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PART I: STEREOCHEMISTRY OF ALLENES PART II: THE REACTION OF PHENYL(PHENYLETHYNYL)-TERT-BUTYL CARBINOL WITH PEROXYACIDS

EUGENE WILLIAM BYRNES

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PART II - THE REACTION OF PHENYL(PHENYLETHYNYL)-t-BUTYL CARBINOL WITH PEROXYACIDS

BY

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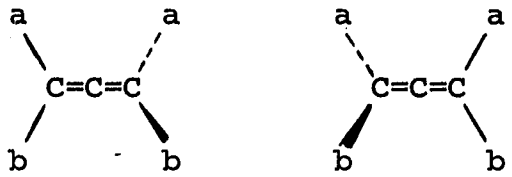
SECTION I

STEREOCHEMISTRY OF ALLENES

Introduction

In 1874 van't Hoff (4) predicted, as a corollary of his hypothesis about the tetrahedral nature of the carbon atom and the source of optical activity in carbon compounds, that an allene of the type I must show optical activity. Because the terminal substituents of I lie in

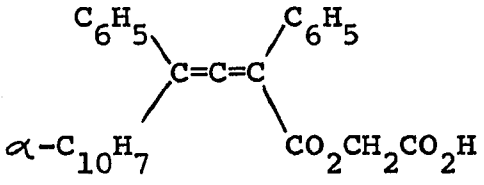


Ia Ib

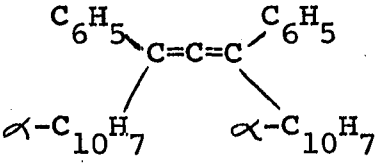
planes perpendicular to each other, Ia and its mirror image (Ib) are not superimposable and therefore must display optical activity (3).

All attempts to prove this prediction failed until, almost simultaneously, Maitland and Mills (5) in Great Britain and Kohler, Walker, and Tishler (6) in this country reported verifications of van't Hoff's prediction: Kohler's group synthesized and resolved the allenic acid II; Maitland

and Mills obtained the allenic hydrocarbon III in an optically active state by a partial asymmetric synthesis.



II



III

In 1951 Bijvoet, Peerdeman, and van Bommel (9) determined the absolute configuration of (+)-tartaric acid by studying the anomalous X-ray diffraction pattern of the dihydrate of its sodium rubidium salt. Using the configurations of Emil Fischer's convention, the anomalous diffraction patterns for the (+) and (-) salts were predicted with the aid of quantum mechanics. The pattern observed for the salt of (+)-tartaric acid corresponds with that of the convention adopted by Emil Fischer.

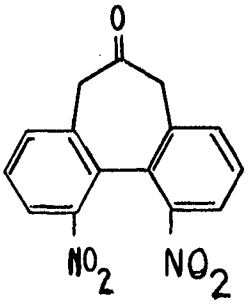
Thus, the absolute configuration of any compound that had been correlated chemically with tartaric acid became known and interest in absolute configurations rapidly developed. Prelog (18) developed a theory of asymmetric synthesis, which can be used to predict absolute configurations, based on conformational analysis of the transition state. This method was used to show that the convention

for steroids, in which the α-substituents lie below and the β-substituents above the plane of the paper, is correct. The use of optical rotatory dispersion for correlating configurations has been developed by Djerassi (27) and for six-membered ring ketones it can even be used to predict absolute configurations without the need of comparison with another asymmetric center of known configuration.

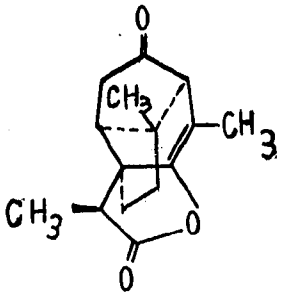
These techniques have been used to determine the absolute configurations of at least two classes of compounds that do not have asymmetric atoms but whose optical activity is due to molecular asymmetry, i.e., compounds whose whole molecule rather than one specific atom has an asymmetric configuration. These two classes are the optically active biphenyls and the allenes.

In 1958 Mislow (10) determined the absolute configuration of the biphenyl IV by a Meerwein-Pondorf-Verley reduction of the ketone IV with (+)-pinacolyl alcohol. It was assumed that the enantiomer of IV which was reduced faster was that one in which there was less steric repulsion in the transition state between the t-butyl group of the pinacolyl alcohol and the phenyl group of the biphenyl. The configuration of this ketone was later confirmed (11) by optical rotatory dispersion correlation with santonide

(V), whose absolute configuration was obtained independently.

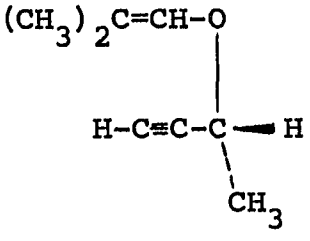


IV

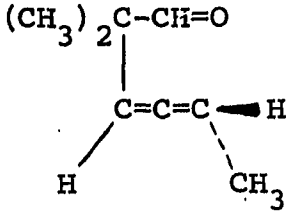


V

In the field of allenes, E. R. H. Jones (12) was the first to report a chemical correlation of an allene with a compound of known configuration and thus to determine the configuration of an allene. The reaction involved in his work was the conversion of Vla to Vlb through a six-membered ring transition state, similar to the Claisen rearrangement.



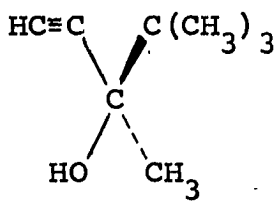
R-(+)-Vla



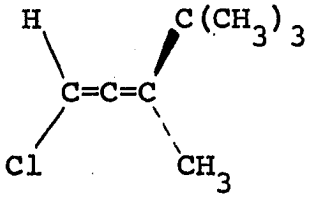
R-(-)-Vlb

At about the same time, Eliel (13) proposed an assignment of the absolute configuration of the allene VIII. This

allene was synthesized stereospecifically by Landor and Taylor-Smith (14) from the alcohol VII. Using Brewster's rules (15), Eliel proposed the S configuration for VII and, asserting that the reaction with thionyl chloride, regardless of whether it was SNi' or SN2', would give the same product, he deduced, from these considerations, that (+)-3-methyl-3-t-butyl-1-chloroallene has the (R) configuration.

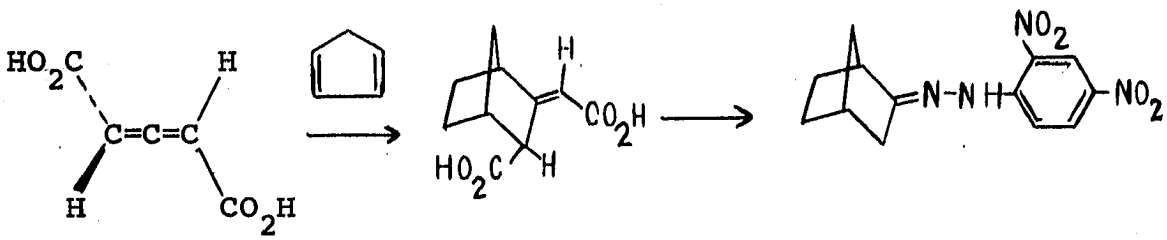


S-(+)-VII



R-(+)-VIII

Agosta (16) has determined the absolute configuration of glutinic acid (XXII) by a Diels-Alder reaction with cyclopentadiene and degradation of the resulting bicyclo derivative to norcamphor dinitrophenylhydrazone (XXIII).

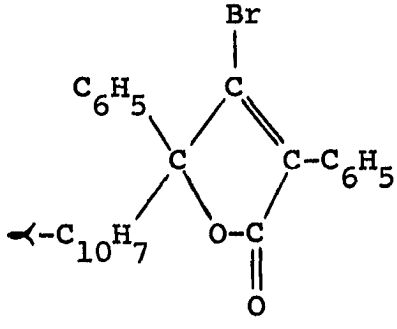


R-(+)-XXII

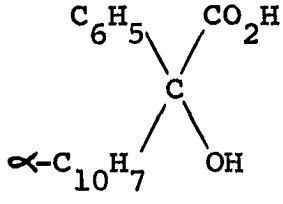
(+)-XXIII

Gianni (17) attempted to determine the absolute configuration of the optically active allene (II) by a chemical correlation with α-naphthylmandelic acid (X).

He converted the allene II by a stereospecific internal cyclization to the lactone (IX) containing an asymmetric atom but failed to attain the desired degradation to X. He did find, however, that the optical rotatory dispersion curves of the lactone IX and the diol obtained from it by lithium aluminum hydride reduction displayed Cotton effects similar to (+)-α-naphthylmandelic acid (X) and assigned the configuration on this basis.



IX



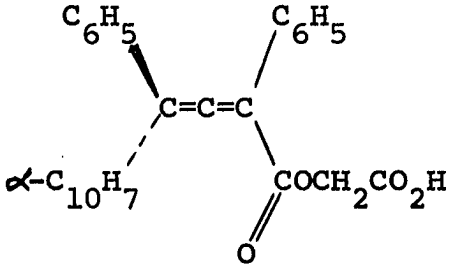
X

Background

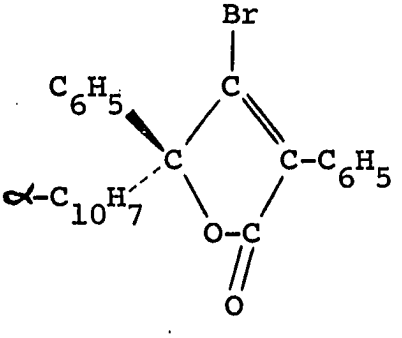
As support for his assignment of configuration, Gianni attempted to convert the allene II to α-naphthylmandelic acid (X) by chemical means.

A necessary step in such a scheme is the conversion of the allene, which has no asymmetric carbon atom, to a compound containing an asymmetric carbon atom which is similar to that of α-naphthylmandelic acid. This conversion must

take place in a manner such that the spatial relationship between the asymmetric arrangement of the allene molecule and that of the newly formed asymmetric carbon atom can be clearly and unequivocally understood. This situation was realized in the lactonization of the allene. Since the terminal substituents of the allene lie in planes perpendicular to each other and cannot rotate freely, the carboxyl oxygen in a given enantiomer can approach the other terminal carbon from only one side and can only form one enantiomer of the bromolactone IX. That is, the allene II in the "R" configuration must give the lactone IX in the "R" configuration.



R-II



R-IX

Following the first step, the chemical correlation would require that the lactone IX be degraded to a compound whose absolute configuration is known. In this particular situation, the end product would have been α-naphthylmandelic acid, whose absolute configuration was established by Prelog

(18). This direct correlation was never attained because of difficulties in the cleavage of the carbon-carbon double bond in the lactone ring. Even when the lactone ring was cleaved by lithium aluminum hydride reduction of the lactone function, the double bond was unaffected by ozone. The difficulty of ozonolysis of this double bond was attributed to its steric protection by the bulky groups surrounding it. More vigorous conditions of ozonolysis or of oxidative cleavage brought on the destruction of the naphthalene nucleus.

Preliminary Investigations

The failure of Gianni's attempt to degrade the allene to α-naphthylmandelic acid prompted a search for an alternate pathway for the determination of the absolute configuration of this allene.

One of the first thoughts involved conversion of α-naphthylmandelic acid to the allene. If the acid could be converted to the allene by a pathway such that the stereochemistry of each step was known, then the absolute configuration of the allene could be inferred from that of the acid.

Another idea involved the conversion of both the α-naphthylmandelic acid and the allene to a common product,

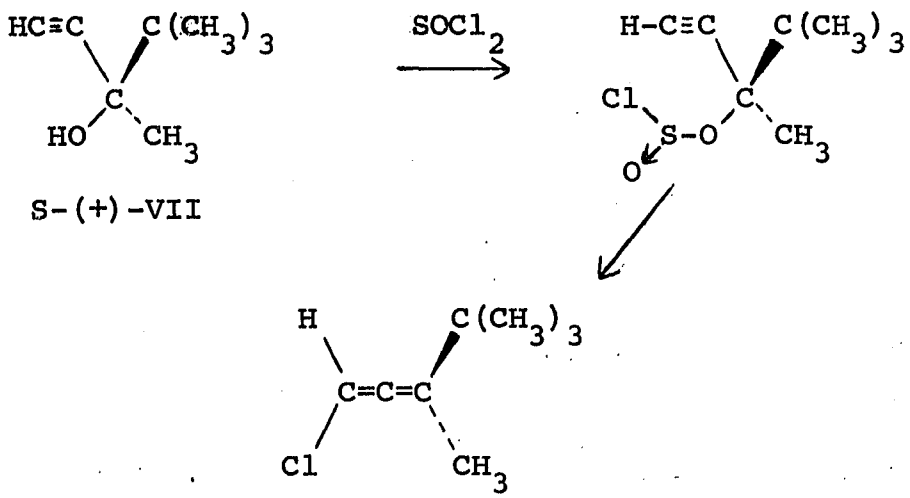
both conversions taking place by paths whose stereochemistry is known in every step.

Each of these possibilities was considered and discarded for the following reasons. First, the preparation and resolution of the α-naphthylmandelic acid were not high yield processes (17). Even after several crystallizations the acid had only a low optical rotation and the values reported in the literature did not give promise of obtaining a material of high optical purity or of high rotation. Second, there is a great chance of racemization of the acid in any reaction attempted on it because of the ease of ionization of the hydroxyl group. Third, an undetected anchimeric effect might cause retention of configuration at the asymmetric center when inversion is anticipated.

The apparent solution to the problem was found in the synthesis of both the allene and the α-naphthylmandelic acid from the same starting material by reaction paths that would allow one to derive the absolute configuration of the allene from that of the starting material and that of the starting material from the known absolute configuration of the α-naphthylmandelic acid.

Landor (14) demonstrated that an allene could be

synthesized stereospecifically from an acetylenic alcohol by reaction with thionyl chloride. The reaction was presumed to take place by either an SNi' or an SN2' reaction.



S-(+)-VII

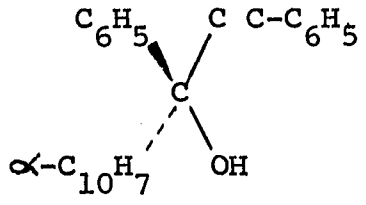
R-(+)-VIII

$$\text{R-(+)-VIII} + SO_2$$

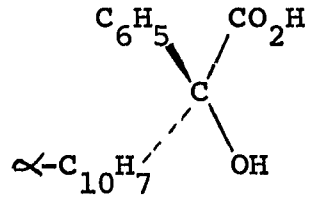
An SN1 reaction is excluded by the fact that the allene obtained is optically active and the SN1 mechanism involves a carbonium ion intermediate which would cause the loss of stereochemical integrity. In the SNi' reaction the cyclic transition state allows one to deduce the stereochemistry of the allene if one knows the stereochemistry of the optically active acetylenic alcohol. In the case of the SN2' reaction, Stork and White (19) have shown that the displacing ion approaches the substrate from the same side as that from which the leaving group departs. Consequently, whichever mechanism prevails, SNi' or SN2', the stereochemical

relationship between the starting acetylenic alcohol and the final allene will be the same. Eliel (13) used this same reasoning to deduce the absolute configuration of the allene VIII.

