SYNTHESIS OF SUBSTITUTED CYCLOHEPTATRIENE DERIVATIVES

by

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Major Professor

To my wife, Betty, whose patience

and understanding have made this possible.

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INFRARED SPECTRA

N.M.R. SPECTRA

HISTORICAL

The discovery of the aromaticity of the tropylium ion[1] and its subsequent structure determination[2] has aroused new interest in the parent hydrocarbon, tropilidene. Tropilidene was first synthesized by Ladenburg[3] in 1881, but it was not until 1901 that Willstatter[4] through a series of reactions and logical deductions eliminated all the possible isomers of C_7H_8 except that of 1,3,5-cycloheptatriene.

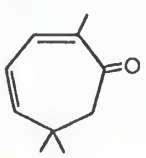
In 1950, Doering and Knox[5] synthesized tropilidene by a photochemical addition of diazomethane to benzene. Since the reaction of diazomethane with double bonds usually gives rise to cyclopropane derivatives, Doering and Knox concluded that the chemical evidence to date was not sufficient to distinguish between the monocyclic 1,3,5-cycloheptatriene structure (I) and bicyclo[4,1,0]hepta-2,4-diene or norcaradiene structure (II).

I

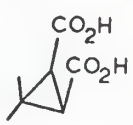
II

With the advent of more sophisticated spectrometric methods, Corey, et al.[6], using nmr spectroscopy, found no evidence of the norcaradiene structure in a series of enol esters of eucarvone (III), although low temperature ozonolysis yielded cis-caronic acid (IV) in good yields.

Alder[7] reported that tropilidene gave Diels-Alder adducts which appeared to have been derived from a norcaradiene structure,



III



IV

but permanganate oxidation of tropilidene produced none of the cyclopropane-1,2-dicarboxylic acid that would be expected for a norcaradiene structure.

With most of the evidence in favor of a monocyclic structure, Doering, et al.,[8] proposed that tropilidene existed in the form of 1,3,5-cycloheptatriene (V) with a resonance stabilization contribution by C-1, C-6 π-orbital overlap. Such a compound would be "pseudo aromatic" since it contains six delocalized π-electrons in a cyclic structure. This structure proposal is analogous to the homo-allylic and homo-aromatic systems that have more recently been suggested by Winstein.[9,10]

V

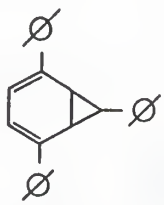
A number of molecular orbital calculations[11,12] on the structure proposed by Doering and Knox followed, but no agreement could be reached on the approximations necessary to account for the strain and non-planarity effects. Heats of hydrogenation of tropilidene[13] produced values which were very close to those found for a non-cyclic triene, but Turner, et al.,[14] attributed this low value to underestimation of the strain energy in the seven-membered ring. Then, Conrow[15] reported thermodynamic data for the tetramethyl substituted tropilidenes. In these compounds, the resonance stabilization due to 1,6 overlap must be quite small, on the order of 1.3 kcal per mole.

Davis and Tulinsky[16] have suggested that a "half π-bond" may best explain the C-1, C-6 bonding; in such a system, π-orbital overlap would only occur on one side of the molecule (VI).

VI

Although both δ-cycloheptatriene carboxylic acid[17] and eucarvone enol triphenylmethyl ether[18] had been reported as having stable norcaradiene structures, this work was later proven to be in error by Doering, et al.[18,19] It was not until 1965 when Ciganek[20] reported the synthesis of 7,7-dicyanonorcaradiene that a simple norcaradiene derivative was unequivocally shown to exist. Prior to 1965, the only reports of norcaradiene structures found to be stable were those that either incorporated one or more of the double bonds of the diene into a condensed aromatic system[21,22,23] or bound C-1 and C-6 by a three atom bridge.[24,25]

More recently, Mukai[26] has reported a stable phenyl substituted norcaradiene, 2,5,7-triphenylnorcaradiene (VII). Also, Ciganek[27] has reported a system where a norcaradiene-cycloheptatriene valence-tautomeric



VII

equilibrium (VIII) can be observed. Such a system had been expected for many years, but in all previous systems the equilibrium was either too far in one direction or no equilibrium was in operation. While Ciganek's

VIII

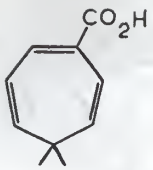
work appears to solve the question of whether a tautomer equilibrium can exist, the structural proposals for the cycloheptatriene ring skeleton still appear to contain discrepancies.

In 1956, Doering, et al.,[8] had proposed that the Buchner acids had the planar "pseudo aromatic" structure. In 1958, Abel, et al.,[28] suggested from the nmr and vibrational spectra that the methylene must be out of the plane of the other six carbons. They also proposed that the six carbon atoms composed a delocalized six π-electron system that by-passed the methylene group.

A similar structure was proposed for cycloheptatriene molybdenum tricarbonyl, $C_7H_8Mo(CO)_3$, by Dunitz and Pauling.[29] Since the ir spectrum of the complex resembled that of free cycloheptatriene, they suggested that the free cycloheptatriene might have a similar structure.

A detailed study of the ir and Raman spectra of cycloheptatriene by Evans and Lord[30] appeared in 1960. While the spectra could be explained using the planar "pseudo aromatic" model, the possibility existed that the technique used might not be able to discern small distortions.

Davis and Tulinsky[31], using x-ray crystallography, studied the structure of thujic acid (IX). Their results showed that the molecule existed in a boat conformation with the methylene group and the C_3-C_4



IX

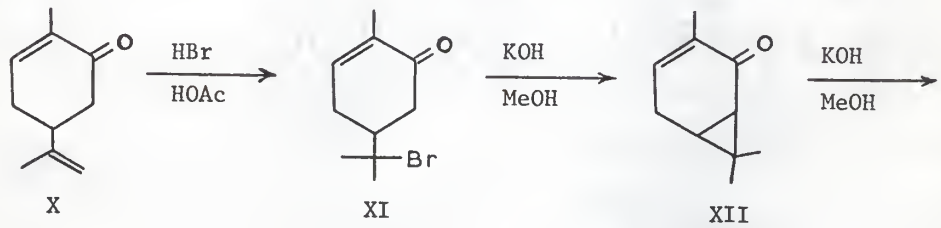
double bond tilted 49.7 and 23.7° away from the plane of carbon atoms 1,2,5 and 6.

The sector electron diffraction method used by Traetteberg[32] yielded similar results to those reported by Davis and Tulinsky. The difference in the angles that were reported was thought to be due to the substituent effects in the thujic acid derivative.

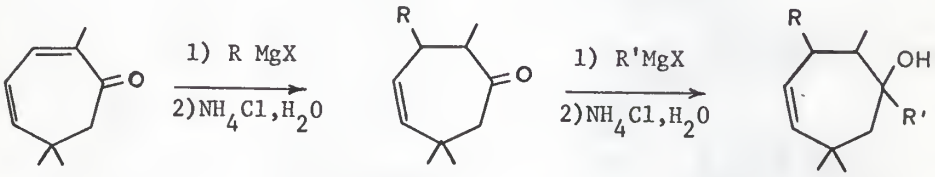
Substituent effects were also noted in the work reported by Conrow, et al.,[33] in 1963. In the 2-t-butyl-3,7,7-trimethyl tropilidene system, the seven membered carbon ring skeleton was shown to be non-planar in the groundstate but rapidly inverting at ordinary temperatures.. The uv spectral data also showed substituent effects, particularly with the addition of the bulky t-butyl group to the substituted cycloheptatriene system.

INTRODUCTION

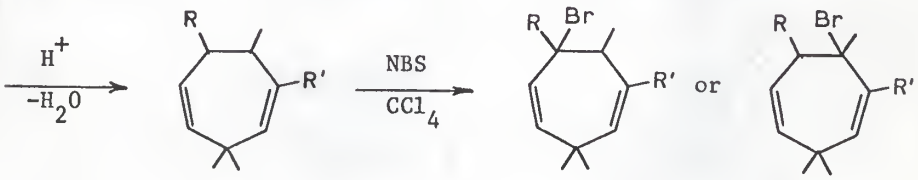
In order to study the substituent effects upon the cycloheptatriene ring skeleton and to develop synthetic techniques for producing substituted cycloheptatrienes, E. D. Lorance[34] undertook the project of synthesizing 2,3,4,7,7-pentasubstituted tropilidenes. The reaction sequence attempted is shown below.



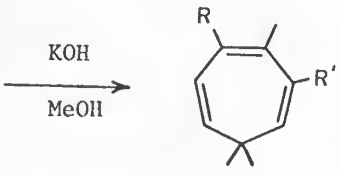
X XI XII



XIII XIV XV



XVI XVII XVIII



XIX

While the possibility of obtaining mixtures was foreseen, it was hoped that the product distribution would converge to that of the desired product, a pentaalkyl tropilidene. Therefore, Lorance proceeded to run the sequence of reactions with only crude purification between steps. Final analysis showed little or none of the desired product. Variation of substituent groups by changing Grignard reagents was also unsuccessful.

Consequently, the present work was initiated to determine why the reaction sequence had failed. It was further hoped that the findings might produce a method for the synthesis of the substituted tropilidenes.

DISCUSSION OF RESULTS

The first problem studied was that encountered by Lorance in the attempted synthesis of 3,7,7-trimethyl-2,4-diisopropyl-1,3,5-cycloheptatriene (XIX, R = R' = isopropyl). In this sequence, the series of reactions was halted when the dehydration of the proposed tertiary alcohol (XV, R = R' = isopropyl) could not be accomplished, even after 13 days in the presence of p-toluenesulfonic acid and refluxing xylene.

