TITLE PAGE

SENIOR THESIS: γ,γ-DIPHENYLALLYL-CARBINYL FREE RADICAL -- SYNTHESIS AND N M R DETERMINATION OF ITS NATURE

SUBMITTED TO DR. JOHN D. ROBERTS IN PARTIAL SATISFACTION OF THE REQUIREMENTS FOR 9 UNITS OF CH. 80 (CHEMICAL RESEARCH)

BY -- EDWARD MEDOF -- MAY, 1964.

ACKNOWLEDGMENTS

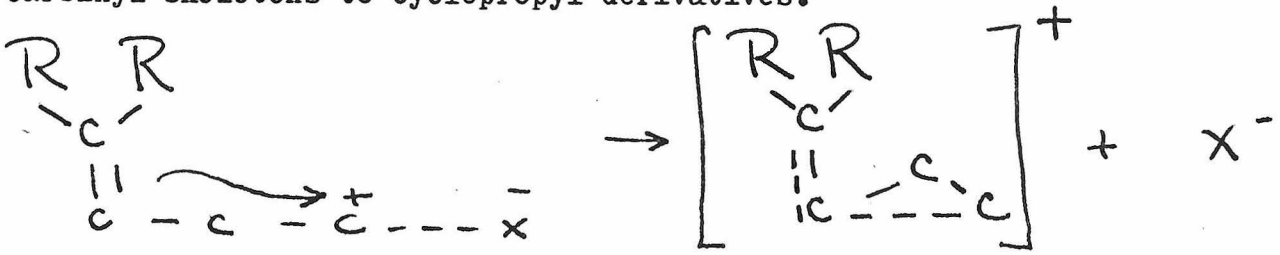
Most of the information in the discussion and background section was taken from Merlin Howden's thesis, Carbanion and Free Radical Rearrangements in Homoallylic Systems. A great deal of the expermental procedures were taken directly from Howden's notebooks.

I would like to gratefully acknowledge the technical assistance of Dr. Marjorie Caserio and Dr. Donald Gwynn and other members of the Roberts group who helped to make my work possible and thereby substantially increased my ability to do synthetic work in organic chemistry.

The idea for the project came from Dr. John D. Roberts, and it was through his support that I was able to obtain the opportunity to undertake it.

INTRODUCTION

Double bond participation has been hypothesized as the reason for making the system below very much more reactive than the corresponding saturated system and for promoting rearrangements of allylcarbinyl skeletons to cyclopropyl derivatives.



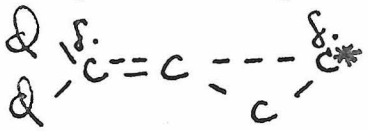
This type of participation has been well established in the case of carbonium ions and has been unequivocably shown to involve non-classical intermediates. Relative to saturated analog, rates of SN-1 reactions go up to 16,000 times faster* and β and γ substituted allylcarbinyl compounds have been shown to yield cyclopropyl derivatives upon reaction with various reagents.** In the reverse direction, diphenylcyclopropylcarbinol treated with phosporus tribromide has been found to afford only γ,γ diphenylallyl-carbinyl bromide.**

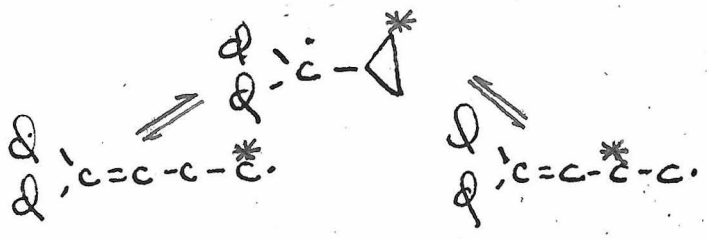
Recently, this concept of double bond participation has been extended to carbanion and free radical systems in order to explain similar phenomena encountered in reactions which normally proceed by these mechanisms. Merlin Howden undertook this problem as part of the work for his Ph.D. thesis. He attempted to determine if the rearrangements observed really did take place by participation as shown in the carbonium system and if so, whether the intermediate involved was actually a non-classical carbanion or free radical analogous to the carbonium ion described above. For this work Howden logically chose to study Grignard and free radical reactions of vinyl and phenyl substituted allyl-carbinyl compounds. These groups substituted in the γ position would be expected to stabilize the carbanion or free radical thereby making its formation easier and making rearrangements more facile. Howden's work yielded several important results. (i) He clearly showed that the above rearrangements were taking place

* Servis, K., Roberts, J. D., J. Am. Chem. Soc., To Be Published.

** Howden, M., Carbanion and Free Radical Rearrangements in Homoallylic Systems, CIT, 1962.

in these systems by means of the proposed double bond participation. (ii) The intermediate involved was one of two types in both the carbanion and free radical case. Indirect evidence was provided supporting the first possibility.

1. 

2. 

(The two possibilities can be distinguished in that the first represents a single resonance stabilized species which can be attacked by reagent at either end and the second represents three separate species ((since the ring can open either way)) in very rapid equilibrium). (iii) He provided implications that the preparation of the substituted allyl-carbinyl Grignard reagents might have proceeded by a mechanism which involves free radicals.