In this particular situation the appropriate acetylenic alcohol is phenyl-∝-naphthylphenylethynyl carbinol (XI). The absolute configuration of the alcohol XI is obtainable if it can be converted to ∝-naphthylmandelic acid while maintaining stereochemical integrity. The triple



XI



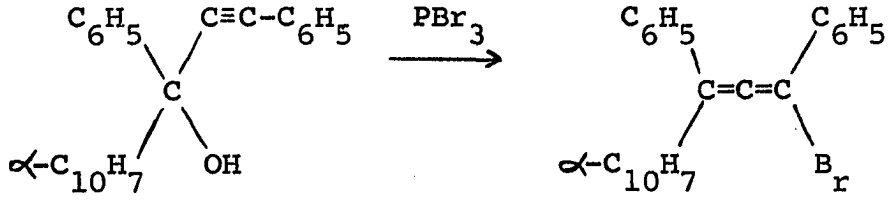
X

bond provides the functional group upon which to work in order to perform this conversion. A simple oxidative cleavage of this bond would perform this conversion in one step without disturbing the asymmetric center. Several oxidizing agents are obvious potential reagents for this purpose: ozone, peroxyacids, permanganate, osmium tetroxide.

The resolution of the alcohol appeared to present no particular problem. The alcohol has been synthesized in a simple reaction from the sodium, lithium, and Grignard

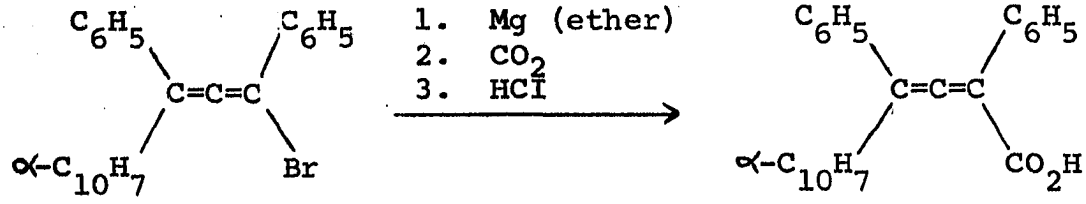
reagents derived from phenylacetylene reacting with phenyl-α-naphthyl ketone. The hydrogen phthalate ester would be easily obtainable and this could be resolved in the usual manner by fractional crystallization of a salt of this ester with an optically active base such as brucine.

The actual conversion of the racemic alcohol XI to the allenic bromide XII was brought about by phosphorus tribromide.



XI XII

The product of the reaction showed in its infrared spectrum the absorption band expected for an allene. Confirmation of the structure of the allenic bromide was obtained by conversion to the allene carboxylic acid XIII by carbonation of the Grignard reagent formed from XII.



XII XIII

The acid was identical to a sample of the allene carboxylic acid obtained from Gianni.

Difficulty in the oxidative cleavage of the acetylene alcohol XI was anticipated. The ozonolysis of a triple bond is more difficult than that of a double bond (39). Gianni (17) found, in addition, that the naphthalene nucleus of the lactone IX was more readily attacked than the double bond when it was subjected to ozonolysis conditions.

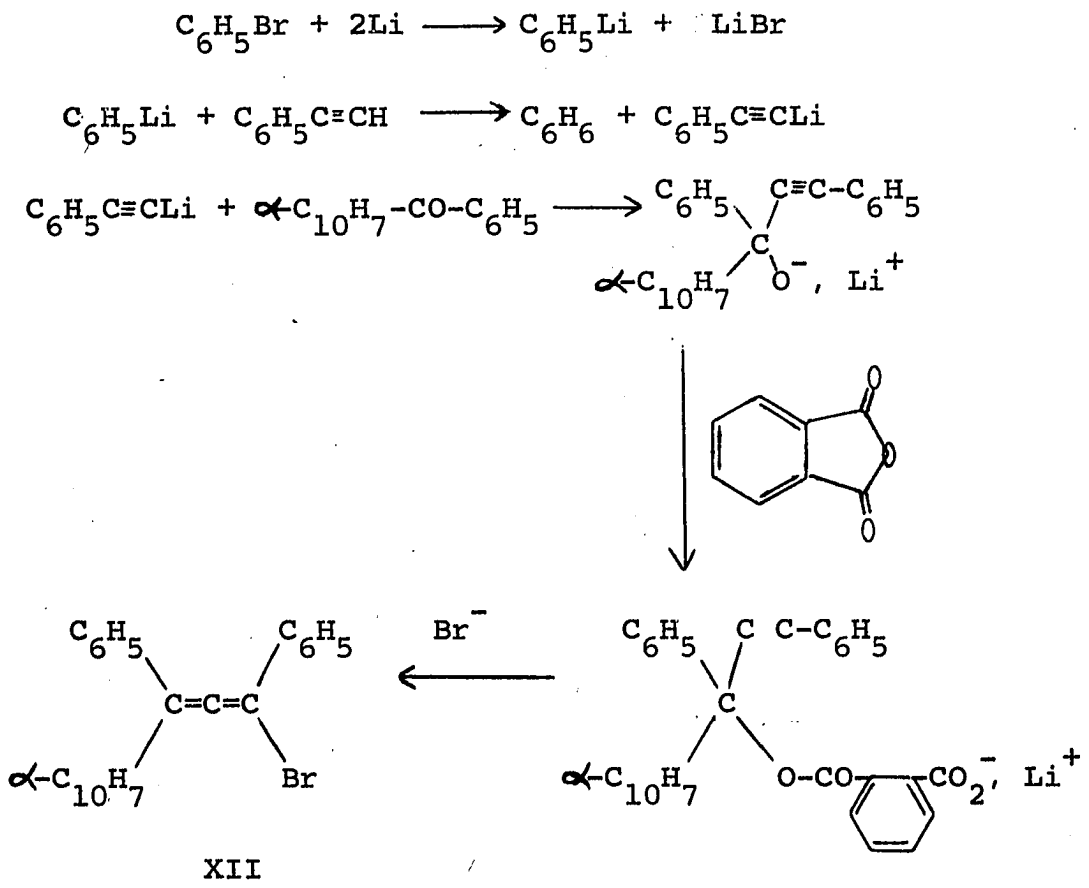
The resolution of the alcohol, which was not expected to present any difficulties, forced a re-appraisal of the goal of this project. The hydrogen phthalate ester, which was necessary for the resolution, could not be synthesized. The usual procedure for such a synthesis is treatment of the alkoxide of the alcohol with phthalic anhydride. Several methods of making the alkoxide were tried in the anticipation that some form of the alkoxide would react with phthalic anhydride. Only the alcohol and phthalic acid could be obtained from various reaction mixtures. The alkoxide was formed by reaction of the alcohol with ethyl magnesium bromide, with lithium hydride powder, with a lithium hydride dispersion in mineral oil, with lithium metal dispersed in mineral oil, and with sodium amide. In all cases, when the reaction mixture was hydrolyzed after

allowing powdered phthalic anhydride to stir overnight with the alkoxide, the alcohol was recovered.

In all these attempts to synthesize the ester, the reaction mixture was heterogeneous since neither the alkoxide nor phthalic anhydride is appreciably soluble in ether. It was observed during the synthesis of the alcohol that the reaction mixture immediately before hydrolysis was homogeneous, indicating that the alkoxide as it is formed in this reaction is soluble in ether. Consequently, instead of hydrolysis of this mixture, phthalic anhydride which is slightly soluble in ether was added to see if the hydrogen phthalate ester could be formed in a homogeneous medium. The product that was obtained from this reaction was found to be not the expected hydrogen phthalate nor the acetylenic alcohol, but the allenic bromide XII.

A deeper investigation of this reaction showed that indeed the lithium alkoxide had been formed from the phenylethynyllithium and α-naphthophenone. Hydrolysis of a portion of the reaction mixture at this point produced the alcohol, showing that the allenic bromide did not form until after the phthalic anhydride had been added. This suggests that the alkoxide does react with the phthalic anhydride to form as an intermediate the salt of the phthalate ester. The

phthalate ion which is a good leaving group, might be displaced from this intermediate by the strongly nucleophilic bromide ion, which is present in the solution from the first step of the reaction sequence, the formation of phenyllithium.



XII

Alternatively, an ionic mechanism can be pictured, in which the asymmetric carbon atom becomes ionized upon the departure of the phthalate ion and a bromide ion attacks the terminal acetylenic carbon atom to form the allenic product. Because of the resonance stabilization of the carbonium ion by the phenyl and α-naphthyl groups and by propargyl-allenic resonance,

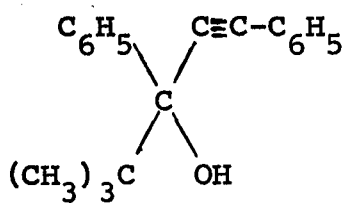
the latter mechanism is more probable.

The facility with which this phthalate ester decomposes is shown by the fact that the phthalate ion, a doubly negative ion, is formed in ether-benzene solvent, a relatively non-polar solvent. The ease of displacement of the phthalate group by a nucleophile suggested that the ester might not be obtainable because of its instability. Even if it were obtainable, the nitrogen base used to resolve it, being a good nucleophile too, would probably displace the phthalate group instead of forming a salt.

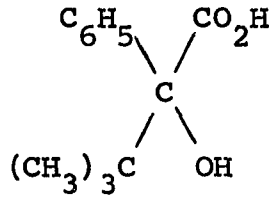
For these reasons: the inability to obtain the hydrogen phthalate ester; the probability that the ester even if obtained could not be resolved; and the anticipated difficulty in oxidative cleavage; it was decided to change to a substrate without the α-naphthyl group for the continuation of this project. If, using an alternate substrate, reagents and conditions were found that might be applicable to this system, then it could be returned to at a later date. At the time, at least, it seemed that the α-naphthyl group was preventing the completion of the project.

In the choice of an alternate system, several factors of importance were considered. If the carbon atom adjacent

to the carbinyl carbon of the alcohol contains a hydrogen atom, there is great danger that dehydration might take place leading to an enyne or to a Rupe rearrangement. Similarly, if there is a hydrogen atom in the corresponding location in the allene, then there is a great possibility that the allene might rearrange to a conjugated diene. In either event optical activity would be lost. To circumvent these difficulties a system was needed that contained no hydrogen atoms in the positions beta to the hydroxyl group. Three alternative groups present themselves as likely candidates: β-naphthyl, phenyl, and t-butyl. The β-naphthyl would probably present the same difficulties that were encountered with the α-naphthyl. If a phenyl group were used in place of the α-naphthyl, the resulting alcohol would not be capable of displaying optical activity. The t-butyl group is not as susceptible to oxidation as the α-naphthyl and the alcohol would be capable of displaying optical activity. An important point in favor of the t-butyl group is that the absolute configuration of the acid XIV is known (18) and that of the alcohol XV can be determined. The new substrate for the investigation then was phenyl-t-butylphenylethynyl carbinol (XV).



XV



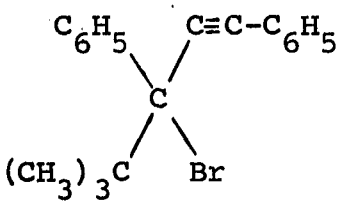
XIV

The same considerations that applied to the ∝-naphthyl substituted alcohol apply also to the t-butyl substituted alcohol. Its stereospecific conversion to the allenic bromide should give an allene of known configuration. Likewise, the oxidative cleavage of the alcohol will not disturb the asymmetric center of the molecule. In addition to these necessary features, the absence of the naphthalene nucleus would eliminate the complications in the oxidation reaction.

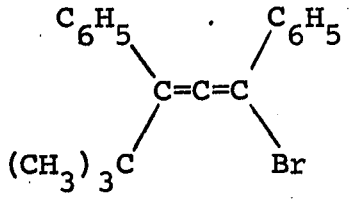
The starting material of the new system, 4,4-dimethyl-1,3-diphenyl-1-pentyn-3-ol (XV), was originally characterized by Willemart (8). He reported that the treatment of pivalophenone with the phenylethynyl Grignard reagent gave the best yields of the alcohol XV. In view of the poor results obtained in this laboratory with the phenylethynyl Grignard reagent and the much better results with phenylethynyllithium, it was decided to use the latter for the synthesis of the starting alcohol. The alcohol was prepared in this way in

46% yield. The high solubility of the alcohol in all the common organic solvents made its crystallization difficult, but cooling to -78° in hexane gave satisfactory results.

Willemart (8) reported that the alcohol is converted to the corresponding acetylenic chloride by the action of PCl_3. Since the rearrangement to the allenic halide is necessary for this work, and since Wotiz (20) had shown by infrared analysis that the substance that Ford, Thompson, and Marvel (21) thought was the acetylenic bromide (XXI) was actually the allenic bromide (XVI), the reaction of this alcohol with PBr_3 was immediately investigated.



XXI

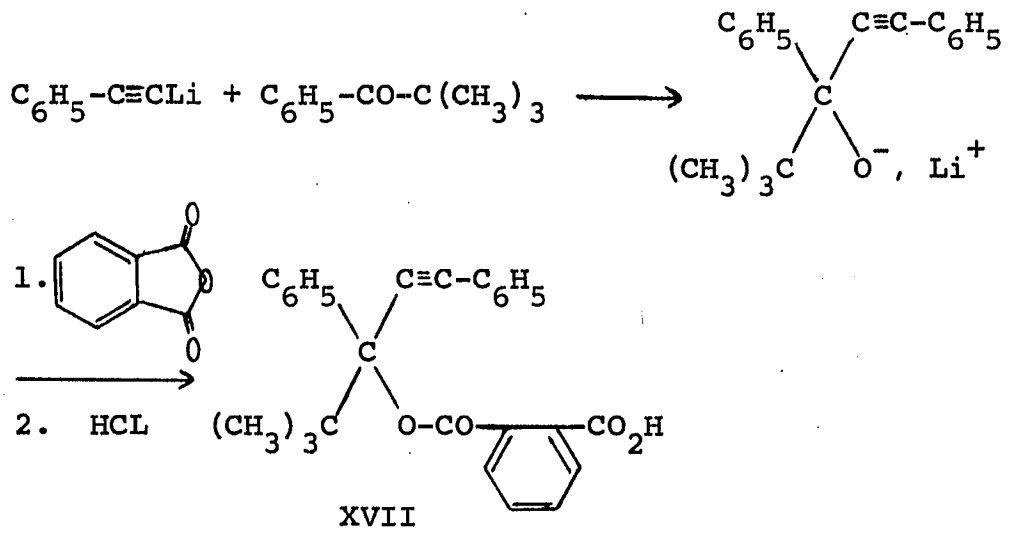


XVI

The infrared absorption spectrum of the reaction product showed clearly that an allene structure was present: the absorption band at 1950 cm^{-1} is attributed to the stretching of the cumulative double bonds of the allene. The absence of the acetylenic absorption at 2200 cm^{-1} suggests, although it does not prove, the absence of the triple bond. In addition, there is a strong absorption band at 848 cm^{-1}

which is attributed to the allenic carbon-to-bromine bond.

