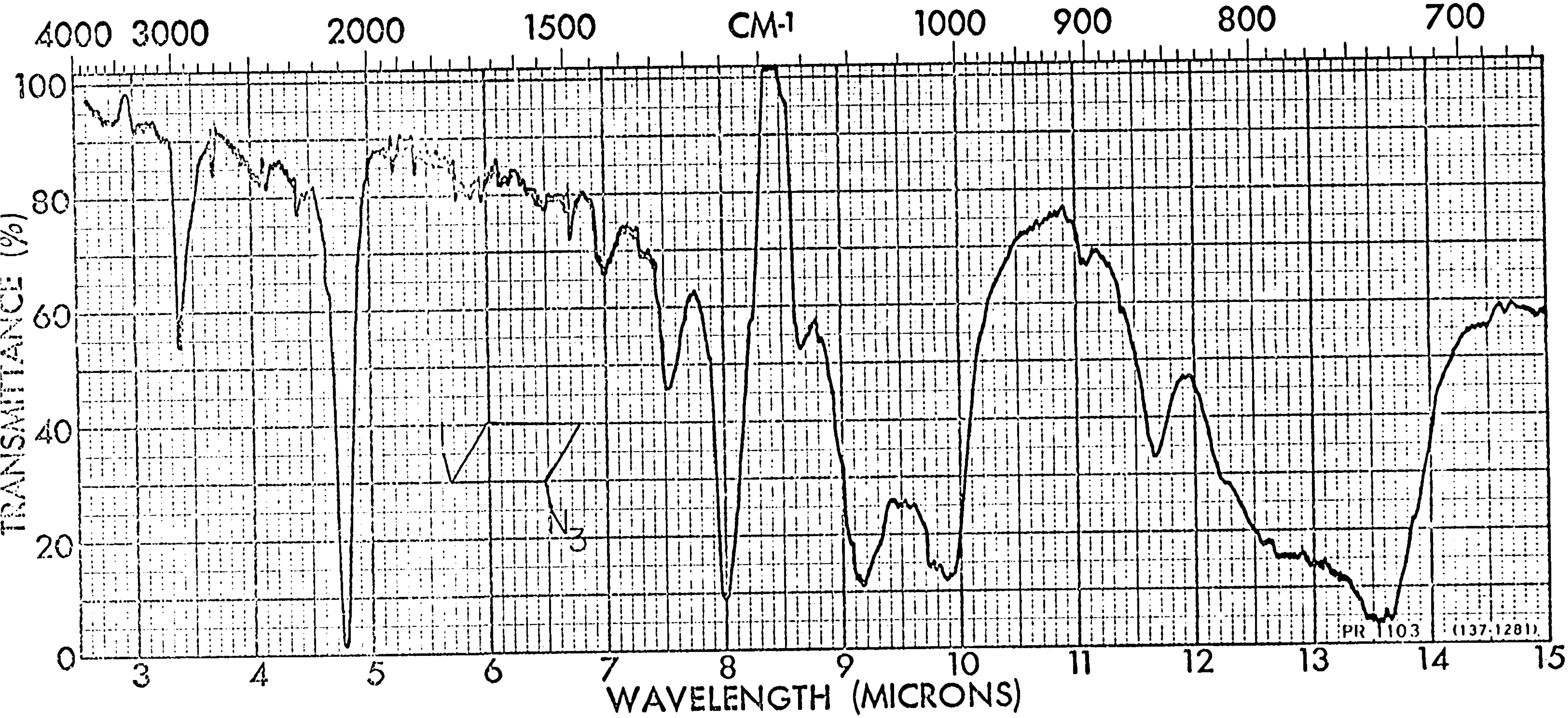
IR Spectrum of 2, 3-Dichloro-5-phthalimidyl-5-azabicyclo[2. 1. 0]pentane (<u>10b</u>) in Dichloromethane.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
Cl
Cl
N
N
O
O
PR 1103
(137-1281)

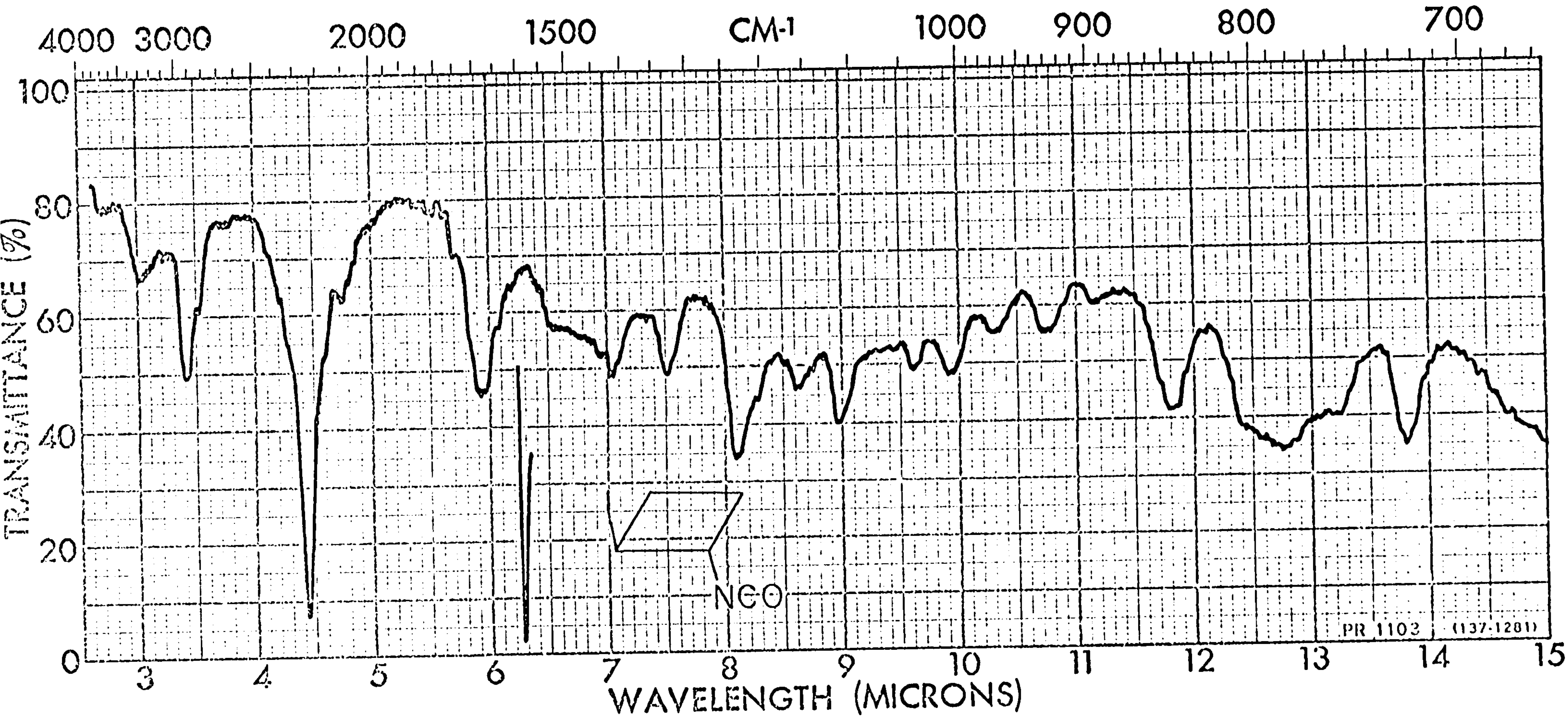
IR Spectrum of 2, 3-Dichloro-5-phthalimidyl-5-azabicyclo[2. 1. 0]pentane, After Heating With D_2O, Sodium Deuteroxide, in Chloroform.


CM-1
4000
3000
2000
1500
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
PR 1103
(137.1201)

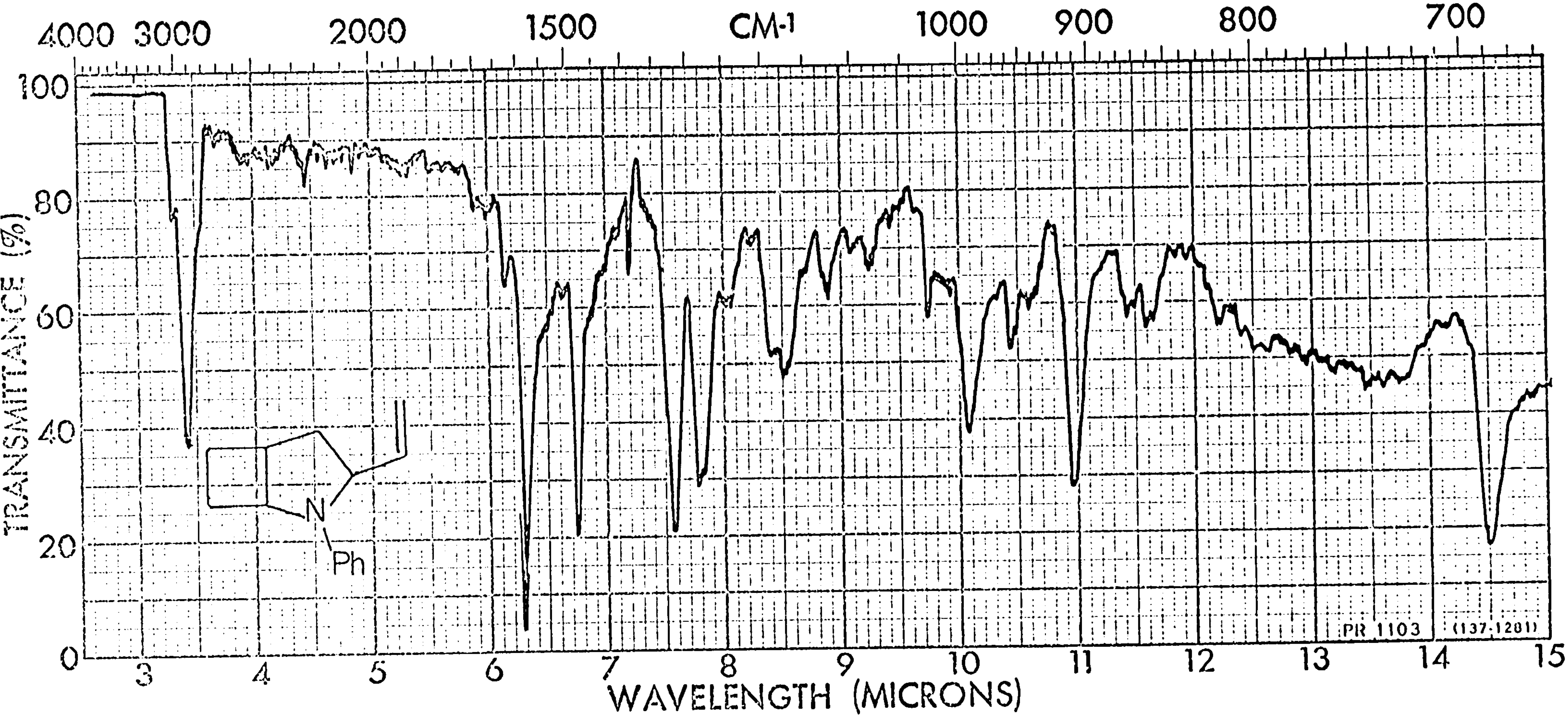
IR Spectrum of 1-Azido-2-iodocyclobutane (15) in Carbon Tetrachloride.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
N3
PR 1103
(137-1281)

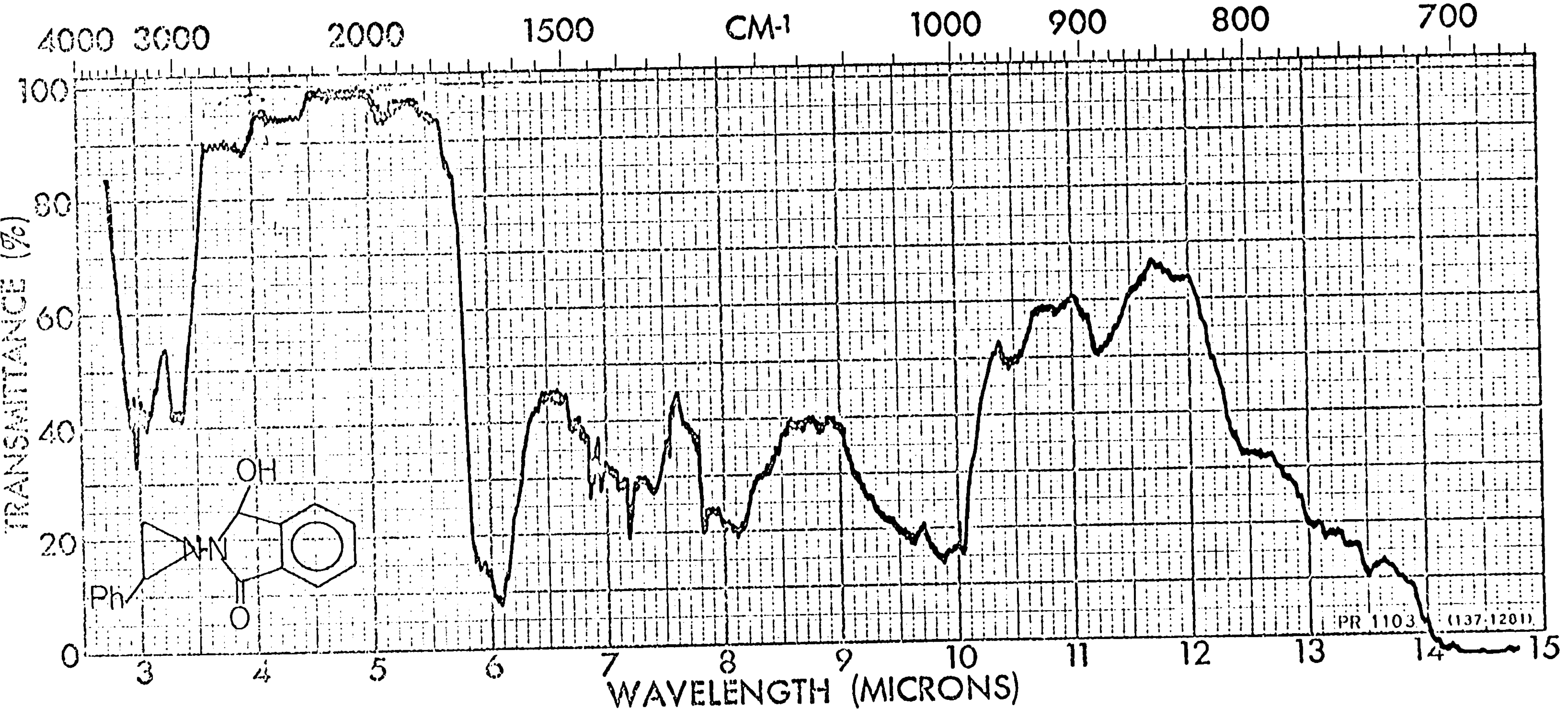
IR Spectrum of 2-Iodocyclobutyl Isocyanate (<u>19</u>) as a Thin Film.


CM-1
4000
3000
2000
1500
1000
900
800
700
TRANSMITTANCE (%)
100
80
60
40
20
0
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
NCO
PR 1103
(137-1281)

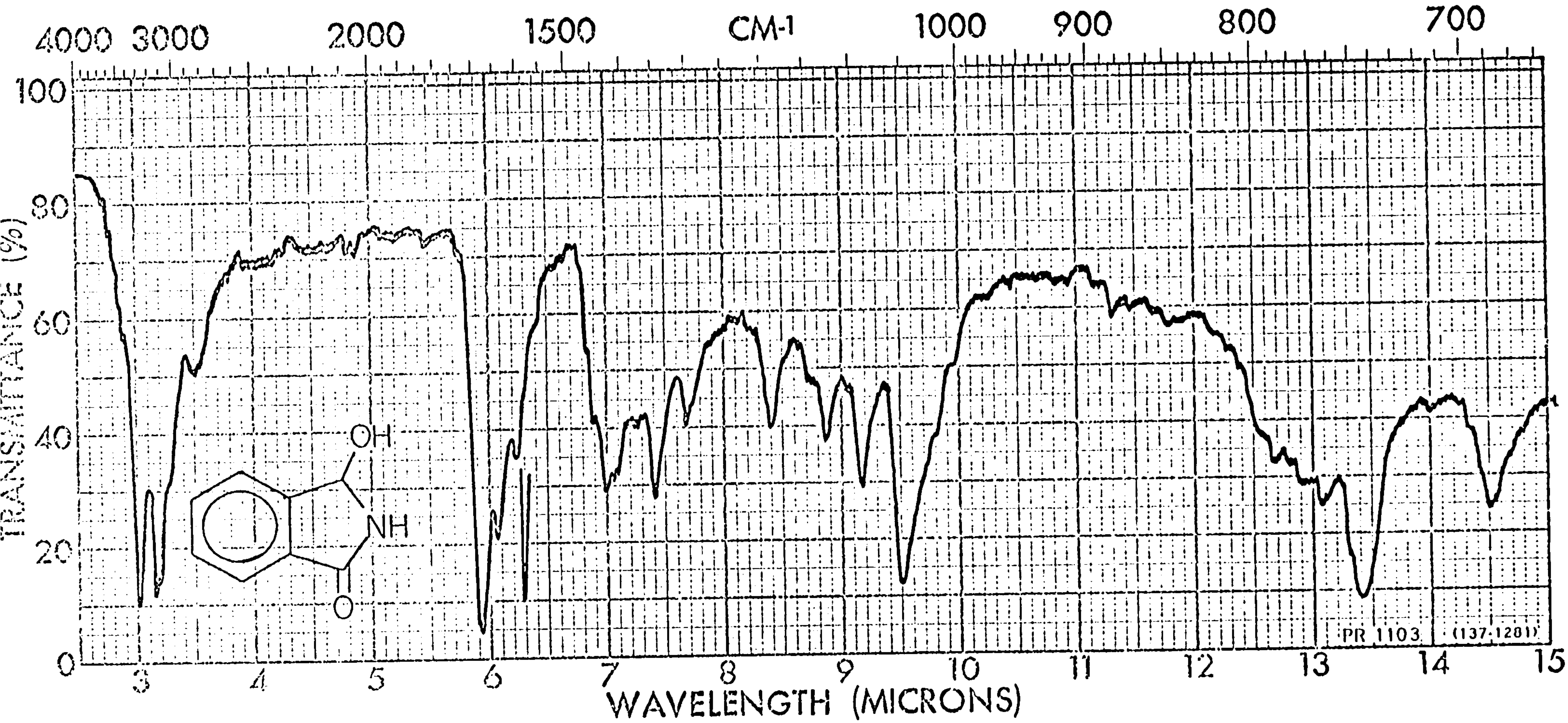
IR Spectrum of 2-Phenyl-3-vinyl-2-azabicyclo[3. 2. 0]heptane (25) in Carbon Tetrachloride.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
N
Ph
PR 1103
(137-1281)

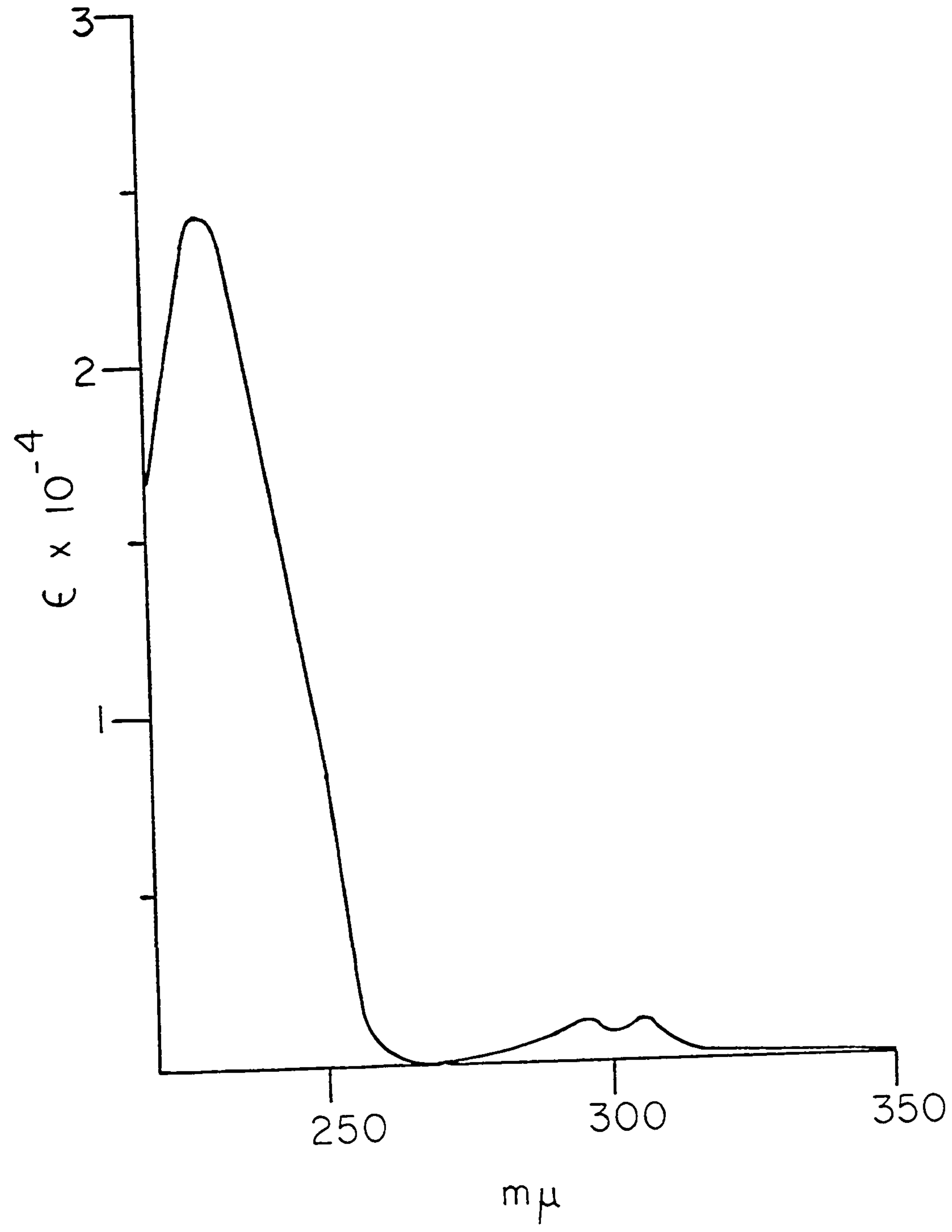
IR Spectrum of N-(3-hydroxyphthalimidinyl)-2-phenylaziridine (<u>35</u>) in Dichloromethane.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
OH
N
N
Ph
O
PR 1103
(137.1201)

IR Spectrum of 3-Hydroxyphthalimidine (<u>36</u>) in Potassium Bromide.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
OH
NH
O
PR 1103
(137-1281)

UV Spectrum of 2, 3 -Dichloro -5 -phthalimidyl -5 -azabicyclo[2. 1. 0] -pentane (<u>10b</u>) in Acetonitrile.