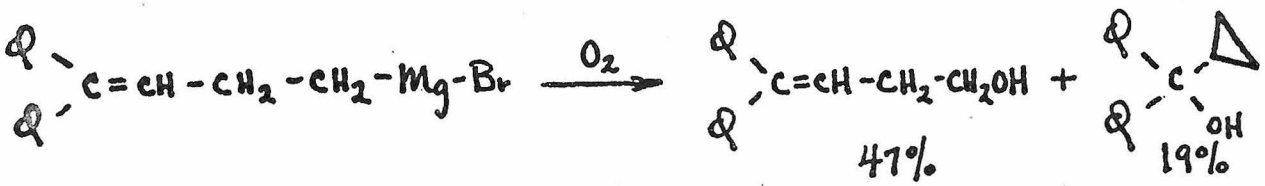
This study was initiated as an extension of Howden's work -- an experiment using the same compounds and techniques that Howden used which would provide direct evidence supporting one of the two intermediates proposed. The free radical system was chosen for practical reasons. The result of the experiment would have a good deal of significance in that it might provide the first unequivocal evidence of a non-classical free radical and that it would yield information concerning the mechanism and type of bonding involved in the formation of Grignard reagents.

DISCUSSION AND BACKGROUND

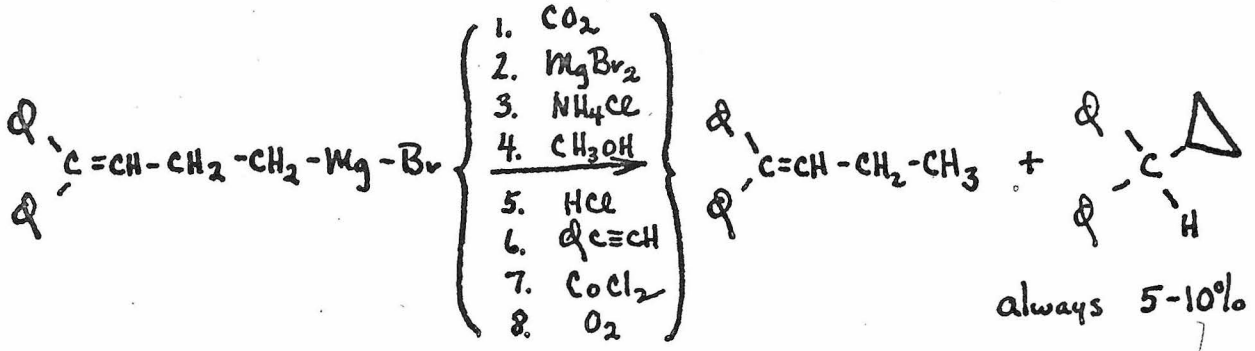
A great deal of evidence led to the conclusions drawn above.

Howden found that reaction of γ,γ diphenylallyl-carbinyl Grignard reagent (1), prepared from γ,γ diphenylallyl-carbinyl bromide and magnesium in ether, with oxygen yielded two products: γ,γ diphenyl-allyl-carbinol and diphenylcyclopropylcarbinol in 47% and 19% yields respectively. He also found that the same Grignard reagent (2) when treated with carbon dioxide, mercuric bromide, ammonium chloride, methanol, hydrochloric acid, phenylacetylene, cobaltous chloride, or oxygen yielded substantial amounts of hydrocarbon composed of a mixture of 1,1-diphenylbutene and diphenylcyclopropylmethane, with the total yield of the latter remaining always between ~5-10%. Clearly rearrangement had been occurring, the extent of which was not a function of the reagent used.

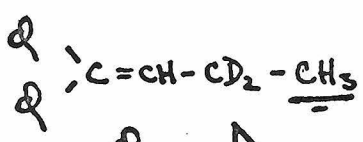
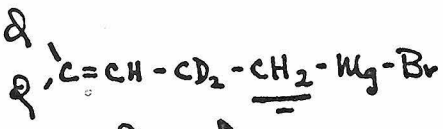
(1)

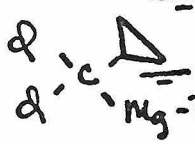


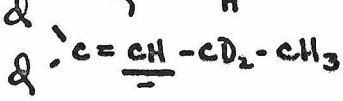
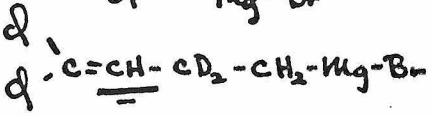
(2)



To gain an idea of what was happening, an n m r study of the Grignard reagent prepared from 4,4-diphenyl-1-bromo-3-butene-1,1-d_2 (the above Grignard reagent doubly labelled in the 1 position with deuterium) was made and yielded the following information. There was a sizable methylene singlet at high field (+25cps) indicating the equilibration of α and β d_2(3). There was a sizable singlet at -25cps indicating the presence of some cyclopropane methylene (4). There was a broad peak at the center of the vinyl triplet, also indicating the equilibration of α and β d_2 (5).