Having shown that the alcohol could be converted to the allenic halide, the optically active alcohol was then needed to test the stereospecificity of the reaction. The hydrogen phthalate ester (XVII) of the alcohol XV was synthesized directly from the lithium alkoxide formed from phenylethynyllithium and pivalophenone without isolating the alcohol. The infrared spectrum, carbon-hydrogen analysis, neutralization equivalent, and saponification equivalent were all consistent with the structure assigned to XVII.



XVII

In addition, hydrolysis of the ester gave phthalic acid (identified by melting point and conversion to the anhydride) and the acetylenic alcohol XV (identified by melting point and infrared spectrum compared to an authentic sample).

Since it had been observed in the α-naphthyl system that the phthalate intermediate was directly transformed into the allenic bromide, a similar type of reaction was sought in this instance. Treatment of the ester with lithium bromide in ether at room temperature for five days did not bring about a reaction. Phosphorus tribromide did, however, give an oil whose infrared spectrum was identical to that of the allenic bromide XVI.

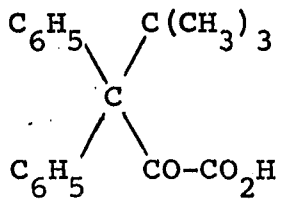
Several attempts were made to resolve the phthalate ester by fractional crystallization. The phthalate ester and brucine were mixed in a ratio of 2:1 in hope that at least a partial resolution could be obtained by preferential formation of one salt. Since the desired salt did not precipitate, the solvent was removed by evaporation, leaving an oil. The ether soluble portion of this oil was dextrorotatory. Both the soluble and the insoluble portions of this oil had spectra that were identical to each other and different from both brucine and phthalate ester. The brucine salt of the phthalate ester was obtained as an oil, which was crystallized by trituration with ether. No satisfactory solvent system was found, however, for the fractional crystallization of the salt. Addition of iso-propyl ether to a solution of the salt in carbon tetrachloride caused the

crystallization of four fractions of salt, all of which had the same specific rotation within experimental error. Slow evaporation of the solvent from a solution containing equimolar amounts of the phthalate ester and cinchonine again gave no indication of salt formation but yielded only an oil. Simultaneously, other observations, which are reported in detail in the second part of this thesis, led to a change in emphasis of the research and these attempts at resolution were abandoned.

As a part of this investigation, the degradation of the alcohol XV to t-butylmandelic acid (XIV) was attempted. Two oxidizing agents were used: ozone and peroxyacid; and an alternate path was tried.

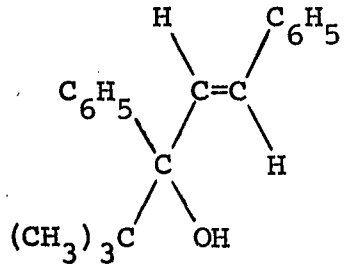
Ozonolysis of the alcohol gave two products, one of which could be identified as benzoic acid. The other product, also acidic, was not the expected t-butylmandelic acid as shown by its infrared spectrum. To confirm this, t-butylmandelic acid was synthesized by an alternate path and was shown to be different from this new product. Although the new product was not obtained in sufficient quantity to allow a complete elucidation of its structure, the following information was obtained. Its empirical formula is $C_{19}H_{20}O_3$, as deduced from carbon-hydrogen analysis. Its

infrared spectrum indicated the presence of the following groups: carboxylic acid (1700 cm^{-1}); unconjugated carbonyl (1720 cm^{-1}); t-butyl (1365 and 1395 cm^{-1}). From this information, the structure appears to be XVIII, although the manner of its formation from XV by a simple path cannot be visualized.



XVIII

In an attempt to circumvent the abnormal ozonolysis of the triple bond, the acetylenic alcohol was reduced with lithium aluminum hydride. Acetylenic alcohols of this type are reduced by lithium aluminum hydride to the corresponding trans olefinic alcohol (XIX) (39). Using a twenty-fold excess of lithium aluminum hydride, a product was obtained which was shown to be a mixture of XIX and the corresponding saturated alcohol. Repetition of this reduction using a five-fold excess of lithium aluminum hydride gave a product



XIX

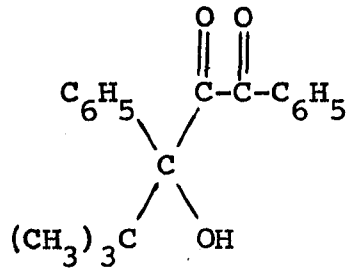
that had the characteristic infrared absorption band of a trans olefin at 965 cm^{-1} and the ultraviolet absorption band of the styrene chromophore at 252 mμ (ε=15,500). The intensity of the styrene chromophore, in addition, is almost the same as that of phenyl styryl carbinol. The reductive hydrolysis of the ozonide of this material had a definite odor of benzaldehyde, but neither benzaldehyde nor t-butyl mandelic acid (XIV) could be isolated from it. Young, et al., (28) reported the abnormal ozonolysis of allylic alcohols with loss of the allylic carbon atom. This route was not considered promising, then, for the degradation of the acetylenic alcohol to t-butylmandelic acid.

At this point a new oxidizing reagent was tried in the hope of finding a pathway to the cleavage of the triple bond without disturbance of the adjacent asymmetric carbon. The work of Schlubach and Franzen (22) on the oxidation of acetylenic compounds suggested that a peroxyacid might prove to be an appropriate reagent.

Because of the difficulties noted in previous work with the sterically hindered triple bond of XV, it was decided to use at the start the strongest of the peroxyacid oxidizing agents known, peroxytrifluoroacetic acid. This acid is commonly used in solution in anhydrous methylene

chloride (the peroxyacid decomposes at higher temperatures and in the presence of water) in the presence of solid anhydrous disodium phosphate (to reduce the acidity of the reaction medium). From the acidic portion of the reaction product, there were obtained small amounts of benzoic acid and phenol. The non-acidic portion of the reaction product (which was not basic but neutral) was shown to contain several compounds which are described in the second part of this thesis. The main points to note here are that the reaction is vigorous and complex.

Since peroxytrifluoroacetic acid is a very strong oxidizing agent, a weaker one of the same type was tried; peroxyacetic acid. Using peroxyacetic acid (dissolved in acetic acid) similar results were expected and found, excepting that the reaction proceeded more slowly and there was no apparent tar formation. Among the products isolated were compounds with the formulas $C_{19}H_{20}O_2$ and $C_{19}H_{20}O_3$. The compound $C_{19}H_{20}O_2$ was extremely interesting because a destruction of the t-butyl group was indicated. The nature of this compound and its formation are described in the second part of this paper. The compound $C_{19}H_{20}O_3$, whose structure is XX, is important because it can potentially be cleaved to give the desired t-butylmandelic acid.



XX

At this point a review of the situation was called for. The oxidative degradation of the acetylenic alcohol appeared to be very promising because of the isolation and identification of the compound, $C_{19}H_{20}O_3$. A variety of oxidizing agents are available and under varying conditions one was certain to bring about the cleavage of this compound to t-butyl mandelic acid. In addition, there was good reason to believe that the conversion of the acetylenic alcohol to the allenic bromide could be brought about stereospecifically and that the allenic halide could be converted to the corresponding carboxylic acid without loss of activity. In fact, vinyl halides have been converted to the corresponding acids through the use of Grignard reagents and lithium reagents. The situation with respect to the resolution of the alcohol was different, however, since continuing efforts had not succeeded in giving results either as far as obtaining a nicely crystalline salt or providing a solvent system that would allow the recrystallization of the salt.

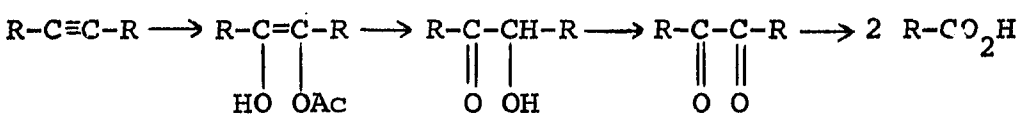
Taking into consideration these difficulties and the opportunity opened up by the discovery of the peroxyacid reaction of studying a new reaction, which appeared to involve an unusual rearrangement, it was decided at this point to discontinue the allene studies and to examine the reaction of this acetylenic alcohol with peroxyacids in greater detail.

SECTION II

PART II - THE REACTION OF PHENYL(PHENYLETHYNYL)-t-BUTYL CARBINOL WITH PEROXYACIDS

Introduction

The first report of any studies of the action of peroxyacids on acetylenic compounds appeared in 1930. Böeseken and Slooff (23) investigated the reaction between peroxyacetic acid and several acetylenic compounds. They concluded that monosubstituted acetylenes reacted only sluggishly with peroxyacetic acid but that disubstituted acetylenes readily underwent oxidative cleavage. They pictured the reaction in the following manner.



The diketone was considered to be a probable intermediate because of the fact that it reacted with the peroxyacid more rapidly than did the acetylene, forming the acid product quantitatively.

In the oxidation of stearolic acid (XXXVIII) they found that sixty percent of the stearolic acid was cleaved

to azelaic (XXXIX) and nonanoic (XXIV) acids. Nine percent

$$CH_3(CH_2)_7\text{-}C{\equiv}C\text{-}(CH_2)_7CO_2H \longrightarrow CH_3(CH_2)_7CO_2H + HO_2C(CH_2)_7CO_2H$$

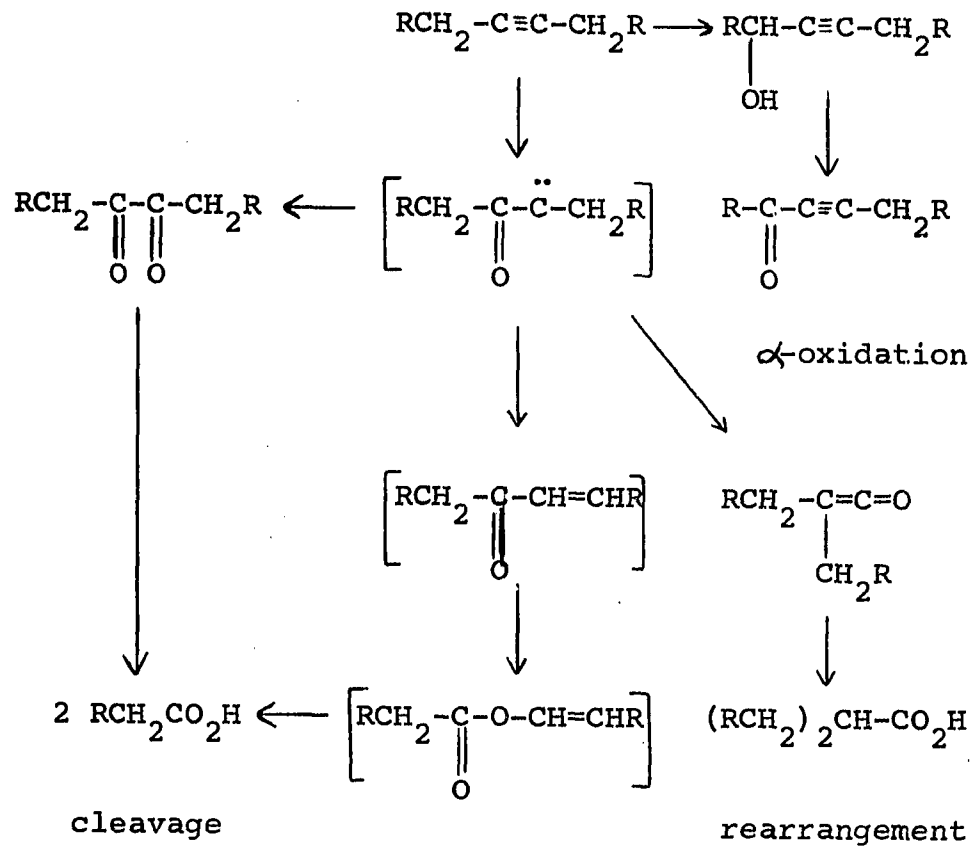
XXXVIII XXXIX XXIV

of another (unidentified) monobasic acid was also obtained. The fact that not all of the acetylene is cleaved to the expected product indicates that an alternate reaction is taking place. In addition, the rapid and quantitative formation of products from the diketone indicates that forty percent of the time the diketone is not formed. Thus, there are two indications that more than one path for the oxidation is involved in the reaction.

In 1952 Schlubach and Franzen (24) reported the reaction between peroxyacetic acid and acetylenic hydrocarbons and concluded that two reaction paths were involved. One is the simple oxidative cleavage of the triple bond that Böeseken and Slooff had found. The other involves a rearrangement through presumed ketocarbene and ketene intermediates to a branched-chain acid. The similarity of this rearrangement to the Wolff rearrangement is obvious.

Further studies of this reaction by Franzen (25) indicated that three reactions, α-oxidation, cleavage, and rearrangement, were taking place simultaneously. The

following scheme shows the actual or possible reaction paths.



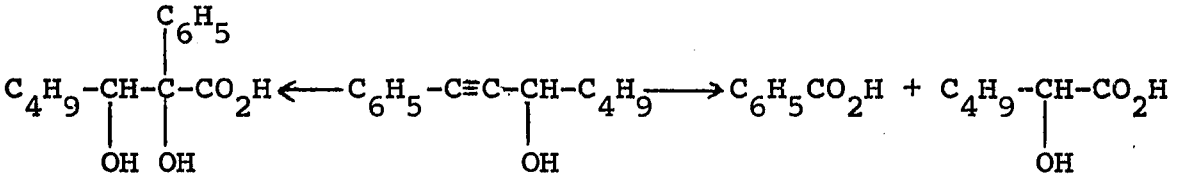
Two of these paths, those leading to the rearrangement and to the cleavage reactions, involved an attack at the triple bond. Both of these reaction paths are easily understandable as proceeding through an actual or incipient ketocarbene intermediate. In fact, the α,β -unsaturated ketone was isolated from the reaction mixture and shown to be an intermediate.

The third path, that leading to alpha oxidation, involves an attack at the α-methylene group: the intermediate

acetylenic alcohol undergoes oxidation to the corresponding acetylenic ketone. In this case it is noteworthy that the ∝-methylene group is attacked by the electrophilic reagent while the triple bond is left untouched. An analogous situation is found in the allylic halogenation reactions of the free radical type. It seems unreasonable then that both an electrophilic attack at the unsaturated linkage and an attack (possibly free radical) at the ∝-hydrogen are taking place simultaneously.