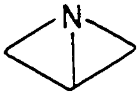

3
2
1
ε x 10⁻⁴
250
300
350
mμ

PART II. STUDIES OF SOME SYNTHETIC PATHS LEADING TO 2-AZABICYCLO[1.1.0]BUTANE

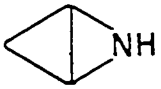
INTRODUCTION

A great deal of attention has been devoted to the properties and reactions of small ring bicyclic nitrogen compounds in the recent chemical literature.[24] It was decided to attempt the synthesis of the 2-azabicyclo[1.1.0]butane system (37) to extend the knowledge in this area. The chemical literature to date contains only three reports of 2-azabicyclo[1.1.0]butane systems as postulated transitory intermediates, none of which could be isolated.[51] In all three cases, other mechanisms could not be ruled out and thus it appears that the bicyclic system is attractive as an intermediate to an appreciable extent because of its novel structure. Illustrative properties of this system which would be of interest include strain energy, bond lengths and angles, nitrogen basicity, and reactions of the bridging bond.

The isomeric 1-azabicyclo[1.1.0]butane (38) system has been synthesized by Hortmann and also by Funke.[24] The latter has reported uncatalyzed addition of such reagents as thiophenol, tosyl chloride, and acetic anhydride across the 1,3 bond of the system. This high reactivity indicated possible similar behavior for the 2-aza system.



37



38

Synthetic routes considered were: 1) via a nitrene by either insertion of a nitrene moiety into a cyclopropene double bond or intramolecular insertion of a nitrene into a C-H bond, and 2) dipolar addition of an azide to a cyclopropene followed by photolysis of the intermediate triazoline, if it proved isolable. The routes will be considered in more detail at the beginning of the section for each.

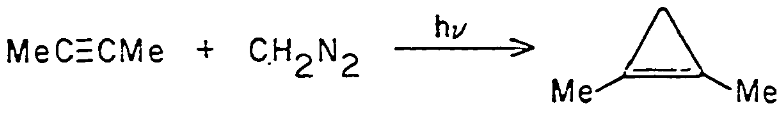
Since one would expect the 2-azabicyclo[1. 1. 0]butane system to be quite strained, the above two approaches were chosen from the variety of aziridine-forming reactions as having the least steric and strain requirements.

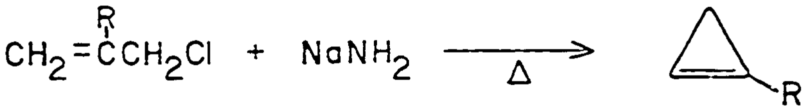
A third method of aziridine formation, reduction of an iodoazide by lithium aluminum hydride, was attempted in order to help elucidate the proposed rearrangement of the [1. 1. 0] system, as explained later.

DISCUSSION OF RESULTS

Synthesis of Cyclopropene Starting Materials

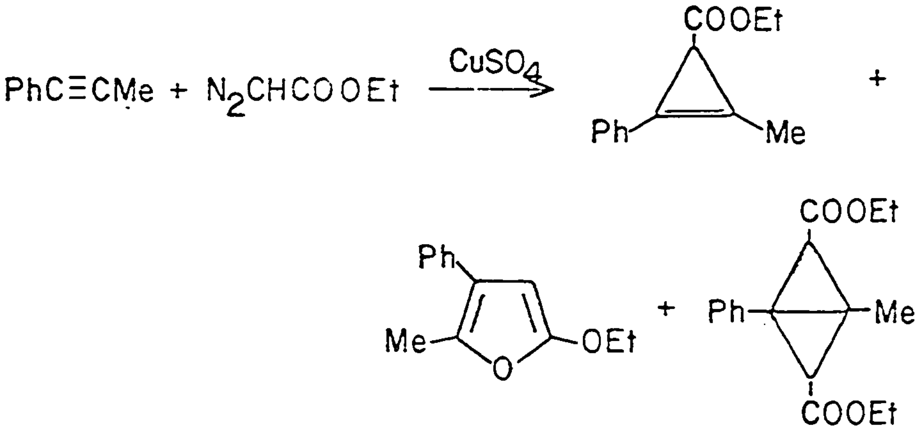
The literature methods of cyclopropene synthesis generally rely on either carbene or carbenoid reagents reacting with acetylenes, or on allylic carbenes undergoing intramolecular double bond insertion. For example:[52]

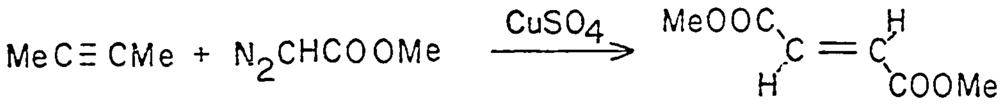


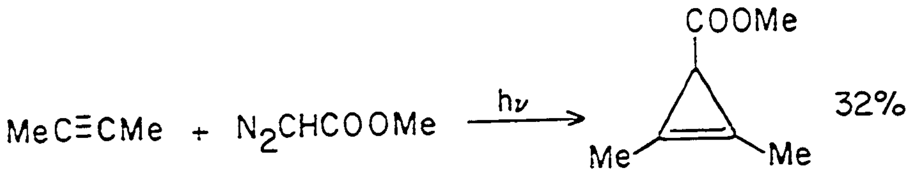


In the present study both methods of synthesis were attempted, the first with no success.

The carbene or carbenoid reaction with an acetylene has some unfortunate characteristics. The cyclopropene is as reactive or more reactive than the starting acetylene and so significant amounts of the bicyclo[1. 1. 0]butane may be produced. The following reactions serve to illustrate some of the problems of this type of synthesis.[52]

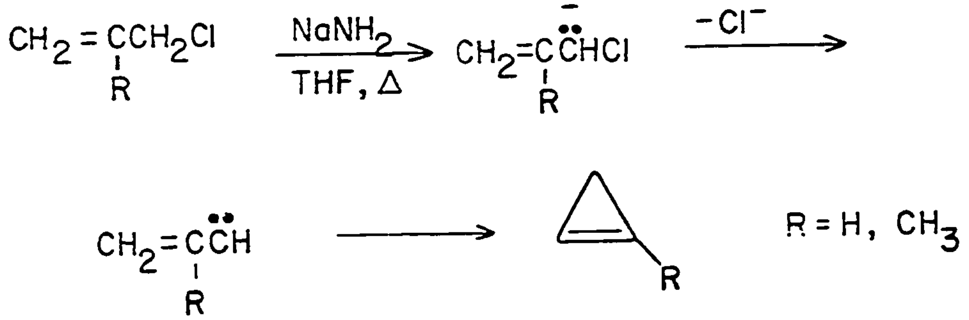






If the concentration of the carbene reagent is too high, coupling can occur to give an olefin. Also hydrogen abstraction from the solvent followed by radical coupling to give an alkane occurs readily. Because of all these side reactions, a large excess of acetylene over the carbene precursor is required to obtain reasonable results. Typical yields are still low however.

A more convenient route to two cyclopropenes is through the intramolecular insertion of an allylic carbene. This procedure has been used successfully by Closs,[53] and by Fisher and Applequist[54] to make the parent hydrocarbon and methylcyclopropene respectively.



From the standpoint of obtaining the parent 2-azabicyclo[1.1.0]-butane system, cyclopropene would be the desired starting material. There are, however, certain overriding factors which dictate that, for exploratory synthesis at least, the better material is methylcyclopropene.

Cyclopropene boils at -36° and must be stored in liquid nitrogen to prevent evaporation and rapid side reactions of the material that lead to loss of the olefin.[55] The yield of the olefin in the literature procedure is 10-12%. On the other hand, methylcyclopropene boils at 12°, can be stored at the Dry Ice-acetone temperature if desired, and the literature yield is "about 50%".[54] Thus for ease of handling and production of large quantities of material, methylcyclopropene was the olefin of choice for the attempted synthetic routes.

It was quickly found that the literature synthesis was not reproducible with respect to yield. Using purified reagents and dried tetrahydrofuran (THF) a consistent yield of 20-26% was realized. Quite by accident, it was noted that a jump to 30-40% was obtained when impure methallyl chloride was substituted for the purified material. The rate of production of the olefin was also increased. This was accounted for by assuming that a more soluble base was formed by reaction of an impurity in the allylic chloride. This base was probably hydroxide ion since during distillation the crude material gives a milky forerun. The hydroxide ion acts then as the effective base and is regenerated by the sodium amide which is expected to be less soluble in THF than sodium hydroxide.

The olefin as collected contained substantial amounts of THF swept over by the gas stream, so two trap-to-trap distillations were required for purification. The last traces of methylcyclopropene in the remaining THF could not be removed without contaminating the olefin with additional THF. Therefore, the slowest possible nitrogen stream was used in order to keep to a minimum the amount of THF contamination.

The material exhibited the published NMR spectrum,[54] and by NMR checks it was determined that samples of the pure material could be kept without appreciable change for periods of up to three weeks when cooled by Dry Ice-acetone. The change observed on long standing consisted of the appearance of peaks at 9.05 τ and 4.70 τ amongst other smaller signals. After long standing, the methyl signal collapsed to a multiplet at the same position in the spectrum.

Nitrene Approach

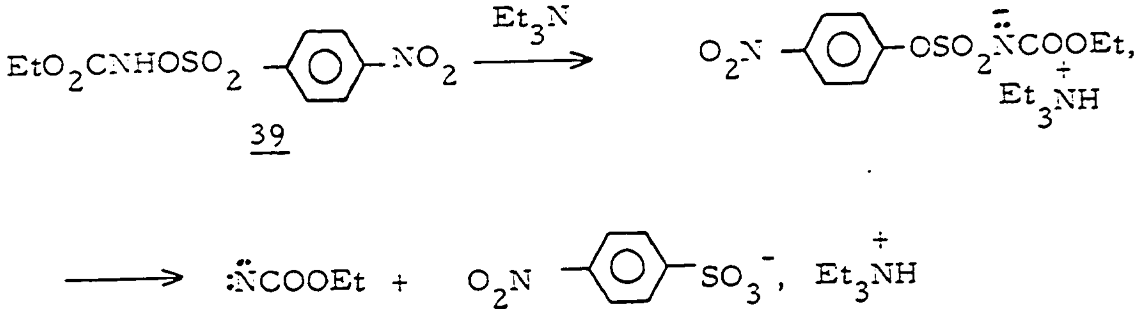
Introduction

Nitrenes, neutral nitrogen compounds having only six electrons in their outer shell, have received interest of late from several investigators.[19,20] Early work established that very few nitrenes could be of potential synthetic use in aziridine synthesis. (see Part I, p. 10)

For the reasons outlined in the first part of this thesis, carboethoxynitrene and phthalimidylnitrene were considered for synthesis studies. In addition it was decided to attempt generation of a nitrene attached to a tertiary carbon that was substituted with only aliphatic groups. This would, of course, prevent imine formation from α-hydrogen abstraction and hopefully would allow C-H insertion to go faster than any alkyl group migration.

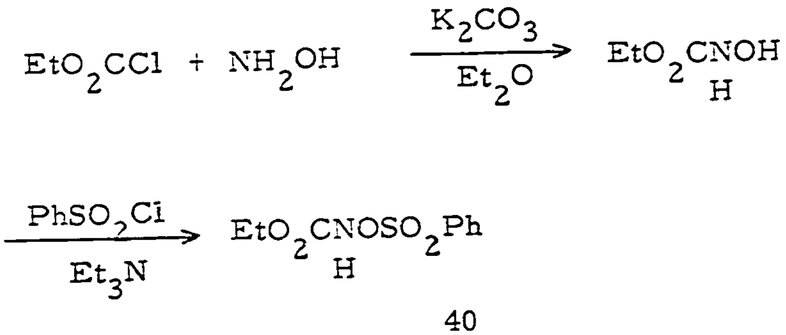
Reaction of Carboethoxynitrene With Methylcyclopropene.

Lwowski and coworkers have generated carboethoxynitrene by reaction of the sulfonoxyurethane (39) with base:[56]



39

The appropriate sulfonyl chloride not being readily available, the benzenesulfonoxy compound (40) was synthesized by substituting the readily available benzenesulfonyl chloride in the sequence.



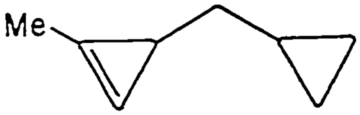
$$EtO_2CCl + NH_2OH \xrightarrow[Et_2O]{K_2CO_3} EtO_2C\underset{H}{N}OH \xrightarrow[Et_3N]{PhSO_2Cl} EtO_2C\underset{H}{N}OSO_2Ph$$

40

When compound 40 was stirred with triethylamine in dichloromethane solution, carboethoxynitrene was produced as shown by the detection of diethyl hydrazodicarboxylate. (see Experimental Section)

When 4 was treated with triethylamine in the presence of excess methylcyclopropene in dichloromethane or ether, a heavy precipitate formed which was indicative of nitrene production. Attempts to isolate a product by distillation did not succeed with pressures as low as 2 torr at a temperature of 100°. By VPC, the fractions collected from the distillation gave only solvent and THF. THF was a normal contaminant of the olefin. (see Experimental Section) The pot residue was a thick yellow solid which when treated with potassium hydroxide in methanol gave a white precipitate. An analysis of this precipitate indicated that it was not simply the dipotassium salt of hydrazodicarboxylic acid. An IR spectrum (nujol) showed peaks at (cm^{-1}) 3450, 1720, and 1640. Due to the non-volatility of the original pot residue, it was assumed not to have consisted of any of the desired bicyclic amine.

By preparative VPC of some of the filtered reaction mixture on either Carbowax or SE 30, a volatile material was isolated. An IR spectrum was taken (see Experimental Section) and the NMR (τ) was: 3.52 (m, 1), 7.90 (d, 3), 8.47 (m, 1), 8.95 (s, 1), 9.02 (d, 2), 9.45 (m, 2), and 9.92 (m, 2). The data best correspond to a dimer of methylcyclopropene via an ene-reaction.



Mass spectrometric analysis was not fruitful since some high molecular weight contaminant was present, probably due to the sample decomposing upon coming in contact with the hot gallium inlet system or the hot source. Peaks from m/e 410 on down were observed. The "ene" dimer of cyclopropene also shows high mass peaks when spectra are taken on samples warmed above -60°.[55]

The results seemed to indicate the absence of a monomeric product of the desired composition. It is pertinent to note that 5-carboethoxy-5-azabicyclo[2.1.0]pentane has the same molecular weight and is volatile at 0.1 torr and 40°. Also 6-carboethoxy-6-azabicyclo[3.1.0]hexane with an added molecular weight of 14 has a boiling point of 110-112° at 60 torr. In light of this it is reasonable to assume that the desired product should be easily volatile at 2 torr and 100°.

If an analogy held between the 2-azabicyclo[1.1.0]butane system and its carbocyclic analog, the aza system should easily survive the temperature conditions of attempted isolation since the three hour $T_{\frac{1}{2}}$ temperature for bicyclo[1.1.0]butane is 210°. As will be discussed later, this analogy is proposed not to hold because of electronic factors which are not present in the carbocyclic analog.

Reaction of Phthalimidylnitrene With Methylcyclopropene.

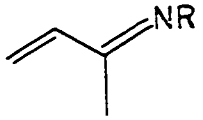
C. W. Rees and coworkers have been able to form aziridines in moderate to good yields with olefins and N-imidyl and N-amidylnitrenes.[20] The products were always solids of fairly high melting points and good stability.

When the nitrene was generated by the lead tetraacetate (LTA) oxidation of N-aminophthalimide in the presence of excess methylcyclopropene, a yellow solution was obtained after filtration which quickly turned dark red-brown on short exposure to air. Evaporation gave a red-brown mass which upon Soxhlet extraction with ether gave a crystalline product showing exclusively aromatic absorptions in the NMR and was identified as phthalimide. As discussed in Part I, phthalimide is a normal byproduct of N-phthalimidylnitrene reactions.

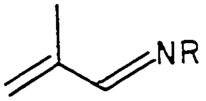
In attempting to shed further light on the product of the reaction and its fate after formation, the reaction was rerun using lead tetrabenzoate (LTBz) as the oxidant. LTBz was chosen for the reaction since it is fairly soluble in dichloromethane whereas LTA is only sparingly soluble. Also there would be only aromatic signals present so it would not interfere with the NMR observation of the region above dichloromethane.

The reactants were mixed at -78° in a flask immersed in Dry Ice-acetone. A 0.5 ml aliquot of solution plus suspended solid was observed by NMR. Observation at -50° indicated no change in any signals over 30 minutes and no evident oxidation. The sample was progressively warmed until at 10° a singlet was seen to appear just below the methyl doublet of the olefin. No other signals at higher field appeared during the entire course of observation. After standing overnight at room temperature, multiplets appeared in the 8-9 τ region and the methyl singlet signal seemed to disappear completely. (see Spectral Section) Observation of the olefinic region of the NMR spectrum was obscured by the methylene chloride solvent.

A proposal to explain the results would be that the bicyclic system rearranges as fast or faster than the rate of oxidation of the amine to the nitrene. The unsaturated imines <u>41</u> and <u>42</u> would reasonably be expected



41



42

to give a methyl signal in the NMR spectrum in the region where the singlet was experimentally observed to grow. After standing overnight, extensive polymerization could easily destroy the methyl singlet by "saturating" the adjacent double bond.

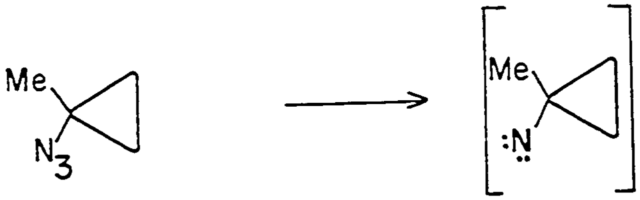
In an attempt to isolate a reduction product of the imines, the rest of the reaction mixture was allowed to warm to room temperature with vigorous stirring, and the yellow mixture was poured into methanol, and hydrogenated. A slow hydrogen uptake was observed but only inconclusive results were obtained. The fractions isolated by preparative TLC containing phthalimidyl protons contained no substantial aliphatic signals, i.e. 7 τ or greater, whereas fractions showing strong aliphatic signals showed only a benzoic acid-type pattern in the aromatic region.

It is possible that the hydrogen uptake observed was due to reduction of formaldehyde produced from LTBz oxidation of methanol and that the imine was extensively polymerized in the course of the slow hydrogenation, since there was benzoic acid present to act as a catalyst for the process, or that the imine was polymerized before hydrogenation was attempted.

Except for the difficulty in isolating the N-alkyl phthalimides, this seemed to be very good evidence for the rapid spontaneous rearrangement of the 2-azabicyclo[1. 1. 0]butane system once formed. This apparent tendency to rearrange would point toward the necessity of a good low-temperature method for rapid nitrene formation to allow observation of the bicyclic system by low-temperature NMR before its destruction by rearrangement.

Generation of a Cyclopropylnitrene.

The third nitrene, whose generation was attempted, was one attached to a tertiary carbon substituted with alkyl groups. A logical choice for this nitrene would be from the decomposition of the azide, 43, formed by formal addition of hydrazoic acid to methylcyclopropene.



43 44

In dilute solutions the nitrene, 44, would have only three alternative reaction paths: 1) hydrogen abstraction from the solvent; 2) C-H insertion; and 3) alkyl group migration. The C-H insertion reaction could give either the desired product or 2-azaspiro(2. 2)pentane.

The rate of 2° C-H insertion is faster by a factor of 9 to 11 than 1° C-H insertion for carboethoxynitrene.[57] This would favor formation of the desired product even though the 1° C-H bonds are favored three to two on a statistical basis.

It was further felt that since alkyl migration for nitrenes seemed to be very much slower than aryl migration, that the rate of C-H insertion could be at least competitive with the rate of migration.[18]

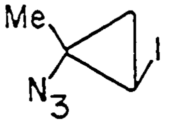
The simplest possible route leading to 1-azido-1-methylcyclopropane, 43, would be to add hydrazoic acid directly to methylcyclopropene.

Hydrazoic acid itself is highly toxic and constitutes a high explosion hazard. However, in following the procedure and precautions for its synthesis found in Inorganic Synthesis[58] a solution was made without incident, and methylcyclopropene added to it. The resulting product after workup was indicated to contain ten compounds by a VPC analysis. Due to the difficulties in attempting a chromatographic separation of so many compounds, the mixture was not worked up further.

An alternate means of introduction for the azide was thus necessary. Iodonium azide was easily generated in situ in acetonitrile according to the procedure of Hassner.[26] When methylcyclopropene was added to this solution, a very exothermic reaction resulted. The crude product could be isolated in good yield and purified to a fair extent by column chromatography.