(3)  or 

(4)  or 

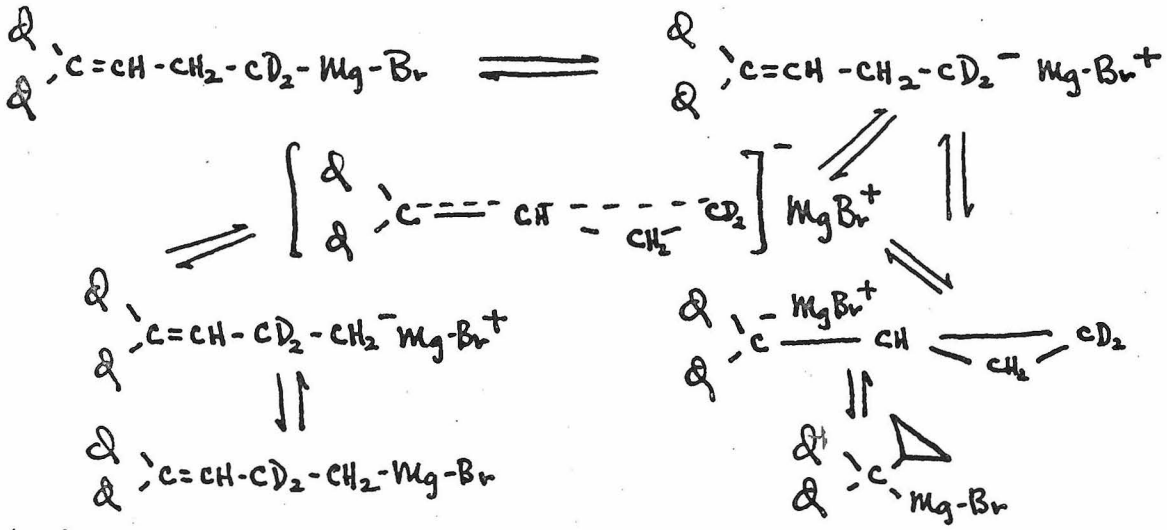
(5)  or 

It was found that this spectrum did not change with time but that a spectrum of the same compound that was not substituted with phenyl groups at the 4 position did change with time, having a half life of ~30hr. This fact indicated that the Grignard reagent of interest had equilibrated before its n m r spectrum had been taken and that the rate determining step of equilibration was ring formation since the two phenyl groups would facilitate this conversion.

From area comparisons of the peaks, one could observe that the cyclopropane singlet at -25cps accounted for a 7% molar ratio of cyclopropane compounds to the total of other compounds in the solution. This fact coupled with the fact that 1,1-diphenyl-4,5-d_2-butene was isolated from the system implied that the cyclopropane resonances might be due to diphenylcyclopropylmethane rather than diphenylcyclopropymethyl Grignard reagent since, as seen above, all the previous reactions of the Grignard reagent had yielded 5-10% diphenylcyclopropylmethane. It was quite conceivable that the 1,1-diphenylbutene and diphenylcyclopropylmethane were forming during the formation of the Grignard reagent by a free radical mechanism involving hydrogen abstraction from ether. This hypothesis seemed to satisfy all previous results. However, area measurements comparing the peak at -25cps to that at +25cps (cyclopropyl products to 4,4-diphenyl-3-butene-2,2-d_2 Grignard reagent) yielded a 1:3.74 ratio, correcting for the proper number of hydrogens for each type of molecule. This ratio was too high to be consistent with preparative data and might well indicate the presence of some diphenylcyclopropylmethyl Grignard reagent. Since the spectrum of the Grignard reagent necessarily had to be taken in ether, whose large methyl and methylene resonances with spinning side bands and carbon 13 peaks covered up a good deal of the pertinent information and confused

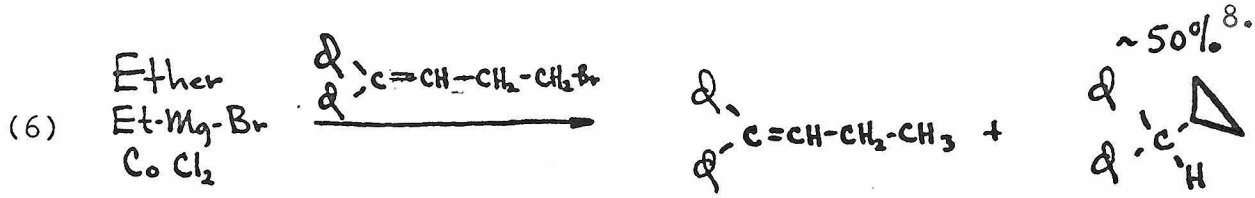
the spectrum, no further conclusions could be drawn from this experiment.

One is able to set up the following hypotheses from the above data, however. (i) The mechanism of rearrangement of the Grignard reagent must proceed by one of two possible routes. The Grignard reagent forms the corresponding anion and then is either in equilibrium with the rearranged diphenylcyclopropylmethyl anion or forms a non-classical carbanion which has character corresponding to both of the above forms and can go to either.



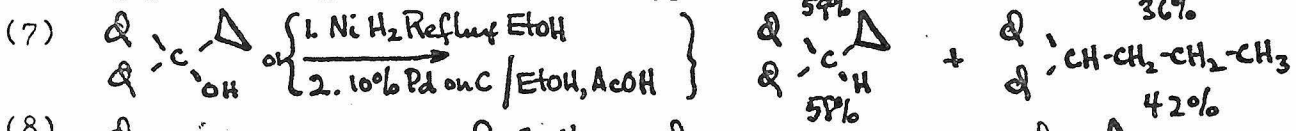
(ii)Formation of the hydrocarbon species of 1,1-diphenylbutene and diphenylcyclopropylmethane probably occurs during formation of the Grignard reagent and might proceed by means of hydrogen abstraction from solvent by a free radical mechanism.