The same workers (26) studied the reaction of acetylenic alcohols with peroxyacetic acid. Here again they found more than one reaction path: one path led to simple cleavage of the triple bond, the other to rearrangement without loss of carbon. In this case, however, both pathways began with attack at the triple bond; no product was found in which attack was at the ∝-position. The products can be explained by an electrophilic attack at the triple bond with the actual or incipient formation of a ketocarbene. In one case, the carbene carbon is oxidized to a carbonyl function with products being formed by oxidative cleavage of the ∝-diketone. In the other case, a Wolff-type rearrangement takes place, leading to a ketene intermediate, which, in the presence of the peroxyacetic acid, is oxidatively hydrolyzed. The final

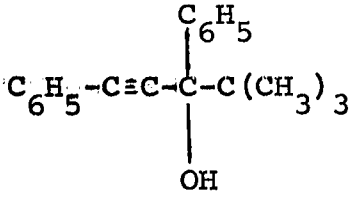
product of the rearrangement is an α,β-disubstituted glyceric acid.



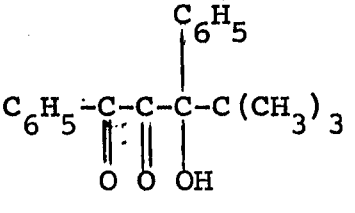
Background

As indicated in Part I of this paper, the reaction of phenyl(phenylethynyl)-t-butyl carbinol (XV) with peroxy-acids gave indications that an unusual reaction was taking place. The multiplicity of products immediately suggested that several competing reactions were involved. The two C_{19} products mentioned previously gave another indication of the uniqueness of the reaction.

The compound, $C_{19}H_{20}O_3$, whose structure was shown to be XX, is formed by a simple oxidation of the triple bond. In effect, an oxygen atom is added to each carbon of the acetylene with no change in the carbon skeleton.



XV



XX

The appearance of benzoic acid as a product can be explained by the cleavage of the triple bond, perhaps through this diketone intermediate.

The compound $C_{19}H_{20}O_2$ was known from its infrared spectrum to be a hydroxyketone. The manner in which one carbonyl oxygen could be added to the alcohol XV was not apparent, as was the case with the compound $C_{19}H_{20}O_3$. Since the infrared spectrum of this compound (hereafter called compound A) did not give enough information to elucidate its structure completely, the proton magnetic resonance spectrum was obtained through the courtesy of Dr. Michael H. Gianni at the University of Notre Dame. It showed the presence of two nonequivalent methyl groups in contrast to the three equivalent ones of the t-butyl group. Obviously then, the t-butyl group was destroyed in this reaction and isomerization of the carbon skeleton has taken place without loss of carbon.

A third reaction is indicated by the presence of phenol among the reaction products. In this case, an attack at the hydroxylic carbon is indicated with subsequent cleavage of the carbon-phenyl bond.

With at least three reaction paths being indicated

by the products of the reaction, a more detailed study of the reaction was undertaken.

The Reaction

The acetylenic alcohol XV was treated both with peroxytrifluoroacetic acid and with peroxyacetic acid. The two reagents react in the same manner with the alcohol XV. The former is, however, a much more vigorous oxidizing agent and is completely used up within several hours, while the latter reacts more slowly and is still present after one week. In order to moderate the reaction of peroxytrifluoroacetic acid, an insoluble inorganic base, disodium phosphate, was added to the reaction mixture to decrease its acidity.

Two and one half molar equivalents of peroxytrifluoroacetic acid, freshly prepared from trifluoroacetic anhydride and 90% hydrogen peroxide in methylene chloride, were added dropwise to a solution of the alcohol XV in methylene chloride. The reaction generated heat but the temperature did not rise above 42°, the boiling point of the solvent. After several hours, a negative test with starch-iodide paper showed that the peroxyacid was all consumed and that oxidation had ceased.

Peroxyacetic acid was prepared by the addition of hydrogen peroxide to acetic anhydride without solvent. The reaction with the acetylenic alcohol was carried out by dissolving the alcohol in glacial acetic acid and adding to this three and one half molar equivalents of peroxyacetic acid solution. For several hours there was no evidence of reaction, after which the solution became pale yellow. Usually, after one to two days, a white flocculent precipitate formed, amounting to about 15% yield; this precipitate is the compound, $C_{19}H_{20}O_2$, compound A.

Reaction Products

In the work-up of the reaction with peroxytrifluoroacetic acid the solid disodium phosphate was removed by filtration. The filtrate was washed with water to remove the trifluoroacetic acid and then with dilute sodium bicarbonate to remove any strongly acidic products. Evaporation of the dried methylene chloride solution and crystallization of the residue from ether gave compound A. Evaporation of the filtrate from compound A and the crystallization of the residue from petroleum ether gave the compound, $C_{19}H_{20}O_3$, designated compound B. The remainder of the products were separated by chromatography on alumina or silica gel.

Compound A usually precipitated from solution after about twenty-four hours when peroxyacetic acid was the oxidizing agent. After this product was filtered off and washed, the rest of the products were obtained from the acetic acid by diluting the solution with a large amount of water and extracting the organic materials with ether. The ethereal solution was separated into an acidic fraction and a neutral fraction by extraction with dilute sodium hydroxide. The neutral fraction was further separated by chromatography on silica gel.

The chromatography of the neutral fraction in each case was performed in the same manner. Silica gel was used as the adsorbent and the material was eluted with solvent of varying composition. Whenever possible the fractions were taken by observing when the several colored bands were eluted from the column. The elution was begun with pure petroleum ether and the polarity of the solvent was increased gradually by addition of diethyl ether until the solvent contained 25% ether. In this way the neutral portion of the product was resolved into its components which were identified and which are described in the following paragraphs. First are described the products which were compared with known compounds; second, those which have been assigned structures from their physical (spectral) and chemical properties;

and third, those for which only tentative structural assignments can be made because they were not obtained in sufficient quantity or in sufficient purity to determine their structure.

Benzoic acid was isolated from the base soluble portion of the reaction mixture. It was obtained as a crude solid with a light tan color, melting at 114-118°. Its isolation was made difficult by the presence in the reaction mixture of large amounts of acetic or trifluoroacetic acid. Although the sample was not pure, its infrared spectrum compared favorably with that of an authentic sample of benzoic acid.

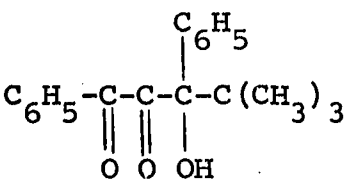
A small amount of phenol was obtained as an oil. It was identified by its odor and by the fact that it reacted readily with bromine water to form a solid derivative. Again the sample was not pure but its infrared spectrum compared favorably with that of a pure sample of phenol.

A small amount of pivalophenone (phenyl-t-butyl ketone) was obtained, insufficient to determine its boiling point or to prepare a derivative. The sample was sufficiently pure that its infrared spectrum was identical to that of an authentic sample of pivalophenone.

Two of these three substances, benzoic acid and

pivalophenone, besides being identified by comparison with known compounds, are reasonably expected products of this reaction: benzoic acid as a cleavage product and pivalophenone as an oxidation product of the other cleavage product, t-butylmandelic acid. The third product, phenol, however, was not anticipated as a product of the reaction. The manner of its formation will be described below.

All available evidence indicates that compound B, $C_{19}H_{20}O_3$, has the structure XX. The data leading to the structural assignment are described here.

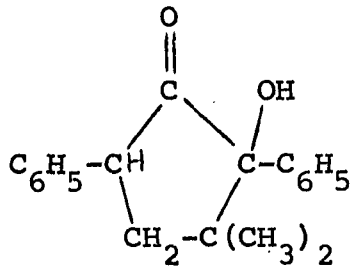


XX

First, its analysis indicated that two oxygen atoms have been added to the acetylenic alcohol. The easiest way to account for them is by the addition of the two oxygen atoms to the triple bond. Second, the infrared spectrum indicated that there was in the molecule a hydroxyl function and two carbonyl functions, one conjugated to an aromatic ring (1665 cm^{-1}) and the other not conjugated (1705 cm^{-1}). The characteristic absorptions of the t-butyl group at 1365

and 1395 cm^{-1} were also present in the spectrum. Third, the proton magnetic resonance (PMR) spectrum showed three absorptions: τ=2.65, 7.58, and 8.95. These correspond to the ten aromatic hydrogen atoms, the single hydroxylic hydrogen, and nine equivalent methyl hydrogen atoms of the t-butyl group. All of this information quite clearly supports the assignment of the structure of this compound.

Compound A, $C_{19}H_{20}O_2$, was isolated from both the peroxyacetic and the peroxytrifluoroacetic acid reactions. The structure XXV was assigned to this substance on the basis of its molecular formula, and its infrared and proton magnetic resonance spectra.



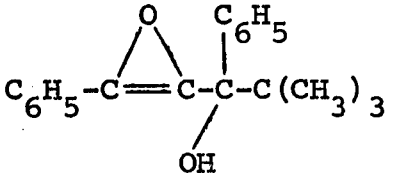
XXV

Carbon-hydrogen analysis and molecular weight determination showed that its molecular formula was $C_{19}H_{20}O_2$. Its infrared spectrum showed absorption maxima at 3410 and 1735 cm^{-1}. The PMR spectrum showed two non-equivalent methyl groups: τ=8.84 and 9.23. A saturated open-chain hydrocarbon

having nineteen carbon atoms must have forty hydrogen atoms. For every double bond and for every ring in a carbon compound the number of hydrogen atoms is two less than in a saturated open-chain hydrocarbon with the same number of carbon atoms. Since compound A has twenty hydrogen atoms less than the saturated open-chain hydrocarbon, it follows that there must be ten double bonds and/or rings in the molecule. Each benzene ring accounts for three double bonds and one ring; the carbonyl function, indicated by the 1735 cm^{-1} absorption band accounts for one double bond. Since this makes a total of nine known double bonds and rings, the molecule of compound A must contain one or more ring or double bond but not both.

Since the starting acetylenic alcohol has the molecular formula $C_{19}H_{20}O$, we must consider ways in which a single atom of oxygen can be added to it, perhaps with a change in the carbon skeleton, but without the loss or gain of any hydrogen atoms.

The simplest way to envision the addition of a single atom of oxygen is through a reaction similar to the epoxidation of an alkene. This reaction would give a product (XXVII) containing an unsaturated, three-membered, oxygen heterocyclic ring which would be called an oxirene or an "acetylene oxide". Franzen (25b) reported that he obtained

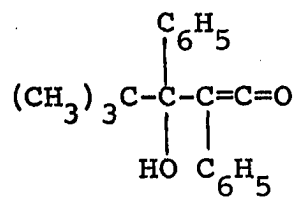


XXVII

an acetylene oxide from the reaction of peroxyacetic acid with di-n-butylacetylene and that its infrared spectrum contained both an acetylenic and a carbonyl absorption. He reported later (25c), however, that his presumed acetylene oxide was actually a mixture of the di-n-butylacetylene and 4-decen-6-one. In addition to the fact that no oxirene compound has been isolated, this structure for compound A seems unlikely because of the conditions under which it is formed. In analogy to an ethylene oxide, an acetylene oxide would be expected to undergo an acid catalyzed ring cleavage, probably more readily. One would not expect to isolate it from acetic acid solution. Besides, the IR and PMR spectra cannot be reconciled with the acetylene oxide structure (XXVII). Elimination of the acetylene oxide structure as a final product isolated, however, does not preclude its existence as an intermediate. Schlubach and Franzen (24, 25, 26) presume this to be an intermediate in the reaction of acetylenes with peroxyacids. The susceptibility of the acetylenic bond to electrophilic attack and the electrophi-

licity of peroxy acids both lead one to expect the point of initial attack to be the triple bond.

The two oxygen atoms of compound A are known from the infrared spectrum to be contained in a carbonyl group and in an alcohol. If it be assumed that the hydroxyl group of the product is the same one as in the starting alcohol, then the carbonyl oxygen must be attached to one of the carbon atoms that formerly made the triple bond. In this case, the other former acetylenic carbon atom would be left with two unshared electrons. If these electrons happen to be paired, this carbon atom has the "open sextet" of the classical Whitmore mechanism and a 1,2-shift of an adjacent group would be expected. The product of this reaction would be the ketene XXVIII.

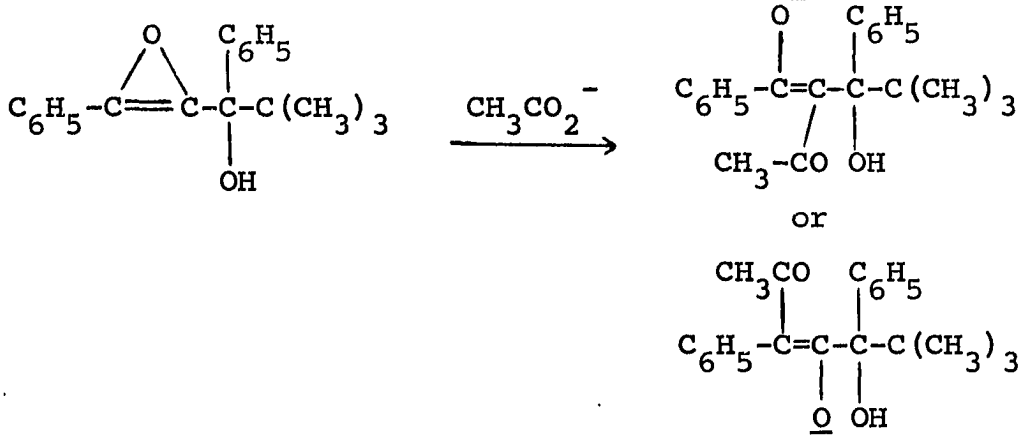


XXVIII

Here again, the infrared and proton magnetic resonance spectra do not support this structural assignment and the fact that the product was isolated from acetic acid solution would lead one to expect not a ketene but an acid as the

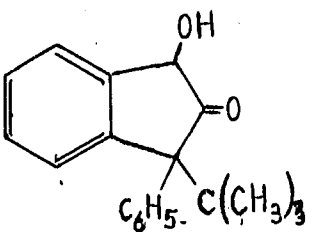
product of the reaction. Schlubach and Franzen (24, 25, 26) did isolate from their reaction mixtures acids formed by just such a reaction path. In one case the acid formed by simple hydration of the ketene was found and in another the acid from oxidative hydration (by peroxyacid or peroxide) of the ketene. Here again, the elimination of the ketene as the final product does not eliminate the possibility of its being an intermediate.

Another possibility to consider is that the triple bond becomes dihydroxylated. This could take place through the acetylene oxide intermediate (XXVII) by ring cleavage by an acetate ion, the acetate group being subsequently hydrolyzed. This intermediate would then ketonize to an acyloin.