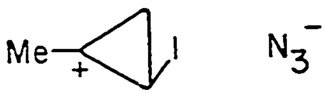
The crude semi-purified material showed two major peaks by VPC. The second peak (25% of the sample) was thought to arise from thermal decomposition upon injection. Material run through a short silica gel column using petroleum ether (pet. ether) elutant gave highly purified adduct which showed one major spot on TLC. (see Experimental Section)

The NMR spectrum of the purified material showed one isomerically pure compound. This may be readily seen by inspection of the spectrum of the material in the Spectral Section. Note that the multiplet at 8.43 is distorted vertically since it lies partly on the upfield trailing edge of the singlet for the methyl group. Since iodonium azide is known to add Markovnikov and trans, the adduct would be:



45

This was substantiated by the following reasoning. The adduct could not logically be all cis since the only likely mode of production of cis compound would be through an open carbonium ion. This ion would be expected to have at least as good a chance, if not better, to add the nucleophile trans to the iodine, especially due to steric bulk of iodine which would give partial shielding to attack on the cis side.



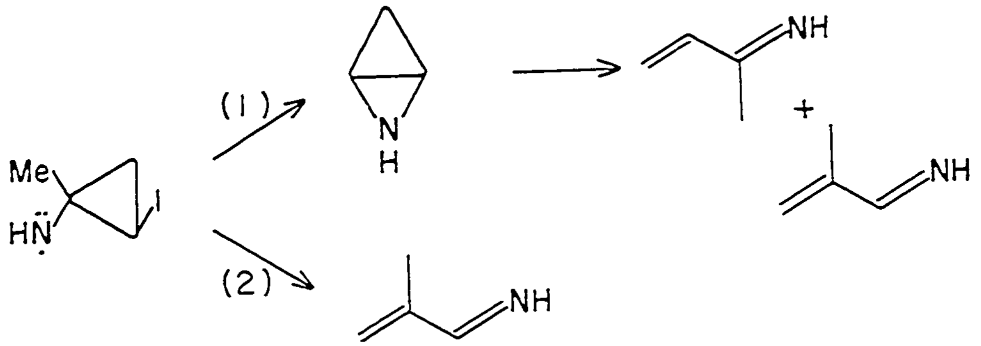
The IR spectrum confirmed the presence of azide, and the presence of iodine was confirmed by sodium fusion and mass spectrometry. The mass spectrum of the compound showed a parent peak at 222.9603; calculated for $C_4H_6N_3I$: 222.9608. The base peak with 127 m/e corresponding to I^+. A major fragment was at 96 m/e corresponding to $C_4H_6N_3^+$, compound 45 minus iodine.

The fact that the iodoazide, <u>45</u>, was 100% <u>trans</u> indicated that the intermediate ring system, a 2-iodoniumbicyclo[1.1.0]butane, was probably formed as a reaction intermediate, and also indicated that it may be possible to form the bicyclo[1.1.0] system with a heteroatom in the 2 position. The intermediacy of a highly shielded monocyclic carbonium ion cannot of course be ruled out.

In an attempt to replace the iodine by hydrogen, the iodozide, <u>45</u>, was treated with tri-n-butyltin hydride. When the reaction was run at 30°, a very marked heating occurred causing much decomposition and gas evolution. Running of the reaction with ice cooling lead to reduced discoloration but a gas was still given off. An IR spectrum indicated that the gas was probably butane. A positive identification could not be made due to the weak spectrum obtained. The yield of volatile azide removed by vacuum and caught in a trap was very small and the main pot residue was hexa-n-butyldistannane. The same results were obtained running the reaction at -65° for an extended period.

In both of the runs, at 0° and -65°, a peak slowly appeared at 1610 cm^{-1} reaching less than medium intensity at the end of the reaction. This peak was postulated to arise from radical attack on the azide function to give the radical <u>45a</u> which then further reacted <u>via</u> either path (1) or path (2) to give an α,β-unsaturated imine. This imine should be stable to the tin hydride.

Since the imines were not isolated, experimental verification of this postulate was not obtainable.



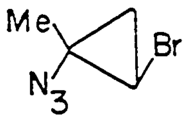
45a

The iodoazide, 45, did not react with magnesium in dry ether or in dry THF. It reacted rapidly with lithium in THF, however, and upon hydrolysis in water gave varying yields of impure azide, 43. The NMR spectrum of the azide was (τ); 8.5 (s, 3), 9.13 (m, 2), and 9.33 (m, 2). This further confirms the Markovnikov addition of the iodonium azide to methylcyclopropene.

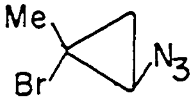
The reason for the varying yields, mostly lower with lower temperature and longer reaction times, was thought to be due to carbon dioxide in the nitrogen line used to keep the reaction free of moisture and oxygen. Tests on the nitrogen line showed that Ascarite was used up by a steady flow of nitrogen over a short period of time. Since the azide was always purified by column chromatography, the acid resulting from lithium reagent carbonation would be held in the column until long after the azide was through and would not be detected.

With the hope of improving the yield of azide from the tin hydride reaction, the bromoazide of methylcyclopropene was synthesized. It was theorized that since the bond energy of the tin-iodine bond is very low, perhaps the reaction thermodynamics would be helped by formation of a tin bromide instead of an iodide. The synthetic use of bromonium azide had been reported by Hassner, but experimental details were poor at best, only being alluded to in the footnote of a communication.[59]

Using the conditions stated in the Experimental Section, a moderate yield of bromoazide was obtained. Its NMR spectrum was similar to that of the iodoazide but indicated about 25% anti-Markovnikov adduct. The IR spectrum was very similar to that for the iodoazide. From these two data the structures were inferred to be those shown below for 46a and 46b:



46a



46b

The material exploded upon heating. This was observed while injecting a sample into a VPC apparatus. For this reason a mass spectrum was not taken.

The adduct, when treated with tri-n-butyltin hydride behaved identically to the iodoazide except that reaction time was prolonged.

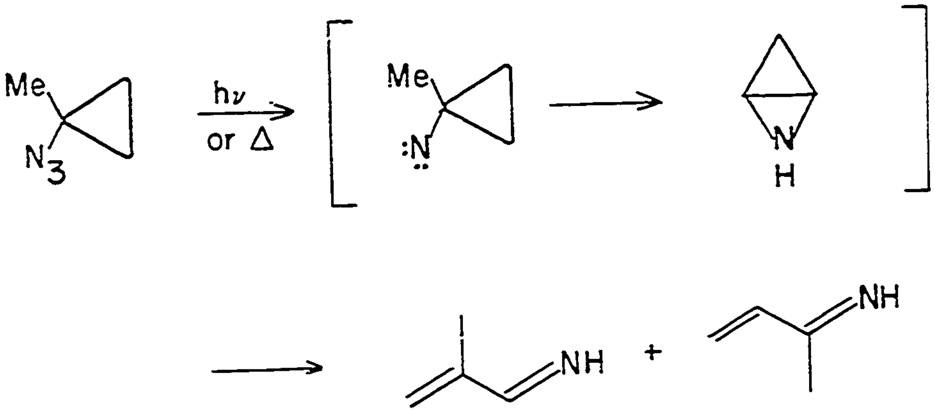
Thus no superior method of synthesis resulted but the small amounts obtained were adequate for a few further exploratory reactions.

When a small sample of the crude azido compound, 43, was refluxed in dry glyme for several hours, the azide band completely disappeared and two bands at 3550 cm^{-1} (m) and 1610 cm^{-1} (m) appeared. (see Spectral Section) Attempted isolation of a product gave only a dark solid residue, no amine odor having been noticed over the solution.

Photolysis of a sample of the azide, 43, in ether with a 450 watt lamp and a Vycor filter stopped at one-fifth the theoretical nitrogen evolution when a yellow solid coated the jacket of the immersion well.

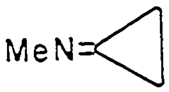
It is of interest to note that while attempting to follow the progress of the iodoazide, 45, down a silica gel column with a UV blacklight, the material partly decomposed and the dark eluant showed, in addition to some iodoazide remaining, new peaks at 3400 and 1700 cm^{-1} in the IR spectrum. Again no product could be isolated. The imine band being much higher, the species observed is probably an imine formed by group migration.

The pyrolysis and photolysis of the azide were proposed to have lead to an α, β-unsaturated imine by a spontaneous rearrangement of the 2-azabicyclo[1.1.0]butane formed as a reaction intermediate.

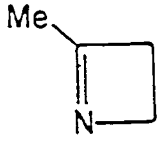


47

Since the imines were not isolated but only spectral evidence of their existence obtained, it cannot be determined that the bicyclic system was ever formed. Imine 47 for example could arise without intermediate cyclization. The formation of an imine, 48 or 49, by alkyl group migration would not account for the bands observed in the IR spectrum since they would be expected to absorb somewhat higher. Imines absorb in the region around 1700 cm^{-1} and α, β-unsaturated imines mostly in the region around 1650.[60]



48



49

The carbocyclic analog has a much greater thermal stability but thermally rearranges to a butadiene system. For example, bicyclo[1.1.0]butane has a 3 hour $T_{\frac{1}{2}}$ temperature of 210°[61] and rearranges to 1,3-butadiene.

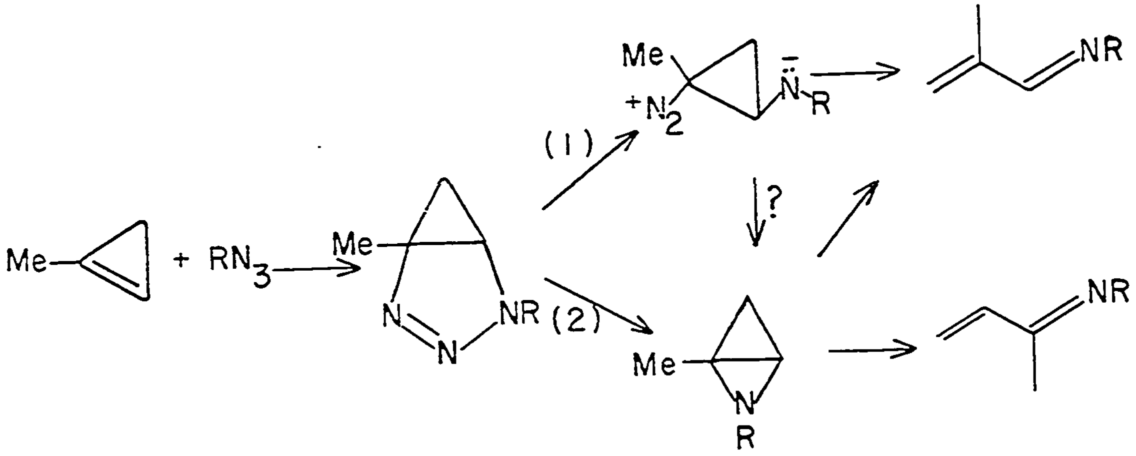
Attempted Synthesis by Dipolar Addition

An alternative route of synthesis attempted was the use of dipolar addition. Huisgen and others have shown that aziridines may be synthesized in good yield by reacting azides with strained olefins.[30,31]

When methylcyclopropene and tosyl azide[31] were allowed to react, as the azide peak decreased in the IR spectrum a peak grew at 1540 cm^{-1}. This peak was not due to the tosyl amide found present at the end of the reaction. It was ascribed to an α, β-unsaturated imine. Attempts to hydrolyze the solid product of the reaction to isolate the α, β-unsaturated carbonyl compounds were unsuccessful. Methyl vinyl ketone, an expected product, gave only a tarry black-brown material under the conditions of the hydrolysis reaction, and so would have escaped detection.

When methylcyclopropene in dichloromethane was treated with cyanogen azide[62] in cold acetonitrile (using adequate precautions due to the hazardous nature of the azide) a red-brown tarry precipitate was observed. Upon filtration and IR examination of the filtrate no azide remained. The desired product would reasonably be expected to be soluble in acetonitrile-dichloromethane. A sample of the filtrate was distilled to give fractions of pungent smelling material. VPC analysis showed them to be mixtures of dichloromethane and acetonitrile with a peak also coming out well before dichloromethane and probably representing hydrogen cyanide or hydrogen azide gas from the inadvertent hydrolysis of cyanogen azide. Nothing else could be detected by VPC of the pot residue.

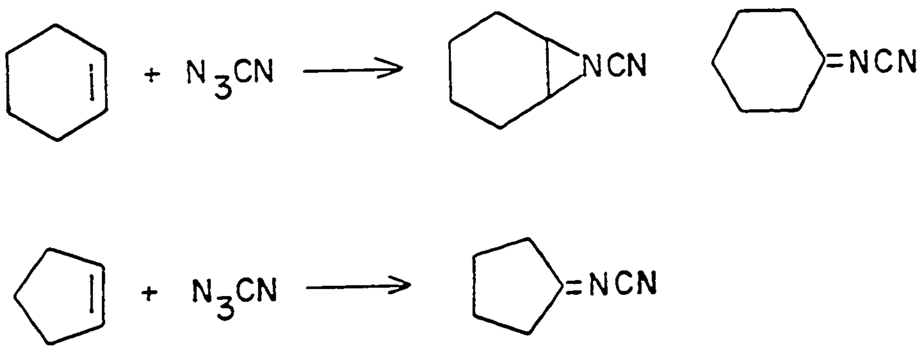
In both cases the results could be explained by the following scheme, Path (1) seeming more likely.



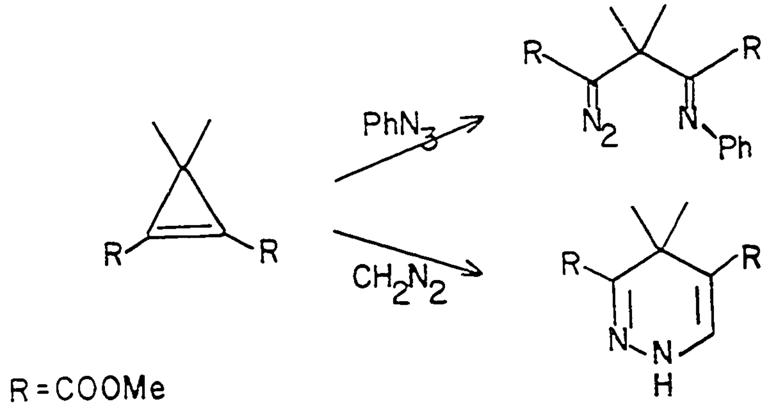
Hydrolysis in the case of the tosyl azide reaction would produce the tosyl amide observed and the unhydrolyzed unsaturated imine could account for the IR spectral band at 1540 cm^{-1}.

With cyanogen azide, the solid precipitate could be a polymer of the imine. Its greater ease of formation than with tosyl azide would be due to the stabilization of the transition state by the nitrile function giving it a much lower activation energy for the polymerization reaction.

It must be pointed out that in neither case is the bicyclic compound a necessary intermediate. In fact with cyanogen azide the following have been observed:[62]



An interesting alternative explanation is based on reactions recently observed with an electronically different cyclopropene.[63]

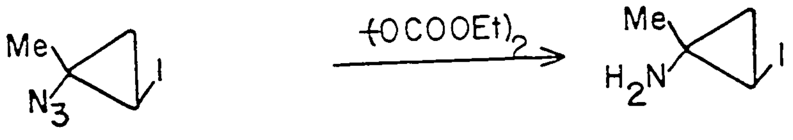


Since the potential diazocompound generated in the reaction in this thesis would not be stabilized by an α-ester function, they would be expected to be very reactive and could lead to formation of a polymer. This could explain the large excess of olefin required in the reaction with tosyl azide Since the polymer would have an imine function, hydrolysis upon chromatography would give the two observed products aliphatic proton containing polymer and tosyl amide. The IR spectral band at 1540 cm^{-1} however is very low for a non-conjugated imine.[60]

Since no good products could be isolated, the proposed rearrangements must remain an unproved hypothesis. It is, however, definite that this route is not a fruitful one for synthesis of the desired system. Because of the extreme slowness, dipolar additions at low temperatures, e.g. -78° for more product stability, would be highly impractical.

Attempted Reduction of 1-Azido-2-iodo-1-methylcyclopropane With Diethyl Peroxycarbonate

Reduction of the azide function of the iodoazide, 45, should yield an iodoamine which might be cyclized by base to the desired compound.



45

The reaction was run in either refluxing methanol or isopropanol, the mixture became very dark but a TLC check revealed little reduction.

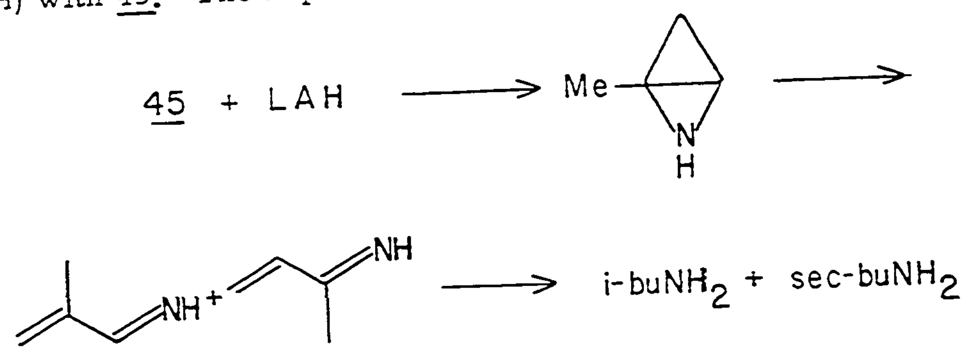
A solution of the product in dry ether produced no precipitate or oil when treated with dry hydrogen chloride gas, indicating no amine was produced in the reaction.

Reduction of 1-Azido-2-iodo-1-methylcyclopropane With Lithium Aluminum Hydride

Several attempts to establish the production of the 2-azabicyclo-[1.1.0]butane system by isolating a stable compound made from the proposed rearrangement product, an α,β-unsaturated imine, were made.

An attempted hydrolysis is referred to in the section on dipolar additions. (see page 138). Likewise an effort to hydrogenate the product of a nitrene reaction failed. (see page 130)

A third attempt involved the reaction of lithium aluminum hydride (LAH) with 45. The hoped for reaction was:

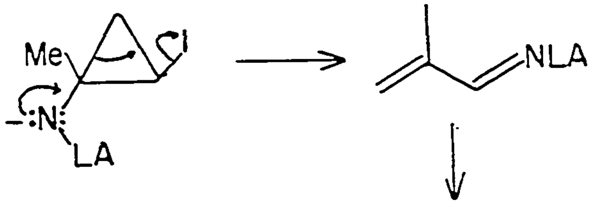


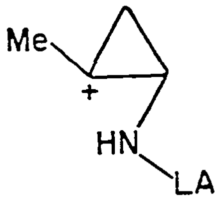
From the product observed in the attempted synthesis of 5-azabicyclo[2.1.0]pentane by LAH reduction, (see Part I, p. 28), it was felt that the Lewis acidity of species present would cause rearrangement of the system even if the system were stable in the absence of acid. The major product expected was isobutylamine assuming the azabicyclic system to react analogously to larger ring systems where the path is influenced by the production of the most stable carbonium ion. This is of course not necessarily the case.

It was hoped that LAH would allow the reduction to stable products to proceed at a faster rate than other side reactions such as polymerization. Also verification of isobutylamine as a product would establish the intermediacy of the ring system.

When the reaction was carried out, a VPC check indicated one major product and a minor product. Comparison of VPC retention times with authentic samples, and also with added known reference amines, showed the major product to be neither isobutylamine nor isobutenylamine. This was confirmed by the NMR of the hydrochloride of the crude amine mixture which was <u>ca.</u> 80% sec-butylamine hydrochloride as shown by comparison with an authentic sample.

This result then does not establish the necessary intermediacy of the ring system as another path is available for formation of sec-butylamine.



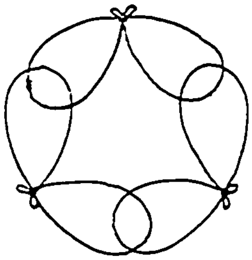


<u>50</u>

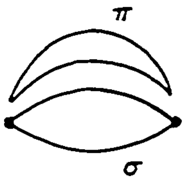
The result also does not, however, exclude the ring system formation since the system need not find the path through ion <u>50</u> to be the low energy one, or even indeed pass through an intermediate corresponding to ion <u>50</u> during rearrangement.

NMR Studies

A cyclopropane ring or aziridine ring is generally considered to have "bent" sigma bonds due to energy considerations. The angles between orbitals in cyclopropane has been calculated to be 106° and a depiction of the orbital overlap would be:[64]

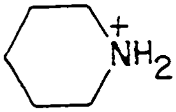
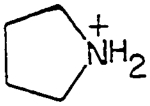
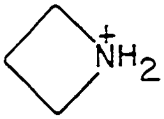
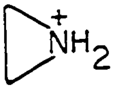


The resulting bonds are given the term "bent bonds" because of their asymmetry along the interatomic axes.[64] Since the bonds are not symmetrically distributed about the interatomic axes, they can be thought of as a sum of two wave functions, one of a sigma-bond type, i.e. cylindrically symmetrical about the interatomic axis, and one of a p-p type overlap that is however different in that the usual symmetry of the normal π-bond is not preserved.[65] Only one "half" of the function is present.



The presence of this π-function leads to a ring current in cyclopropanes.[64]

An experimental substantiation of this π-character of the bonds for aziridines is found in, amongst other things, a series of pKa measurements on ammonium salts.[66]

				
pKa	11.22	11.27	11.29	8.04

The authors explained the vastly different pKa of the aziridinium ion as a result of this π-character of the bonds in the aziridine ring.

It is also known that cyclopropane will react readily with bromine and acids in a manner quite similar to that of a double bond.[67] Cyclobutane or higher cyclic hydrocarbons will not react in this manner under the same conditions.