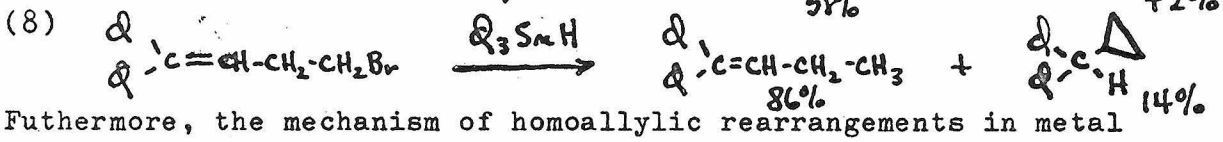
The idea of this free radical hydrogen abstraction mechanism involved in homoallylic Grignard formation could be very significant. In the previous synthetic work, described above, γ,γ diphenylallyl-carbinyl Grignard reagent had been treated with cobaltous chloride, a reaction which is known to proceed by a free radical mechanism, and had yielded hydrocarbons of the same types and in the same proportions as those yielded from the other reagents. To check the hypothesis that these hydrocarbons had actually formed during the synthesis of the Grignard reagent, the cobaltous chloride reaction was again run but in a modified form (6). γ,γ diphenylallyl-carbinyl chloride was added to an ethereal solution of ethyl magnesium bromide and cobaltous chloride.

(6) 

It seemed reasonable that if a free radical mechanism were operative in the formation of the Grignard reagent producing hydrocarbon fractions, this modification of the cobaltous chloride reaction should enhance this free radical mechanism and yield the same hydrocarbon products in greater amounts. Indeed this turned out to be the case; the total yield of hydrocarbon was increased from 35% to 60%, and of this amount, the yield of rearranged product increased from 35% to 89%. This reaction provided the first example of not obtaining the rearranged diphenylcyclopropylmethane in 5-10% yield but instead in ~50% yield and therefore lent support to the above hypothesis.

It was thought by Howden that the free radical mechanism and non-classical carbanion or free radical intermediate might have some bearing on two other types of reactions which have been observed and thought to proceed by means of carbonium ion intermediates (7), (8), thus lending greater significance to his hypothesis.

(7) 

(8) 

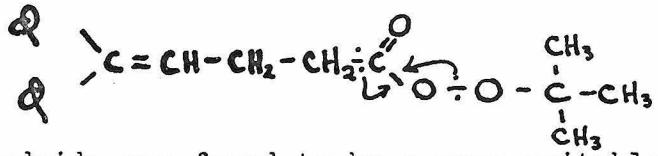
Futhermore, the mechanism of homoallylic rearrangements in metal reductions, although having been observed in several systems, is not known.

The above results called for experimentation with the free radicals, themselves, that were thought to be involved. The study of these radicals would certainly be pertinent and significant even in the event that they were not involved in the above phenomena. Demonstration of the existence of a non-classical free radical would be of great significance in itself to Organic Chemistry.

Difficulties were encountered in attempts to produce a diphenylcyclo-

propylmethyl free radical, so the problem was attacked from the other end -- the formation of γ,γ diphenylallyl-carbinyl free radical. The method of choice turned out to be thermal decomposition of t-butyl-γ,γ diphenylallyl-peracetate. Several substituted acetic acid t-butyl peresters have been found to thermally decompose with the simultaneous liberation of carbon dioxide gas, substituted carbinyl free radical, and butoxide ion (9).

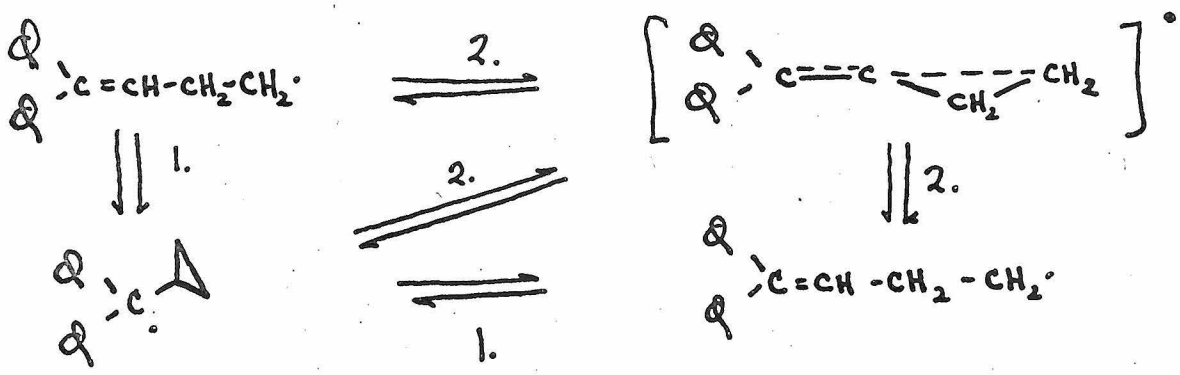
(9)



Tributyltin hydride was found to be a very suitable hydrogen donor to react with the free radical and thereby study the products formed.