Initially, the procedure of Corey and Burke[35] was followed for the conversion of readily available l-carvone (X) to eucarvone (XIII). The eucarvone was purified on a high speed spinning band column, and purity was checked by gas chromatography. This eucarvone was allowed to react with isopropyl magnesium bromide, and the subsequent salt was hydrolyzed with ammonium chloride and water. The product, 2,6,6-trimethyl-3-isopropylcyclohept-4-enone (XIV, R = isopropyl), was purified by spinning band distillation and found to be homogenous by gas chromatography. The 2,6,6-trimethyl-3-isopropylcyclohept-4-enone was treated with isopropyl magnesium bromide. The workup was completed as before, and the ir spectrum verified that the product was an alcohol. However, the nmr spectrum

(page 23) showed an eight peak multiplet for a hydrogen on a carbon which also bears a hydroxyl function. Since no hydrogen would have been at this position if the addition had occurred, the conclusion was that a reduction had resulted. Subsequent reactions proved that a gas which decolorized bromine in carbon tetrachloride evolved during the course of the reaction. So, instead of the addition of the Grignard reagent to the ketone, the reaction had proceeded to give the secondary alcohol, 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol and propene gas. This type of reaction, the simultaneous reduction of a ketone to the corresponding alcohol and the oxidation of the Grignard reagent, has previously been studied by Whitmore and George.[36] Their findings indicate that this reaction is often the principal reaction in situations where sterically hindered ketones are allowed to react with bulky Grignard reagents.

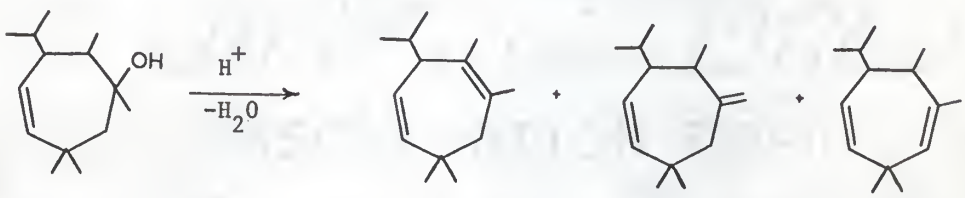
To prove that the product was indeed the reduction product, 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol, the ketone was treated with sodium borohydride in ethanol. The resulting alcohol was identical to the product isolated from the reaction of 2,6,6-trimethyl-3-isopropylcyclohept-4-enone and isopropyl magnesium bromide.

Attempted dehydration of this secondary alcohol, 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol, with p-toluenesulfonic acid was unsuccessful. Therefore, it appears that the product isolated by Lorance was a secondary alcohol rather than the desired tertiary alcohol.

Since the methyl Grignard reagent is smaller sterically than the isopropyl Grignard reagent and is also less likely to effect reduction, the next attempt was to make 2,3,7,7-tetramethyl-4-isopropyl-1,3,5-cycloheptatriene (XIX, R = isopropyl, R' = methyl). The previously prepared 2,6,6-trimethyl-3-isopropylcyclohept-4-enone (XIV, R = isopropyl)

was allowed to react with methyl magnesium iodide. Initially, workup followed by vacuum distillation produced a mixture of dienes and the desired alcohol, 1,2,6,6-tetramethyl-3-isopropylcyclohept-4-en-1-ol (XV, R = isopropyl, R' = methyl). Since the dehydration was thought to be acid catalyzed, workup was later done under slightly basic conditions. These conditions were successful in discouraging dehydration, and the desired alcohol was obtained.

Dehydration of the tertiary alcohol (XX) to a specific diene was never achieved. Each method attempted produced mixtures of the three possible



XX XXI XXII XXIII

dienes (XXI, XXII and XXIII). Vacuum distillation from potassium hydrogen sulfate yielded predominately starting material, while heating the alcohol in the presence of potassium hydrogen sulfate for 165 minutes at atmospheric pressure produced the diene with an exocyclic double bond, 1-methylene-2, 6,6-trimethyl-3-isopropyl-4-cycloheptene (XXII), as the major product. Distillation of the alcohol from catalytic amounts of iodine also did not produce dehydration since the alcohol underwent decomposition during attempts to distill at atmospheric pressure. At reduced pressure, the iodine either sublimed from the distilling flask or reacted with the sites of unsaturation before distillation could be achieved.

Refluxing the alcohol in benzene with a catalytic amount of p-toluenesulfonic acid was most successful in producing the diene, 1,2,6,6-tetramethyl-3-isopropylcyclohepta-1,4-diene (XXI), which appeared most likely to produce a substituted tropilidene after allylic bromination and dehydrohalogenation. However, even this method seemed to produce changing product distributions from one run to the next. The two major products from the p-toluenesulfonic acid dehydration were always the 1,2,6,6-tetramethyl-3-isopropylcyclohepta-1,4-diene (XXI) and the 1-methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene (XXII). The former was found in the greatest yeild.

Separation of the dienes was only accomplished by repeated injections and collections from the gas chromatograph. The mixture boiled at a constant temperature, and no vacuum distillation technique ever changed the product distribution in the distillate. Since Lorance[34] only reported bands in the ir spectrum for the diene that he isolated, it is impossible to say what product distribution he might have obtained, but the bands reported suggest that the major product was XXI rather than 1,3,3,7-tetramethyl-6-isopropylcyclohepta-1,4-diene (XVI, R = isopropyl, R' = methyl) that he had shown in his reaction diagram.

Although the allylic bromination was never repeated in this work, this mixture of three dienes, each with three allylic sites for bromination, probably yielded many bromides in Lorance's work that would not produce a substituted cycloheptatriene upon dehydrohalogenation. Multiple bromination of the dienes would only enhance these difficulties.

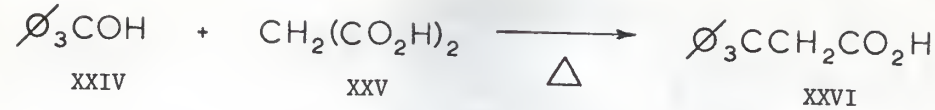
Since the allylic bromination-dehydrohalogenation route did not appear productive, an alternate method of dehydrogenation was desired. Since trityl perchlorate is known to be a good hydride extractor, it was

thought that trityl perchlorate in the presence of a hindered amine might produce an especially mild chemical method of dehydrogenation. A literature search revealed that ethyldicyclohexylamine is one of the most hindered amines and is also a fine proton acceptor. The latter characteristic was required since a proton would have to be removed from the molecule to complete the dehydrogenation.

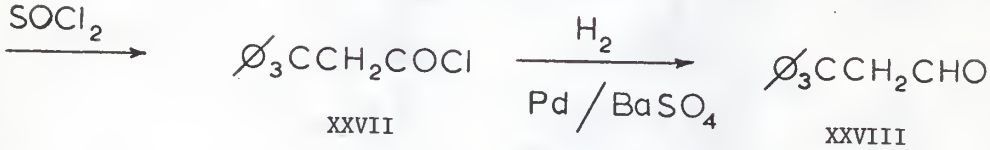
Preparation of ethyldicyclohexylamine was carried out from commercially available dicyclohexylamine and ethyl sulfate as reported by Hunig and Kiessel.[37]

For the initial attempt, the diene mixture obtained from the p-toluenesulfonic acid dehydration was added to dried acetonitrile. The amine was then added, followed by addition of the solid trityl perchlorate. A reaction was readily visible since the flask warmed and the solution turned from orange to dark purple. Within ten minutes a white solid precipitated. Workup produced the unreacted diene mixture and a compound which was the reaction product of ethyldicyclohexylamine and trityl perchlorate. Further preparations of this material and subsequent spectral analysis indicated that the product might be N,N-dicyclohexyl-3,3,3-triphenylpropenylamine (XXIX).

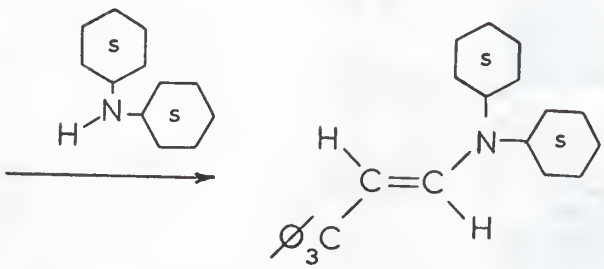
To prove that the product of the reaction of trityl perchlorate and ethyldicyclohexylamine was XXIX, an alternate synthesis was devised. Since the reaction of aldehydes and amines is known to yield enamines and since dicyclohexylamine was already available, the only remaining compound required was β,β,β-triphenylpropionaldehyde (XXVIII). β,β,β-Triphenylpropionic acid (XXVI) was synthesized from triphenylcarbinol (XXIV) and malonic acid (XXV). The β,β,β-triphenylpropionic acid (XXVI) was converted to the acid chloride (XXVII) by treatment with thionyl chloride. The solid



XXIV XXV XXVI



XXVII XXVIII

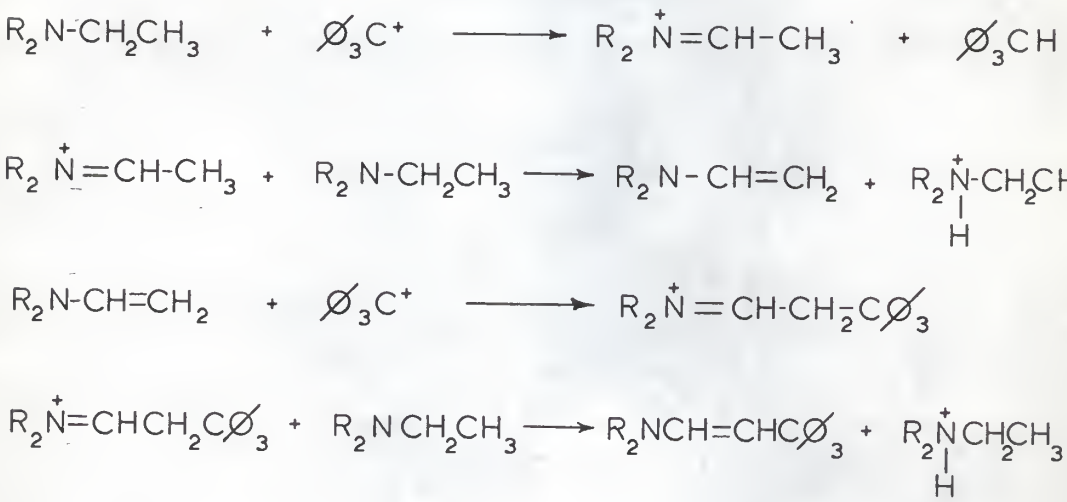


XXIX

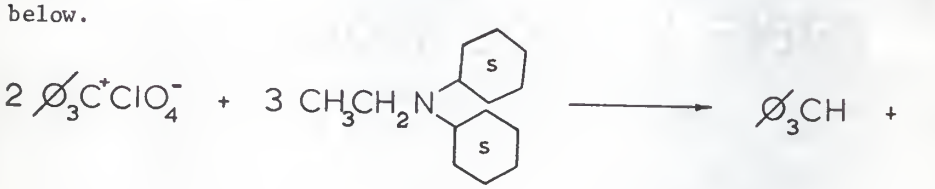
acid chloride was reduced to β,β,β-triphenylpropionaldehyde (XXVIII) via the Rosenmund reaction. The β,β,β-triphenylpropionaldehyde was then heated under reflux in benzene with dicyclohexylamine. Recrystallization of the product from absolute ethanol yielded the same compound, XXIX, as was previously isolated from the reaction of trityl perchlorate and ethyldicyclohexylamine.