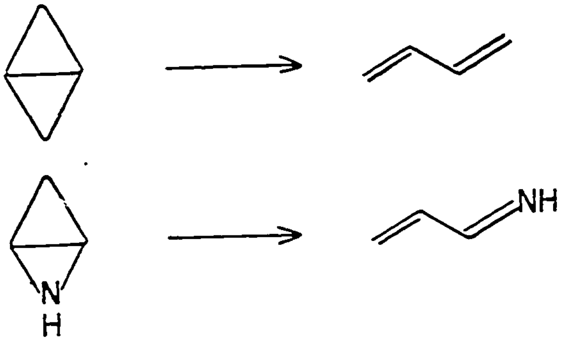
When the π-character hypothesis is applied to a bicyclic aza-compound, the bond of interest becomes the bridging or "zero" bond. This bond possesses certain π-character which will interact with the nitrogen lone pair electrons. The extent of interaction should be directly proportional to the π-bond character of the "zero" bond, *i. e.* a greater interaction should accompany an increase in π-character of that bond.

The greater the interaction, the greater the electronic destabilization that should occur based on analogy to the 2-aziridine system, 51, which is calculated to be antiaromatic by LCAO-MO-SCF calculations using Gaussian functions for the orbitals.[68]

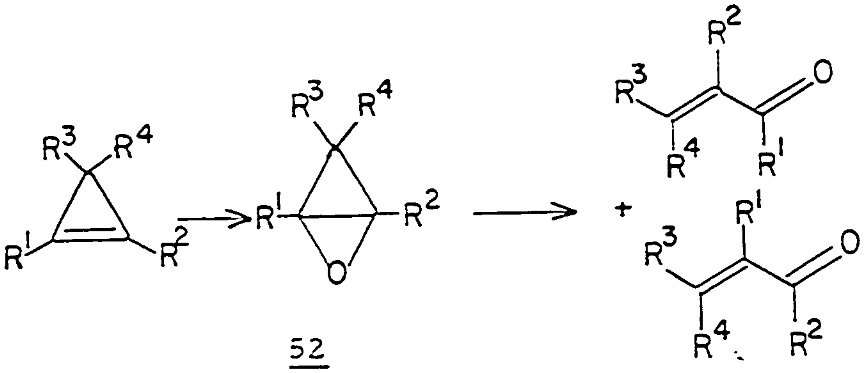
51

In the bicyclic case the "π-orbital" of the "zero" bond is not symmetrical and thus the direct correlation between the saturated bicyclic and the unsaturated monocyclic systems is not possible. The same sort of electronic interaction would, however, be expected to occur and result in increased destabilization with increasing π-character of the "zero" bond.

With the system under consideration, 2-azabicyclo[1.1.0]butane, based on experimental evidence, it is proposed that this interaction becomes of sufficient magnitude to cause considerable decrease in the energy of activation for rearrangement, making the product not isolable at ordinary temperatures; i.e. the ground state of the molecule is raised from what it would ordinarily be by an amount equal to the net electronic destabilization energy, making the rearrangement correspondingly easier. If the molecule is formed the rearrangement is proposed to proceed analogously to the thermal rearrangement of bicyclo[1.1.0]butane.



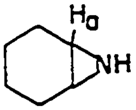
It is of interest to note that an analogous heterosystem, 52, a 2-oxabicyclo[1.1.0]butane has not been isolated in epoxidation attempts on cyclopropenes.[69] The products show the identical rearrangement of the bicyclic intermediate as proposed for the aza-system.



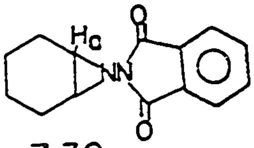
52

In order to test for a correlation in increase in π-bond character over other aziridine systems which results in the instability of the 2-azabicyclo[1.1.0]butane system, a series of compounds was synthesized and the NMR spectra of the bridgehead proton absorption values were compared.

Since there are electronic effects in the absorption position of the bridgehead protons due to the nitrogen substituent in the bicyclic systems, it was necessary to prepare compounds with the identical group attached to the nitrogen to cancel out these difficulties.



7.92 τ



7.30 τ

Three series of compounds were convenient for study since several of the compounds were already reported and missing members were easy to synthesize. Rees reported the synthesis of 7-phthalimidyl-7-azabicyclo-[4.1.0]heptane but gave no data.[20] It was necessary to synthesize the 6-phthalimidyl- and 6-carboethoxy-6-azabicyclo[3.1.0]hexanes and the 5-azabicyclo[2.1.0]pentanes. (see Experimental Section of Part I and Part II) The synthesis and purification of the N-phthalimidyl compounds was especially facile. The N-carboethoxy compounds were more difficult to purify since they were liquids.

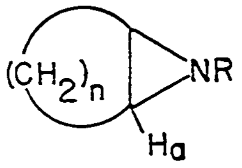
The NMR spectra were taken on a Varian T-60 in dichloromethane solution with internal TMS. The scale was corrected where necessary to agree with a separation of 320 hz between the solvent and TMS.

The bridgehead absorption values are shown in the table below. The full NMR spectra of the new compounds are recorded in the appropriate Spectral Section.

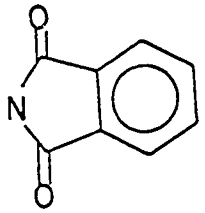
A graph of these values vs. ring size of the large ring is presented on page 149.

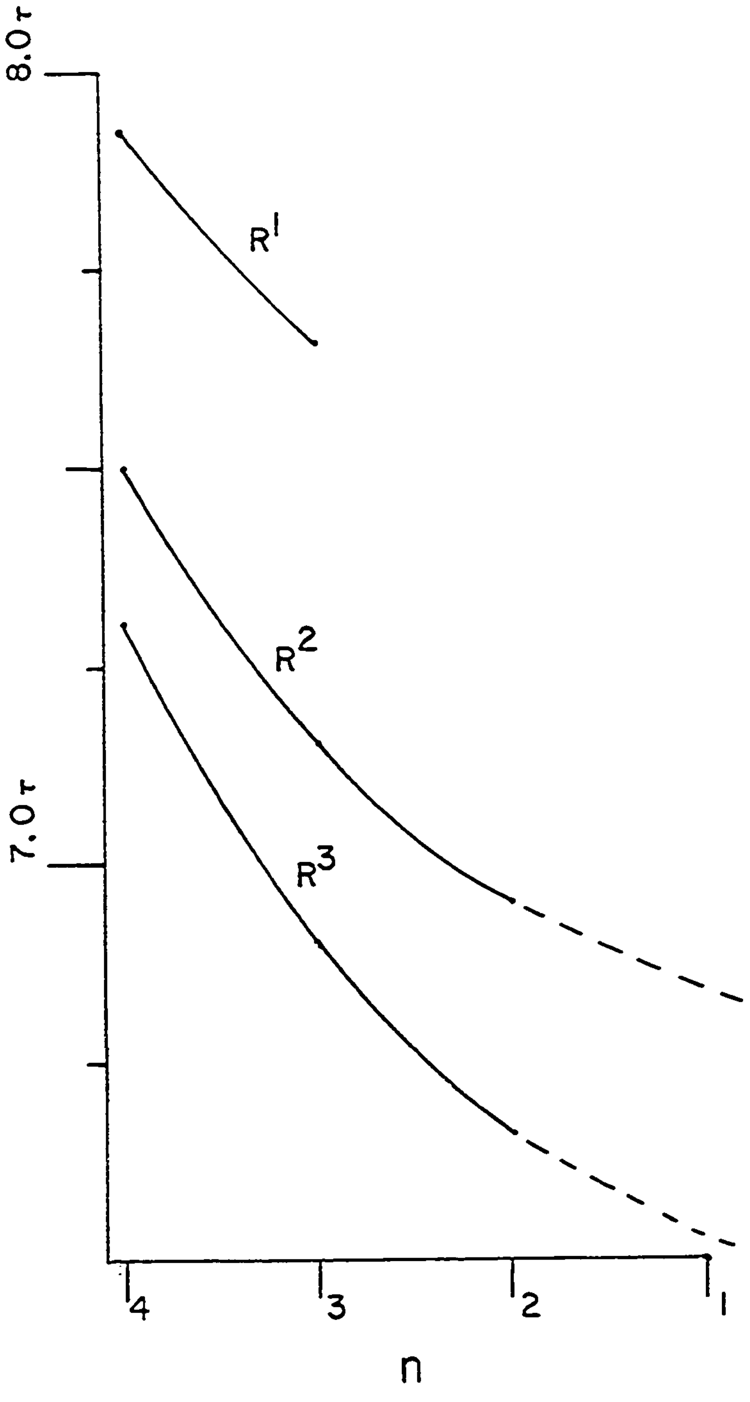
TABLE 6

Bridgehead Absorption Positions



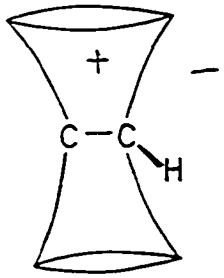
		$H_a(\tau)$	
n	R^1	R^2	R^3
4	7.30	7.50	7.93
3	6.89	7.15	7.65
2	6.66	6.95	

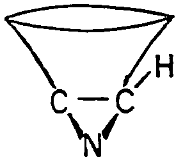
R^1 =  , R^2 = COOEt, R^3 = H


8.0τ
7.0τ
R¹
R²
R³
4
3
2
1
n

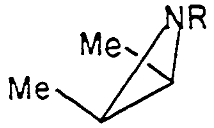
As the large ring of the bicyclic compound is contracted, a certain amount of rehybridization occurs. As this occurs the major change expected would be an increase in the s-character of the bridgehead C-H bonds and an increase in the π-character of the "zero" bond. The situation thus changes from one analogous to a hydrogen attached to an sp^3 hybridized carbon as in an alkane, to one more analogous, except for the asymmetry of the " π-bond", to a hydrogen attached to an sp^2 hybridized carbon as in an alkene.

By extending the graph and using the monocyclic aziridine, 53, as a standard of reference, one calculates a predicted π-character increase of 22% for the 2-azabicyclo[1.1.0]butane over the "normal" aziridine. This assumes 4.0 τ units to be the difference between a hydrogen on an sp^3 carbon and a hydrogen on an sp^2 carbon. In the case considered, however, the π-bond increase is most likely greater than the calculated 22% because of the different geometries present. In the case of the alkene, the hydrogen is well into the deshielding cone of the π-cloud. In the bicyclic compound, as can be seen above, the hydrogen is much closer to the boundary of and may even be in the shielding cone of the bond. This could lead to a difference of much less than 4.0 τ units for a 100% increase

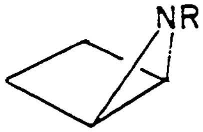




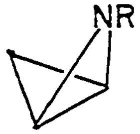
in π-bond character.



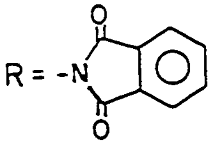
53



10a



54



Differences arising from different nitrogen invertomers need not be considered for the following reason. In the aziridine, 53, due to the cis-character of the methyl groups, one expects both the monocyclic system and the bicyclic systems to have the same stable N-invertomer, i. e. with the phthalimidyl group cis to the aziridine-ring hydrogens. Indeed in the literature report of 53[21] only one invertomer is present; also for 10a only one invertomer is observed in the NMR spectrum. Steric considerations dictate that the invertomers be the ones shown in the figure above. For an excellent review on the factors influencing nitrogen inversion barriers, the interested reader is referred to the one by S. J. Brois.[70]

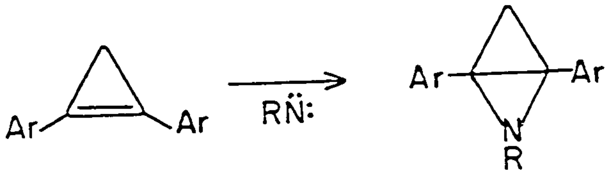
Since the amount of π-bond character of the C-C bond of the monocyclic aziridine is not known, the total π-character cannot be accurately estimated, only that a large increase is predicted in going to the 2-azabicyclo[1.1.0]butane system. This electronic factor of course is only one of the two factors influencing the stability of the system. The other to be considered is the added strain involved in making a [1.1.0]-system. The large difference in the strain energy of a [1.1.0] system even over a [2.1.0] system is reflected in the three hour $T_{\frac{1}{2}}$ temperature for bicyclo[2.1.0]pentane and bicyclo[1.1.0]butane which are 270° and 210° respectively.[17] The strain energy difference has recently been determined by calorimetric methods to be 10 kcal/mol.[71]

The electronic factor and the strain factor combine to make the 2-azabicyclo[1.1.0]butane system possess a higher ground state energy, apparently such that either the energy of activation for rearrangement was too low to allow observation of the compound even at temperatures as low as the 0° experimentally used, or that the ground state was too high allowing competing reactions to become the exclusive reaction mode.

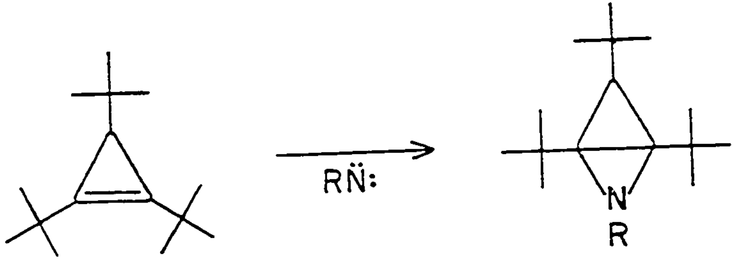
CONCLUSIONS

From the experimental evidence it is not possible to verify the production of the 2-azabicyclo[1.1.0]butane system. Comparison to the mode of reactivity of known compounds and spectral evidence, however, indicate the production of the system and subsequent rapid rearrangement to an α,β-unsaturated imine. It would thus seem that direct evidence for the existence of this system awaits the use and/or development of a good low temperature synthetic method.

Possible methods of room temperature stabilization might involve use of a cyclopropene substituted to provide electron withdrawal from the "zero" bond. Until very recently the desired 1,2-diarylcyclopropenes were unavailable.[72] A second possibility would be a cyclopropene substituted



with t-butyl groups to raise the energy of the transition state leading to rearrangement by having to have bulky t-butyl groups pass by each other.



The synthesis of the starting material would be quite difficult by presently known methods.

EXPERIMENTAL SECTION

The following chemicals were used in the experiments detailed in this section: methallyl chloride was a developmental sample from Shell Chemical Company; sodium azide, iodine monochloride, and cyanogen bromide were obtained from Eastman Organic Chemicals; sodium amide and phenylacetylene from Farchan Research Laboratories; lithium wire (1% sodium) and lithium aluminum hydride from Alfa Inorganics; and tri-n-butyltin chloride from Aldrich. Lithium aluminum hydride was also obtained from Metal Hydrides Corporation. All other chemicals were reagent grade from various suppliers.

Petroleum ether (pet. ether) was commercial 30°-60° material. Acetonitrile was dried by refluxing 24 hr. over and distilling from calcium hydride, then stored over Linde molecular sieves, type 4Å. Ether, THF, and 1,2-dimethoxyethane (glyme) were predried over sodium wire, decanted into a clean flask and refluxed over and distilled from lithium aluminum hydride, the THF and ether being kept at reflux in a suitable apparatus and drawn off as needed. Dichloromethane was refluxed 24 hr. over and distilled from phosphorus pentoxide, then stored over Drierite. Triethylamine was refluxed 16 hr. over and distilled from barium oxide.

All melting points are uncorrected. Those below 210° were taken on a Thomas Hoover Uni-melt apparatus, those above on a heated stage similar to a Fisher block.

VPC analyses were carried out on a Varian Aerograph with the column specified using a helium flow rate of 60 ml/min.

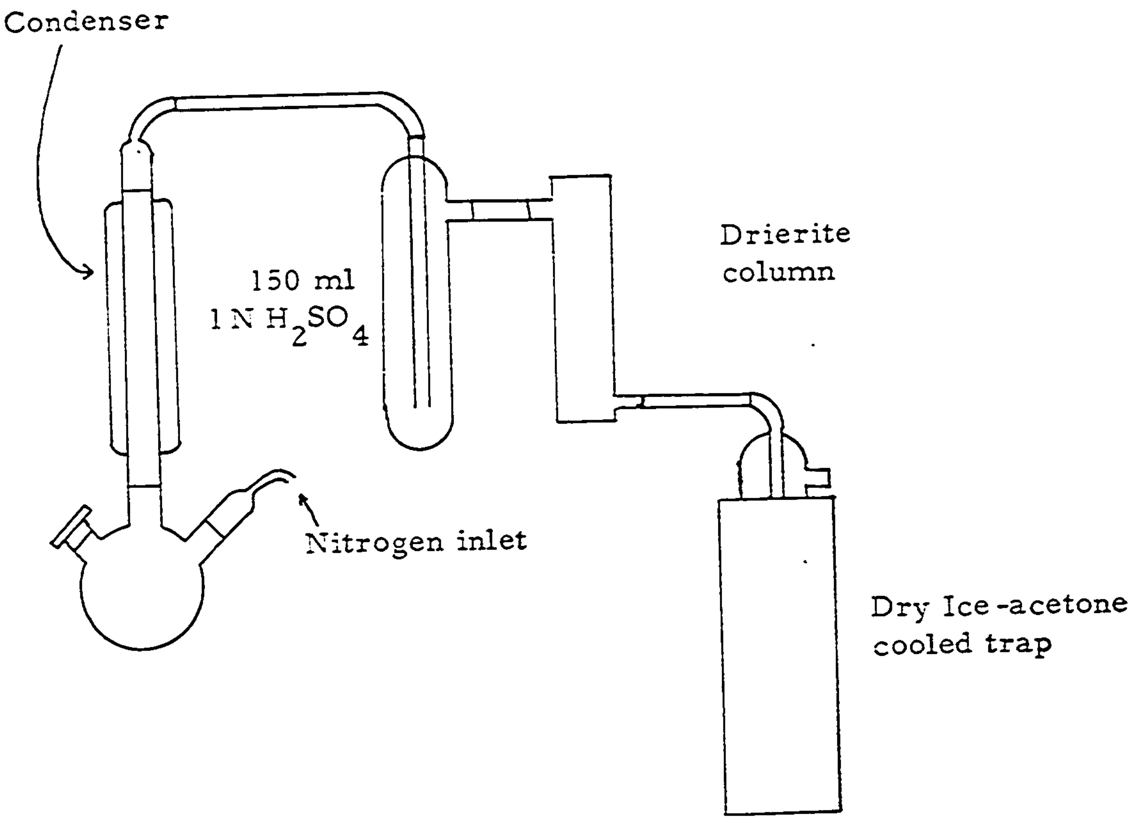
NMR spectra were taken on Varian HA-60, A-60, and T-60 spectrometers with internal references as indicated, and recorded as τ values in ppm. UV spectra were taken on a Cary Model 14, and IR spectra on Perkin-Elmer Model 137 or Model 225 spectrophotometers. Mass spectra were taken on an AEI MS-9 mass spectrometer at 70 eV ionizing voltage.

Methycyclopropene.[54] - Methallyl chloride, 50 ml (46.2 g, 0.51 mol), was dissolved in 100 ml dry THF and placed in the flask of the apparatus shown on the following page. Sodium amide, 20 g (0.50 mol), was added as a slurry in 60 ml dry THF. After stoppering, the flask was heated and magnetic stirring begun along with a slow nitrogen flow. Upon gentle reflux of the solution gas evolution was observed. The reaction took about 12 hr. to go to completion and was noticed by no further decrease in the pot solution volume. The trap liquid was purified by two trap-to-trap distillations with a Dry Ice-acetone bath. Yield 5-7 g (20-26%). Using impure methallyl chloride the yield was 30-40% and the reaction time was *ca.* 6 hr.

Reaction of Phenylacetylene With Ethyl Diazoacetate. - Phenylacetylene, 2.0 g (20 mmol), was mixed with 2.0 g (18 mmol) of ethyl diazoacetate[73] in 40 ml of dry carbon tetrachloride. The reaction flask was exposed to sunlight for 10 da. (*ca.* 12 hr. each day) The yellow

FIGURE 2

METHYCYCLOPROPENE APPARATUS



The flask is 500-ml. All tubing must be rubber (no Tygon!) and is wired tight to the glass tubing to prevent leaks.

solution gradually turned orange and then red-brown. IR spectra showed a decrease in the diazo peak but not in the C-H acetylene peak. The solution was evaporated to a thin red-brown liquid. The NMR spectrum showed phenylacetylene and a component with a singlet at 6.4 τ and ethoxy protons.

N-Benzenesulfonoxyurethane (40). - The procedure for *para*-nitro-N-benzenesulfonoxyurethane[56] was used except that the appropriate molar amount of benzenesulfonyl chloride was used in place of *para*-nitrobenzenesulfonyl chloride.

The product was a yellow syrupy liquid which could be easily crystallized by mixing thoroughly with a small amount of carbon tetrachloride. For a preparation with 21 g (0.20 mol) of N-hydroxyurethane,[56] 24 ml (0.195 mol) of benzenesulfonyl chloride, and 19 ml (0.135 mol) of triethylamine, the syrup was mixed with 150 ml of carbon tetrachloride and filtered with suction. The white crystals were recrystallized from *ca.* 50 ml of benzene. The yield was 23.5 g (66%) after a second recrystallization from benzene, m.p. 88-93°. IR spectrum ($CHCl_3$) showed peaks (cm^{-1}) at 3300 and 1730. NMR (acetone, τ in ppm, area): -0.20 (s, 1), 2.11 (m, 2), 2.40 (m, 3), 6.00 (q, J = 7, 2), and 8.93 (t, J = 7, 3). Mass spectrum 245.0346, calc. for $C_9H_{11}NO_5S$, 245.03577. Major fragments were observed at 141 ($C_6H_5O_2S^+$), 94, 77 (base peak, $C_6H_5^+$), 65, 62, 45 (EtO^+), 44 (CO_2^+), 43 ($CONH^+$), and 31 (HNO^+). A metastable peak appeared at 42 corresponding to the transition 141 to 77, loss of SO_2 from $C_7H_6SO_2^+$.