Upon decomposing the t-butyl-γ,γ-diphenylallyl-peracetate at 110°C. in the presence of varying concentrations of tributyltin hydride, it was found that there was less than 10% change in the ratio of rearranged product (diphenylcyclopropylmethane) to total product (diphenylcyclopropylmethane + 1,1-diphenylbutene). It is noted that again the same products as seen in the above systems were forming.

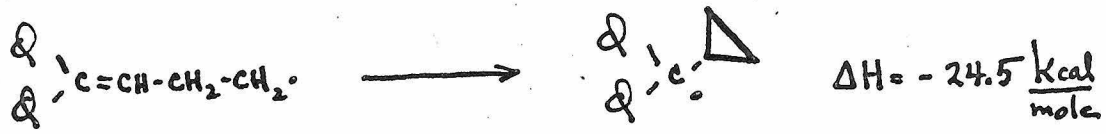
From this result it was concluded that the mechanism in which diphenylcyclopropylmethyl radical is formed slowly and irreversibly, being a lower energy state, was not possible. Again in very close analogy to the carbanion system of the Grignard reagent, it was concluded that the rearrangement could proceed only by one of two very closely related mechanisms, one of which involves the proposed non-classical intermediate.



A study of the products formed upon decomposition of t-butyl-γ,γ diphenylallyl-peracetate in the presence of tributyltin hydride as a function of temperature over a 40°C. range provided the fact that the ratio of products was not a function of temperature. This result turned out to be very significant in light of the following discussion.

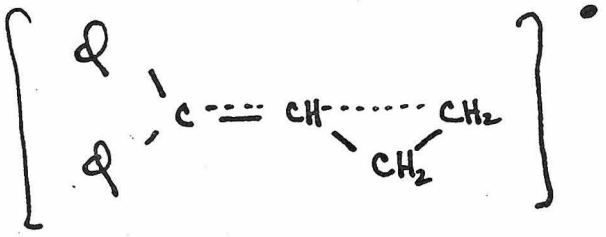
Bartlett and Hiatt had found that with a series of t-butyl peresters, the rate of decomposition was a function of the stability of the alkyl free radical formed. Howden ran rate experiments with t-butyl-γ,γ diphenylallyl-peracetate and with the corresponding saturated compound, t-butyl-5,5-diphenylperpentanoate, under the same conditions used by Bartlett and Hiatt. He found that the rate of decomposition of t-butyl-γ,γ diphenylallyl-peracetate was faster than its saturated analog by a factor of only 1.4 and a factor of only 1.45 over that found for t-butyl-peracetate by the above authors. Surely this modest increase was less than that expected. The effect of the two phenyl groups combined with the hypothesized action of the double bond would be expected to stabilize the radical considerably and thereby increase the rate by a significant factor. The very small increase was ascribed to formation of γ,γ diphenylallyl-carbinyl free radical in the initial step.

The ΔH value for the conversion of γ,γ diphenylallyl-carbinyl free radical to diphenylcyclopropylmethyl free radical (10) was then calculated using bond dissociation energies in the literature. It was found that the transformation gave a ΔH value of -24.5 Kcals/mole indicating that the equilibrium should lie far to the right or that if a non-classical free radical were involved, it should have a good deal of cyclopropyl character.

(10) 

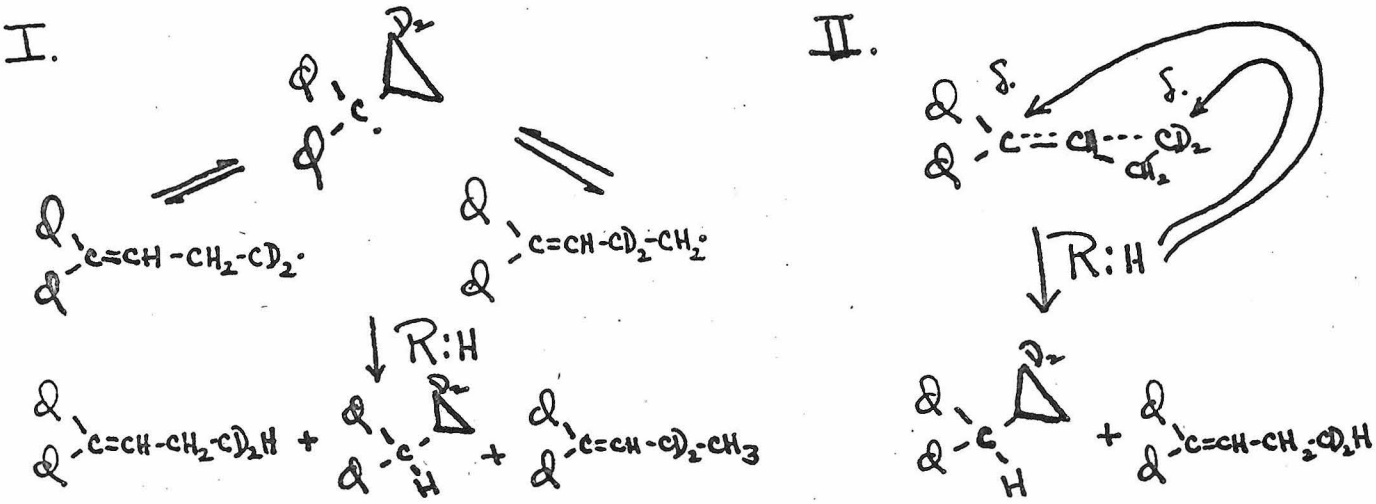
Since the above result showed that there was no temperature coefficient