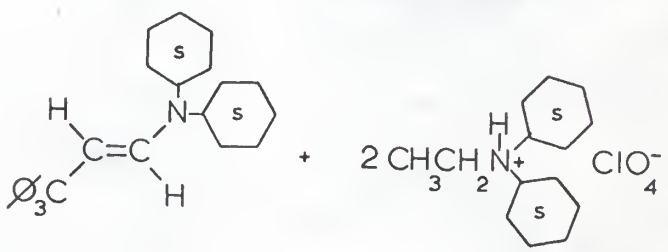
While the reaction of trityl perchlorate and ethyldicyclohexylamine was not the reaction originally desired, it was found that no report of such a reaction had previously been published. A similar type of amine oxidation with subsequent nucleophilic attack of the oxidized amine upon the oxidizing reagent has been reported by Henbest, et al.,[38] for ethyl amines and the halogenated p-benzoquinones.

The mechanism proposed for the formation of XXIX is similar to the mechanism proposed by Henbest for the reaction of ethyl amines and the halogenated p-benzoquinones.



The stoichiometric equation for this particular reaction is shown below.





A similar reaction was found to occur with trityl perchlorate and triethylamine, only in this case the reaction proceeds more than once for each molecule of triethylamine. The nmr spectrum (page 27) suggests that the reaction proceeds three times per molecule of triethylamine, but either the reaction is not complete, the compound is not stable, or the necessary methods for purification have yet to be devised. Attempts to recrystallize this product have generally been unsuccessful. This compound, like XXIX, is quite easily hydrolyzed. Column chromatography on alumina results in isolation of β,β,β-triphenylpropionaldehyde with the amine presumably staying on the column. Sublimation only results in thermal decomposition.

One of the intermediates in the triethylamine reaction would be diethylvinylamine. Weyand and Daniel[39] and Wittig and Tochtermann[40] have reported that dialkylvinylamines are difficult to prepare due to their tendency to hydrolyze, oxidize and polymerize. Such a side reaction or the presence of fairly high concentrations of a quaternary amine perchlorate in the reaction media may be responsible for the difficulties encountered.

Since an ethyl amine is obviously unsatisfactory as the proton acceptor for a dehydrogenation reaction, 2,4,6-trimethylpyridine appeared to be a good alternative. This reaction was attempted, but only triphenylcarbinol and the perchlorate salt of 2,4,6-trimethylpyridine was isolated. It was later found that the humidity during the summer months required special precautions to avoid hydrolysis of the trityl perchlorate to triphenylcarbinol. Therefore, the possibility still exists that 2,4,6-trimethylpyridine might function as the hindered amine in a dehydrogenation reaction with trityl perchlorate. Another amine which might prove to have the desired qualities is tribenzylamine. Henbest, et al.,[38] reported that

complex formation between chloranil and tribenzylamine was very slow compared to the trisubstituted ethyl and methyl amines.

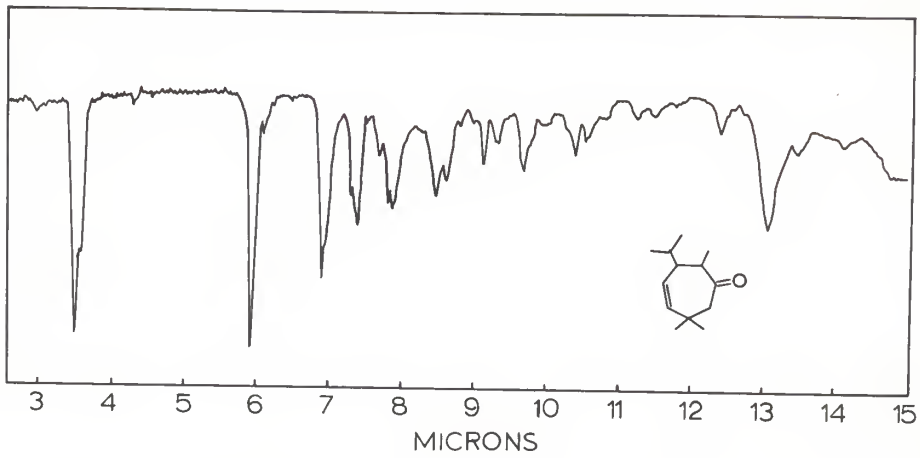
While an actual synthesis of a substituted tropilidene was not accomplished, this work has clarified several difficulties encountered by Lorance, has resulted in the synthesis and characterization of several new substituted cycloheptene and cycloheptadiene compounds, has reported a new tritylation reaction and has accomplished the initial reaction studies which should be helpful in the formulation of a new method of dehydrogenation.

INFRARED SPECTRA

2,6,6-Trimethyl-3-isopropylcyclohept-4-enone (neat)

2,6,6-Trimethyl-3-isopropylcyclohept-4-en-1-ol (neat)

1,2,6,6-Tetramethyl-3-isopropylcyclohept-4-en-1-ol (neat)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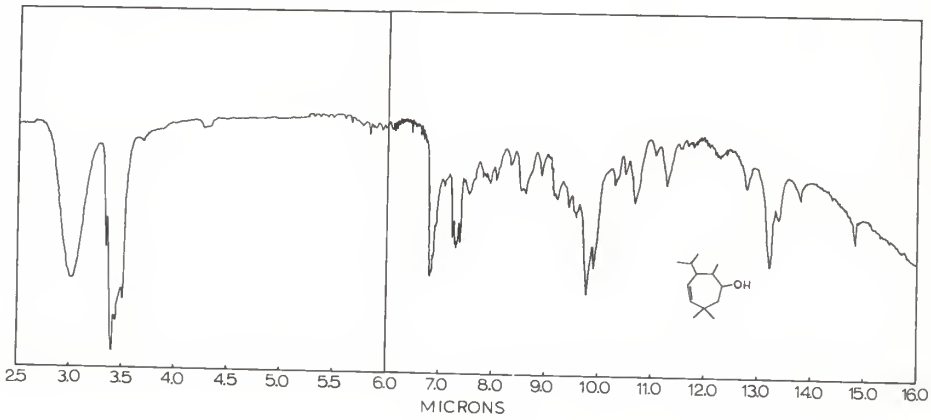
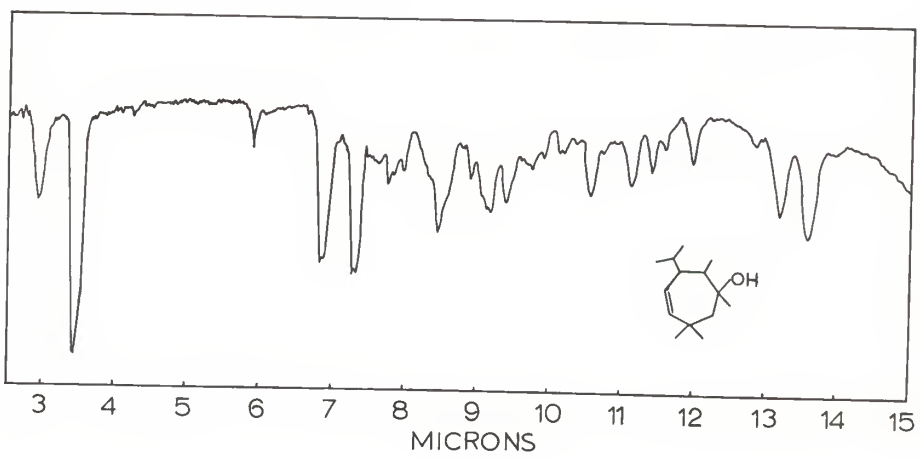
MICRONS


OH
2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0
MICRONS

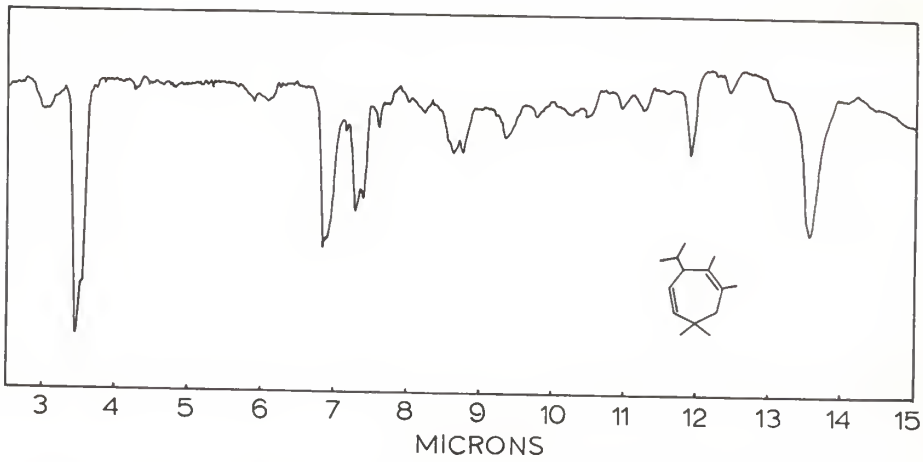

OH
3 4 5 6 7 8 9 10 11 12 13 14 15
MICRONS

INFRARED SPECTRA

1,2,6,6-Tetramethyl-3-isopropylcyclohepta-1,4-diene (neat)