The material should be stored in the cold (below 0°) in a taped bottle. In this condition a sample of 18.6 g after 14 mo. storage was recrystallized to give 14.5 g, m.p. 85-93°.

Reaction of Methylcyclopropene With Carboethoxynitrene Generated In Situ. Run 1. - Ten ml of impure methylcyclopropene (80 mmol) was dissolved with 2.0 ml (15 mmol) of dry triethylamine in 20 ml of dry ether. The flask was placed in a salt-ice bath and magnetic stirring begun. N-benzenesulfonoxyurethane, 5.2 g (20 mmol) was added in portions over a few minutes and a reflux condenser attached. After stirring overnight, the heavy white precipitate was filtered off, weight 5.0 g (97%) of triethylammonium benzenesulfonate (by NMR in D_2O). A portion of the yellow filtrate was evaporated on a Rotovac, the resulting oil showing urethane carbonyl absorptions in the IR spectrum. A VPC of the oil on 10% Carbowax at 100° showed six peaks, one major, two minor, and three trace. None of the peaks were starting materials.

The rest of the original solution was distilled. The material collected was examined by VPC and consisted of ether and THF. A vacuum was applied and the viscous yellow distillation residue did not distill at 2 torr and 100°. The pot residue was treated with 1.2 N potassium hydroxide in methanol and after a short time 0.4 g of white crystals precipitated and were filtered by suction. The material was recrystallized two times from methanol, m.p. >210°.

Anal. Found: C, 36.38; H, 2.76; residue (gray) 41.93.

Run 2. - The experiment was repeated using the same amounts except for 1.0 g (19 mmol) methylcyclopropene. The results were essentially identical to those above. A TLC of the crude reaction mixture showed the presence of a large amount of diethyl hydrazodicarboxylate.

Run 3. - Methylcyclopropene, 5.5 ml (80 mmol), and 1.2 ml (8 mmol) of triethylamine were stirred together with Dry Ice cooling and 2.1 g (8 mmol) of N-benzenesulfonoxyurethane in 15 ml dry ether was added over several hours with stirring. After overnight stirring followed by filtration to remove precipitated salt, the filtrate smelled of triethylamine. A preparative VPC separation of 300 l gave three fractions (10% Carbowax, 62°, 3/8" x 12'). The third fraction showed NMR peaks for THF and a component with peaks (CCl$_4$): 3.52 (m, 1), 7.90 (d, 3), 8.47 (d of d, J = 1.5, J = 2.5, 1), 8.95 (s, 1), 9.02 (d, 2), 9.45 (m, 2), 9.92 (m, 2). IR spectrum 1800 cm^{-1} (thin film). Evaporation with a nitrogen stream gave a small amount of thick liquid, NMR spectrum (CDCl$_3$): 9.6 (br m) plus ethoxy peaks. An IR spectrum showed a urethane carbonyl but no N-H absorption. Preparative VPC separation on SE 30, 5%, of 3 ml of filtrate gave: methylcyclopropene, 2.1 min.; ether, 2.7 min.; THF, 7.7 min.; triethylamine, 13.2 min.; minor broad lump, 25.4 min. (not collected), and a fraction identical in NMR spectrum to that for the Carbowax separation (see above) but with no THF present, 32.3 min. An attempted MS-9 analysis gave the highest peak at 410 m/e (magnet range 5) with other major peaks at (P to P+1 matching): 263, 219, 145, 93, 91, and 77.

Reaction of Methylcyclopropene With N-phthalimidylnitrene In Situ. - N-aminophthalimide,[47] 1.6 g (10 mmol), was stirred in 65 ml of dry dichloromethane with 3.2 g (50 mmol) of potassium hydrogen phosphate with salt-ice cooling. When the temperature reached -5°, slow portion-wise addition of 4.4 g (10 mmol) of lead tetraacetate was carried out over 10 min. The temperature rose to a maximum of 1°. After 15 min. additional stirring, the salts were filtered off by suction leaving a yellow filtrate which quickly turned deep red on short exposure to air. Evaporation produced a gooey red solid. Attempted recrystallization from ethanol and ethanol-pet. ether failed. An attempted sublimation at 10^{-2} torr and 60° failed. Sodium fusion showed the presence of lead.

Six-tenths of a gram of the red solid was Soxhlet extracted with ether giving 0.25 g of slightly yellow crystals. NMR spectrum (DMSO-d_6): 2.2 (s, 4), 6.7 (br s, 1) and was identical to that for phthalimide. TLC examination on silica gel with several elution systems showed only one spot.

NMR Study of the Reaction of Methylcyclopropene With N-phthalimidylnitrene In Situ. - Methylcyclopropene, 0.8 g (15 mmol) was diluted with 1 ml of dry dichloromethane, transfered to a 50-ml flask precooled in Dry Ice-acetone, and 0.817 g (5.05 mmol) of N-aminophthalimide was added followed by 3.46 g (5.0 mmol) of lead tetrabenzoate[22] in

11 ml of dry dichloromethane. The mixture was swirled for 1 min. and a 0.5 ml aliquot was withdrawn and placed in an NMR tube precooled in Dry Ice-acetone.

The NMR tube was transfered to the probe of an HA-60 spectrometer at -50° and an initial NMR spectrum was taken. After 0.5 hr. at -50° no change was seen in the spectrum. The sample was warmed to -30° and observed for 0.5 hr. after which no change was noted. The sample was then warmed to 30°. The time lapse of the observation at -30° and 30° was ca. 30 min. The 30° spectrum exhibited a new singlet at 7.73 but no additional peaks between the 7.90 τ and 9.02 τ peaks of methylcyclopropene or above the 9.02 τ peak up to 10τ. The flask mixture was stored overnight in Dry Ice-acetone and another aliquot was removed for NMR examination the next day.

An initial NMR spectrum at -50° showed no apparent oxidation overnight. The temperature was raised to -10° and held there for 0.5 hr. Little or no change was observed in the spectrum so the sample was warmed and held at 0° for 0.5 hr. A spectrum revealed the appearance of a peak at 7.73 τ (s) which after 20 min. had increased. The sample was quickly warmed to 10° and a spectrum taken 10 min. from the second 0° spectrum. The singlet appeared not to have increased any further in size. No other peaks were observed to increase or decrease between the 7.90 and 9.02 τ peaks of the olefin or above its 9.02 τ peak.

The previous days sample upon examination showed the 7.73 singlet apparently absent. Several new peaks appeared and are given with their approximate integrations (τ): 7.2 (m, 2), 8.0-8.4 (m, 18), 8.4-8.6 (m, 5), and 8.85 (m, 20). The volume of thick material noted in the bottom of the tube was about 1/8th the total solution volume.

The remainder of the reaction mixture was allowed to warm to room temperature with vigorous stirring. The light yellow solution became dark orange. An IR spectrum of the crude solution showed peaks at (cm^{-1}) 1785 (m), 1735 (s, br), 1705 (s), and 1605 (s). A sample (ca. one-half of the solution) complete with suspended matter was dissolved in 35 ml of methanol, 50 mgm of 5% Pd• C was added, and the whole hydrogenated at atmospheric pressure. Initial uptake was 0.9 ml/min. dropping rapidly to 0.17 ml/min. and slowly declining to zero. The total uptake was 56.4 ml (2.32 mmol). The solution was filtered to remove catalyst and suspended solid matter and evaporated to a semi-solid dark material. The material was taken up in chloroform and shaken with a few drops of water. A white precipitate, 53 mgm, appeared which was identified as phthalimide by TLC.

The dark red filtrate was evaporated to dryness and dissolved in 4 ml of THF. One half of the solution was applied to two preparative TLC plates and eluted with 5:1 pet. ether-acetone. The plate was visualized under a UV blacklight and cut into six bands as shown in the table on the following page.

An NMR spectrum was taken of each fraction as was except band 4 which was dissolved partly in carbon tetrachloride, filtered, and recrystallized from carbon tetrachloride followed by recrystallization from water, m.p. 118-21° (lit. for benzoic acid 122°). Band 3's composition was infered from the data on band 4. The results are shown in Table 8 on the following page. The 0.8 spot was the only component of the recrystallized band 4. The 0.6 spot was phthalimide by TLC comparison to authentic material.

Reaction of Methylcyclopropene With Hydrazoic Acid. - The entire reaction was carried out behind a sturdy blast shield in a good fume hood. Hydrazoic acid,[58] 0.1 mol in 100 ml of ether was stirred and cooled in a salt-ice bath in a flask equipped with a thermometer. Methylcyclopropene,

TABLE 7

TLC-Plate Bands

Band	R_f	UV	Weight	TLC[a]
1	1.0	wf[b]	ca. 10 mgm	1.0, 0.95
2	1.0 - 0.8	--	ca. 10 mgm	0.95, 0.8
3	0.8	wf	37 mgm	0.8, 0.6
4	0.8 - 0.3	--	252 mgm	0.8, 0.6
5	0.3	a[c]	35 mgm (yellow)	0.45, 0.3
6	0.3 - 0.0	wf	(d)	0.45, 0.3 (heavily streaked)

[a] 3:1 pet. ether-acetone on silica gel.

[b] White fluorescing under UV blacklight.

[c] Absorbing under UV blacklight.

[d] Too gooey to weigh. More than band 5, however.

TABLE 8

Protons Present in TLC-Plate Bands

Band	Aliphatic	Benzoyl	Phthalimidyl
1	x	x	none
2	x	x	none
4	none	x	none
5	trace	x	x
6	trace	x	x

6.2 ml (0.1 mol), was added in small portions with no temperature rise noted. After stirring for 5 hr. the solution was yellow and cloudy. Stirring of the stoppered flask was continued overnight.

The next day the solution was washed with a saturated salt solution that was 5% in potassium hydroxide. After drying the ether layer over magnesium sulfate, it was gently evaporated to a yellow liquid. A VPC showed six or seven components.

The material was distilled at aspirator vacuum with a 100° oil bath. Most of the liquid rapidly turned into a thick dark red oil. A few drops of yellow distillate were obtained which showed several peaks attributable to 1-azido-1-methylcyclopropane in the IR spectrum but also peaks at (cm^{-1}): 1695, 1667, 1640 and 1560. A VPC of the yellow liquid showed ten components, the largest one of which was 45% of the total mixture, the next one constituted 22% of the total peak areas. An attempt to make a phenyurethane of the oil gave crystals after washing with ligroin and 50% ethanol that showed only one sharp peak in the phenyl region in the NMR spectrum, m.p. 231-4° (literature for 1,3-diphenyl urea, 237-7.5°)

1-Azido-2-iodo-1-methylcyclopropane, (45). - The literature procedure for 0.1 mol preparations of iodonium azide was followed.[26] To the orange iodonium azide solution was added 5.4 gm (0.1 mol) of methylcyclopropene over a period of 3 hr. Additions should not exceed 0.5 ml at a time as the reaction is very exothermic. The temperature was maintained below 10° with salt-ice cooling. After stirring overnight, the mixture was worked up according to the literature report for iodoazides. The crude product was run through an alumina column (Woelm neutral) with pet. ether-ether (1:1 by volume) eluant. The yellow fractions were evaporated to a yellow oil, yields 9.9 g (44%) to 18.9 g (85%); average of several preparations, 70%. The reaction could also be run successfully on a 0.05 mol scale. Elution of the yellow oil through a silica gel column with pet. ether (200-325 mesh, 1 x 2 cm) gave a colorless product which discolored in air quickly. The NMR spectrum (CCl_4) showed peaks: 7.20 (d of d, J = 6, J = 10, 1), 8.37 (s, 3), 8.43 (d of d, J = 8, J = 10, 1), 9.18 (d of d, J = 6, J = 8, 1). An IR spectrum (thin film) showed a peak at 2050 cm^{-1} (s). A mass spectrum showed a parent peak at 222.9603, calc. for $C_4H_6N_3I$: 222.9608. The base peak was 127 (I^+) with a major fragment at 96 (P-I, $C_4H_6N_3^+$). Very few other peaks were present in the spectrum. Sodium fusion was positive for nitrogen and iodine.

Reaction of 1-Azido-2-iodo-1-methylcyclopropane With Tributyltin Hydride. Run 1. - The iodoazide, 2.2 g (10 mmol), was stirred in a flask heated to 30° and 2.9 g (10 mmol) of hydride[74] reagent slowly dropped in. The reaction was very exothermic and the temperature rose to a maximum of 70°, staying mostly at about 50°. Gas evolution was rapid, 180 ml being collected in 4 hr. The dark solution was stirred overnight without heating. When 50 ml of the gas was removed and ignited, it burned with a yellow flame. 130 ml of the gas mixed with 120 ml of air was taken into a gas bulb and transferred *via* vacuum line connections to an IR gas cell (10 cm path length). The IR showed peaks at (cm^{-1}): 2960, 2920, 2870, 1460, 1385, and 1010.

A small amount of liquid was collected by vacuum separation and caught in a liquid nitrogen-cooled trap. Almost all of it evaporated at room temperature.

The pot residue on standing deposited crystals that were dirty brown. They were insoluble in common organic solvents and could not be sublimed at 80° and 0.01 torr even after several days. The remaining solution showed a strong azide peak in the IR spectrum.

Run 2. - The iodoazide, 2.2 g (10 mmol), was stirred in a flask packed in Dry Ice and 2.9 g (10 mmol) of the hydride was dropped in over 4 hr. Gas evolution was not detected over several hours. The mixture was allowed to stir 3 days more packed in Dry Ice. IR spectra taken daily showed the Sn-H peak slowly decreasing. The flask was packed in an ice-salt bath and stirred two days more after which the stoppered flask was transfered to a refrigerator at -20°. The mixture upon warming to room temperature evolved gas. An IR check after 14 days total reaction time showed no Sn-H peak. The mixture was allowed to warm to room temperature but no gas evolution was observed. Vacuum separation as before gave a small amount of clear colorless liquid with a strong ammonia smell which dissipated upon warming to room temperature. The residue, 50μl, showed a small amount of ether, THF, and NMR peaks at (τ): 8.5 (s, 3), 9.13 (m, 2), 9.33 (m, 2).

A small sample of pot residue was run through a silica gel column with pet. ether-ether (9:1) and several 1 to 1.5 ml fractions were collected. TLC indicated the first and second fractions to consist of one pure component. An IR spectrum showed the presence of a tributyltin grouping identical to the spectra of tributyltin hydride and chloride from 1600 to 670 cm^{-1} and no azide peak. A sodium fusion showed a negative test for halogen and a positive test for tin. Attempted mass spectral analysis gave no peaks beyond ca. 200 m/e strong enough to be distinguished from background of the instrument. The sixth fraction from the column showed a medium peak at 2070 cm^{-1} and peaks for a tributyltin moiety in addition to several others. Sodium fusion was positive for iodine and tin but negative for nitrogen.

An IR spectrum of the crude pot residue revealed a peak at 1640 cm^{-1} (m) which had been observed to grow slowly during the course of the reaction.

Run 3. - The iodoazide, 2.2 g (mmol), was stirred in a pear flask in an ice bath, with a dropping funnel fitted was a gas outlet tube leading to a gas collection apparatus attached. A thermometer was placed in the side neck of the flask and when the temperature reached 2°, addition of 2.9 g (10 mmol) of tributyltin hydride was carried out over 20 min. Small bubbles were observed in the reaction mixture after an additional 30 min. An IR spectrum at 1 hr. indicated a large amount of hydride still present (monitored peak at 1803 cm^{-1}). The solution was stirred an additional two days, packed in ice, after which a total of 156 ml of gas was collected. An IR spectrum of the mixture showed no Sn-H absorption. The orange-red solution was separated by vacuum and approximately 0.5 ml of a clear, colorless liquid with a strong ammonia smell was collected in the liquid nitrogen-cooled trap. Upon warming to room temperature the trap liquid reduced in volume and the ammonia smell was replaced by that for 1-azido-1-methylcyclopropane synthesized from the hydrolysis of the lithium reagent of 45 (see page 169). An IR spectrum revealed the azide to be impure.

An IR spectrum of the pot residue showed an azide present and also a peak at 1640 cm^{-1} (m). A TLC with pet. ether on silica gel showed spots at 1.0 (major), 0.5 (iodoazide), and one at the origin.

Reaction of 1-Azido-2-iodo-1-methylcyclopropane With Magnesium.

In Ether. - Crude iodoazide, 45, 2.2 g (10 mmol), was stirred in 55 ml of dry ether with 0.25 g (10 mmol) of magnesium turnings under nitrogen. A few crystals of freshly sublimed iodine were added to initiate the reaction. After stirring over the weekend the solution was poured into 200 ml of water with 10 ml of 6 N sulfuric acid added to decompose excess magnesium. The solution was extracted two times with ether, the combined ether extracts washed with 10% sodium bicarbonate, the ether dried over magnesium sulfate and evaporated to a small volume, giving 1.3 g of recovered iodoazide of better purity (IR and NMR) than starting material.

In THF. - A second run was attempted with the same amounts except it was run in 50 ml of dry THF. After stirring two days, 0.25 g (100%) of magnesium was recovered by filtration and washing with ether.

Reaction of 1-Azido-2-iodo-1-methylcyclopropane With Lithium.

Run 1. - Crude 45, 2.2 g (10 mmol), was dissolved in 15 ml of dry THF and added under nitrogen slowly to 10 ml of THF stirred with 0.1 g (10 mmol) of lithium wire in small pieces. A vigorous reaction ensued and the mixture was cooled with an ice bath. After the reaction was complete, ca. 45 min., the smell of methylcyclopropene was evident above the solution. The mixture was poured into water and extracted with ether. The ether extracts were combined and dried over magnesiumsulfate. Evaporation gave a dark red liquid which gave a negative sodium fusion test for halogen. A VPC on 5% SE 30 at 105° showed one major component and five minor ones. The material was placed on an alumina column and eluted with pet. ether-ether (1:1 by volume). The yellow fractions were evaporated and a VPC check on 5% SE 30 at 108° showed one major product, which was not starting material. Two impurities were present totaling ca. 25% of the mixture.

Run 2. - A rerun of the reaction using 1.5 ml (0.067 mol) of iodoazide with 1.0 g (0.1 mol) of lithium in 25 ml of dry THF with the flask packed in Dry Ice using the same workup gave the same product by VPC retention time comparison.

The combined yields were 0.8 g (49%).

Run 3. - Iodoazide, 5.5 g (25 mmol), was treated with 0.5 g (50 mmol) of lithium wire in 50 ml dry THF. The reaction was packed in Dry Ice. After 20 hr. reaction time the mixture was worked up as before. The workup yielded 2.2 g of crude product with some solid present. Upon column chromatography, only a few drops of yellow azide were obtained.

Reaction of Methylcyclopropene With Bromonium Azide In Situ, (46a, 46b). - This reaction was carried out behind a sturdy blast shield in a good fume hood. Sodium azide, 32.5 g (0.50 mol), was stirred in 100 ml of dichloromethane and 25 ml of water added. The flask was fitted with a thermometer and placed in a salt-ice bath. Concentrated hydrochloric acid (21 ml) was added dropwise followed by 8.0 g (50 mmol) of bromine added over 5 min. with stirring. (The temperature remained at 5°) After stirring 1 hr., the mixture was poured into a separatory funnel and the bottom dark red layer separated into a three-neck 200-ml round bottom flask in a salt-ice bath fitted with a thermometer.

When the temperature reached -2° a solution of 4.0 ml (58 mmol) of methylcyclopropene in an equal volume of dichloromethane was added portionwise not allowing the temperature to exceed 15°. The reaction was very exothermic. The pot mixture gradually lightened during the addition and decolorized completely at the end of the olefin addition. The mixture was stirred 2 hr. more after which the light yellow solution was washed with 25 ml of 5% potassium hydroxide in 100 ml of water in a separatory funnel followed by 25 ml of 5% potassium hydroxide. The aqueous solution was found (Hydrion paper) to be pH 11. (It should be at least slightly basic to avoid any hazard from hydrazoic acid). The light colored organic layer was evaporated to a yellow liquid, 4.7 g (53%). The material was stored in a refrigerator as its carbon tetrachloride solution darkened markedly at room temperature over several days.

A TLC on silica gel with pet. ether-ether (1:1 by volume) showed spots at 0.95, 0.8, and 0.6 with a small spot at the origin. The 0.8 spot was major; the 0.6 spot was very small.

The compound detonated in a syringe upon VPC injection into a 220° port.

An IR spectrum of the crude adduct is shown in the Spectral Section. The NMR (CCl_4) showed peaks at: 6.55 (d of d, J = 4.5, 8), 7.43 (m), 8.20 (s), 8.27 (s), 8.57 (t, J = 8), 8.83 (m), 9.13 (d of d, J = 4.5, 8). No integrations were possible due to instrument malfunction. The singlet at 8.27 was 1/3rd the height of the 8.20 singlet. Other small peaks were also present.

Reaction of Bromonium Azide Adduct With Tributyltin Hydride. - Crude bromoazide, 46a, 46b, 1.7 g (9.7 mmol), was stirred in a salt-ice bath and tributyltin hydride,[37] 2.6 ml (10 mmol), dropped in over a 1 hr. period. After several hours the bath was removed and the flask, loosely stoppered with a cork, was placed in a refrigerator at -18°. Periodic IR spectra indicated a slow decrease in the Sn-H peak. After eighteen days reaction time no Sn-H peak was noted. The mixture was separated by vacuum as with the reaction of the iodoazide, 45, with the hydride. (see page 166). A strong ammonia smell was present over the cloudy, colorless trap liquid. After warming to room temperature the ammonia smell dissipated and the residue, 0.3 g, showed spots on TLC (silica gel, pet. ether-ether, 9:1) at 0.8 and 0.65 (both small) plus a heavy streak to 0.55 from the origin.