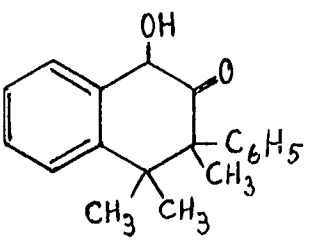
This of course requires that the original alcohol function be removed. That this hydroxyl should ionize is not unreasonable as it is a tertiary hydroxyl located alpha to

a benzene ring. The carbonium ion thus formed could react in two ways. First, by an electrophilic attack at the ortho position of the gamma benzene ring, forming the indane derivative XXIX. Alternatively, a Wagner-Meerwein rearrangement might take place with the migration of one of the t-butyl

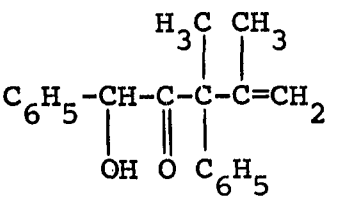


XXIX

methyls to the ionized carbon atom. The newly formed carbonium ion could then cyclize to the tetralin derivative XXX or expel a hydrogen ion from a methyl group and form a terminal double bond (formula XXXI).



XXX



XXXI

Structure XXXI can be eliminated on the basis of the lack of evidence for a double bond, least of all a terminal double bond, which would give a clearly discernible

and characteristic absorption in the infrared due to the out-of-plane bending of the terminal hydrogens. Structures XXIX and XXX are consistent with the infrared spectrum as far as the carbonyl and alcohol absorptions are concerned: the absorption at 1735 cm^{-1} can be attributed to a five-membered ring ketone; the alcohol absorption is that of an intramolecularly hydrogen-bonded hydroxyl group. In addition, it is known that allenes containing aromatic substituents cyclize under acidic conditions to indene derivatives. Since it was obvious that more information was needed in order to elucidate the structure of compound A, it was decided to obtain its proton magnetic resonance spectrum.

Since the proton magnetic resonance spectrum distinguishes between hydrogen atoms in different parts of the molecule, it was anticipated that it would give valuable information toward the elucidation of the structure. Also, since the amount of energy absorbed is directly proportional to the number of hydrogen nuclei of a given type, the PMR spectrum in effect counts the number of hydrogen atoms of each type and the areas under the curve for the various absorption peaks are in ratios of small whole numbers corresponding to the number of hydrogens of different types. Thus, the PMR spectrum indicates not only the type of hydrogen

atoms present, but also the number of each type. The PMR spectrum of the starting alcohol XV is shown in Figure 1. Figures 2 and 3 show the PMR spectrum of compound A in perdeuteroacetone and in pyridine, respectively.

The PMR spectrum of the starting alcohol is rather simple, having only three peaks. The starting alcohol XV has hydrogen nuclei in three different magnetic environments: the nine equivalent hydrogen nuclei in the t-butyl group; the single hydroxylic hydrogen; and the ten aromatic hydrogens of the two phenyl rings. Since the three methyl groups of the t-butyl group are attached to the same carbon atom, there is no difference between their magnetic environments and, since there is no hydrogen on the carbon adjacent to the three methyl groups (the central carbon of the t-butyl group), there is no splitting of the absorption peak. Thus, the nine hydrogens on a t-butyl group appear in the PMR spectrum as a single absorption peak, and this at high field. The absorption due to the single hydroxylic hydrogen is unaffected by neighboring hydrogen nuclei and appears as an unsplit peak in the center of the spectrum. The magnetic resonance of the aromatic hydrogens appears as a complex absorption, since each individual hydrogen nucleus is affected by the others in the same ring. The integrated area

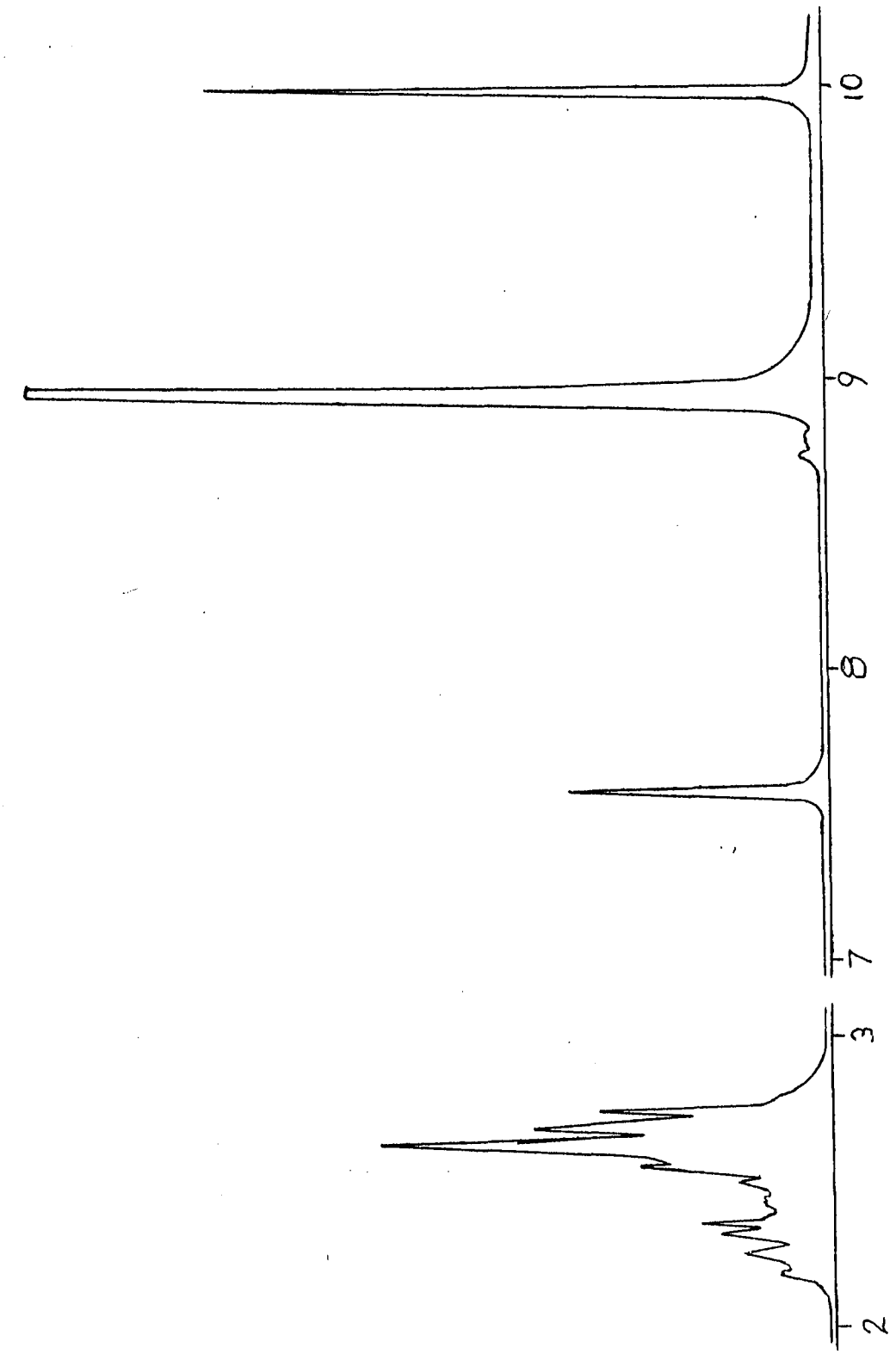


Figure 1. Proton Magnetic Resonance Spectrum of Phenyl-(phenylethynyl)-t-butyl Carbinol (XV) in Carbon Disulfide.

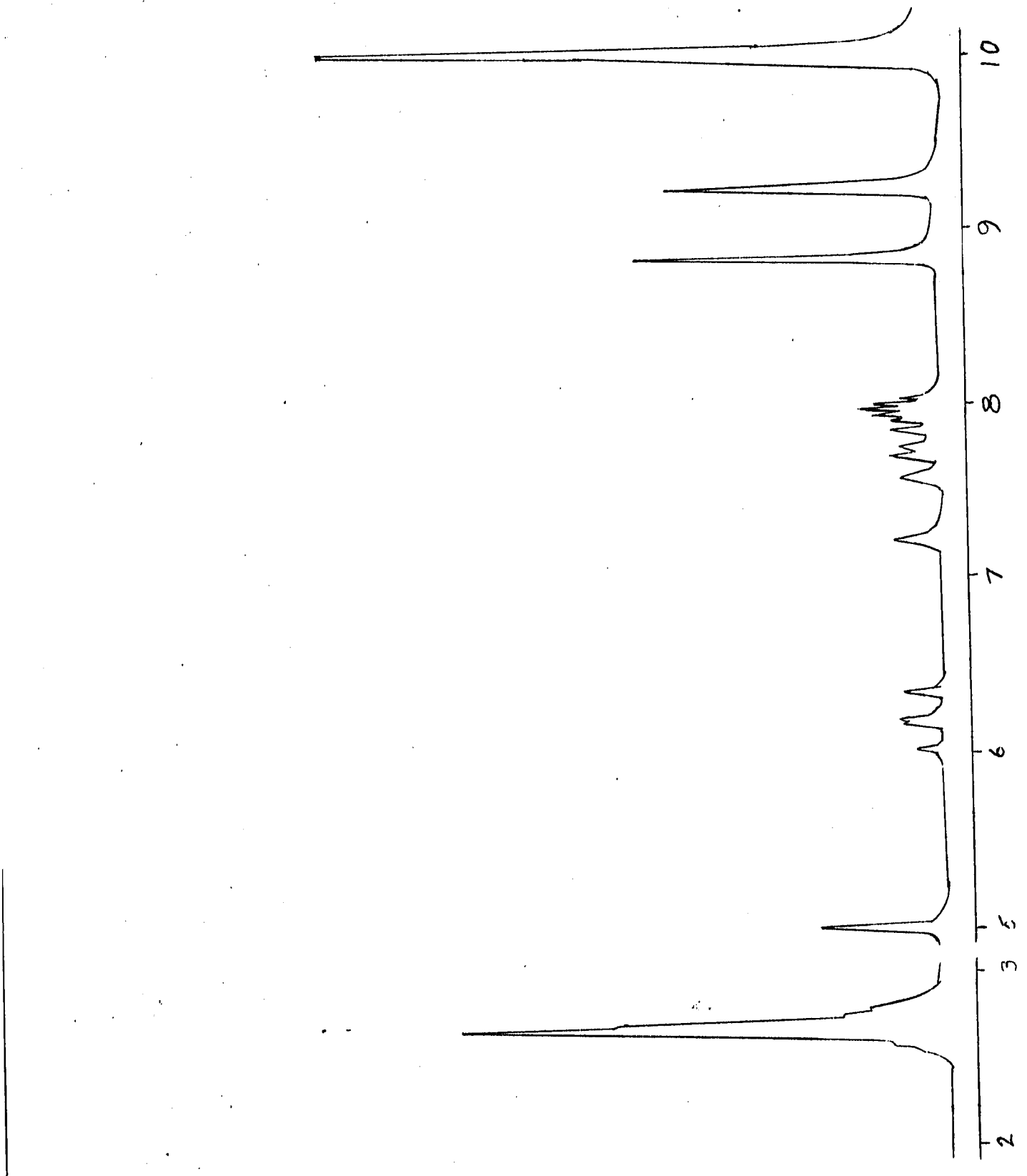


Figure 2. Proton Magnetic Resonance Spectrum of Compound A (XXV) in d_6-Acetone

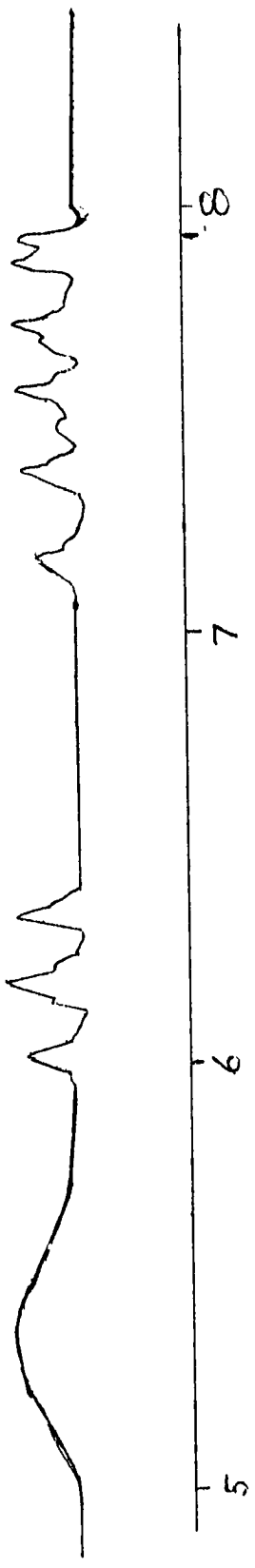


Figure 3. Proton Magnetic Resonance Spectrum of Compound A in Pyridine.

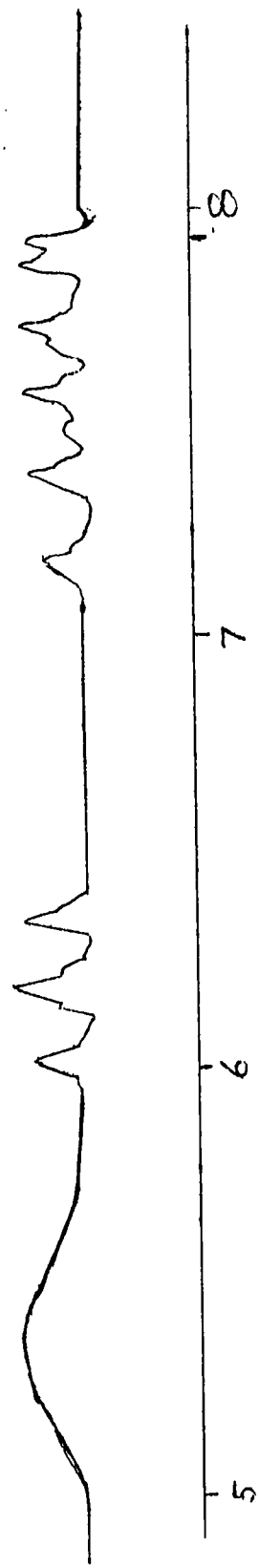


Figure 3. Proton Magnetic Resonance Spectrum of Compound A in Pyridine.

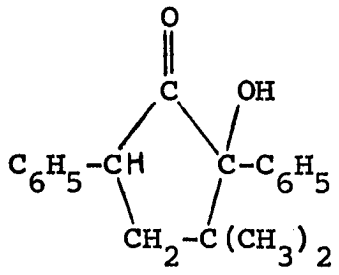
the three methyl groups are not the same distance from the benzene ring at any given moment, over a finite period of time, because of rotation about the bond, the three methyl groups have a time-average equal distance from the phenyl group and thus are equivalent.