1-Methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene (neat)

1,3,3,7-Tetramethyl-6-isopropylcyclohepta-1,4-diene (neat)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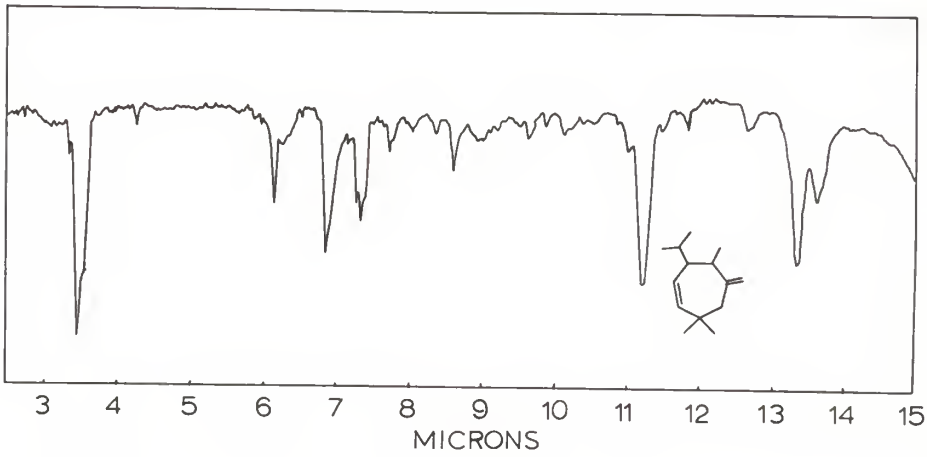
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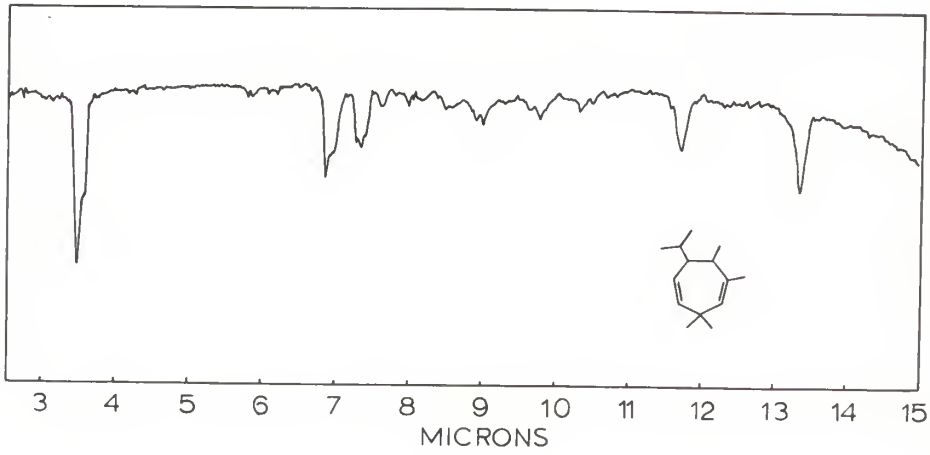
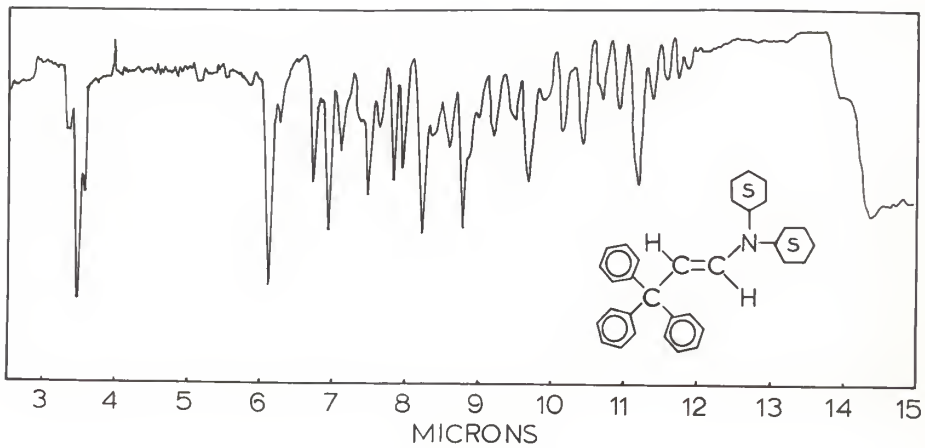
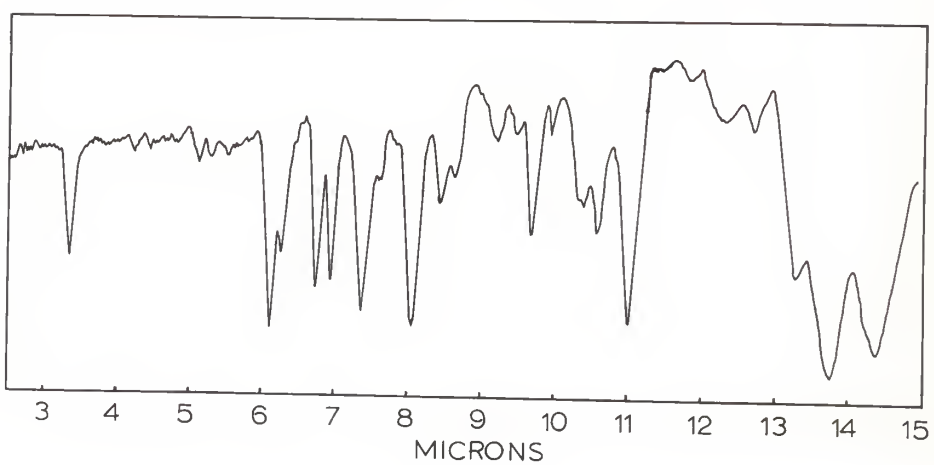

3 4 5 6 7 8 9 10 11 12 13 14 15
MICRONS

INFRARED SPECTRA

N,N-Dicyclohexyl-3,3,3-triphenylpropenylamine (CCl_4)

Reaction product of trityl perchlorate and triethylamine


S
N
S
H
C=C
H
C
3 4 5 6 7 8 9 10 11 12 13 14 15
MICRONS

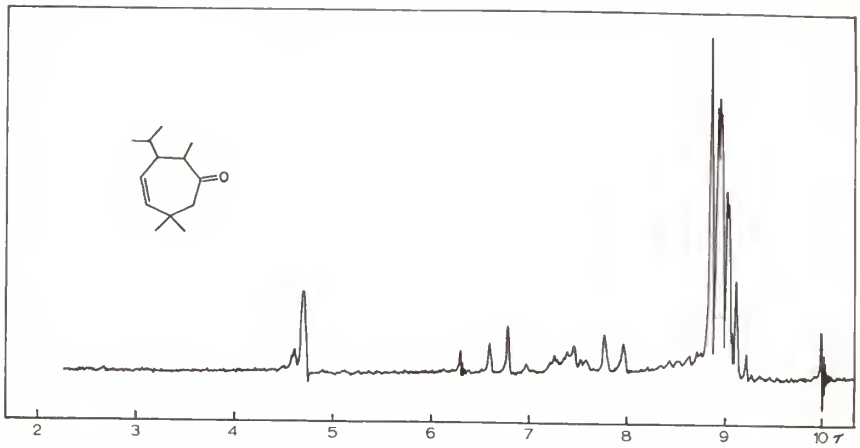

3 4 5 6 7 8 9 10 11 12 13 14 15
MICRONS

N.M.R. SPECTRA

2,6,6-Trimethyl-3-isopropylcyclohept-4-enone ($DCCl_3$)

2,6,6-Trimethyl-3-isopropylcyclohept-4-en-1-ol ($HCCl_3$)