A VPC on 5% SE 30 at 100° showed thirteen components, six of which may be considered to be in trace amounts. Eight peaks occurred together with an area of 40 units, 20 of which belonged to the major peak of that group. The major peak was separated from the group and had an area of 45 units.

Pyrolysis of Semi-purified 1-Azido-1-methylcyclopropane. - The azide, 0.1 g, was dissolved in 25 ml of dry 1,2-dimethoxyethane (glyme) and refluxed gently for 3 hr. An IR spectrum of the orange solution against glyme did not give good results since the glyme blanks out a large portion of the spectrum. Peaks were however noted at 3450 and 1610 cm^{-1}. A TLC on alumina using pet. ether-ether (1:1 by volume) gave no spot movement at all. Starting material moves with the solvent front under the same conditions.

The solution was distilled and fractions to 60° collected. Their analysis by VPC showed only ether and glyme. The pot residue after standing was treated with benzoyl chloride in pyridine-benzene. The only product isolated was benzoic anhydride (confirmed by NMR and melting point). No amine smell was detected but the pot residue when treated with hydrogen chloride gas in ether gave an oily precipitate. The precipitate was gooey even after long drying in a vacuum desiccator and was not further analyzed.

Photolysis of Semi-purified 1-Azido-1-methylcyclopropane. - The crude product, 0.7 g, from the hydrolysis of the lithium reagent of 45 was dissolved in 100 ml dry ether and placed in an ice-cooled photoreactor and irradiated with a 450 watt hi-pressure Hanovia lamp type 679-1 through a quartz jacket. Nitrogen evolution ceased at 30 ml (theoretical, 161 ml) after 2 hr. with the formation of a heavy yellow coating on the jacket surface.

The solution was distilled through a platinum gauze column, the only low boiling fraction collected being ether. The thick pot residue had no amine smell nor did the original photolysis solution.

Tosyl azide. - Tosyl azide[31] was prepared according to the literature except that the product oiled out upon pouring into water instead of crystallizing. The oil and water were extracted with ether and the ether evaporated after drying over sodium carbonate. The yellow oil was crystallized by cooling in an ice bath followed by vigorous stirring and scratching with a spatula. The mass was broken up and filtered through a Büchner funnel precooled in ice and a filter paper wetted with ice water. The liquid in the filter flask was returned to a beaker in an ice bath and crystallization was induced with a product crystal. This was filtered as before through fresh filter paper, the process being repeated until the liquid no longer crystallized. Yield 31.0 g (86.5%).

Reaction of Tosyl Azide With Methylcyclopropene. Run 1. - Methylcyclopropene, 1.0 g (18 mmol), was mixed together with 2.6 g (13 mmol) of tosyl azide in 5 ml of carbon tetrachloride and sealed in a stoppered pear-flask with beeswax. After less than 0.5 hr. the stopper blew out, and one-half of the mixture was lost. The flask was stoppered loosely at room temperature and after two days 2.0 g (36 mmol) of the olefin was added. An IR spectrum failed to show any azide present after an additional day. An NMR spectrum of an evaporated aliquot of the solution showed broad absorptions. A dark oil was evident in the bottom of the flask which showed peaks in the IR spectrum at 3250, 1700 and 1600 cm^{-1}. A portion of this oil purified by column chromatography showed no aryl protons in the NMR spectrum, only absorptions at 8.0, 9.0, and 9.1-9.8 .

Evaporation of the reaction solution gave two immiscable oils an aliquot of which when run through a silica gel column (pet. ether-ether, 1:1) gave a yellow liquid showing one major spot by TLC in addition to 3 to 5 minor spots. An attempted molecular distillation at 1.5 torr and 90° gave a large amount of tarry residue and a few drops of a yellow liquid which showed a strong peak at 1660 cm^{-1} that was not present prior to distillation. An NMR spectrum showed no protons below 7 .

The column elutant was changed to benzene-ether (1:1) and the yellow fractions evaporated to a small gooey mass. TLC showed the major component to be tosyl amide by comparison with authentic material.

The remainder of the oil mixture was separated by preparative TLC (silica gel, pet. ether-ether 1:1). All the bands desorbed from the plate formed crystals and except for tosyl amide could not be matched by TLC to any components of the column separation. IR spectra of the bands isolated did not indicate the presence of a vic-triazoline.[19]

Run 2. - Tosyl azide, 4.95 g (25 mmol), was dissolved in 15 ml of carbon tetrachloride in a 50-ml flask. The flask, fitted with a long condenser having a nitrogen inlet tube on the top, was placed in a large Dewar flask, packed in ice, and magnetic stirring begun through the bottom of the Dewar. Methylcyclopropene, 8.8 ml (140 mmol), was added according to the following schedule: 1.8 ml, first day; 2.0 ml, second day; 1.0 ml, third day; 2.0 ml, eleventh day; 2.0 ml, thirteenth day. The ice in the Dewar was replenished when necessary. IR spectra showed the azide peak decreasing and a peak at 1540 cm^{-1} slowly growing. On the twentieth day a small azide peak was still present so the flask was removed from the bath and placed in a -20° refrigerator for ten additional days.

After sitting in the refrigerator a thick film was noted on the surface of the reaction mixture. The film was evaporated on a Rotovac to a dry, orange, flakey material. Sodium fusion gave positive sulfur and nitrogen tests and a negative halogen test.

A sample of the crystals placed on a Florisil column were eluted with ether followed by ether-chloroform (1:1). The fractions collected gave essentially identical IR spectra except for the last small ether-chloroform fraction. The amount of the material coming through the column was considerably smaller than that put on. An NMR of the combined identical fractions showed two broad peaks at 8.75 and 9.1 with an extremely small signal for the aromatic protons. The dissimilar fraction showed aromatic protons but could not be concentrated enough for a good spectrum. It was later shown by TLC to be tosyl amide by comparison with an authentic sample.

A sublimation of the original flakey material at 65° and 0.006 torr gave after long running several mg of white crystals, m.p. 123-4°. By comparison of IR spectra and TLC data the material was identified as tosyl amide.

Evaporation of the remaining liquid from the reaction at 0.1 torr with a trap immersed in liquid nitrogen in between the flask and the vacuum line gave several ml of liquid with the characteristic smell of methylcyclopropene. An NMR spectrum showed the presence of the olefin, THF (an olefin contaminant), and some low amplitude unidentified peaks which could not be fitted to the desired compound in total or in part.

Distillation of the liquid down to 5 ml pot volume gave a yellow solution which by VPC on 5% SE 30 at 130° showed THF, carbon tetrachloride, and two very small components following carbon tetrachloride. The solution gave a negative test for nitrogen.

Reaction of Cyanogen Azide With Methylcyclopropene. - This entire experiment was carried out behind a sturdy blast shield in a good fume hood. Sodium azide, 3.2 g (50 mmol), was suspended in 50 ml of dry acetonitrile in a 100-ml flask. Cyanogen bromide, 5.3 g (50 mmol), in 10 ml of dry acetonitrile was added through a dropping funnel slowly while stirring and cooling with salt-ice. (Note: the acetonitrile must be completely dry to avoid formation of explosive precipitates. For handling precautions with cyanogen azide the experimenter is urged to refer to the original literature.)[62] The ice was allowed to melt and the solution, after reaching room temperature, was filtered by gravity into a three-neck flask fitted with a thermometer and a dropping funnel. The flask was cooled with ice while stirring, and after the temperature was below 5°, 4.0 g (74 mmol), of methylcyclopropene in 4 ml of acetonitrile was added over 5 min. The solution gradually darkened to a final dark red after 2 hr. of stirring. The temperature during this process did not exceed 7°.

A small aliquot of solution when treated with chloroform after evaporation on a Rotovac produced a gooey precipitate.

Dry dichloromethane was added to the pot mixture and allowed to stand overnight. A large amount of gooey material was precipitated by morning and was filtered off. A VPC of the filtrate showed three peaks: one coming out before dichloromethane, dichloromethane, and acetonitrile. The filtrate had a very pungent smell as did the peak before dichloromethane. No other materials could be found by concentrating the filtrate by distillation and checking the residue by VPC.

Reaction of 1-Azido-2-iodo-1-methylcyclopropane With Diethyl Peroxycarbonate. Run 1. - Iodoazide, 45, 1.0 g (4.5 mmol), was refluxed in 25 ml of absolute methanol with the peroxide[75] generated in a small amount of chloroform from 1.2 g ethyl chloroformate and 0.5 g of powdered sodium peroxide. Within 10 min. 70 ml of gas were collected. The solution turned from light yellow to dark orange. Gas evolution seemed to cease at 0.5 hr. with 94 ml collected.

A small aliquot of the pot solution when dissolved in ether gave no precipitate with hydrogen chloride gas. A TLC indicated only iodoazide present along with a small amount of color at the origin of the plate.

Run 2. - A second attempt was run with 2.2 g (10 mmol) of 45 with 1.3 g (7.3 mmol) of diethyl peroxycarbonate in 10 ml of refluxing isopropanol. After 6 hr. 150 ml of gas was collected. The black solution showed by TLC (silica gel, ether) in addition to the iodoazide at 1.0 only trace spots at 0.8, 0.65, and 0.4.

Reaction of 1-Azido-2-iodo-1-methylcyclopropane With Lithium Aluminum Hydride. - Lithium aluminum hydride, 1.0 g (26.3 mmol), was weighed in a dry box directly in a 50-ml three-neck flask which had been previously flamed out. To the flask, after removal from the dry box with stoppers in all necks, was added 25 ml of dry ether. One neck was connected by means of a gas outlet tube to a U-tube mineral oil bubbler, one fitted with a dropping funnel, and the third with a thermometer. The flask was placed in an ice bath and while stirring 1.8 g (8.1 mmol) of freshly purified 45 dissolved in 4 ml of dry ether was added slowly as soon as the solution temperature reached 3°. Too rapid addition caused a rapid rise in the solution temperature. The solution after addition was allowed to warm to room temperature and stir overnight.

An aliquot was removed the next day and hydrolyzed with 40% potassium hydroxide. An IR spectrum of the dried ether showed no azide remaining. Several 2 or more ml aliquots were removed, hydrolyzed, and carefully evaporated to a small amount of amine smelling liquid. Of the columns tested for VPC analysis 3% and 5% SE 30 columns proved satisfactory when run at 35° column temperature. The precipitated salts from the hydrolysis when shaken with water gave a strong positive test for iodine.

The rest of the mixture was carefully hydrolyzed with 50% potassium hydroxide and the salts filtered off. The ether solution was carefully distilled through a metal helices column to *ca.* 0.5 ml pot residue. A VPC check on 3% SE 30 at 35° showed ether and two product peaks, the second being broad and minor. Added sec-butylamine increased the size of the first peak. Added iso-butylamine gave a separate peak of slightly longer retention time than the major peak. The known amines were added by drawing a sample into the syringe and then removing most of it by suction. Pot residue was then drawn into the syringe. In this manner, contamination of the pot residue was avoided. The minor peak did not correspond in retention time to methallylamine.

Attempted preparative separation of 100 µl of solution gave merged amine and ether peaks.

Treatment of the remaining ether solution with hydrogen chloride gas gave a white precipitate, 50 mg, whose NMR spectrum in D_2O showed it to be 80% sec-butylamine hydrochloride by comparison to authentic material.

<u>6-Phthalimidyl-6-azabicyclo[3.1.0]hexane.</u> - Cyclopentene,[76] 1.70 g (25 mmol), was dissolved in 20 ml of dry dichloromethane and stirred at room temperature. N-aminophthalimide, 1.05 g (6.48 mmol), was added followed by addition portionwise of 2.76 g (6.25 mmol) of lead tetraacetate over 9 min. The mixture was stirred an additional 20 min. after which the salts were filtered off and the filtrate evaporated to yellow crystals. These were reevaporated twice with 25 ml of benzene. The crude crystals were eluted through a silica gel column (200-325 mesh, 6.7 x 13.5 cm) with 3:1 pet. ether-acetone. The yellow fractions were evaporated to bright yellow crystals. Yield 0.7 g (49%), m.p. 119-26°. A sample recrystallized from carbon tetrachloride by slow addition of pet. ether gave crystals of m.p. 126-28.5°.

An NMR spectrum (CH_2Cl_2 or $CDCl_3$) with TMS showed peaks: 2.31 (s, 4), 6.86 (m, 2), 7.50-8.97 (m, 6).

Analysis. Calc. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.28; H, 5.37; N, 12.40.

7-Phthalimidyl-7-azabicyclo[4.1.0]heptane.[20] - Cyclohexene, 2.06 g (25 mmol), was dissolved in 20 ml of dry dichloromethane and stirred at room temperature. N-aminophthalimide, 1.05 g (6.48 mmol), was added followed by 2.76 g (6.25 mmol) of lead tetraacetate in portions over 8 min. The mixture was stirred an additional 10 min. after which it was worked up and the product purified as in the preparation above. The yellow fractions when evaporated gave 0.55 g (36%, lit. 40%[11]) of yellow crystals, m.p. 132-4°.

An NMR spectrum (CH_2Cl_2) with TMS present showed preaks at: 2.35 (s, 4), 7.30 (m, 2), 7.93 (br m, 4), 8.68 (m, 4).

A sample rechromatographed and recrystallized from methanol had m.p. 133-6°. Mass spectrometric analysis gave a strong parent peak at 242.1100, calc. for $C_{14}H_{14}N_2O_2$: 242.1055, by matching to 264 m/e of perfluorotributylamine. The spectrum was clean above the parent peak.

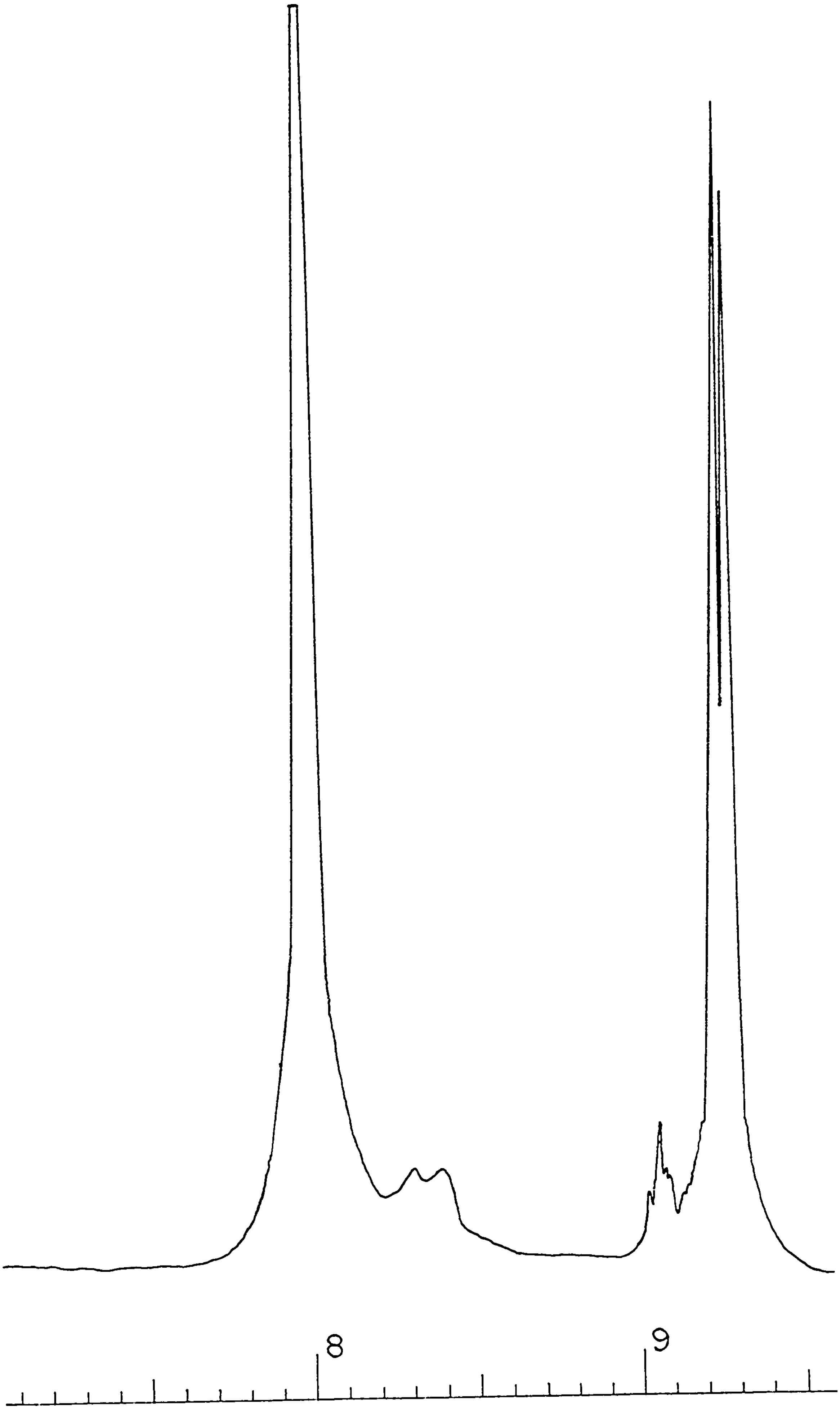
6-Carboethoxy-6-azabicyclo[3.1.0]hexane. - 6-Azabicyclo 3.1.0 - hexane (prepared by the method of Hassner[27]), 0.86 g (10.3 mmol), was added to a stirred mixture of 1.09 g (10 mmol) ethyl chloroformate, 0.4 g (10 mmol) of sodium hydroxide, 15 ml of benzene, and 20 ml of ice in an ice bath at 7°. After stirring one hr. the temperature dropped to 4° and remained there for the final hr. of stirring. The mixture was poured into 20 ml of water, the benzene layer separated, and the water extracted twice with ether. The combined organic layers were dried over magnesium sulfate.

The organic layer was combined with that from the above preparation repeated on twice the scale and the solvents were distilled off through a column packed with metal helices. The dark residue was vacuum distilled yielding 1.40 g (30%) of a clear colorless oil, b.p. 110-112°/60 torr. The material showed NMR absorptions (CCl_4)at: 5.97 (q, J = 7, 17), 7.15 (br s, 14), 7.80-9.00 (m, 82).

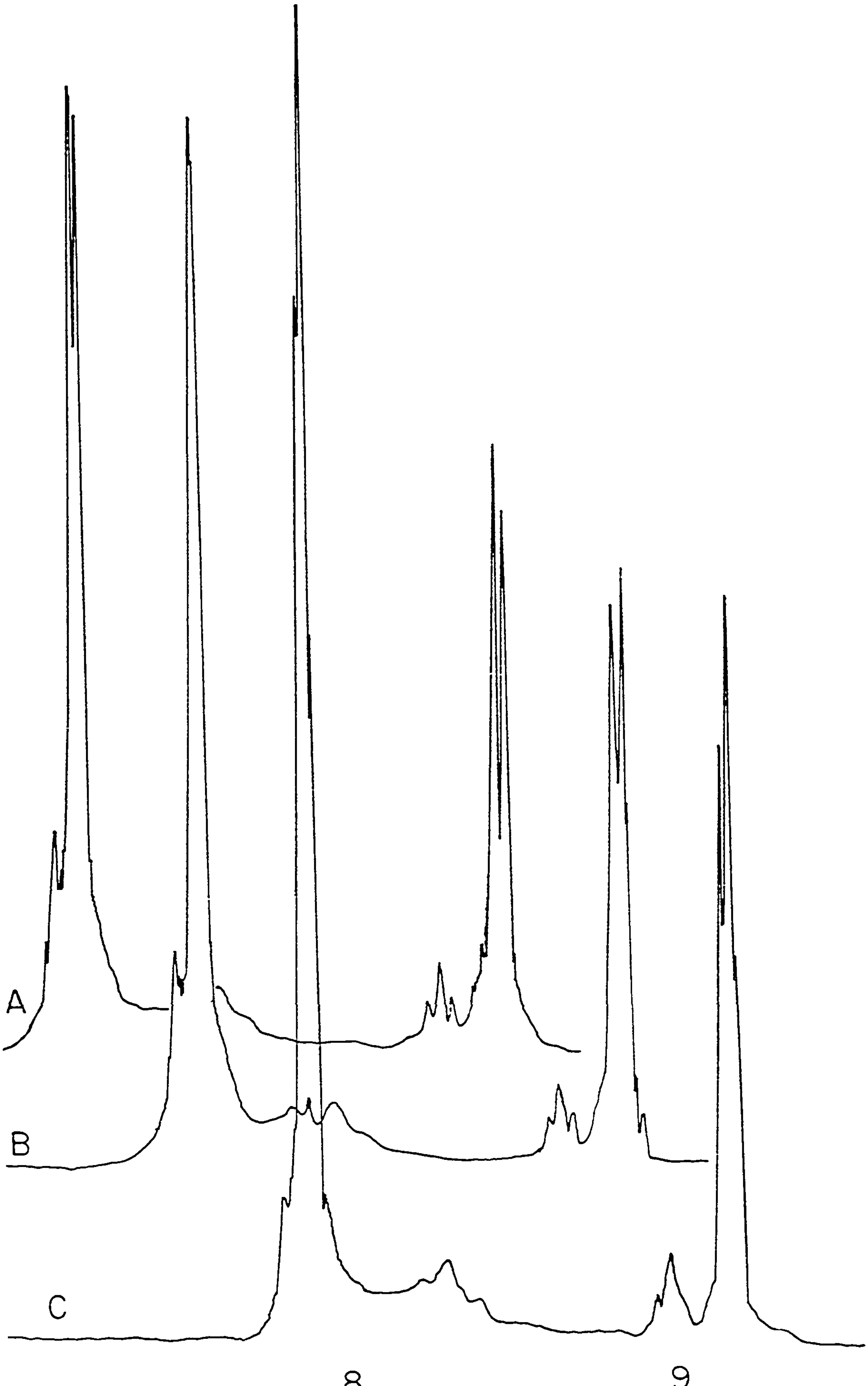
Material of analytical purity, slightly yellow in color, was obtained from preparative TLC on silica gel by visualizing the edges of the plate with iodine vapor by passing nitrogen through a transfer pipet containing iodine crystals. The iodine developed areas were not desorbed. NMR spectrum (CCl_4) showed peaks (τ, area): 5.97 (2), 7.15 (2), 7.80-9.00 (9).