describing the products formed, Howden inferred the existence of the non-classical intermediate. If classical radicals were in rapid equilibrium with a ΔH difference -24.5 Kcals/mole and since hydrogen abstraction reactions are of the order of 5-10 Kcals/mole, one would expect a marked difference in products with increasing temperature. The expected products should form in the ratio of the two free radicals. The lack of temperature dependence seemed to rule out the equilibration of classical radical intermediates and imply the existence ot the other possible intermediate -- the non-classical free radical (11).



EXPERIMENT

The proposed experiment was simply the following: The t-butyl-γ,δ diphenylallyl-acetic acid perester, which Howden had studied, would be prepared -- doubly labelled with deuterium on the α carbon -- a compound analogous to that which Howden used for n m r study of the Grignard reagent. The perester would be thermally decomposed in the presence tributyltin hydride; the products would be isolated and their n m r spectra taken. If it is assumed that the mechanism of the reaction is one of the two possibilities presented by Howden, then the result of this experiment would yield information implicating the correct alternative.

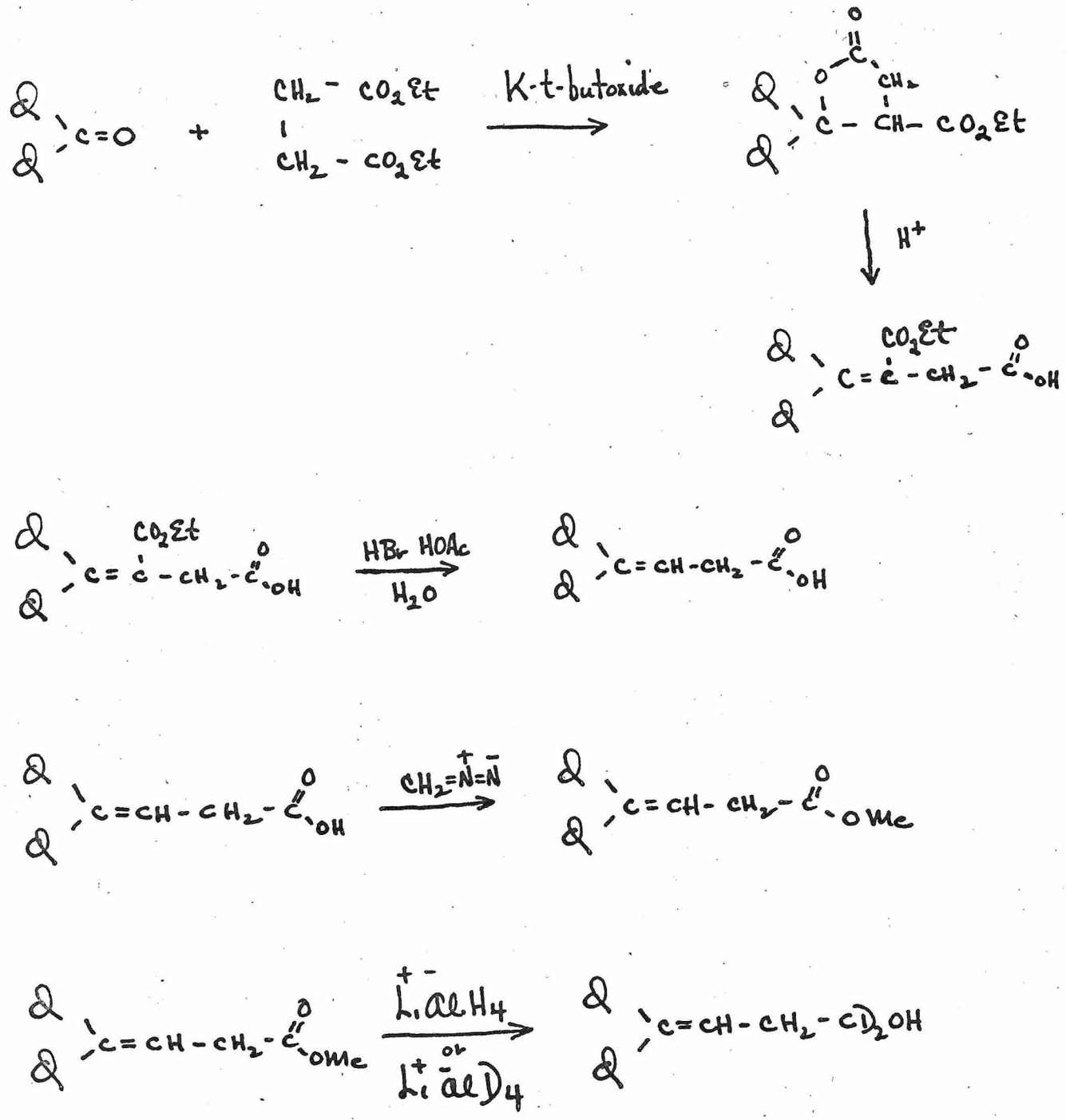


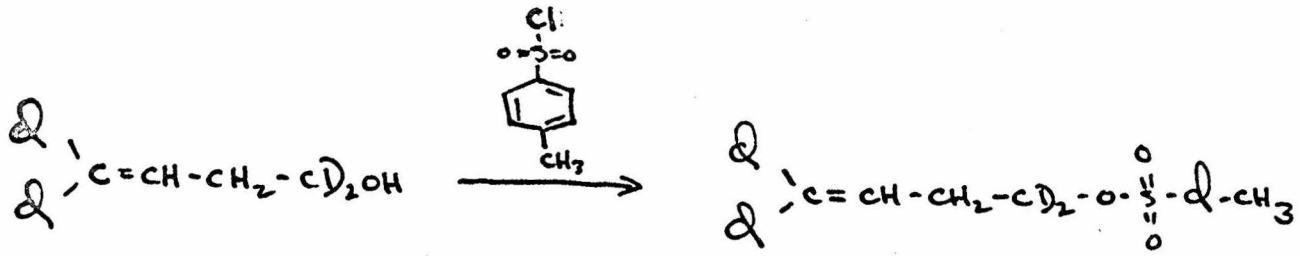
If classical radicals are involved as shown in case I, then one would expect, upon the addition of hydrogen donor, to get 1,1-diphenyl-3,3-d_2-butene containing three methyl hydrogens. A spectrum of the products taken in carbon tetrachloride, chloroform, or possibly a deuterated solvent should yield a very clear result. All of the practical disadvantages encountered by Howden using the Grignard reagent would be eliminated. One would not have to contend with ether nor would the great variety of products be possible. A much higher sensitivity could be used.

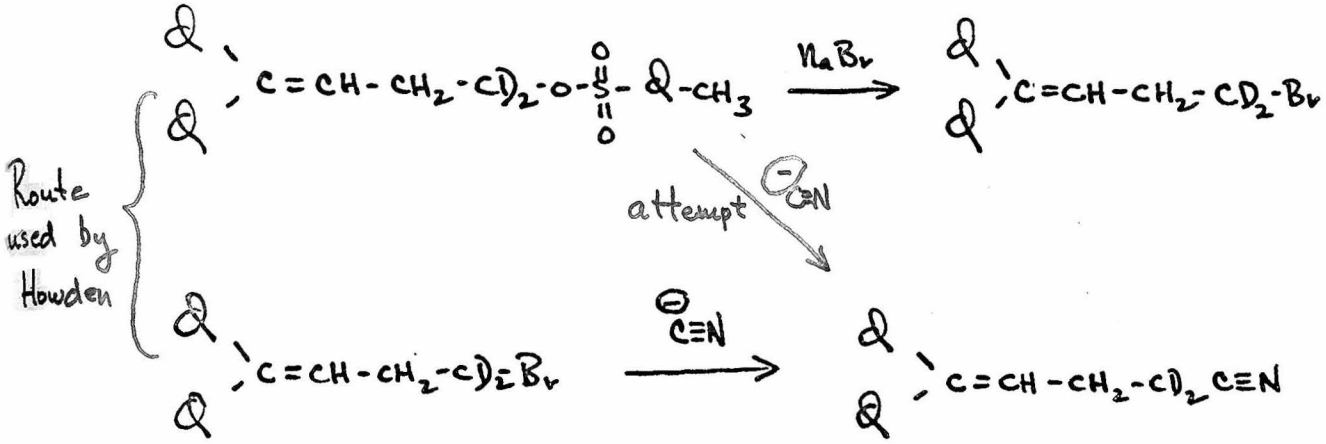
Aside from resonance due to 4-position hydrogens seen if the classical mechanism is in fact the correct one, one would be able to observe a larger than normal central peak in the vinyl triplet due to part of the molecules containing deuterium in the 3-position. Cyclo-

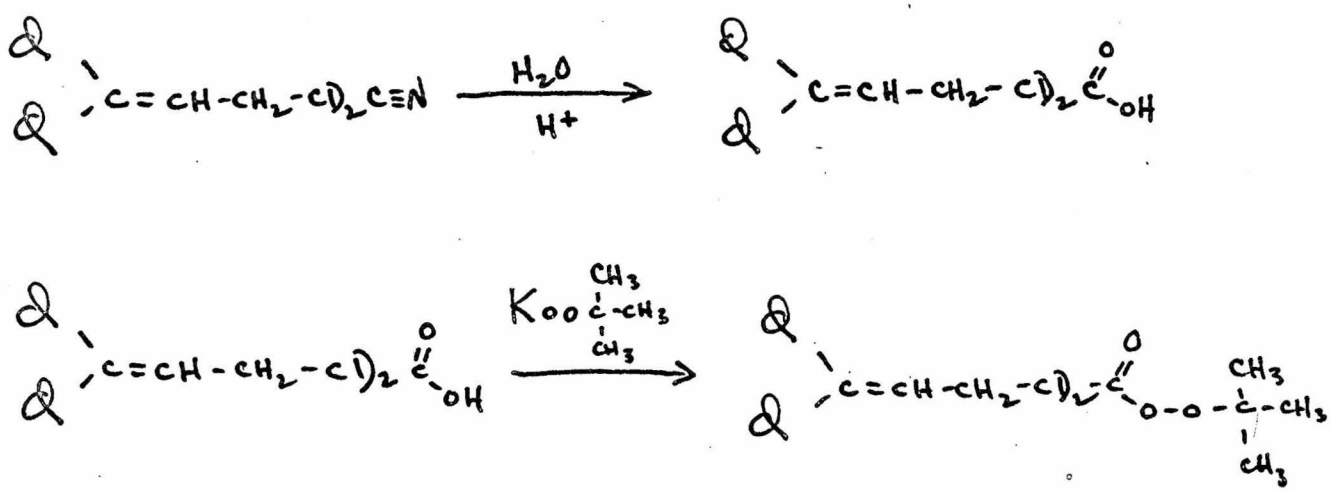
propane peaks should be seen in both possibilities. Area measurements could be utilized effectively in determining the state of equilibrium in the event of the classical case and difference in ease with which either side of the radical can be attacked in the event of the non-classical case.