1,2,6,6-Tetramethyl-3-isopropylcyclohept-4-en-1-ol ($DCCl_3$)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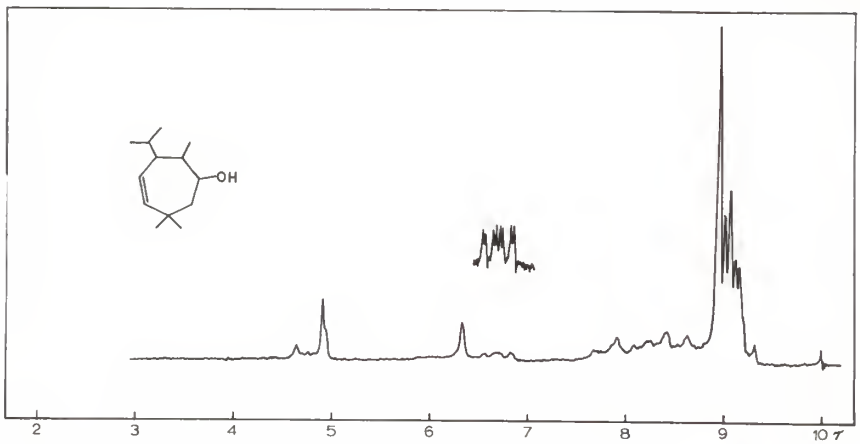
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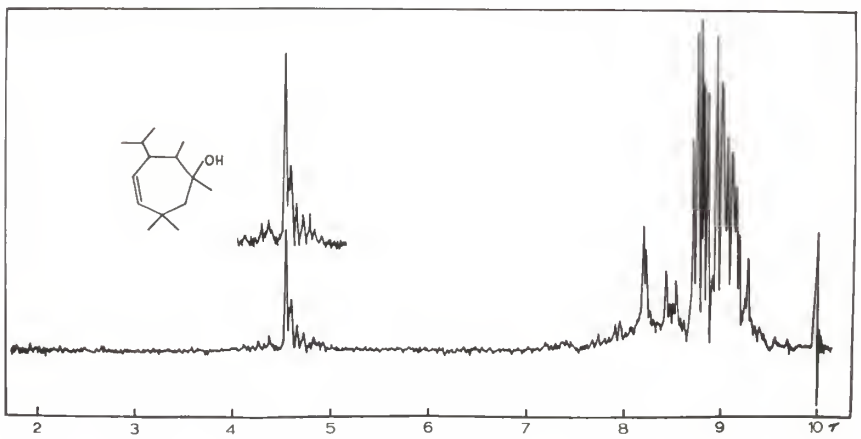
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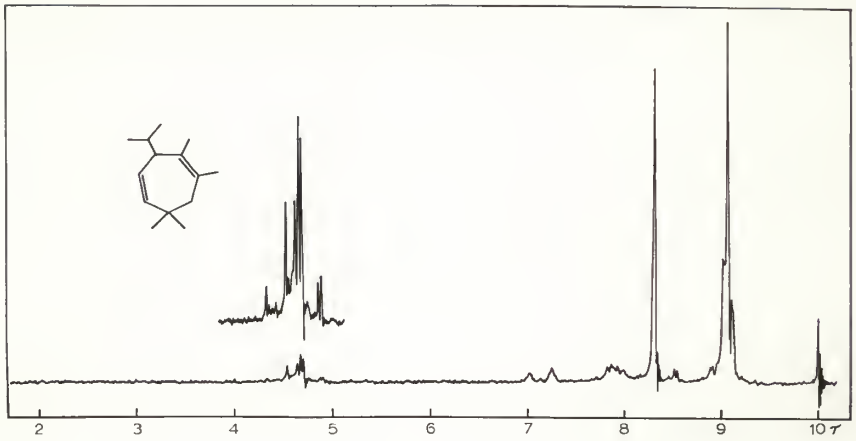
N.M.R. SPECTRA

1,2,6,6-Tetramethyl-3-isopropylcyclohepta-1,4-diene ($DCCl_3$)

1-Methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene ($DCCl_3$)

1,3,3,7-Tetramethyl-6-isopropylcyclohepta-1,4-diene ($DCCl_3$)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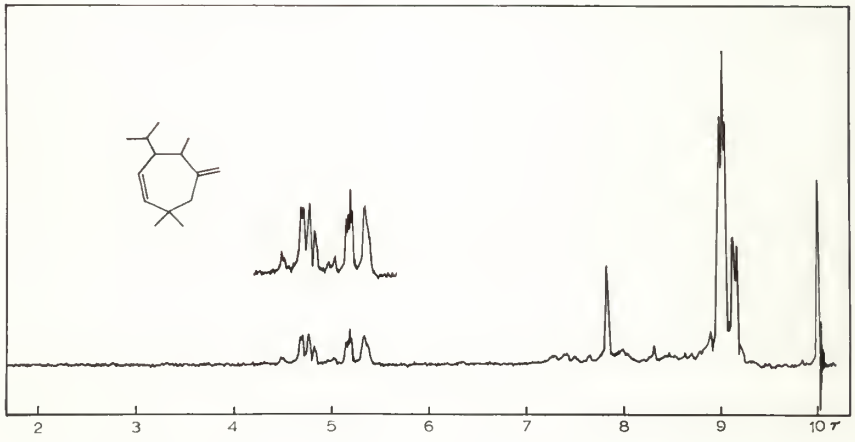
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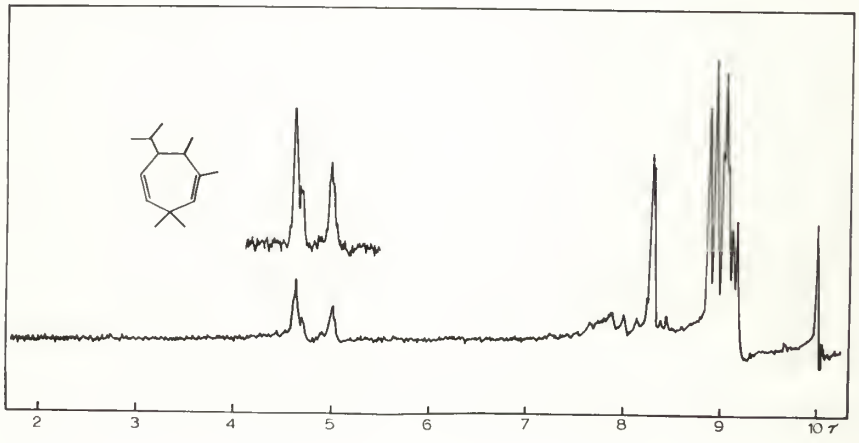
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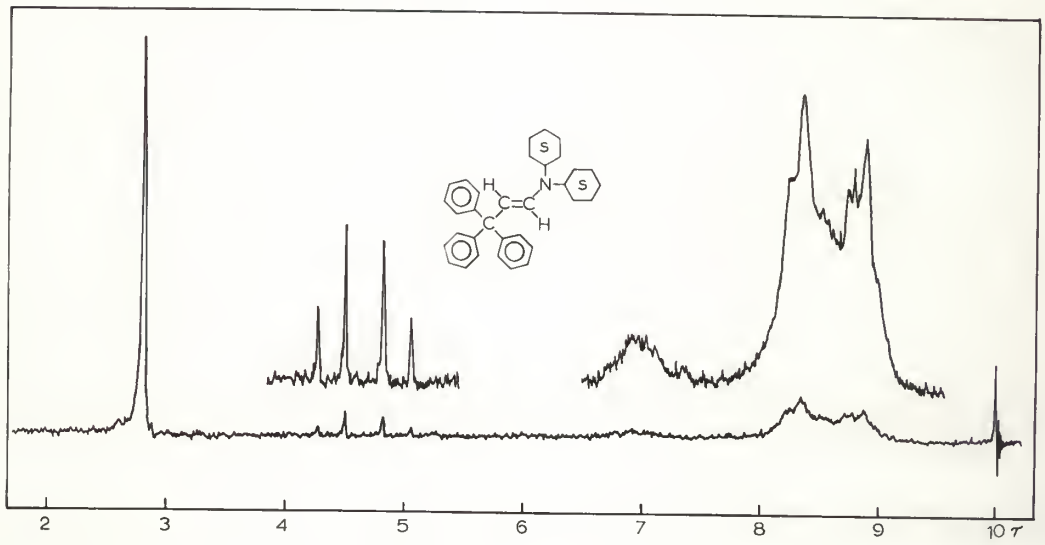
N.M.R. SPECTRA

N,N-Dicyclohexyl-3,3,3-triphenylpropenylamine ($DCCl_3$)

Reaction product of trityl perchlorate and triethylamine ($DCCl_3$)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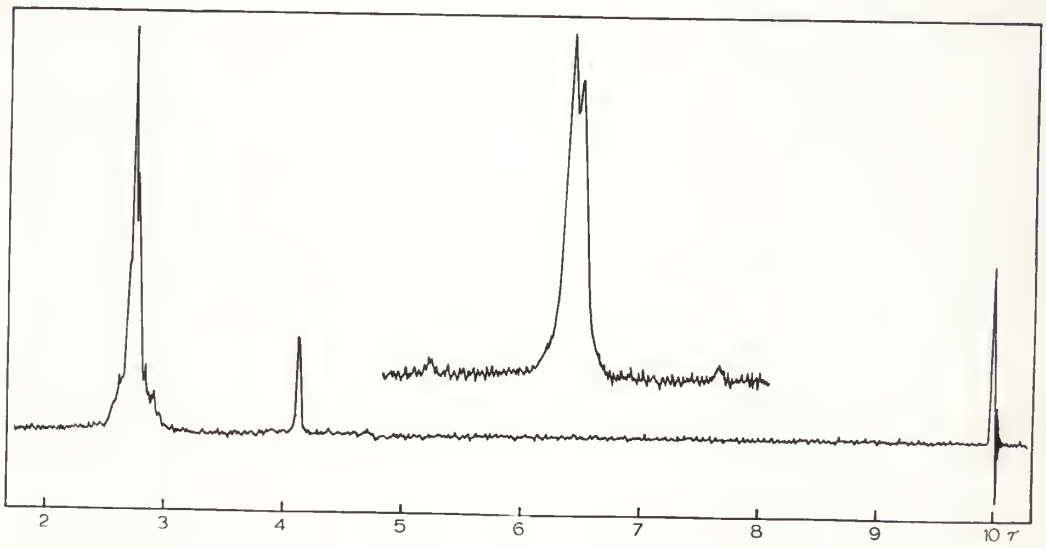
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EXPERIMENTAL

GENERAL: Infrared spectra were taken on a Perkin Elmer Model 137 and 237. Solids were run as potassium bromide pellets and as solutions in carbon tetrachloride. Liquid samples were placed between sodium chloride plates, and the spectra were taken of thin films without solvent. Nuclear magnetic resonance spectra were obtained from a Varian A-60. Ultraviolet data was taken from a Cary Model 14. Elemental analyses were determined by Galbraith Laboratories, Inc. A Fisher-Johns Melting Point Apparatus was used for melting point determinations. All melting points and boiling points are uncorrected.

EUCARVONE: Following the procedure of Corey and Burke[35], l-carvone (101 g, 672 mmoles) was added to a solution of hydrobromic acid (500 g of a 30-32 percent solution of hydrogen bromide in acetic acid) at -30° C.