The strong absorption at τ=2.8 is undoubtedly due to the aromatic hydrogens. The area under this peak is ten relative to three for each methyl group. The absorption at τ=5.03 in d_6-acetone is certainly the hydroxyl hydrogen. That this is so is confirmed by the spectrum in pyridine where the absorption is very broad at about τ=4.6. The group at τ=6.2 corresponds to one hydrogen; it is in the range for methine hydrogens. The absorptions between τ=7 and 8 are in the range for methylene hydrogens. Although the d_6-acetone spectrum is beclouded in this region by d_4-acetone absorption, the pyridine spectrum shows this area clearly. Their presence provides a convenient explanation for the disappearance of the methyl group without the loss of the carbon atom; it has been changed into a methylene group.

The explanation of the splitting of these absorptions follows somewhat along the same lines as that for the geminal methyl groups. A phenyl group on the adjacent carbon

atom, through the magnetic field generated by its circulating pi-electron cloud, has a greater effect on the adjacent cis-hydrogen than on the trans-hydrogen. Consequently, the two methylene hydrogens are not equivalent even though they are on the same carbon and they cause splitting of each other's absorptions. The absorptions are split further, as can be seen more clearly in the pyridine spectrum, due to the adjacent methine hydrogen, whose peak is split by the two methylene hydrogens.

Now by joining together the known fragments of the molecule in a manner which is most similar to the starting alcohol XV, the structure of compound A can be deduced. The methine and methylene carbons are adjacent as demonstrated by the PMR spectrum. The methylene carbon was formerly the methyl group of the t-butyl group and these must be adjacent. The next carbon is the carbinol carbon containing also a phenyl group. The other phenyl and the carbonyl groups account for the remaining carbon atoms. The carbonyl absorption in the infrared is that of a five-ring ketone; it completes the five-membered ring. The phenyl group is in the only vacant spot remaining: the methine carbon. The methine and carbonyl carbons are the former acetylenic carbons. The structure of compound A is represented below.



XXV

In addition to these compounds, there were two more which were not identified completely because they were not obtained in sufficient quantity or purity. One of these, designated compound E, was obtained from the chromatography as an impure oil and on attempted re-chromatography was lost completely. Its infrared spectrum, however, gave a clue to its identity because of the presence in it of two important bands; a strong one at 2190 cm^{-1} and the other at about 1690 cm^{-1}. The 2190 band is due to an acetylenic bond; in comparison with the acetylenic absorption of XV, it is greatly enhanced and thus cannot be attributed to some of XV as an impurity. Such an enhancement of an acetylenic absorption is generally attributed to conjugation with a carbonyl group. The carbonyl group is present as shown by the band at 1690 cm^{-1}; this band is somewhat lower than that normal for a carbonyl due to the conjugation with the triple bond. It is assigned structure XXXII.

$C_6H_5-C\equiv C-CO-C(CH_3)_3$

XXXII

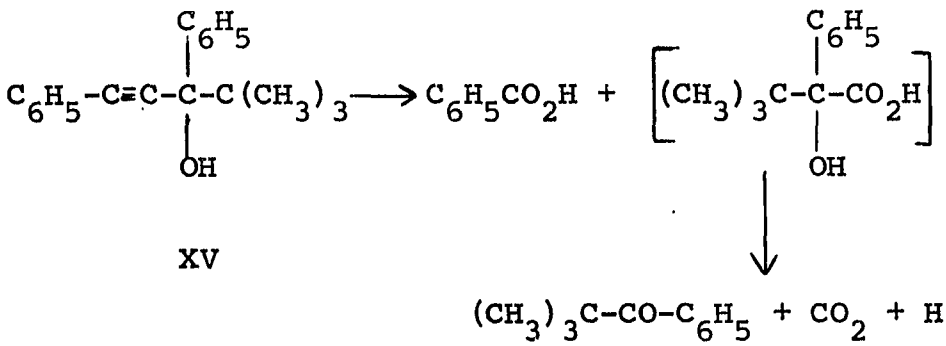
The last compound to be described, compound C, was not obtained in sufficient quantity to identify and its actual structure remains a mystery. It was obtained from the chromatography as a solid melting at 91°; carbon-hydrogen analysis indicates a structure $C_{18}H_{16}O$, but this cannot be so, as indicated by the PMR spectrum, which demonstrates the presence of two methyl groups, two aromatic rings, and another kind of hydrogen atom in the molecule. The methyl and phenyl hydrogens together add up to the 16 which are indicated by the analytical data. There was not obtained sufficient material to purify it for additional analysis and tests to determine its identity.

Mechanism of the Reaction

As indicated earlier, the multiplicity of products of this reaction suggests that several competing reactions are taking place simultaneously. These reaction paths will be described in the succeeding paragraphs.

The first and perhaps the simplest reaction to envision is a simple cleavage reaction of the triple bond.

Products resulting from this type of reaction were reported by Schlubach and Franzen (26), who obtained the two acids that would be expected from a simple oxidative cleavage of the triple bond. The two acids that would be formed by a similar cleavage in the present case of compound XV are benzoic acid and t-butylmandelic acid (XIV). The former of these was isolated from the reaction mixture and,



XV

XXVI

although the latter was not, it might reasonably be expected that under the conditions of the reaction the hydroxy-acid XIV might be further oxidized with loss of carbon to pivalophenone (XXVI), which was actually found among the products of the reaction. Compound XX is reasonably expected as an intermediate in the oxidative cleavage of the triple bond. After an initial electrophilic attack on the triple bond by the peroxyacid, another similar electrophilic attack can easily be seen as giving rise to the

diketone structure without disturbing any other part of the molecule. A similar intermediate was proposed by Schlubach and Franzen (25) and by Böeseken and Slooff (23) for the reaction of the same reagent with acetylenic alcohols. Criegee (30) reported that in the ozonization of acetylenes, a diketone is one of the products that is formed.

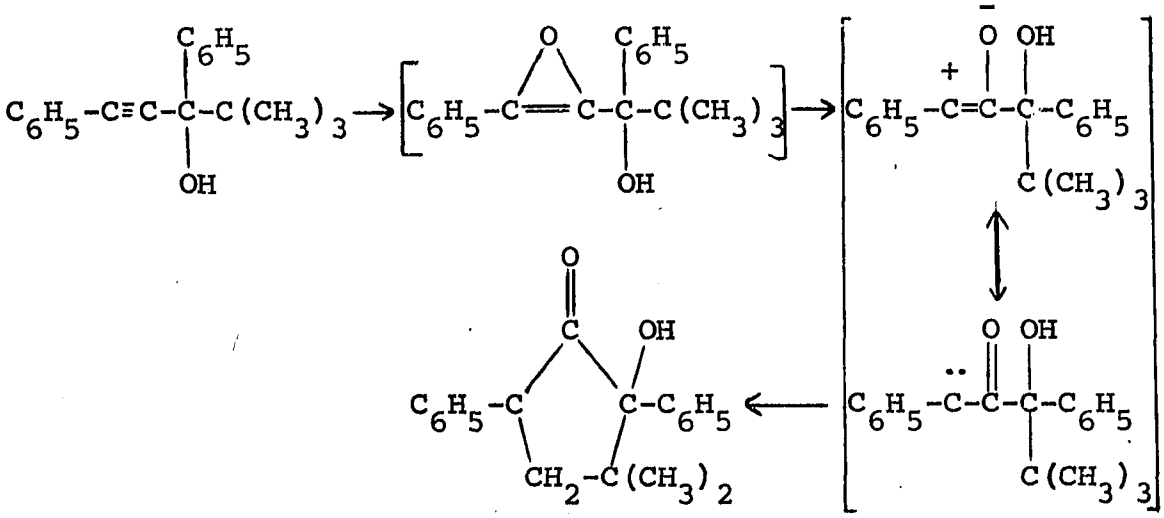
Besides the reaction at the triple bond, there appears to be a reaction at the hydroxyl group also. It is known that peroxyacetic acid and water are in equilibrium with acetic acid and hydrogen peroxide. The analogous equilibrium in the trifluoro system lies greatly to the right, peroxytrifluoroacetic acid being destroyed by water.

$$CH_3CO_3H + H_2O \rightleftharpoons CH_3CO_2H + H_2O_2$$

$$CF_3CO_3H + H_2O \rightleftharpoons CF_3CO_2H + H_2O_2$$

A similar type of exchange reaction at the hydroxyl group of the alcohol XV would bring about the formation of a hydroperoxide at the quaternary carbon of XV. From this intermediate it is easy to picture a 1,2-shift of one of the groups attached to this quaternary carbon to the adjacent oxygen with the expulsion of a hydroxide ion. There is formed simultaneously, of course, a carbonium ion which can pick up the hydroxide ion to form a hemiacetal.

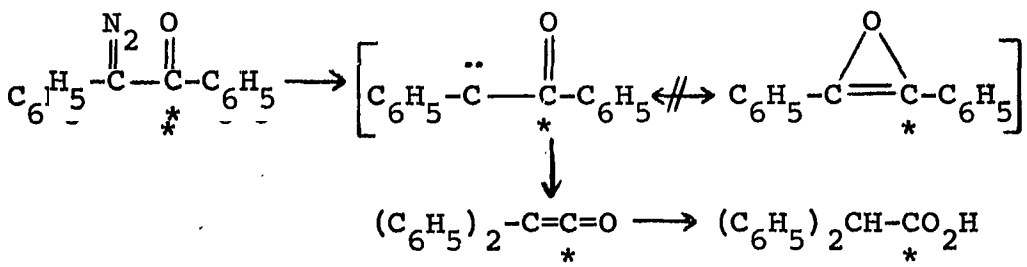
the presence of XXV in the reaction mixture, either as an intermediate or as a final product, a third pathway must be invoked. This reaction path must account for the destruction of a t-butyl group, a rare event except for a Wagner-Meerwein rearrangement accompanying a dehydration or cyclization. Since no Wagner-Meerwein type products were found, an entirely different kind of reaction must be invoked. If, in addition, this reaction can be seen as proceeding through the same intermediate as one of the two mechanisms discussed above, then it will be the more reasonable. This situation is realized in the following mechanism.



The reaction is initiated through the same step as the cleavage reaction, with the exception that before the second mole of peroxyacid can attack the triple bond, the oxirene ring opens up to give a zwitterionic structure that is a resonance form of the well-known ketocarbene. Although

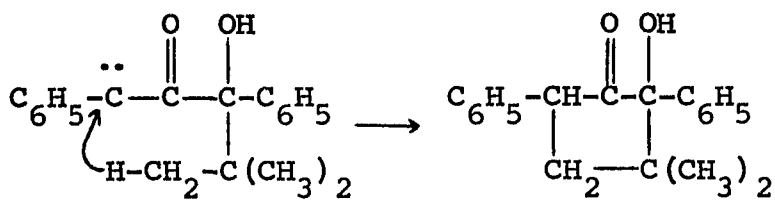
the oxirene ring can open in two ways, the one shown is favored because the adjacent phenyl ring can stabilize both the positive charge of the zwitterionic form and the carbene form, while the alternate cleavage allows no stabilization of either resonance form. This oxirene intermediate has been invoked by Franzen as an intermediate in oxidations of triple bonds by peroxyacetic acid.

Franzen thought at one point that he had isolated an oxirene as an intermediate in the oxidation of di-n-butylacetylene, but reported subsequently that the material was actually an α,β -unsaturated ketone. Since the acetylene oxide changes quite easily to the isomeric ketocarbene, he also attempted to determine whether the two were in fact resonance forms by decomposition of ^{14}C- labeled phenyl benzoyl diazomethane. If they are actually resonance forms,



then the label would be distributed between the two central carbons; it was not.

The ketocarbene intermediate then leads to the final product XXV by an attack on one of the methyl groups of the t-butyl group. The cyclization takes place through the joining of the carbene atom with the carbon atom of the methyl group. The resulting substance has a five-membered ring,

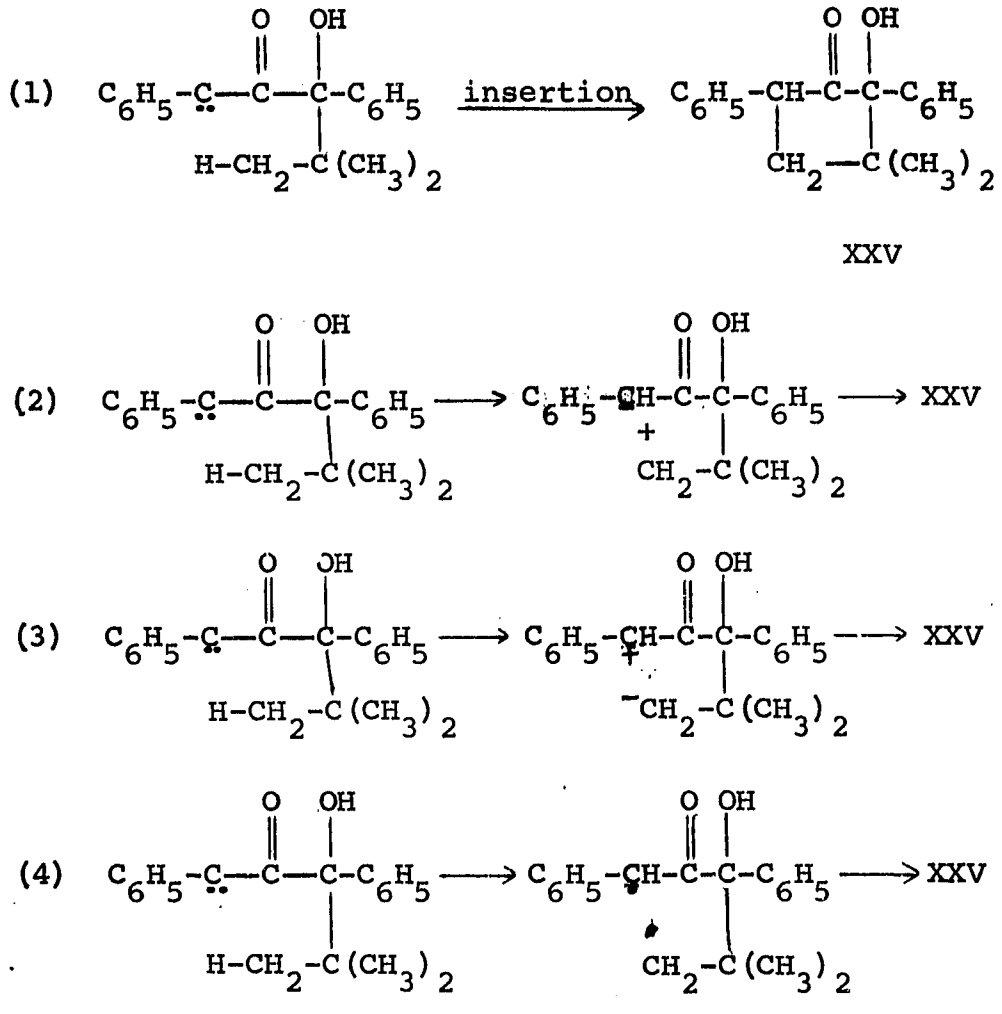


XXV

which, through the cis-trans relationship of its substituents, accounts for the difference in the geminal methyl groups in the molecule. This reaction also satisfactorily explains how one of the three methyl groups in the original molecule can disappear, without being lost to the molecule, by being transformed into a methylene group.

