I. REACTIONS OF 2,4-PENTADIENAL

II. SOME COMPOUNDS RELATED TO MORPHINE

By

Henry Frederick Lederle

Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

1951

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

ACKNOWLEDGEMENT

The author wishes to express his deep appreciation and sincere gratitude to Dr. G. Forrest Woods for suggesting these problems, and for his guidance and assistance during the course of these investigations.

The author is indebted to Dr. Louis H. Schwartzman for many helpful suggestions during the latter part of this thesis.

All microanalyses reported in this research were performed by Mrs. Mary Aldridge and by Mr. Byron Baer. The author would like to take this opportunity to thank them for their efforts.

TABLE OF CONTENTS

HISTORICAL

2,3-Dihydropyran (I) a substance prepared from tetrahydrofurfuryl alcohol has been used in this laboratory to prepare highly unsaturated compounds such as 1,3,5-hexatriene, 1,3,5,7-octatetraene and 3-bromohexatriene. A major portion of this thesis deals with further synthetic work along this line, namely the preparation of 3-vinyl-$\Delta^{1,5,7}$octatrien-4-ol, the dehydration thereof, the synthesis of the 2,4-pentadienyl ester of 2,4-pentadienoic acid, the synthesis of 2,4-pentadienyl acetate, and derivatives of these compounds.

The other portion of this thesis pertains to the attempted synthesis of 1-phenylcyclohexaneacetic acid, and compounds derived from it. These compounds were of interest because they resemble the structure of morphine.

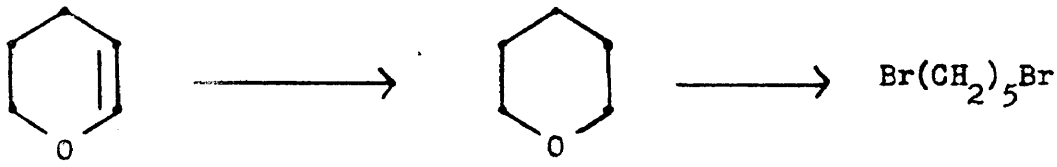
I. THE CHEMISTRY OF PRODUCTS DERIVED FROM 2,3-DIHYDROPYRAN.

2,3-Dihydropyran was obtained by Paul, by dehydration of tetrahydrofurfuryl alcohol over aluminum oxide at 370-380°.[1] Paul also proved its structure. Since the starting material, tetrahydrofurfuryl alcohol can be obtained readily from furfural, which is available in large quantities, dihydropyran potentially could become a cheap industrial chemical. The emphasis of this portion of the historical therefore is placed on the conversion of dihydropyran to other products.

Hydrogenation with Raney Nickel at 100° and several atmospheres pressure led rapidly and quantitatively to tetrahydropyran (II).[2,3] Paul reported that copper-chromite is a great deal less reactive in this reaction.[4] Wilson used nickel, nickel-cobalt, and cobalt catalysts at

100°, the reaction being performed in the vapor phase.[5] Similar results by Bremner, Jones and Taylor[6] were confirmed by Wilson. Two interesting side reactions were observed when the temperature was raised above 200°.[5] The first was a ring fission to yield butane, butene and carbon monoxide, while the other was a rearrangement to cyclopentanone, which, under favorable conditions could be obtained in 33% yield. When noble metal catalysts were used in the reduction, it took place at room temperature and atmospheric pressure. However, Paul reported that n-amyl alcohol may be formed as a by-product up to 10% in the latter instance.[1]

Tetrahydropyran (II) itself is a very useful material. Thus Jurjew[7] reported its conversion to piperidine, and Paul[1] described the synthesis of pentamethylene dibromide from it:



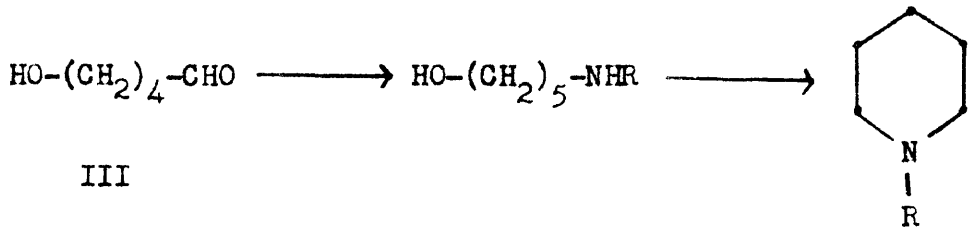
I II

5-Hydroxypentanal (III) was prepared from dihydropyran by acid hydrolysis.[8,9] Catalytic reduction of this compound yielded pentamethylene glycol.[9] This latter compound could also be obtained directly from dihydropyran.[10,11] Paul prepared other 1,5-diols by means of adding an excess of the desired Grignard reagent to 5-hydroxypentanal.[10]