The resulting dark solution was poured into one liter of water, and the lower dark layer was separated. The water layer was extracted with ether, and the ether extract was added to the organic layer. The organic layer was neutralized with 5 percent sodium bicarbonate, washed with water and dried with magnesium sulfate. The ether solution was reduced to 200 ml under vacuum and was added to 75 g (1.3 moles) of potassium hydroxide in 275 ml of methanol at 0° C. The dark red solution was heated to 50° C for 15 minutes. The mixture was cooled to room temperature and poured onto an ice-sulfuric acid mixture (175 ml of concentrated sulfuric acid). A white solid precipitated, and a yellow organic layer separated. The yellow oil was withdrawn, and the water layer was extracted three times with ether. The ether extract was mixed with the yellow oil, and the mixture was washed with 5 percent sodium bicarbonate solution and with water until neutral.

The ether was removed, and the yellow oil was steam distilled. Approximately three liters of distillate were collected. The distillate was salted and extracted with ether, and the ether solution was dried. The ether was removed, and the product was distilled on a spinning band column. Thirty nine grams (38.6 percent yield) of eucarvone was obtained; bp 44° C (0.6 mm). Vpc on a 10 percent neopentyl glycol succinate column at 210° C showed only one component, and the ir spectrum agreed with that reported for eucarvone by Campbell.[41]

2,6,6-TRIMETHYL-3-ISOPROPYLCYCLOHEPT-4-ENONE: Isopropyl magnesium bromide was prepared from 13.4 g (551 mmoles) of magnesium and 61.5 g (500 mmoles) of isopropyl bromide. The magnesium was covered with anhydrous ether, and the halide dissolved in 100 ml of ether was added dropwise with cooling to the flask once the reaction had been initiated. After the spontaneous exothermic reaction had ceased, the reagent was heated for 30 minutes at reflux and was then cooled to room temperature. A solution of 35.2 g (234 mmoles) of eucarvone in 100 ml of ether was added dropwise, and the reaction was stirred at room temperature overnight.

The solution was neutralized with a saturated solution of ammonium chloride; the ammonium chloride solution was added dropwise with cooling and stirring. The ether layer was separated, and the water layer was extracted three times with ether. The ether solutions were mixed, washed with 5 percent sodium bicarbonate, washed with water and dried with magnesium sulfate. The ether was evaporated, and the product was distilled on a spinning band column. The colorless liquid distilled at 62° C (0.5 mm). The ir (page 17), nmr (page 23) and uv max (95 percent ethanol) 293 mμ were consistent with those expected for the γ,δ-unsaturated ketone. The product was checked on a SF-96 and on a 10 percent Carbowax 20M vpc

column and showed only one component. Yields ranged from 52-75 percent.

REACTION OF ISOPROPYL MAGNESIUM BROMIDE WITH 2,6,6-TRIMETHYL-3-ISOPROPYL-CYCLOHEPT-4-ENONE: Isopropyl magnesium bromide was prepared from 825 mg (34 mmoles) of magnesium and 3.81 g (31 mmoles) of isopropyl bromide. The reagent was prepared as before, and then 3.0 g (15.5 mmoles) of 2,6,6-trimethyl-3-isopropylcyclohept-4-enone in 6 ml of ether was added dropwise. The reaction was very vigorous, and the workup was done as before. The product from the reaction was a yellow oil which was separated into one major component and three minor components on a 1/4 in x 6 ft vpc column of 10 percent FFAP on 60/80 firebrick. Preparative gas chromatography on a 3/8 in x 15 ft column of 10 percent FFAP on 60/80 firebrick with a helium flow rate of 200 ml/min, a column temperature of 180° C, detector temperature of 240° C, and an injector temperature of 210° C produced the samples used for identification.

The major fraction (52 percent of products) was a colorless crystalline solid: mp 53° C; ir (page 17); nmr (page 23). Sodium borohydride reduction of 2,6,6-trimethyl-3-isopropylcyclohept-4-enone in ethanol yielded a compound with the same ir and nmr spectra. This compound was determined to be 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol.

Another component (16 percent of products), an alcohol, was isolated in sufficient quantity for an ir, nmr and elemental analysis (C, 78.41; H, 12.32). The compound was a yellow crystalline solid: mp 55-57° C. No structure proposal seemed adequate to explain the data.

2,6,6-TRIMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL: Three grams (15.5 mmoles) of 2,6,6-trimethyl-3-isopropylcyclohept-4-enone was reduced with 3.0 g (79 mmoles) of sodium borohydride. The ketone was dissolved in 7 ml of absolute ethanol, and sodium borohydride dissolved in 70 ml of absolute

ethanol was added dropwise to the ketone. The solution warmed slightly and was stirred at room temperature overnight.

Workup consisted of acidification with sulfuric acid, neutralization with 5 percent sodium bicarbonate, addition of sodium chloride to salt out the organic material, extraction with ether, drying over magnesium sulfate, evaporation of the solvent and vacuum distillation at 78° C (0.04 mm).

The distillation product was a clear viscous liquid that would not crystallize. Attempts were made to crystallize the product from ethanol-water mixtures without success. So, the product was concentrated and redistilled. After one week, the redistilled material had solidified into a clear crystalline solid. The nmr and ir spectra confirmed that the product was the same as the major product from the reaction of isopropyl magnesium bromide and 2,6,6-trimethyl-3-isopropylcyclohept-4-enone.

ATTEMPTED DEHYDRATION OF 2,6,6-TRIMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL WITH 85 PERCENT PHOSPHORIC ACID: One gram (5.1 mmoles) of 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol was treated with 5 ml of 85 percent phosphoric acid. The solution was heated at 110° C for 40 minutes. The reaction was stopped when the solution turned a dark brown color that is often indicative of polymerization. The reaction mixture was neutralized with 5 percent sodium bicarbonate and extracted with ether. The ether solution was washed with water and dried with magnesium sulfate. The ir still resembled that of the starting alcohol. The dehydration has not been achieved.

ATTEMPTED DEHYDRATION OF 2,6,6-TRIMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL WITH p-TOLUENESULFONIC ACID: One gram (5.1 mmoles) of 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol was placed in a 50 ml round bottom flask equipped with a Dean-Stark trap and a magnetic stirrer. Twenty milliters

of benzene and a catalytic amount of p-toluenesulfonic acid was added. The solution was refluxed for two days. Workup yielded only starting material.

1,2,6,6-TETRAMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL: Methyl magnesium iodide was prepared from 2.16 g (15.2 mmoles) of methyl iodide and 410 mg (16.8 mmoles) of magnesium. The magnesium was covered with ether, and once the reaction had been initiated, the halide dissolved in 5 ml of ether was added dropwise to the flask. After the spontaneous exothermic reaction had ceased, the reagent was heated for 30 minutes at reflux and was then cooled to room temperature, and then, a solution of 2.0 g (10.3 mmoles) of 2,6,6-trimethyl-3-isopropylcyclohept-4-enone in 8 ml of anhydrous ether was added dropwise to the Grignard reagent. The reaction was stirred at room temperature overnight.

Workup was accomplished by using ammonium chloride to acidify and very dilute sodium bicarbonate (pH approximately 8 with Accutint Indicator Paper) to make the reaction product slightly basic. All glassware to be used in the distillation of the product was cleaned with chromic acid cleaning solution, washed with distilled water, washed with acetone, washed with a dilute solution of ammonium hydroxide and dried at 115° C. This treatment was found to be necessary to avoid dehydration reactions during distillation.

The reaction yielded 1.5 g (70 percent yield) of a clear viscous liquid that distilled at 55-58° C (0.1 mm). The ir (page 17) and nmr (page 23) were consistent with those anticipated for the desired alcohol. The distilled product was gas chromatographed at 170° C on a 3/8 in x 15 ft column of 10 percent FFAP on 60/80 firebrick. The recorded chromatogram indicated that the alcohol was dehydrating on the column.

DEHYDRATION OF 1,2,6,6-TETRAMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL BY

DISTILLATION FROM POTASSIUM HYDROGEN SULFATE: Distillation of 1.5 g of 1,2,6,6-tetramethyl-3-isopropylcyclohept-4-en-1-ol in the presence of 50 mg of potassium hydrogen sulfate at 0.5 mm yielded predominately starting material.

The recovered starting material was heated in the presence of finely ground potassium hydrogen sulfate at 100° C. The reaction progress was checked by vpc at 30 minutes, 55 minutes and 165 minutes. No alcohol was observable in the reaction after 165 minutes, so the reaction was allowed to cool to room temperature. The ir and nmr showed that the predominant product of the dehydration was the diene with an exocyclic double bond, 1-methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene.

ATTEMPTED DEHYDRATION OF 1,2,6,6-TETRAMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL BY DISTILLATION FROM IODINE: Dehydration by distillation from iodine was unsuccessful because the temperatures required to distill the resulting diene at atmospheric pressure are high enough to cause rearrangements and decomposition. Vacuum distillation was also unsuccessful because the iodine sublimed from the distilling flask or reacted with the sites of unsaturation before distillation could be accomplished.

DEHYDRATION OF 1,2,6,6-TETRAMETHYL-3-ISOPROPYLCYCLOHEPT-4-EN-1-OL WITH p-TOLUENESULFONIC ACID: Eight grams (38 mmoles) of 1,2,6,6-tetramethyl-3-isopropylcyclohept-4-en-1-ol was placed in a 250 ml round bottom flask equipped with a Dean-Stark trap and magnetic stirrer. Dry benzene (150 ml) and 50 mg of p-toluenesulfonic acid were added to the flask, and the reaction was refluxed. Reaction progress was observed by measuring the amount of water collected. The reaction was stopped after 60 hours: eighty-one percent of the theoretical amount of water was collected.

The benzene solution was washed twice with 25 ml portions of water

to extract the acid. The benzene was distilled off, and the product was distilled at 36° C (0.2 mm). Six grams (82 percent yield) of clear colorless liquid diene was collected. The diene mixture was gas chromatographed on a 3/8 in x 15 ft column of 10 percent FFAP on 60/80 firebrick with a column temperature of 145° C, detector temperature of 250° C, injector temperature of 210° C and a helium flow rate of 200 ml/min.