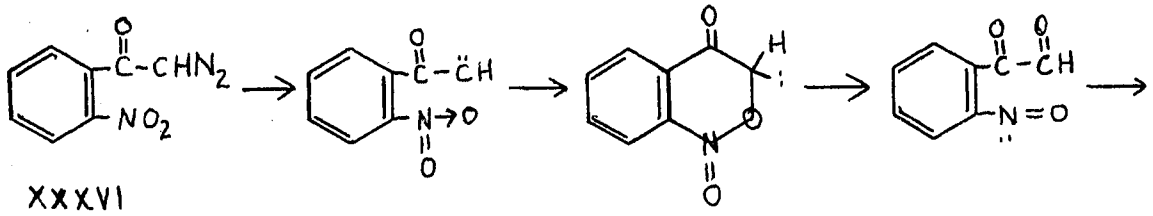
For the actual cyclization step of this reaction, several mechanisms are possible: (1) by a carbene insertion reaction, (2) by a hydride shift with the carbene carbon acting as an electrophile, (3) by a proton shift with the carbene carbon acting as a nucleophile, (4) by a hydrogen radical shift with the carbene carbon acting as a radical. All four

mechanisms give rise to the same final product as is shown by the following scheme.

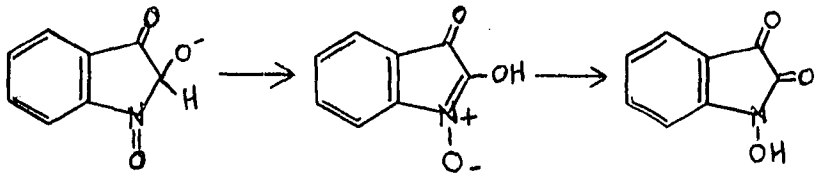


As evidence for these possible paths can be cited the following points from the literature.

Both Franzen, Schmidt, and Mertz (31) and Kirmse and Doering (32) have found that iso-propylcarbene undergoes an intramolecular insertion reaction to methylcyclopropane.

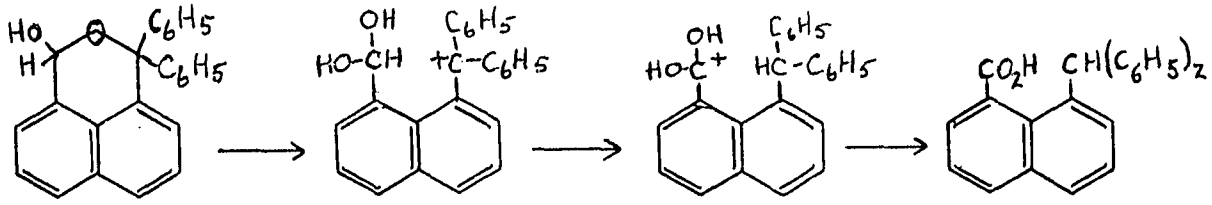


XXXVI

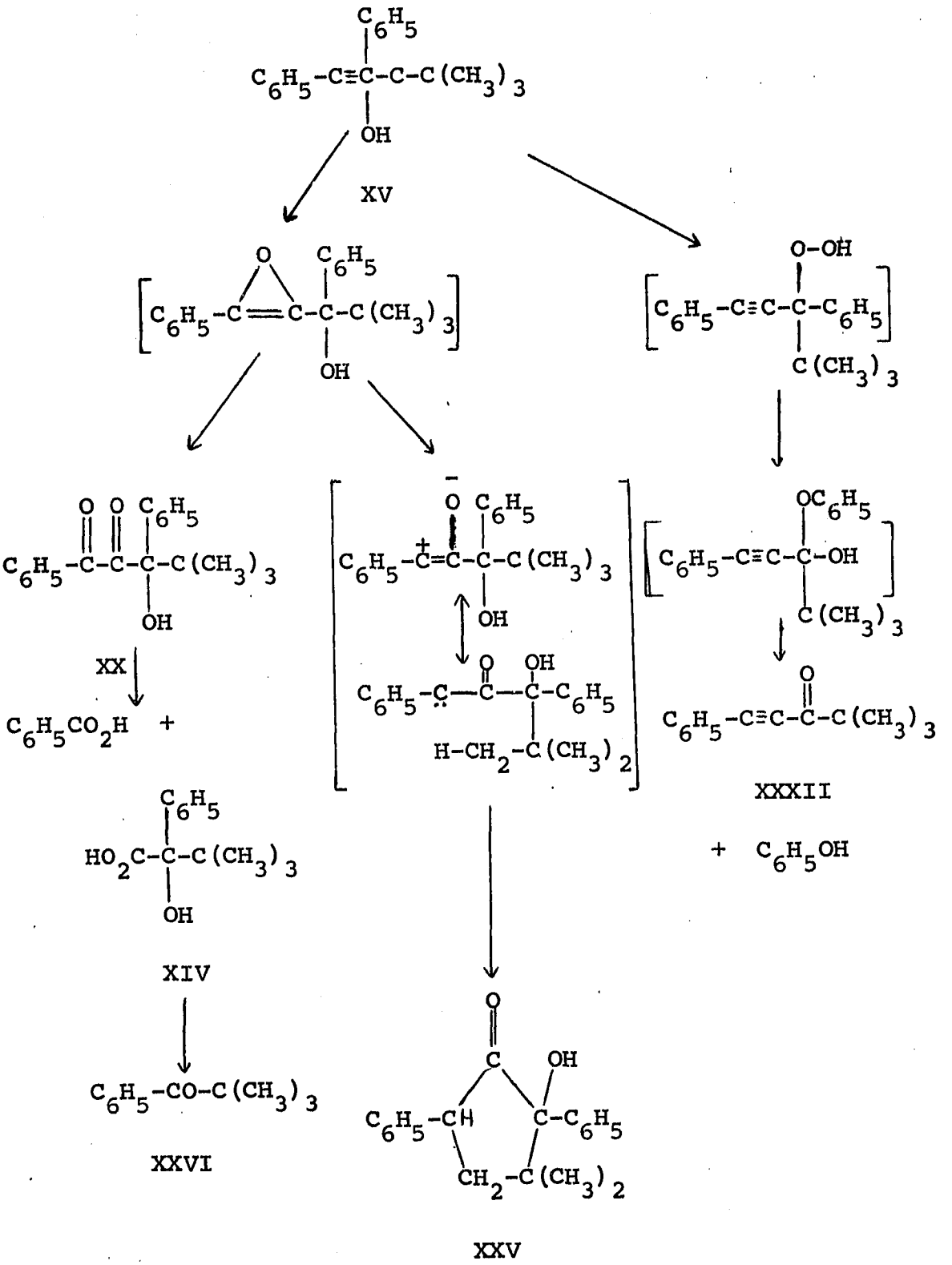


XXXVII

(35) have shown that this is possible in acid solution.



The reaction of phenyl(phenylethynyl)-t-butyl carbinol (XV) with peroxyacids can be seen then as proceeding through three pathways but as being initiated by reaction of the peroxyacid at one of two locations in the molecule: the triple bond or the hydroxyl function. In the case of reaction at the hydroxyl function, only one pathway is followed but in the reaction initiated at the triple bond, two paths can be taken after formation of the oxirene. The scheme below depicts the several reaction paths.



SECTION III

EXPERIMENTAL

Preparation of Pivalophenone

From Benzonitrile and the t-Butyl Grignard Reagent. In a 2 l. 3-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel was placed 24 g. (1 g-atom) of magnesium and 200 ml. of ether. A solution of 92 g. (109 ml.; 1 mole) of t-butyl chloride in 500 ml. ether was placed in the dropping funnel. The reaction was started in a test tube with several magnesium turnings, a few ml. ether, and a few ml. of t-butyl chloride by scratching the magnesium with a glass rod. When the starter was reacting vigorously, it was added to the reaction flask and the t-butyl chloride solution was added dropwise over the course of 2½ hours. Stirring was continued for 15 minutes after the end of the addition and 55 g. (0.53 mole) of benzonitrile was added rapidly. The ether was distilled off and replaced with toluene and the solution was refluxed for two hours, after which time the reaction mixture was hydrolyzed with 200 ml. of 1:1 aqueous HCl. The aqueous layer was extracted with 2x50 ml. ether. The combined organic

layers were dried ($MgSO_4$) and distilled. The fraction boiling up to 115° at atmospheric pressure was solvent. The remainder was fractionally distilled at reduced pressure to give 5.7 g. benzonitrile (b.p. 85.5-91°/22-26 mm.) and 33.2 g. (40%) pivalophenone (b.p. 117-118°/24-26 mm.).

From Pivalonitrile and the Phenyl Grignard Reagent. One mole of the phenyl Grignard reagent was prepared according to the procedure of Organic Syntheses (1). To this ethereal solution was added 83 g. (1.0 mole) of pivalonitrile as fast as possible without causing flooding of the reflux condenser. The reaction mixture was stirred under reflux for 3 hours, during which time the yellow imine complex precipitated. This mixture was then poured into 200 ml. of 50% aqueous HCl mixed with cracked ice and allowed to stand overnight. The aqueous layer was separated and extracted with 2x100 ml. ether. The combined ether layers were washed twice with water and saturated, aqueous sodium bicarbonate. The wet ether was treated with 10 g. of Norite at room temperature for 30 minutes and then filtered. The ether was dried over $CaCl_2$ and distilled. After removal of most of the ether, vacuum was applied and the fraction boiling at 97-100°/8-10 mm. was collected. Yield: 133.5 g. (82.5%); $n_D^{25°}$ 1.5087. Pearson (2) reports $n_D^{25°}$ 1.5082.

Preparation of Phenyl(Phenylethynyl)-t-butyl Carbinol

From Pivalophenone and the Phenylethynyl Grignard Reagent. To the Grignard reagent prepared from 2.4 g. (0.1 atom) of magnesium and 11 g. (0.1 mole) of ethyl bromide in 50 ml. ether, was added 10 g. (0.1 mole) of phenylacetylene. The solution was stirred for two hours until evolution of ethane ceased. After the ether was replaced with dry toluene, 16.2 g. (0.1 mole) of pivalophenone was added and the mixture was stirred under reflux for four hours. The reaction mixture was hydrolyzed with 20 ml. of 1:1 hydrochloric acid. The aqueous layer was extracted with 2x25 ml. ether. The combined organic layers were washed with dilute sodium bicarbonate and water and were dried. The solvent was evaporated to a yellow oil, which was crystallized by dissolving in n-hexane and cooling to -80° in a dry ice-acetone bath. This treatment gave 10 g. of almost white crystals melting at 65-67°. The filtrate was evaporated to a small volume and cooled to -80° giving an additional 2.8 g., melting at 65-68°, (Willimart (8) reports 68-69°). The total yield of 12.8 g. is 49% of theoretical.

From Pivalophenone and Phenylethynyllithium. Phenyllithium was prepared according to the method of Organic Syntheses (7) using 3.5 g. (0.5 atoms) of lithium wire and

40 g. (0.25 moles) of bromobenzene. Titration with 0.25 N HCl of the hydroxide generated by pouring an aliquot into water indicated a consistent yeild of about 0.2 moles (80%) of lithium reagent. To this was added 20 g. (0.20 moles) of phenylacetylene and, after stirring for ½ hour, 32 g. (0.20 moles) of pivalophenone. Stirring was continued for six hours, after which time the reaction mixture was hydrolyzed with water and acidified with HCl. The aqueous layer was separated and extracted with 2x25 ml. of ether. The combined organic layers were washed and dried ($MgSO_4$) and the ether was evaporated. The oil which remained usually solidified overnight and the solid was recrystallized from low-boiling petroleum ether. The yield was 60-65% of a white solid melting at 67-69°. The infrared spectrum (Nujol) showed a hydroxyl band at 3540 cm^{-1}.

Preparation of Phenyl(phenylethynyl)-t-butyl Carbinyl Hydrogen Phthalate

A solution of phenyllithium in ether was prepared according to the method of Organic Syntheses (7) from 3.5 g. lithium wire (0.5 g-atoms) and 40 g. bromobenzene (0.25 moles). The concentration of phenyllithium was determined by adding an aliquot of this solution to water and titrating the base formed with standardized hydrochloric acid. The yield of

phenyllithium prepared in this way was usually found to be about 75 to 80%. The yield of phenyllithium determined by this titration was used as the basis for determining the amounts of reagents added throughout the remainder of the preparation.

To this solution was added the calculated amount of phenylacetylene (usually about 20 g., 0.2 moles). After the vigorous reaction stopped, the solution was heated and stirred for an additional 1 to 2 hours to insure completion of the reaction.

To the phenylethynyllithium solution was added the calculated amount of pivalophenone (usually about 32 g.) diluted with an equal volume of ether. This was heated under reflux for three hours. To the lithium alkoxide solution was then added the equivalent amount of phthalic anhydride (about 30 g.) ground to a fine powder. Since the anhydride dissolved slowly because of its low solubility in ether, the reaction mixture was stirred overnight. There was usually a precipitate formed during this time. Although it was never identified, it was presumed to be the lithium salt of the phthalate ester.

The mixture was hydrolyzed with 1:1 hydrochloric

acid and the layers were separated. The aqueous layer was extracted once with 25 ml. ether. The combined organic layers were washed, and then extracted with 5% aqueous sodium bicarbonate. The aqueous phase was then washed once with ether and acidified with 5% hydrochloric acid. The oily solid was filtered and recrystallized from ether-hexane. The yield based on phenylacetylene was about 57% of material melting at 137-138°.

Analysis: Calc'd. for $C_{27}H_{24}O_4$: C-78.62% H-5.86% N.E. 412

Found: C-78.65% H-5.56% N.E. 399

Preparation of 1,3-Diphenyl-3-t-butyl-1-chloroallene

To a solution of 2.0 g. of phenyl(phenylethynyl)-t-butyl carbinol in 15 ml. of petroleum ether (39-52°) was added 0.4 g. of phosphorus trichloride. After standing for five days at room temperature, the organic phase was decanted from the phosphorous acid which had formed. After the usual washing and drying, the solvent was evaporated leaving a viscous oil which failed to crystallize but whose infrared spectrum indicated an allene. About 500 mg. of this oil was dissolved in a minimum amount of petroleum ether and chromatographed on alumina (27x150 mm.): elution with 250 ml. of ligroin (60-90°) gave 220 mg. of oil; elution

with 250 ml. of benzene gave 260 mg. of oily crystals. Infrared absorption: 1948 cm^{-1} (allene).