$$HO\text{-}(CH_2)_4\text{-}CHO \quad + \quad RMgX \longrightarrow HO\text{-}(CH_2)_4\text{-}CH(OH)\text{-}R$$

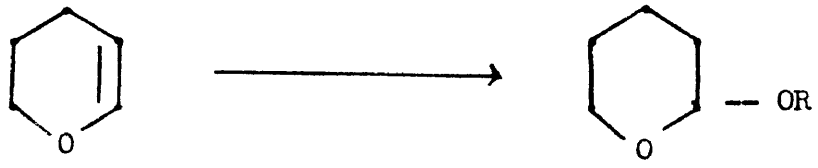
III

By reductive amination N-alkyl-5-hydroxy amines are obtained. When these were passed over alumina at elevated temperatures, N-substituted piperidines were the product:[12]



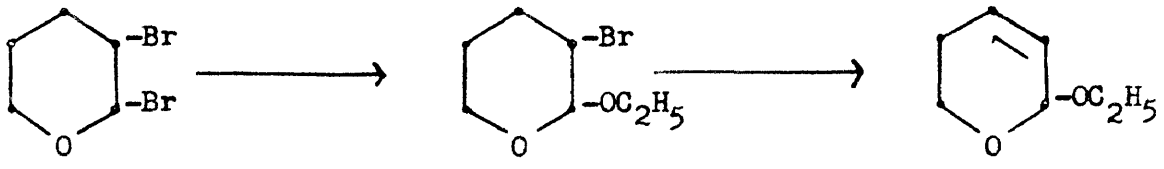
III

Paul showed that under the influence of acid catalysis, water was added to the double bond of dihydropyran, producing a cyclic hemiacetal which was in equilibrium with the open chain 5-hydroxy-pentanal.[13] In the presence of alcohols, acetals were produced. Woods and Kramer prepared a series of these compounds.[14]



I

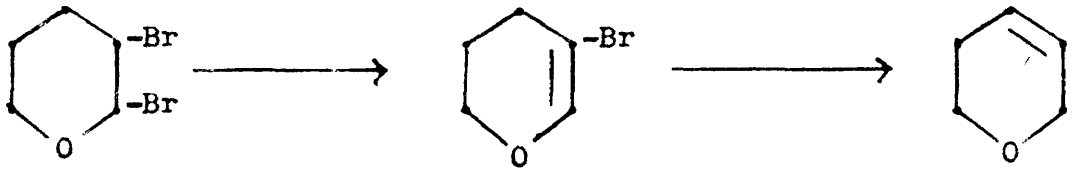
Addition of bromine to the double bond of dihydropyran resulted in the relatively unstable 2,3-dibromotetrahydropyran (IV).[15,16,17] The very reactive α-bromine was easily replaced by alkoxyl groups. When ethanol was used in such a fashion, 2-ethoxy-3-bromotetrahydropyran (V) was obtained. Removal of the second bromine proved rather difficult, but could be effected by refluxing with concentrated base for prolonged periods. This led to 2-ethoxy-Δ^3-dihydropyran (VI), a valuable synthetic intermediate for the preparation of compounds described later.[16]



IV V VI

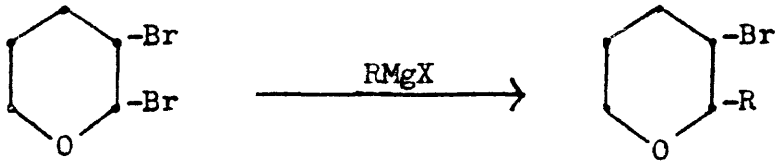
Dehydrohalogenation of 2,3-dibromotetrahydropyran (IV) by means of tertiary amines produced 3-bromo-2,3-dihydropyran (VII).[15] From the

latter substance, Paul and Tchelitcheff prepared 3,4-dihydropyran (VIII).[18]