Each of the three possible dienes was collected, reinjected and collected again. The diene mixture was composed of 46.8 percent of 1,2,6,6-tetramethyl-3-isopropylcyclohepta-1,4-diene, 36.7 percent of 1-methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene, 10.1 percent of 1,3,3,7-tetramethyl-6-isopropylcyclohepta-1,4-diene, and 6.0 percent of unidentified products. The ir spectra (page 19) and nmr spectra (page 25) are of the respective dienes.

Anal. Calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.57. Found (1,2,6,6-tetramethyl-3-isopropylcyclohepta-1,4-diene): C, 87.33; H, 12.53. Found (1-methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene): C, 87.66; H, 12.62. Found (1,3,3,7-tetramethyl-6-isopropylcyclohepta-1,4-diene): C, 88.28; H, 11.78.

TRITYL PERCHLORATE: The procedure used is that of Hofmann and Kirmreuther.[42] Two grams (7.68 mmoles) of triphenylcarbinol was suspended in 15 ml of acetic anhydride. This suspension was cooled in an ice bath. Then, 2.0 cc (26.6 mmoles) of 71 percent perchloric acid was added dropwise with stirring. An orange precipitate formed immediately. The solution was filtered on a medium sintered glass funnel, and the precipitate was first washed with cold acetic anhydride and then washed with cold anhydrous ether. The funnel and precipitate were placed in an Abderhalden and dried under vacuum over phosphorous pentoxide at room temperature. The melting point of the

dried product was 150° C with decomposition. The product decomposed in the presence of atmospheric moisture.

During periods of high humidity, a sintered glass funnel with a standard taper joint attached to the top of the funnel was used for the filtration. The product from the reaction was placed in the sintered glass funnel, and a standard taper calcium chloride drying tube was immediately put in place before filtration was begun.

ETHYLDICYCLOHEXYLAMINE: The procedure used is that of Hunig and Kiessel.[37] Diethyl sulfate (15.42 g, 100 mmoles) was added to 18.13 g (100 mmoles) of dicyclohexylamine heated to 90° C. The reaction was heated at 90° C for 17 hours. Near the end of the reaction period, the solution solidified.

The dark red solid was treated with excess concentrated aqueous potassium hydroxide and extracted with ether. The ether was removed, and the product was distilled at 89° C (0.9 mm). The product was a clear colorless liquid, and the yield for the reaction was 15.5 g (74 percent) of ethyldicyclohexylamine.

The same procedure was later followed for a synthesis using 3.47 moles of each of the reactants. The addition of the diethyl sulfate was done as in the earlier reaction, but without explanation, the reaction temperature rose from 90° C to 160° C, and the reaction became quite violent and was only maintained at 160° C by submersion in a large ice bath. The product from both reactions was the same, but the apprehension could probably be avoided by reacting smaller quantities.

ATTEMPTED DEHYDROGENATION OF 1,2,6,6-TETRAMETHYL-3-ISOPROPYLCYCLOHEPTA-1,4-DIENE: In a 10 ml round bottom flask, 200 mg (1.0 mmoles) of the diene mixture obtained from the p-toluenesulfonic acid dehydration was mixed with 5 ml of anhydrous acetonitrile and 1 ml of ethyldicyclohexylamine.

Then, 0.51 g (1.6 mmoles) of trityl perchlorate was added to the reaction vessel. Instantly, a purple color developed, and within four minutes the color began to lessen. In less than 10 minutes a white solid precipitated. The reaction was allowed to stand for 40 minutes.

Workup of the reaction mixture consisted of the addition of 15 ml of water. The white solid was insoluble in water but was soluble in carbon tetrachloride, so carbon tetrachloride was added to take up the organic material. The water layer was separated and extracted with carbon tetrachloride. The carbon tetrachloride solutions were then washed with 20 percent perchloric acid to change any soluble amines to the corresponding amine salts. The resulting salts were insoluble in the perchloric acid solution and in the carbon tetrachloride layer, so the carbon tetrachloride layer was separated and filtered. The carbon tetrachloride layer was then dried with magnesium sulfate and evaporated. An nmr of the product was the same as that of the starting diene mixture.

Simultaneously, another reaction with the same quantities of diene mixture and trityl perchlorate but with 3 ml of acetonitrile and 3 ml of ethyldicyclohexylamine was run. This reaction initially developed the orange color of trityl perchlorate. No evidence of a reaction was visible for 3 hours. Then, a white solid or milky suspension developed in the lower ethyldicyclohexylamine layer. The same reaction had occurred in both cases, but in the latter case, the larger quantity of amine or smaller quantity of acetonitrile had slowed the reaction.

Further study uncovered the fact that trityl perchlorate and ethyldicyclohexylamine in acetonitrile react without having the diene mixture present. It was also found that the same purple color developed in chloroform, but no precipitate formed. The solid white compound was found

to be soluble in chloroform.

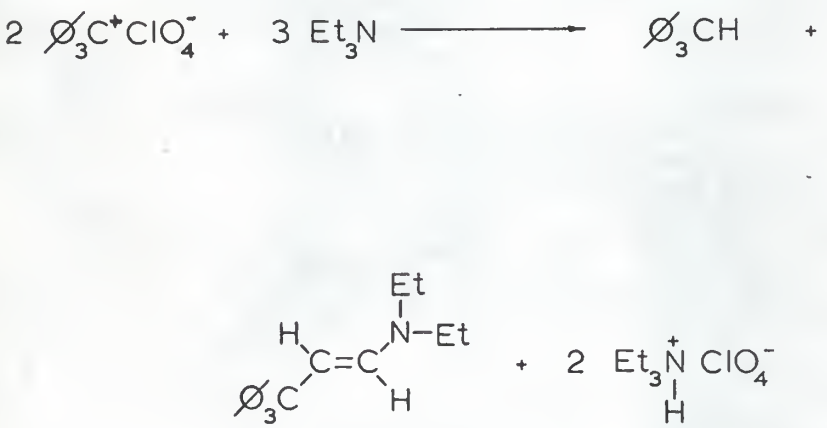
ISOLATION OF THE REACTION PRODUCT OF TRITYL PERCHLORATE AND ETHYLDICYCLOHEXYLAMINE: Since the stoichiometry of the reaction was unknown, 1 ml of ethyldicyclohexylamine was dissolved in 5 ml of anhydrous acetonitrile, and then, 0.51 g (1.6 mmoles) of trityl perchlorate was added to the reaction vessel as in the attempted dehydrogenation reaction. The diene mixture was not added in this synthesis, and the reaction proceeded as before. When the purple color cleared, the reaction mixture was filtered through a sintered glass funnel to isolate the solid. Recrystallization from absolute ethanol yielded fine white crystals with mp 153-155° C. The nmr (page 27) and ir (page 21) indicated that the product might be N,N-dicyclohexyl-3,3,3-triphenylpropenylamine; a subsequent synthesis verified this structure proposal.

N,N-DICYCLOHEXYL-3,3,3-TRIPHENYLPROPENYLAMINE: Trityl perchlorate (2.13 g, 6.22 mmoles) was placed in a 25 ml round bottom flask equipped with a condenser, drying tube and magnetic stirrer. Eighteen milliliters of dried acetonitrile partially dissolved the trityl perchlorate. Then, 1.95 g (9.32 mmoles) of ethyldicyclohexylamine was added dropwise with stirring. The dark purple color developed at once, and following the last addition, the solution cleared, and a white solid precipitated. The reaction took 45 minutes to complete. The solid was filtered off and recrystallized from absolute ethanol. The product had a mp 153-155° C; the ir and nmr spectra were identical to those obtained from the product isolated from the attempted dehydrogenation reaction. Yields for the reaction calculated on the basis of trityl perchlorate ranged from 51.5-63.5 percent.

Anal. Calcd. for $C_{33}H_{39}N$: C, 88.14; H, 8.74. Found: C, 88.10; H, 8.87.

During periods of high humidity, all glassware was ovendried, and the reaction was run in a 3-neck round bottom flask equipped with condenser and serum stopper. The solvent and amine were dried and stored in flasks with similar serum stoppers. Then, transfer of both amine and acetonitrile were accomplished with syringes of appropriate size.

REACTION OF TRITYL PERCHLORATE AND TRIETHYLAMINE: Trityl perchlorate (1.0 g, 2.92 mmoles) was placed in a 10 ml flask equipped with a magnetic stirrer, condenser and drying tube. Six milliliters of dry acetonitrile partially dissolved the trityl perchlorate. Then, 442 mg (4.38 mmoles)



of triethylamine, previously dried over potassium hydroxide and distilled from a mixture of phenyl isocyanate and potassium hydroxide, was added. The solution turned dark purple upon addition of the amine, and within 30 minutes, a white solid percipitated from the reaction mixture.

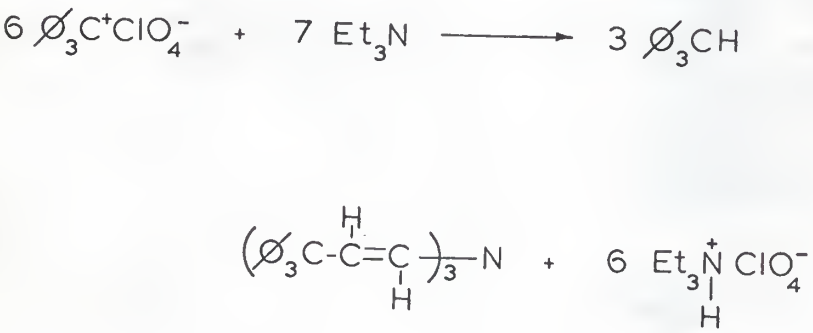
Difficulty was encountered in recrystallizing the product. n-Butyl alcohol slowly dissolved the product, and addition of absolute ethanol and cooling resulted in recrystallization. However, near the boiling

point of n-butyl alcohol, the solution quite suddenly turned yellow, and complete recovery of the product was never achieved. The product recovered was white and crystalline with mp 215-218° C.

Small amounts of methylene chloride also dissolved the product and recrystallization was achieved by addition of n-hexane and boiling of the solution until the product started to precipitate from the solvent mixture. Then, completion of recrystallization was achieved by cooling. Recovery from this solvent system was more complete.