Anal. Calc. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.04. Found: C, 62.18; H, 8.62; N, 9.21.

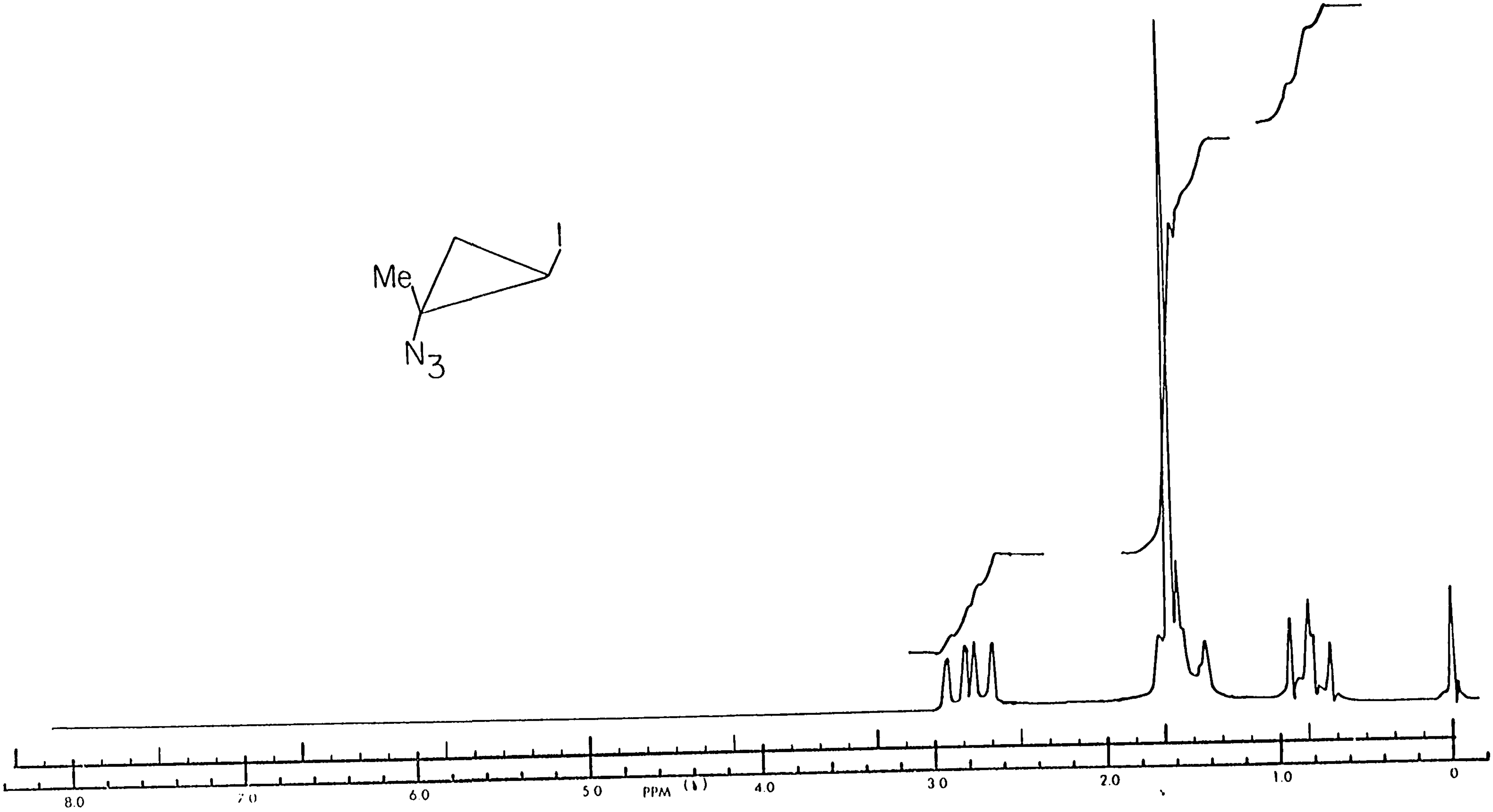
NMR Spectrum of Initial Methylcyclopropene-N-aminophthalimide-Lead Tetrabenzoate Mixture at -50° in Dichloromethane.


8
9

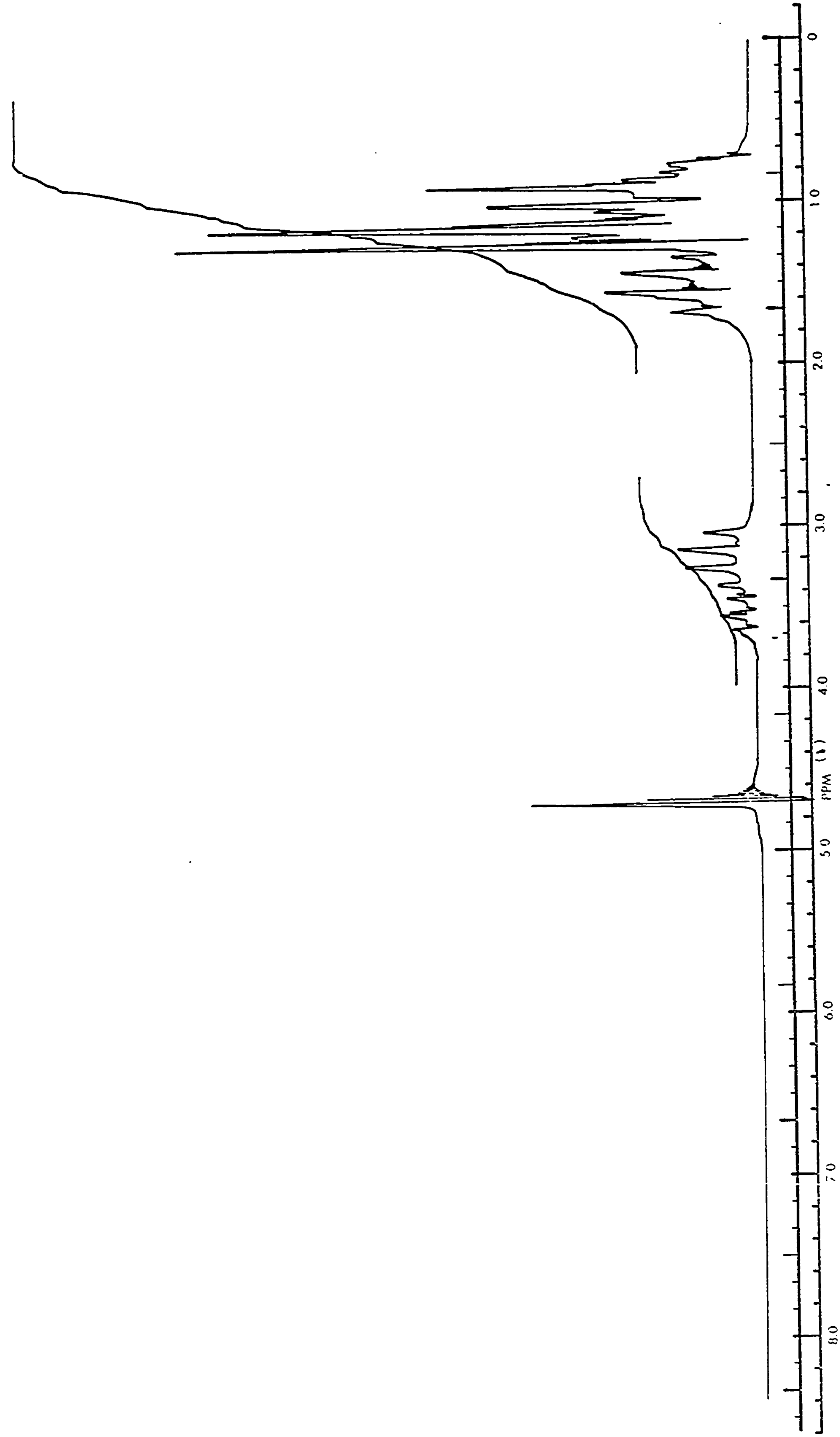
NMR Spectrum of Methylcyclopropene-N-aminophthalimide-Lead Tetrabenzoate Mixture in Dichloromethane: A, Second Spectrum at +10°; B, First Spectrum at +10°; C, Spectrum at 0°.


A
B
C
8
9

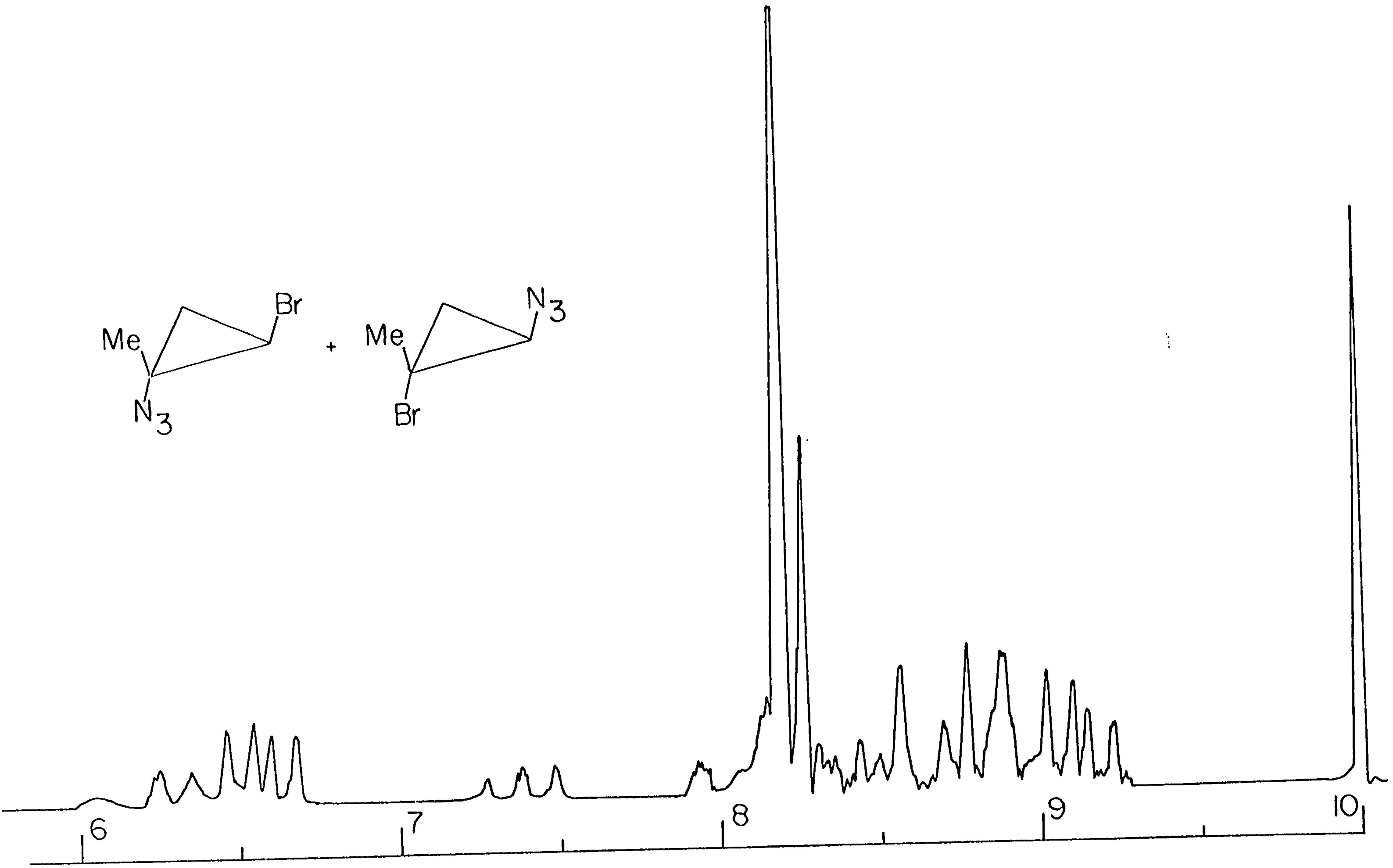
NMR Spectrum of 1-Azido-2-iodo-1-methylcyclopropane (45) in Carbon Tetrachloride.


Me
N3
I
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

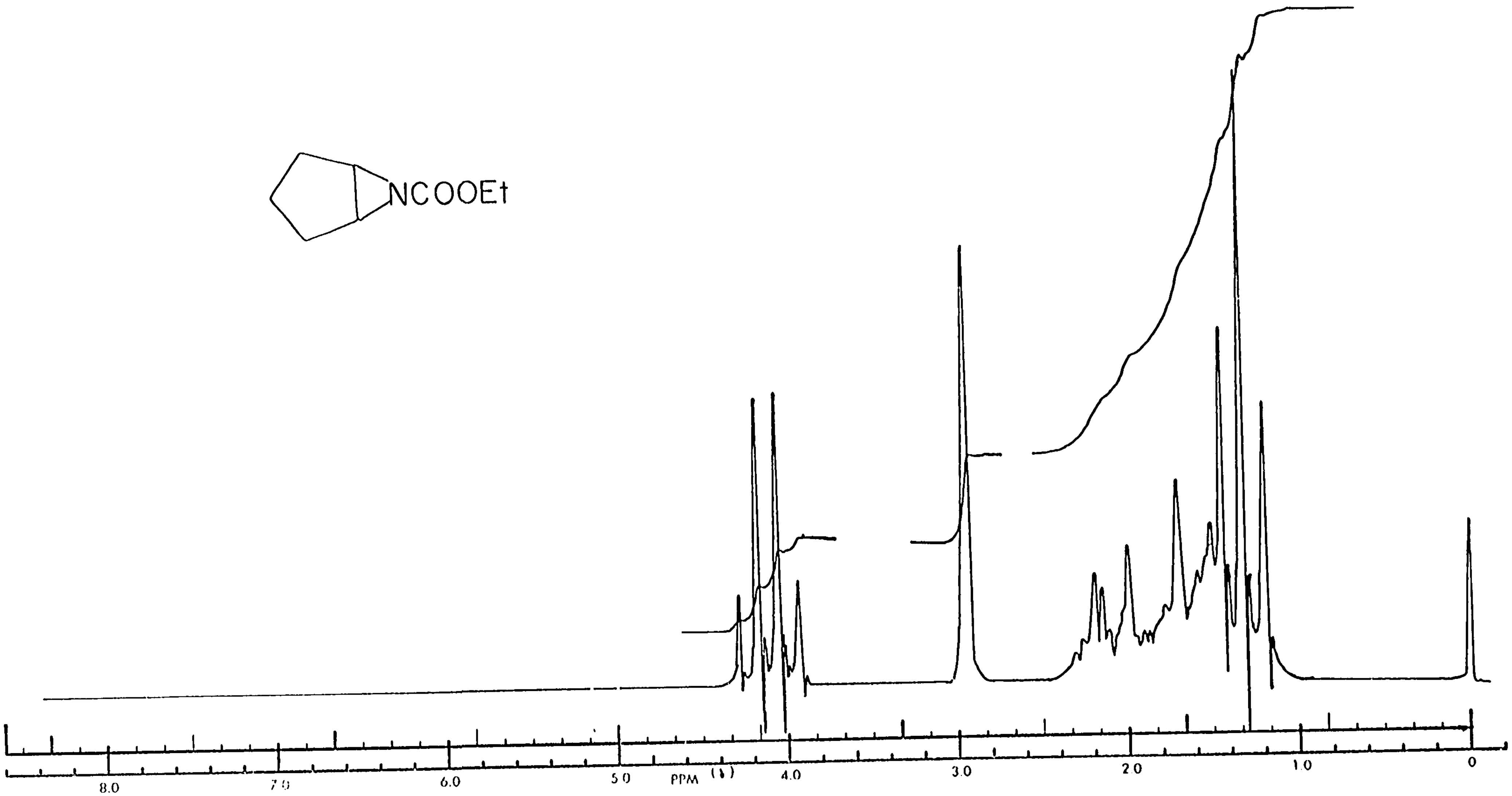
NMR Spectrum of Crude Amine Hydrochloride (see p. 178) in D_2O.


0
1.0
2.0
3.0
4.0
PPM (δ)
5.0
6.0
7.0
8.0

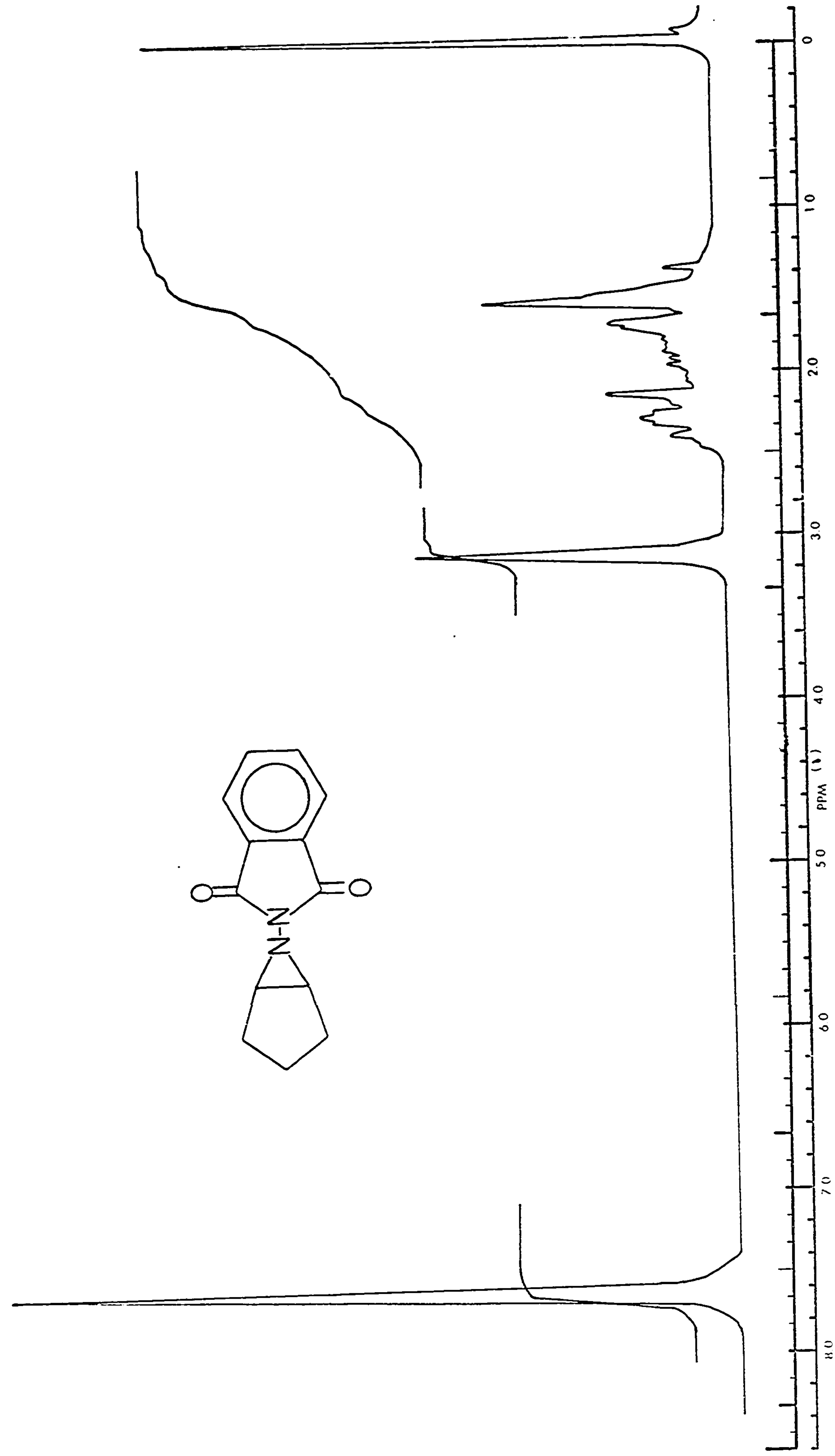
NMR Spectrum of the Bromonium Azide Adduct of Methylcyclopropene (46a, 46b) in Carbon Tetrachloride.