IV VII VIII

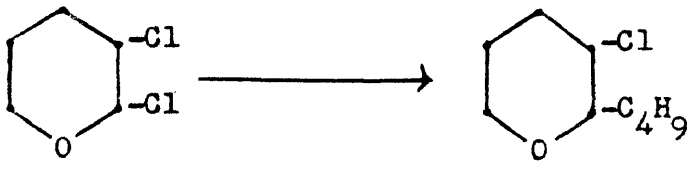
The α-halogen in 2,3-dibromodihydropyran was shown to undergo a Wurtz reaction when treated with Grignard reagents. This led to the 2-alkoxy-3-bromotetrahydropyrans.



IV

Branden, Derfer and Boord used 2,3-dibromotetrahydropyran as starting material for the synthesis of Δ^3-unsaturated alcohols.[17]

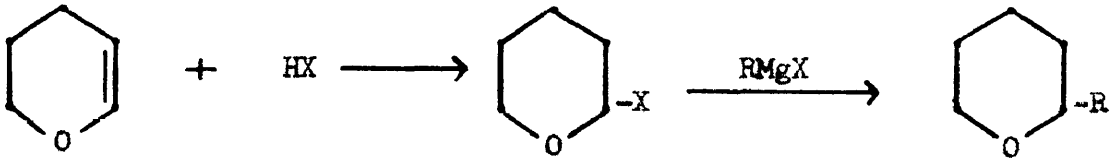
Chlorination of 2,3-dihydropyran afforded 2,3-dichlorotetrahydropyran (IX).[19,20] Jacobson has recently used the latter compound as starting material for the synthesis of one of the pellitorine isomers.[20] The α-chlorine in (IX) may be replaced by alkyl groups by means of an appropriate Grignard reagent. When butylmagnesium chloride was used Paul and Riobe obtained 1,5-epoxy-4-chlorononane (2-butyl-3-chlorotetrahydropyran):



IX

Both hydrogen chloride and hydrogen bromide add to the double bond of dihydropyran, the halogen in each case assuming the α-position.

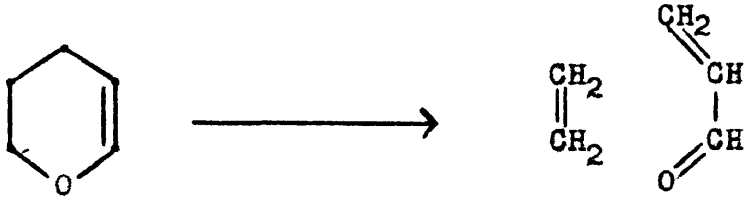
Again, the α-halogen may be replaced by alkyl groups by means of a Grignard reagent, the reaction leading to the 2-alkyl tetrahydropyrans which served as intermediates for the synthesis of 1,4- and 1,5-dienes.[2]



I

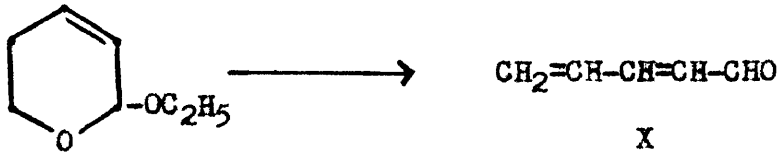
When dihydropyran was passed over aluminum oxide at 400° in a hydrogen sulfide stream, dihydrothiopyran was obtained in 60% yield.[21]

Wilson showed that acrolein and ethylene may be obtained by passing the vapors of dihydropyran (or tetrahydrofurfuryl alcohol) over an aluminum oxide-silica catalyst at an optimum temperature of 450°. With aluminum oxide alone, only a polymer of empirical formula $(C_5H_6)_n$ was obtained.[22]



I

2-Ethoxy- Δ^3-dihydropyran has been used as the starting material for the syntheses of 1,3,5-hexatriene, 1,3,5,7-octatetraene and 3-bromo-hexatriene-1,3,5. When 2-ethoxy- Δ^3-dihydropyran is steam distilled from phosphoric acid, 2,4-pentadienal (X) can be obtained:



X

Woods and Schwartzman reacted methylmagnesium bromide with 2,4-pentadienal.[23] The product of the reaction, 1,3-hexadien-5-ol (XI) was identical with the compound prepared by Heilbron[24] who used a different method of synthesis. The structure of this alcohol was further elucidated by catalytic hydrogenation to the known 2-hexanol, oxidation of the latter to 2-hexanone, and comparison of its derivatives with authentic samples. When passed over activated alumina in the vapor phase, 1,3-hexadien-5-ol (XI) underwent catalytic dehydration very smoothly yielding 1,3,5-hexatriene (XII):

$$CH_2{=}CH{-}CH{=}CH{-}CHO \quad (X) \quad + \quad CH_3MgBr \longrightarrow CH_2{=}CH{-}CH{=}CH{-}CH(OH){-}CH_3 \quad (XI)$$

$$\downarrow$$

$$H{-}(CH{=}CH)_3{-}H \quad (XII)$$

Hexatriene (XII) is of great theoretical importance because of its relationship to benzene, the cis form of hexatriene being the open chain analogue of benzene.

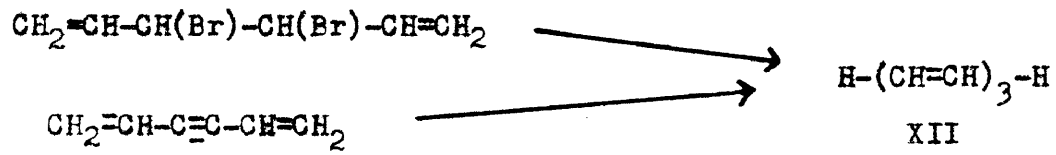
Various other methods for the synthesis of hexatriene have been reported in the literature. Griner first showed that bimolecular reduction of acrolein led to s-divinylethylene glycol (XIII).[25] Van Romburgh and Van Dorssen esterified this substance with formic acid. When the diformate ester was pyrolized, hexatriene was obtained:[26]

$$CH_2{=}CH{-}CH(OH){-}CH(OH){-}CH{=}CH_2 \quad (XIII) \longrightarrow CH_2{=}CH{-}\underset{\displaystyle H{-}C{-}O \atop \displaystyle \quad\; O}{CH}{-}\underset{\displaystyle O{-}C{-}H \atop \displaystyle \quad\; O}{CH}{-}CH{=}CH_2$$

$$\downarrow$$

$$H{-}(CH{=}CH)_3{-}H \quad (XII)$$

Farmer and coworkers prepared the dibromide from s-divinylethylene glycol by means of phosphorus tribromide. Dehalogenation by means of zinc dust yielded hexatriene. They claimed to have synthesized both isomers.[27,28] The same authors also used the selective hydrogenation of divinylacetylene in the synthesis of hexatriene (XII):



In similar fashion, selective hydrogenation of 1,3-hexadien-5-yne has been reported to lead to hexatriene (XII).[29]

Butz and coworkers used the pyrolysis of the half-phthalate of 1,5-hexadien-3-ol to obtain hexatriene (XII).[30] The alcohol was prepared by the Grignard reaction of allylmagnesium bromide with acrolein. However, their hexatriene was contaminated with cyclohexadiene. 1,5-Hexadien-3-ol was also used by Kium Houo, who dehydrated the alcohol by the xanthate method. He reported and interpreted the Raman spectrum of hexatriene.[32,33]

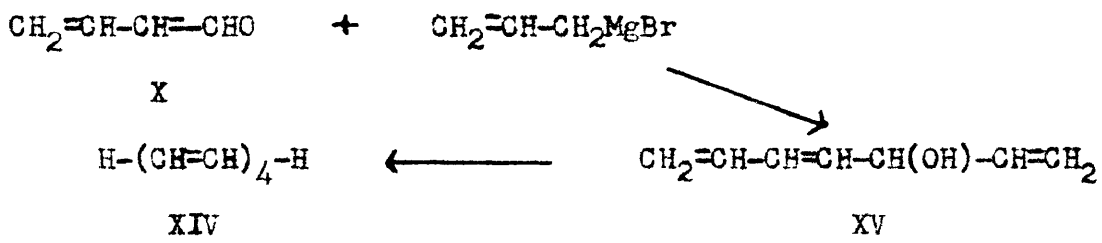
Another synthesis of hexatriene was reported by Kharasch and Sternfeld.[34] They reported an intermolecular dehydrohalogenation of allylchloride as source of hexatriene.