Preparation of 1,3-Diphenyl-3-t-butyl-1-bromoallene

To a solution of 5.0 g. of phenyl(phenylethynyl)-t-butyl carbinol in 20 ml. of petroleum ether was added 2.0 g. of phosphorus tribromide. The solution was allowed to stand overnight, after which time the organic phase was decanted, washed, dried, and evaporated to an oil. Attempts to crystallize the material from petroleum ether, pentane, and acetone failed. About 500 mg. was dissolved in pentane and chromatographed on an alumina column (27 x 157 mm.). Elution with hexane and then with 90-10 hexane-ether gave only small amounts of oil. Elution with 70-30 hexane-ether gave 230 mg. of crystals that melted at 70-73°. Infrared absorptions: 1940-50 cm^{-1} (allene); 848 cm^{-1} (vinyl bromine).

Ozonolysis of Phenyl(phenylethynyl)-t-butyl Carbinol

Ozonized oxygen was passed through a solution of 1.1 g. of the alcohol in 100 ml. of carbon tetrachloride and the emergent gas was passed through 200 ml. of a 4% solution of potassium iodide. Of a total of 9.2 mmole of ozone, 3.3 mmole (by titration with standardized sodium

thiosulfate) was absorbed by the potassium iodide. The organic phase was extracted with 5% sodium hydroxide solution, washed, dried and evaporated to an oil whose infrared spectrum compared favorably with that of the starting material. The basic aqueous phase was washed once with ether, acidified with dilute hydrochloric acid, and then extracted with ether. The ether phase was dried ($MgSO_4$) and evaporated to a red oil. Hexane was added to encourage crystallization. The solid was filtered and washed with cold hexane. The solid material was recrystallized from ether-hexane. Yield: 0.2 g.; m.p. 163.5-165° with gas evolved; N. E. 292; IR: 2200-3600 cm^{-1} (carboxylic acid); 1720-1705 cm^{-1} (carboxylic acid). The filtrate was concentrated and crystallized on standing. It was recrystallized from petroleum ether and melted at 113-118°. Its infrared spectrum is almost identical to that of benzoic acid.

Preparation of Phenyl-α-naphthyl Ketone

In a 1000 ml. Erlenmeyer flask, 56 g. (0.42 moles) of anhydrous aluminum chloride were added to 56 g. (0.40 moles) of benzoyl chloride and the mixture was heated to hasten solution of the aluminum chloride. After cooling, the solution set to a glass. This was dissolved in 320 ml. carbon disulfide and 51.2 g. (0.40 moles) of naphthalene

was added in portions. The mixture was warmed to complete the reaction and then cooled to crystallize the complex. The crystals were filtered and washed with carbon disulfide. The complex was decomposed by adding it to 1200 ml. of water containing 80 ml. of concentrated hydrochloric acid. The light tan crystals of the ketone were filtered, washed, and dried. Yield: 73.3 g. (79%); m.p. 77-78°. This procedure was taken from Fieser (36).

Preparation of Phenyl-α-naphthylphenylethynyl Carbinol

Phenyllithium (7) was prepared from 3.5 g. (0.5 moles) of lithium wire and 40 g. (0.25 moles) of bromobenzene. To this solution was added 20 g. (0.20 moles) of ethynylbenzene rapidly enough to cause refluxing. The solution was heated under reflux for an additional hour or until Gilman's color test #2 (29) was negative. To this solution was added 46.4 g. (0.20 moles) of solid phenyl-α-naphthyl ketone in two or three portions and the mixture was allowed to stir overnight. The reaction was hydrolyzed with 100 ml. of 3:1 hydrochloric acid. The organic phase was washed, dried, and evaporated to an oil. The oil was taken up in toluene; hexane was added to hasten crystallization. Three crops of the alcohol were obtained by concentration of the mother liquors. Yield: 36 g. (54%);

m.p. 113-118°.

Preparation of 1,3-Diphenyl-1-α-naphthyl-3-bromoallene

From 1-Benzoylnaphthalene, Phenylacetylene, Phthalic Anhydride, and Lithium Bromide. The preparation of phenyl-α-naphthylphenylethynyl carbinol was repeated through the addition of the solid phenyl-α-naphthyl ketone. Instead of hydrolysis at this point, 30 g. of phthalic anhydride was added and stirring was continued for three hours. The mixture was hydrolyzed with ice water and the insoluble white precipitate was filtered. It melted at 133.5-136° with decomposition and at 136-137.5° when inserted at 105°. This material showed infrared absorption bands at 1950 cm^{-1} and 845 cm^{-1}.

From Phenyl-α-naphthylphenylethynyl Carbinol and Phosphorus Tribromide. A solution of 6.7 g. of phenyl-α-naphthylphenylethynyl carbinol in 5 ml. of ether was added to a solution of 1.8 g. of phosphorus tribromide in 5 ml. of petroleum ether. After standing at room temperature for one hour, water was added to destroy the excess PBr_3 and to dissolve the phosphorous acid. The organic layer was separated, washed with water, and dried. Evaporation of the solvent left a residue that was recrystallized from

acetone. It melted at 134.5-136.5° when inserted at 105°; the mixture melting point with the material prepared above was 134.5-137° and the infrared spectra of the two samples were identical.

Preparation of 1,3-Diphenyl-3-α-naphthyl allene-1-carboxylic Acid

A solution of 2.0 g. of the allenic bromide was dissolved in ether-benzene and added to 0.25 g. of magnesium in a 350 ml. three-necked flask. A starter, prepared in a test tube from magnesium, ether and ethyl bromide was added to the flask and the mixture was heated under reflux for three hours. The solution was then poured onto 25 g. of powdered dry ice and when the dry ice was all gone it was hydrolyzed with dilute hydrochloric acid. The ethereal phase was extracted with sodium hydroxide solution and the sodium hydroxide solution was acidified with 1:1 HCl. The acidic solution was extracted with ether and the ether was evaporated, being replaced with petroleum ether when the volume became small. The petroleum ether was evaporated to an oil which solidified on standing. The oily solid was washed quickly with cold ether in order to dissolve the oil and leave the solid behind. The solid melted at 184-188°. (Gianni (17) reported a melting point of 192°

for this material.) The infrared spectra of this material and of a sample obtained from Gianni were identical.

The Reaction of Phenyl(phenylethynyl)-t-butyl Carbinol with Peroxytrifluoroacetic Acid

To 5.1 g. of 90% hydrogen peroxide in a 250 ml. Erlenmeyer flask containing 50 ml. of dichloromethane was added 37.8 g. of trifluoroacetic anhydride with cooling in an ice bath. The disappearance of the second phase signalled the completion of the reaction. This solution (0.135 moles CF_3CO_3H) was added to a solution of 13.2 g. (0.05 moles) of phenyl-(phenylethynyl)-t-butyl carbinol in 50 ml. of dichloromethane containing 30 g. suspended anhydrous Na_2HPO_4 over the course of 1½ hours. This was stirred for four hours with cooling in an ice bath. The insoluble Na_2HPO_4 was filtered, washed with dichloromethane and discarded. The filtrate was evaporated leaving an oily solid. The oily solid was taken up in ether and the insoluble material was filtered; evaporation of ether from the filtrate gave more of the same white solid; a third fraction was obtained by evaporation of the filtrate. Total yield: 1.1 g. (8%); m.p. 175-176°. This is the material which is designated compound A (XXV).

Analysis: Calc'd. for $C_{19}H_{20}O_2$: C - 81.39% H - 7.19%

Found: C - 81.11% H - 7.59%

Ether was added to the filtrate from compound A and it was washed with water and $NaHCO_3$ solution to remove acids. After evaporating the ether to an oily solid, addition of petroleum ether and filtration gave 0.8 g. (5.4%) of a light orange material, which was dissolved in ligroin (60-90°). The solution was concentrated by allowing it to evaporate slowly at room temperature. The solid which formed was filtered and washed with ligroin leaving 0.4 g. of solid melting at 111-112°. This solid was dissolved in glacial acetic acid and precipitated with water twice, filtered, and washed with water to remove all the acetic acid. Analysis showed it to have the formula $C_{19}H_{20}O_3$; it was designated compound B (XX).

Analysis: Calc'd. for $C_{19}H_{20}O_3$: C - 77.00% H - 6.80%

Found: C - 76.76% H - 6.70%

The filtrate from compound B was evaporated and its infrared spectrum indicated a mixture of compounds containing hydroxyl, acetylenic and carbonyl functions. A 580 mg. portion of the filtrate was dissolved in petroleum ether and placed on an alumina column (17 x 200 mm.). It was eluted successively with:

100 ml. petroleum ether;

100 ml. 5% ether - petroleum ether;

100 ml. 10% ether - petroleum ether;

100 ml. 15% ether - petroleum ether;

100 ml. 20% ether - petroleum ether.

Fifty-ml. fractions were collected. Fraction 4 contained an oil (5.7%) whose infrared spectrum corresponded with that of pivalophenone. Fractions 7 and 8 contained compound C (13.2%). They were combined and recrystallized from petroleum ether.

Analysis: Calc'd. for $C_{18}H_{16}O$: C - 87.06% H - 6.49%

Found: C - 87.22% H - 6.29%

As indicated on page 55 this formula is inconsistent with the PMR spectrum. No other fractions gave material and the column was eluted with ether; the total recovery of material was 247 mg. (42.5%).

One ml. of the filtrate was chromatographed on a silicic acid column (22 x 190 mm.; 40 g.; Mallinckrodt 100 mesh, containing 20% H_2O). Elution was with 200 ml. of petroleum ether, then 10% ether - petroleum ether. Yellow-colored bands could be seen traveling down the column and fractions were collected visually, so that each band appeared

in a different fraction. The first two bands were very close and together amounted to 1% of the total; they were not identified because of insufficient material. The third band (ca. 5%) was pivalophenone. The fourth band (54%) showed acetylenic, ethylenic, and carbonyl absorption in the infrared spectrum. Upon rechromatography of this material on the same column using 3% ether - petroleum ether, only pivalophenone and compound C could be found; no evidence of the acetylenic and ethylenic absorption bands could be found. The fifth band (9%) was compound C. The sixth band (22%) was compound B. The last band, eluted with ether, amounts to about 10% and it is compound A.

Reaction of Phenyl(phenylethynyl)-t-butyl Carbinol with Peroxyacetic Acid

A peroxyacetic acid solution was prepared by adding dropwise with cooling a mixture of 92 ml. of acetic anhydride and 2 ml. of concentrated sulfuric acid to 30.9 g. of 90% hydrogen peroxide. The solution was analyzed by the procedure of Greenspan and MacKellar (37) and found to contain 0.45% hydrogen peroxide and 45.4% peroxyacetic acid (91% yield). Twenty ml. of the peroxyacetic acid solution (0.12 moles) was added to a solution of 10 g. (0.034 moles) of phenyl(phenylethynyl)-t-butyl carbinol in 75 ml.

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of acetic acid and ten ml. of water. Sometimes compound A precipitated from this solution after two days in approximately 15% yield. If it did not precipitate, the solution was poured into 800 ml. of water and the oily solid that formed was collected and dissolved in ether. After drying of the ether over $MgSO_4$, slow evaporation of the solvent gave compound A in about 15% yield.

A solution of 100 mg. of compound A was dissolved in 20 ml. of glacial acetic acid and 23.8 mg. of chromium (VI) oxide was added to the solution. After two days at room temperature, the original brown color changed to green, indicating reduction of the chromium. The solvent was evaporated in vacuum and the residue was taken up with water, filtered, washed, and dried. A 90% yield of compound A was recovered.

The same 90 mg. of compound A was redissolved in glacial acetic acid and another 23.8 mg. of chromium (VI) oxide was added. The solution was heated to 90° and the reduction of chromium was complete in less than 30 minutes. A similar work-up of the reaction mixture gave 80 mg. of compound A.

To 100 mg. of compound A dissolved in acetone was

added 38 mg. of potassium permanganate and about 0.1 g. of $MgSO_4$ dissolved in water. The mixture was allowed to stand at room temperature until the color of permanganate disappeared. The solvent was removed in vacuum and the residue was taken up with water, filtered, washed, and dried. About 75 mg. of compound A was recovered.

A solution of 67.3 mg. (0.240 mmole) of compound A in 20.0 ml. of a 0.145 N solution of lead (IV) acetate in glacial acetic acid was allowed to stand at room temperature for two days. To this was added 35 ml. of a solution containing 20 g. KI and 300 g. anyhdrous $NaC_2H_3O_2$ per liter. The iodine generated was titrated with 23.98 ml. of 0.1014 N sodium thiosulfate solution. Thus 0.240 mmole of compound A consumed 0.237 mmole of lead (IV) acetate.

A solution of 100 mg. (0.35 mmole) of compound A in 10 ml. of 0.145 N lead (IV) acetate (0.73 mmole) was allowed to stand overnight at room temperature. The reaction mixture was diluted with 100 ml. water and the aqueous mixture was extracted with ether. The ethereal solution was washed with water until the washes were neutral, dried over $MgSO_4$, and evaporated. The infrared spectrum of the residual oil showed absorption bands that correspond to hydroxyl and apparently five or six carbonyl peaks between 1740 and 1660 cm^{-1}. The

reaction obviously is more complex than the previously observed consumption of one mole of lead (IV) acetate would lead one to believe.

To 400 mg. of compound A dissolved in anhydrous ether was added 300 mg. of lithium aluminum hydride. After 48 hours the excess hydride was destroyed with water and the mixture was acidified with 1:1 HCl. Evaporation of the dried ether solution gave 400 mg. of an oily solid that was recrystallized from benzene (m.p.: 156-157°). Its infrared spectrum and analysis correspond to the diol that would be formed by reduction of the carbonyl function of compound A.

Analysis: Calc'd. for $C_{19}H_{22}O_2$: C - 80.81% H - 7.86%

Found: C - 80.73% H - 7.64%

There was dissolved 97.2 mg. (0.347 mmole) of compound A in 25.00 ml. of 0.135 N lead (IV) acetate (1.69 mmole). After one hour and after six hours, five ml. aliquots were removed. Twenty ml. of a solution containing 20 g. KI and 300 g. anhydrous sodium acetate per liter were added to each aliquot and the iodine generated was titrated with 0.1022 N $Na_2S_2O_3$. The titer values, 5.35 ml. and 5.40 ml., respectively, indicated that 0.31 mmole of lead (IV)

acetate were consumed. The remaining 15 ml. were poured into 100 ml. of water. The aqueous solution was extracted with ether and the ether was washed with $NaHCO_3$ solution. The ether phase was dried and evaporated, leaving an oil whose infrared spectrum indicated broad hydroxyl and carbonyl absorptions.

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