Me
N3
Br
+
Me
N3
Br
6
7
8
9
10

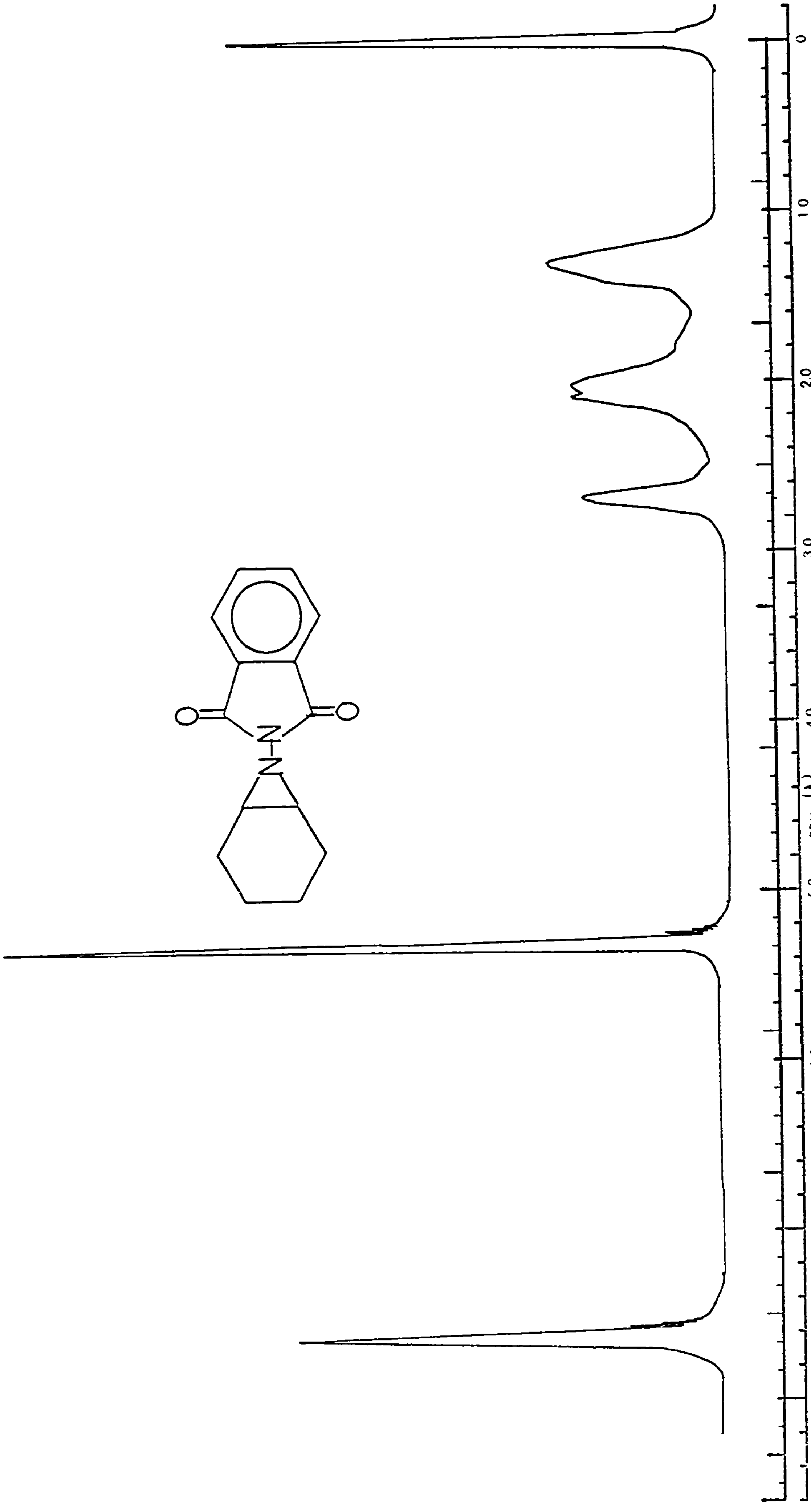
NMR Spectrum of 6-Carboethoxy-6-azabicyclo[3. 1. 0]hexane in Carbon Tetrachloride.


NCOOEt
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

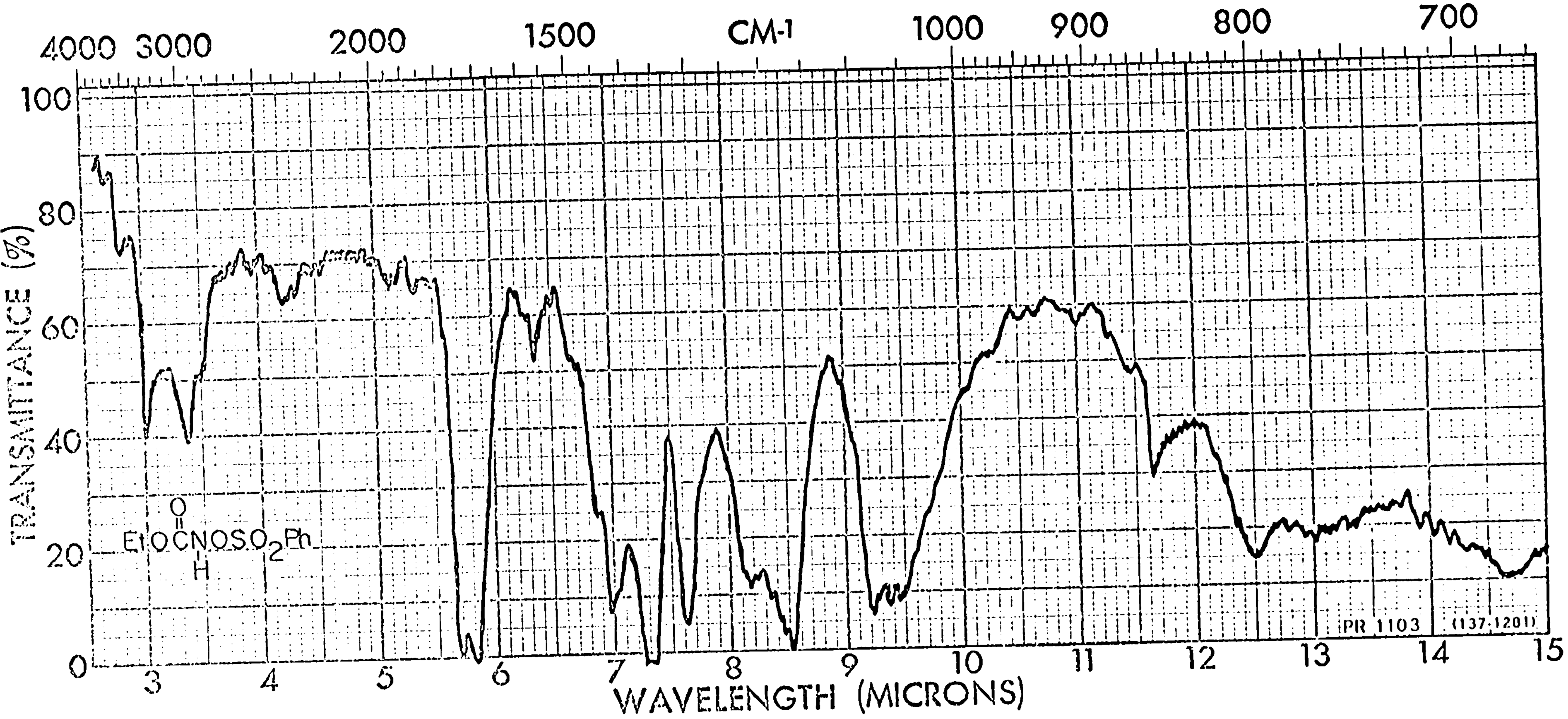
NMR Spectrum of 6-Phthalimidyl-6-azabicyclo[3.1.0]hexane in Deuterochloroform.


O
N-N
O
0
1.0
2.0
3.0
4.0
PPM (δ)
5.0
6.0
7.0
8.0

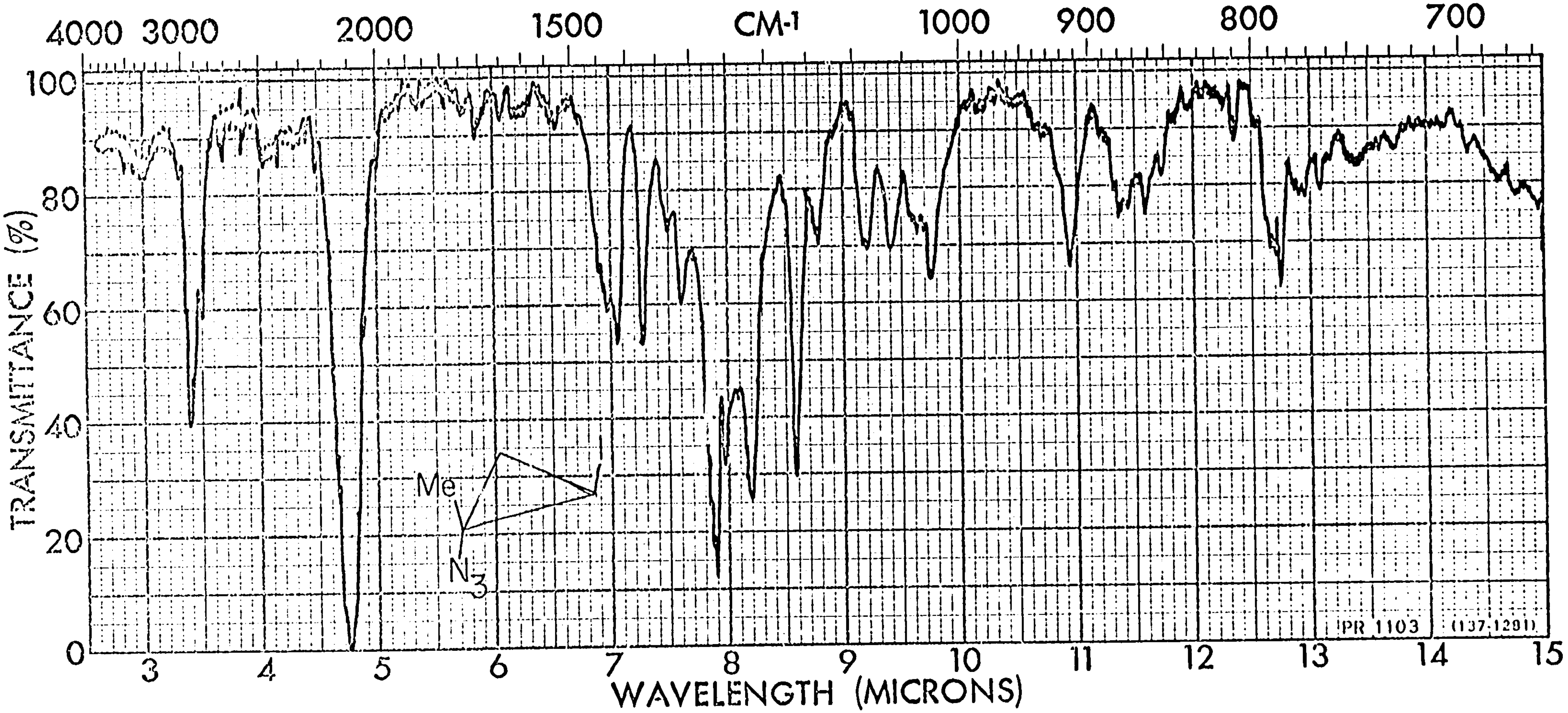
NMR Spectrum of 7-Phthalimidyl-7-azabicyclo[4.1.0]heptane in Dichloromethane.


0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
PPM (δ)
O
O
N
N

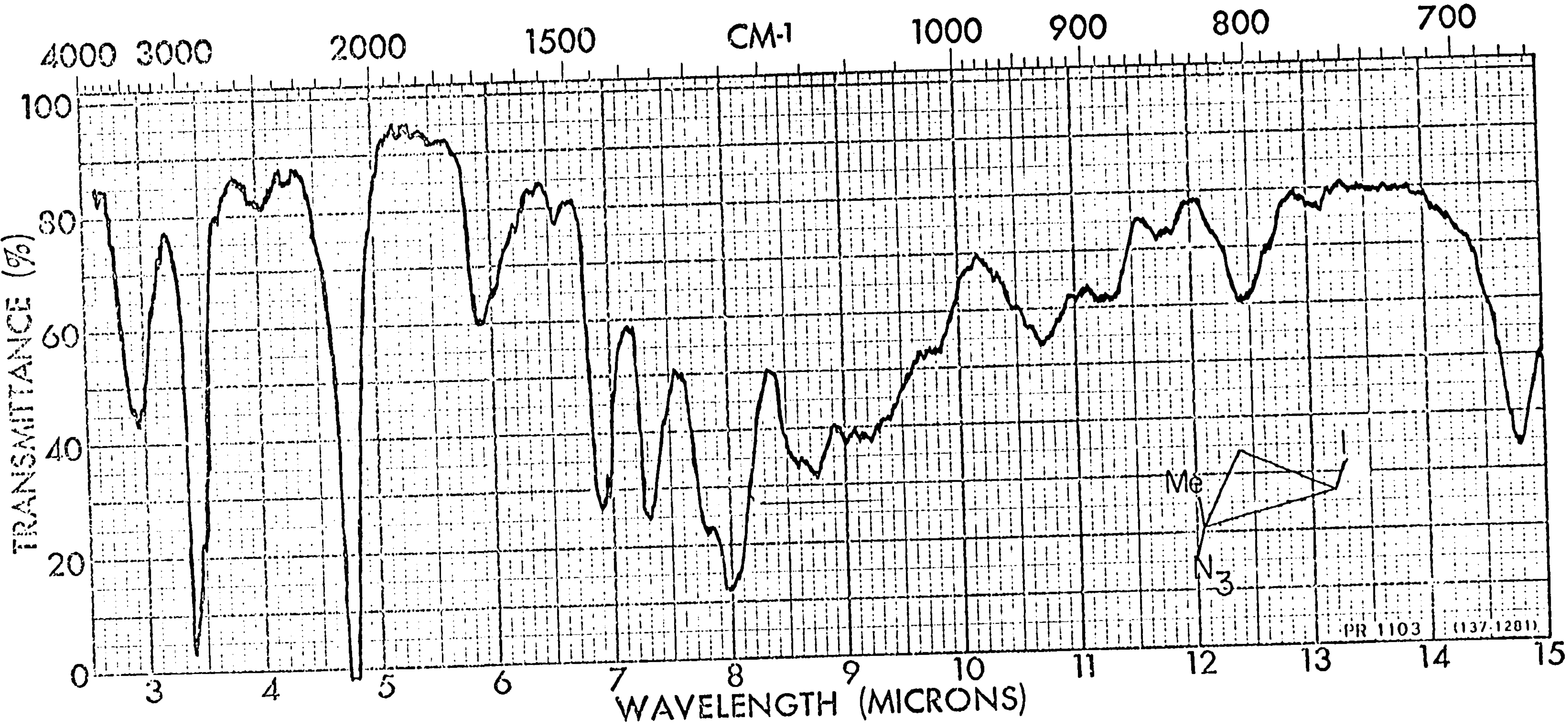
IR Spectrum of N-benzenesulfonoxyurethane (<u>40</u>) in Chloroform.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
$EtO\overset{O}{\overset{\|}{C}}\underset{H}{N}OSO_2Ph$
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
PR 1103
(137-1201)

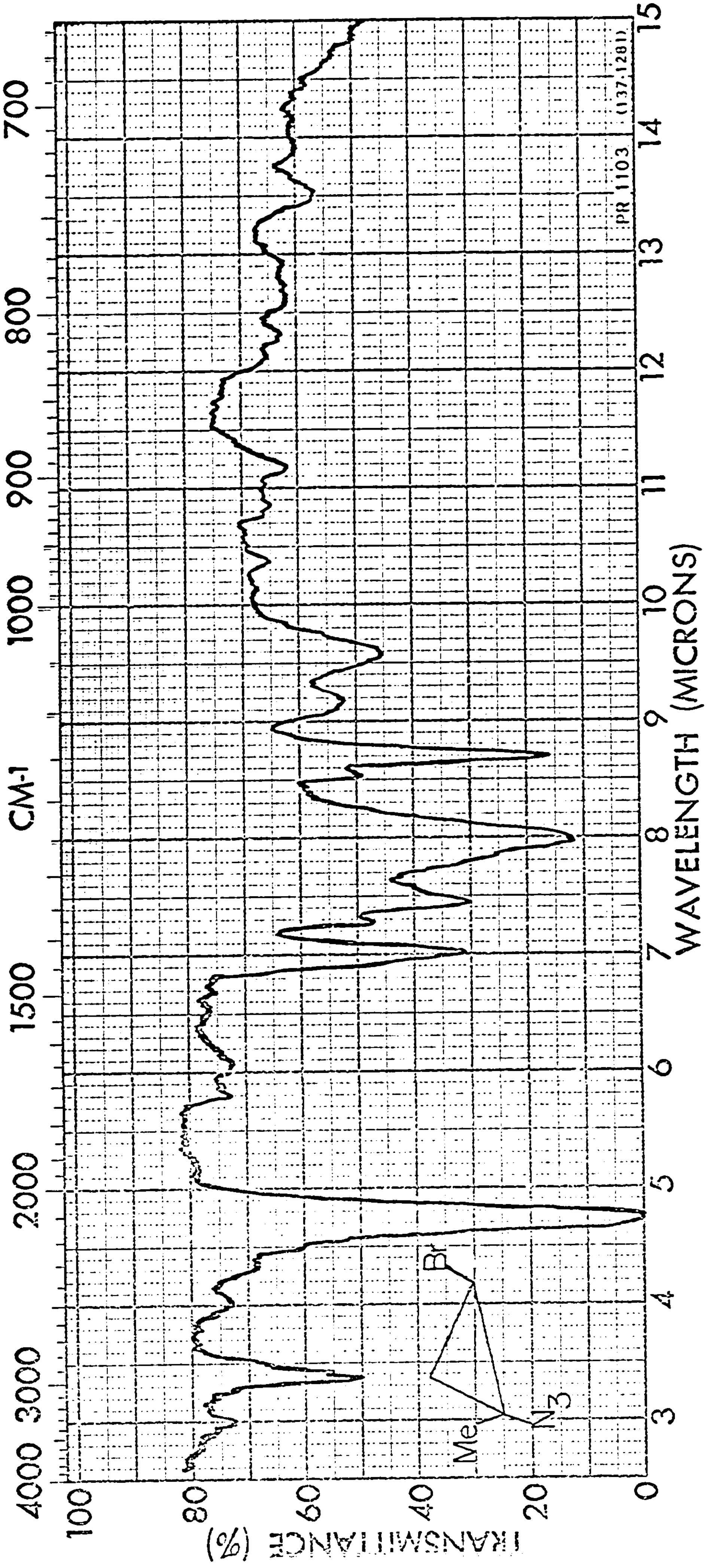
IR Spectrum of 1-Azido-2-iodo-1-methylcyclopropane (45) as a Thin Film.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
Me
N3
PR 1103
(137-1291)

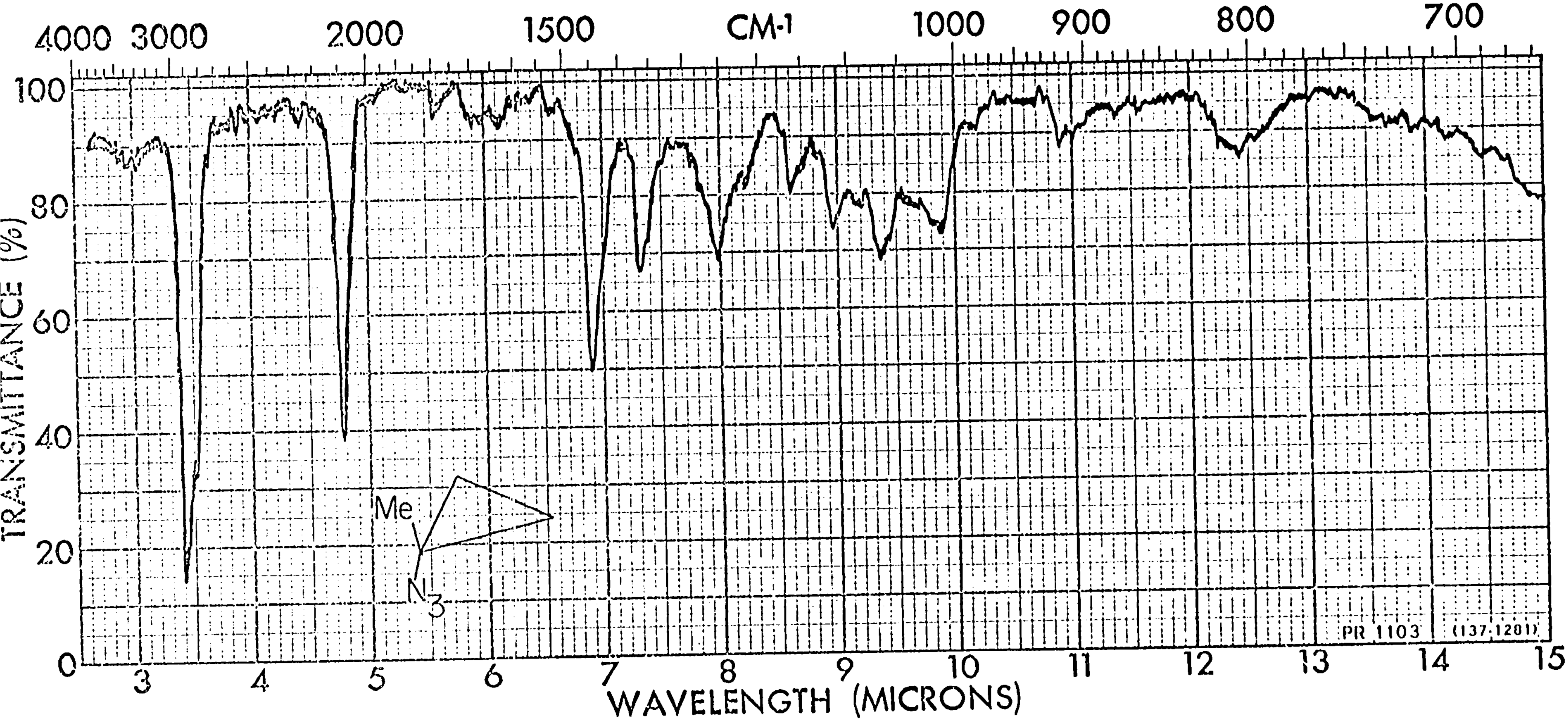
IR Spectrum of 1-Azido-2-iodo-1-methylcyclopropane as a Thin Film After UV Irradiation.


4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
Me
N3
I
PR 1103
(137-1281)

IR Spectrum of the Bromonium Azide Adduct of Methylcyclopropene (46a, 46b) as a Thin Film.


CM-1
4000
3000
2000
1500
1000
900
800
700
WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
TRANSMITTANCE (%)
100
80
60
40
20
0
Br
Me
N3
PR 1103
(137,1281)

IR Spectrum of 1-Azido-1-methylcyclopropene (43) as a Thin Film.



CM-1
4000
3000
2000
1500
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
Me
N3
PR 1103
(137-1281)

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