Woods and Schwartzman made an extensive study of hexatriene.[23] They prepared the dibromoderivative of hexatriene; its melting point agreed with that reported by Farmer for the same compound.[27] Hexatriene absorbed three moles of hydrogen upon catalytic hydrogenation. Infrared studies proved the conjugated nature of the double bonds; but the geometrical configuration of their compound could not be determined with certainty, although theoretical considerations would lead one to believe

that it should be the cis form.

The chemistry of benzene, the cyclic analogue of hexatriene is too well known and too extensive to be included in this thesis. Consequently, no attempt to review it in the limited space available has been made.

Woods and Schwartzman also reported the synthesis of 1,3,5,7-octatetraene (XIV), the next higher homologue of hexatriene.[35] The reaction of 2,4-pentadienal with allylmagnesium bromide yielded 1,3,7-octatrien-5-ol (XV). For purposes of identification this compound was reduced catalytically to the known 4-octanol, which was then oxidized to 4-octanone. Neither the α-naphthylurethan of the saturated alcohol, nor the semicarbazone of the ketone gave a melting point depression when compared with authentic samples. Catalytic dehydration of 1,3,7-octatrien-5-ol (XV) yielded 1,3,5,7-octatetraene (XIV):



Octatetraene was found to be much less stable than hexatriene; it has a tendency to explode on prolonged exposure to air. Oxygen was absorbed very rapidly. A marked tendency to rearrange to ethylbenzene on hydrogenation was noted; only under very mild conditions could the expected n-octane be obtained. In this respect octatetraene resembled its cyclic analogue, cyclooctatetraene, which also has a pronounced tendency to rearrange. The conjugated nature of the double bonds in octatetraene was proven by infrared studies. Three isomers of this coumpound are possible; but no definite structure could be assigned to the entity on

the basis of the experiments.

While the recent synthesis of octatetraene by Woods and Schwartzman is the only one reported for this compound so far, cyclooctatetraene has been known since 1911, at which time Willstatter[36,37] obtained it by a laborious degradation of the natural product pseudopellitierine. However, the compound which he obtained, showed so little of the "aromatic" character expected of it at that time, that the authenticity of the work was doubted for many years. Styrene and other impurities were shown to be present, and generally, the yields were too low for an extensive study of the compound.

Modern concepts of organic chemistry have rationalized the apparent anomalies of cyclooctatetraene. Thus while both benzene and cyclooctatetraene have complete conjugation with their respective rings, it is only the former which is planar without strain. The two major resonating forms of benzene, the Kekule forms, are of equal energy states, and therefore their contribution to the resonance hybrid is relatively large. While the two Kekule forms of cyclooctatetraene also have the same energy content with respect to each other, the energy of cyclooctatetraene itself in the planar form is much higher than that of benzene, because the bond angles of cyclooctatetraene show considerable distortion from the normal valence angles in the planar configuration. It is believed that this causes the apparent divergence from the originally expected aromatic character of cyclooctatetraene.

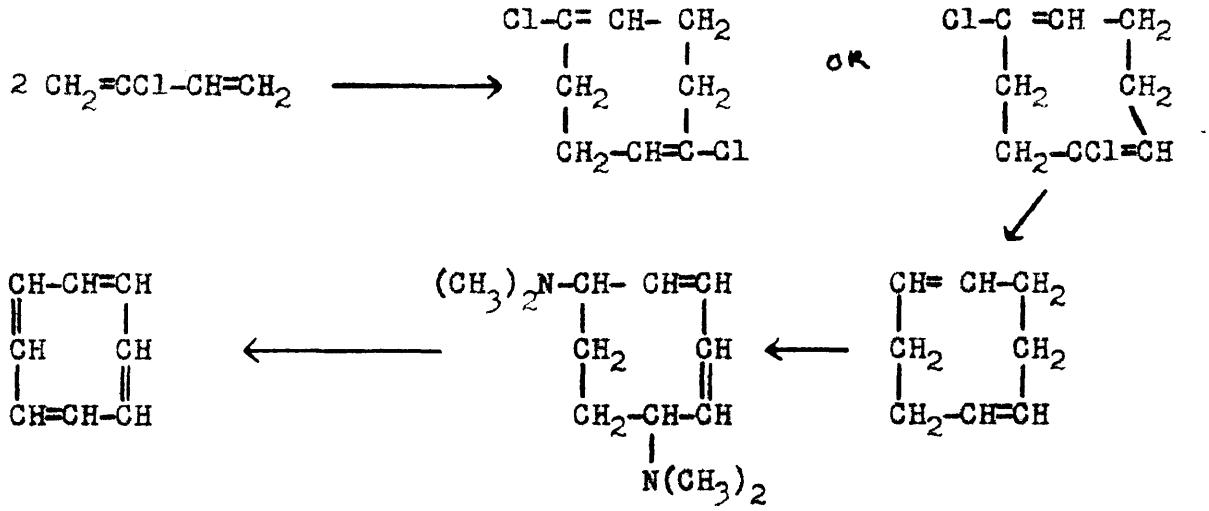
A recent synthesis for cyclooctatetraene was reported by Reppe and coworkers.[38] Their method which yielded up to 90% of the desired product, consisted of reacting acetylene in tetrahydrofuran solvent under 20-30 pounds of acetylene pressure. Nickelous cyanide was one of the catalysts found to be effective. The versatility of cyclooctatetra-