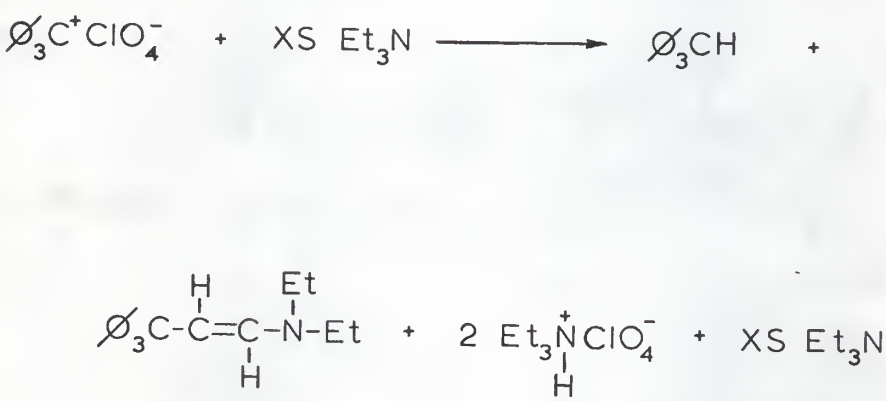
The ir (page 21) and nmr (page 23) of the recrystallized product showed no absorption characteristic of N-ethyl groups. Therefore, it appears that the reaction proceeds three times with one molecule of triethylamine. This would produce tris (3,3,3-triphenylpropenyl)amine, but a satisfactory elemental analysis was not obtained for this structure proposal.

Since the stoichiometry of the reaction did not appear to be the same as with the reaction of trityl perchlorate and ethyldicyclohexylamine, another reaction with 1.0 g (2.92 mmoles) of trityl perchlorate



and (3.40 mmoles) triethylamine was attempted. This reaction took 50 minutes to complete, and the same white solid precipitated as in the initial reaction; in both systems, the triethylamine was sufficient to react with all of the trityl perchlorate.

REACTION OF TRITYL PERCHLORATE WITH EXCESS TRIETHYLAMINE: In order that an excess of amine might be maintained throughout the reaction period, 1.0 g (2.92 mmoles) of trityl perchlorate was completely dissolved in 20 ml of dry acetonitrile, and this was added to a solution of 3.44 g (34.0 mmoles) of triethylamine in 10 ml of dry acetonitrile. All glass-



ware was dried prior to use, and a calcium chloride tube was used to protect the reaction from atmospheric moisture. The trityl perchlorate solution was added dropwise. A purple color developed on the drip tip of the addition funnel as the orange trityl perchlorate solution came in contact with the vapors in the reaction flask. However, no lasting color ever developed in the reaction flask as in the reactions in which the amine was added to the trityl perchlorate in acetonitrile. Likewise, no solid ever precipitated, and attempts to separate the products into different solvents were unsuccessful. So, the organic

material was dissolved in chloroform; the chloroform was evaporated, and the organic product was dissolved in benzene. The benzene solution was chromatographed on an alumina column. The solvent order was: (1) benzene, (2) chloroform, and (3) acetone. The first fraction contained triphenylmethane: mp 90° C. The nmr of this compound was identical with the Sadtler Spectrum. The second fraction contained β,β,β-triphenylpropionaldehyde: mp 100° C. This structure was proven by an alternate synthesis of Hellerman and Garner.[43] The other fractions contained only minor quantities of materials that were not characterized.

The conclusion was that the enamine either hydrolyzed during workup or on the alumina column.

β,β,β-TRIPHENYLPROPIONIC ACID: The procedure used was that of Hellerman.[44] Triphenylcarbinol (25 g, 95 mmoles) was intimately mixed with 16.25 g (156 mmoles) malonic acid in a 300 ml flask. The mixture was heated in an oil bath, at first cautiously at 140-150° C, and was maintained at that temperature until the first evolution of gas had subsided. The oil bath was then heated to 158-160° C for 3 hours. The solid was then treated with 30 g of sodium hydroxide dissolved in 400 ml of water. The mixture was heated to hasten solution, and the unchanged triphenylcarbinol was removed by filtration of the hot solution. The cooled filtrate was treated with excess hydrochloric acid, and the β,β,β-triphenylpropionic acid precipitated. Difficulty was encountered in filtering out the triphenylcarbinol; the pores of the sintered glass funnel filled before the solution could be filtered completely. Only 5.0 g (17.4 percent) of β,β,β-triphenylpropionic acid was isolated from the first run. Since this was sufficient quantity for the subsequent reactions, no attempt was made to further increase the yield. The nmr spectrum of the β,β,β-tri-

phenylpropionic acid had bands at τ 0.90 (1 H, broad singlet), 2.83 (15 H, singlet), 6.33 (2 H, singlet).

ß,ß,ß-TRIPHENYLPROPIONYL CHLORIDE: The synthesis of the acid chloride of ß,ß,ß-triphenylpropionic acid was that of Hellerman.[44] The ß,ß,ß-triphenylpropionic acid (5.0 g, 16.5 mmoles) was allowed to react with 8 ml of thionyl chloride. The reaction was completed by heating to just below the boiling point of thionyl chloride. Crystals formed when the solution was cooled, and the yellow crystals were dried under vacuum over sodium hydroxide pellets in an Abderhalden. The yield for the reaction was 4.2 g (79 percent) of ß,ß,ß-triphenylpropionyl chloride: mp 128° C; ir (CCl_4) 1810 cm^{-1} (C=O); nmr ($DCCl_3$) τ 2.79 (15 H, multiplet), 5.68 (2 H, singlet).

ß,ß,ß-TRIPHENYLPROPIONALDEHYDE: Except for a slight modification of the catalyst, the procedure of Hellerman and Garner[43] was followed for the Rosenmund reduction of ß,ß,ß-triphenylpropionyl chloride to the corresponding aldehyde. The ß,ß,ß-triphenylpropionyl chloride was dissolved in 150 ml of dry xylene, and 0.8 g of palladium on barium sulfate catalyst and two drops of quinoline-sulfur inhibitor (0.1 g inhibitor per milliliter) were added. The reaction mixture was then maintained at 128° C for 6 1/2 hours while hydrogen gas was bubbled in the flask. The catalyst was removed by filtration, and the xylene was distilled under vacuum. The product was obtained in the form of an oil which crystallized when stirred. The aldehyde, washed with a little low-boiling petroleum ether, was obtained in the form of fine, white needles melting at 101° C. The yield of ß,ß,ß-triphenylpropionaldehyde was 2.6 g (75 percent): ir (CCl_4) 1720 cm^{-1} (C=O); nmr (CCl_4) τ 0.64 (1 H, triplet), 2.85 (15 H, multiplet), 6.53 (2 H, doublet).

ALTERNATE SYNTHESIS OF N,N-DICYCLOHEXYL-3,3,3-TRIPHENYLPROPENYLAMINE:

β,β,β-Triphenylpropionaldehyde (500 mg, 1.74 mmoles) was dissolved in 40 ml of dry benzene in a 50 ml flask equipped with a Dean-Stark trap. Then, 350 mg (1.93 mmoles) dicyclohexylamine was added, and the reaction was refluxed for 38 hours. The benzene was distilled off; the product was dissolved in anhydrous ether, cooled overnight in the freezing compartment of the refrigerator and the crystals were collected and recrystallized twice from absolute ethanol. The ir and nmr spectra were taken and were identical with the product prepared from trityl perchlorate and ethyldicyclohexylamine. Melting point of the colorless rod-shaped crystals was 153-155° C.

Anal. Calcd. for $C_{33}H_{39}N$: C, 88.14; H, 8.74. Found: C, 88.24; H, 8.89.

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SYNTHESIS OF SUBSTITUTED CYCLOHEPTATRIENE DERIVATIVES

by

BRYCE EUGENE HARTHOORN

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A scheme for the synthesis of heavily substituted tropilidenes was the object of study. Previous attempts to produce pentaalkyl tropilidenes had proven unsuccessful, and the present work was initiated to define the difficulties in order that a new approach might be devised.

The synthesis of 3,7,7-trimethyl-2,4-diisopropyl-1,3,5-cycloheptatriene was the first to be studied. The starting material, l-carvone, was converted to eucarvone. Then, 1,4-addition of isopropyl magnesium bromide produced 2,6,6-trimethyl-3-isopropylcyclohept-4-enone. An attempted 1, 2-addition of isopropyl magnesium bromide to 2,6,6-trimethyl-3-isopropyl-cyclohept-4-enone resulted in reduction of the ketone and oxidation of the Grignard reagent. Previous study had reported that the proposed tertiary alcohol could not be dehydrated. The reduction product of the ketone was instead proven to be a secondary alcohol, 2,6,6-trimethyl-3-isopropylcyclohept-4-en-1-ol, by an alternate synthesis. The conditions employed in the previous study would not have been expected to cause dehydration of the secondary alcohol.

The second synthesis to be studied was that of 2,3,7,7-tetramethyl-4-isopropyl-1,3,5-cycloheptatriene. The 2,6,6-trimethyl-3-isopropyl-cyclohept-4-enone was allowed to react with methyl magnesium iodide, and the resulting tertiary alcohol, 1,2,6,6-tetramethyl-3-isopropylcyclohept-4-en-1-ol, was dehydrated. The dehydration produced 1,2,6,6-tetramethyl-3 -isopropylcyclohepta-1,4-diene, 1-methylene-2,6,6-trimethyl-3-isopropyl-4-cycloheptene and 1,3,3,7-tetramethyl-6-isopropylcyclohepta-1,4-diene.

Attempts to produce a mild method of dehydrogenation resulted in the discovery of a new reaction between trityl perchlorate and ethyl amines. The product of trityl perchlorate and ethyldicyclohexylamine was proven

to be N,N-dicyclohexyl-3,3,3-triphenylpropenylamine by an alternate synthesis. A mechanism for the new reaction was proposed.

Related reactions of trityl perchlorate and ethyl amines were studied, and modifications for future research were proposed.