The perester would be prepared in the following manner:









Products

RESULTS

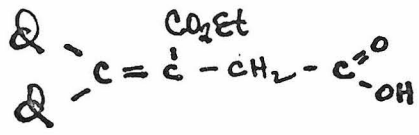
The first five steps of the nonisotopic synthesis were completed. β-carbethoxy-γ,γ-diphenylvinylacetic acid, γ,γ-diphenylvinylacetic acid, methyl-γ,γ-diphenylvinylacetate, and γ,γ-diphenylallylcarbinol, were synthesized, purified and characterized by melting point, n m r, and IR. γ,γ-diphenylallyl-carbinyl-p-toluenesulfonate was prepared but not characterized.

Lack of time would not permit any further work. Approximately 20 grams of the purified carbinol and 25 grams of pure methyl ester were turned over to the Robert's group to be used by subsequent workers. The 20 grams of carbinol represented a 50% overall yield from starting materials, reducing the acid directly. In order to conserve extremely expensive lithium aluminum deuteride, it was decided to reduce the ester and the 25 grams of methyl ester represented 63% yield from starting materials.(based on benzophenone in both cases).

EXPERIMENTAL

1. β-carboethoxy-γ,γ-diphenylvinylacetic acid.

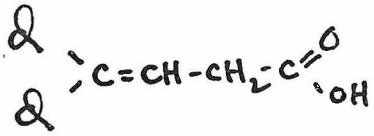
Johnson, W., Daub, S., Organic Reactions, 6, 42.
Johnson, W., Peterson, J., Schnieder, W., JACS, 69, 74, 1947.
Howden, M., Carbanion and Free Radical Rearrangements in Homoallylic Systems. CIT, 184-186, 1962
Howden, M., Notebook II, 49-53.



The compound was prepared by a Stobbe Condensation of benzophenone and diethylsuccinate with potassium t-butoxide as a catalyst. 16ml. of benzene was added to the reaction mixture to keep t-butyl alcohol from crystallizing out.

2. γ,γ-diphenylvinylacetic acid.

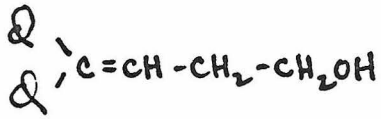
Johnson, W., Peterson, W., JACS, 69, 74, 1947.
Howden, M., Notebook II, 50.



The half ester was decarbethoxylated by refluxing for 24 hours in glacial acetic acid, hydrobromic acid and water. The compound was extracted with ether and recrystallized from ethanol-water.

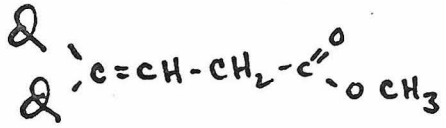
3. γ,γ-diphenylallylcarbinol

Vozza, J., J. Org. Chem., 24, 720-724, 1959
Howden, M., Notebook II, 52.



The carbinol was prepared from an ethereal solution of the acid by dropwise addition of lithium aluminum hydride in ether. The remaining hydride was consumed with acid, the carbinol extracted with ether and washed with acid. The ether was distilled off, leaving the carbinol as a viscous oil.

4. methyl-γ,γ-diphenylvinylacetate

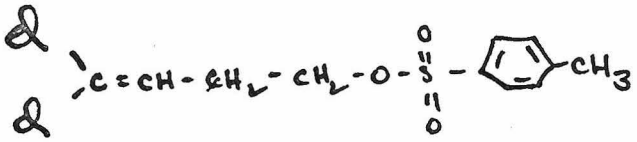


The ester was prepared from the acid by means of a standard diazomethane esterification procedure. The methyl ester was isolated as a thick yellow oil (B.P. = 195° @ 0.5 mm.) yielding the predicted n m r spectrum.

5. γ,γ-diphenylallyl-carbinyl-p-toluenesulfonate

Howden, M., Carbanion and Free Radical Rearrangements in Homoallylic Systems. IIT, 119-120, 1962.

Howden, M,. Notebook II, 54.



The tosylate was prepared by addition of tosyl chloride to a pyridine solution of the carbinol. The tosylate precipitated out from the reaction solution upon addition of ice water as white crystals. They were not characterized.