ene as starting material for the synthesis of other compounds, as well as the relatively easy and cheap mode of preparation may well make this compound of great importance in the future. Reppe went into great detail to prove the structure of his cyclooctatetraene by both chemical and physical methods. The position of the double bonds was proven by studies of the Raman spectrum, which showed no evidence of allenic linkages. Saksena and Narain confirmed Reppe's findings.[39] The equivalence of the four double bonds in the compound also was shown by its behavior on catalytic hydrogenation. The fact that the compound is essentially aliphatic in nature was clearly seen from studies of its diamagnetism.[38,40,41] X-Ray data by Kaufman, Fankuchen and Mark indicated that the bond distances are alternately 1.34 and 1.54 Å, and hence that there is little, if any resonance energy in the compound.[42] The chemical evidence for the structure of cyclooctatetraene is too extensive to be treated here; but it indicated clearly, that the compound has the structure commonly ascribed to it. Thus, both chemical and physical methods showed that Willstatter's original observation of the lack of "aromatic" character was essentially correct.

With the exception of the melting point, Reppe's and Willstatter's physical constants agree rather well; there can be no doubt that the two products are identical. Cope and Overberger recently have repeated both Willstatter's and Reppe's work, and were able to confirm the identity of their products.[43]

Cope and Bailey reported another synthesis of cyclooctatetraene.[44] Chloroprene was dimerized to a cyclic, eight membered ring compound, which was dehalogenated to 1,5-cyclooctadiene, the structure of which was established by ozonization. The 1,5-cyclooctadiene was brominated in the allyl position with N-bromosuccinimide, and the bromine subsequently

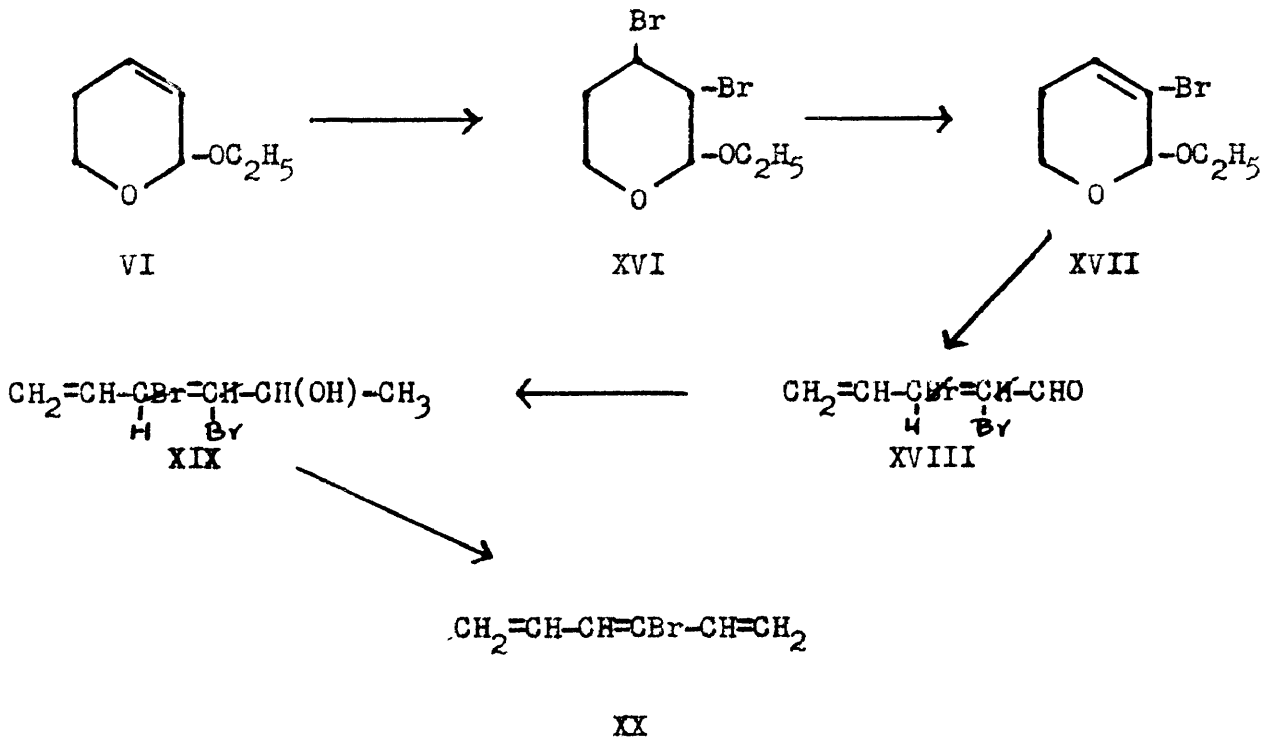
replaced by the dimethylamino group. Exhaustive methylation of this compound yielded cyclooctatetraene in overall yield of 15.5%:



As by-products of the cyclooctatetraene synthesis Reppe and co-workers also obtained three higher hydrocarbons of empirical formula $C_{10}H_{10}$ and $C_{12}H_{12}$.[45] Their structure had not been identified with certainty, but it appeared that they probably were cyclodecapentaene and cyclododecahexaene. Two hydrocarbons of empirical formula $C_{10}H_{10}$ were obtained depending on the conditions used in the preparation. When the cyclooctatetraene synthesis was carried out at temperatures of 60-70° an orange-yellow liquid was isolated from the higher boiling fractions from which the cyclooctatetraene previously had been removed. On the other hand when the reaction was carried out at 120-130°, a light yellow liquid was obtained. The orange-yellow and the light yellow liquids obtained at different temperatures were not identical. While the orange-yellow hydrocarbon gave an addition product with cuprous chloride in ammonium chloride, no such addition product was obtained with the light yellow hydrocarbon. Differences in behavior on catalytic hydrogenation were also noted.

The hydrocarbon of formula $C_{12}H_{12}$ was isolated from the residues from which both the cyclooctatetraene and the hydrocarbons of formula $C_{10}H_{10}$ had been removed. The compound formed an oxide of formula $C_{12}H_{12}O$. The hydrocarbon could be hydrogenated partially or completely, depending on the conditions used.

Two syntheses have been reported for bromohexatriene. The most recent of these, in which the position of the bromine definitely has been established is the synthesis by Woods and Temin.[46] 2-Ethoxy-Δ^3-dihydropyran (VI) was brominated to yield 2-ethoxy-3,4-dibromotetrahydropyran (XVI). Both the cis and the trans isomers of this compound could be obtained. Dehydrohalogenation of this compound proved extremely difficult, but was finally accomplished by reacting the compound with molten potassium hydroxide at 250°. The 3-bromo-2-ethoxy-Δ^3-dihydropyran (XVII) yielded 2-bromo-2,4-pentadienal (XVIII) when steam distilled from an acid solution. When methylmagnesium bromide was reacted with the latter compound, 3-bromo-3,5-hexadien-2-ol (XIX) was obtained. The structure of the latter compound was identified by catalytic hydrogenation to the known compound, 2-hexanol. Hydrogenolysis of the bromine atom occurred simultaneously during this reaction. The saturated alcohol in turn was oxidized to 2-hexanone. The semicarbazone of this compound proved to be identical with an authentic sample. 3-Bromo-1,3,5-hexatriene (XX) was obtained by catalytic dehydration of 3-bromo-1,3,5-hexadien-2-ol (XIX) over alumina at 320°:



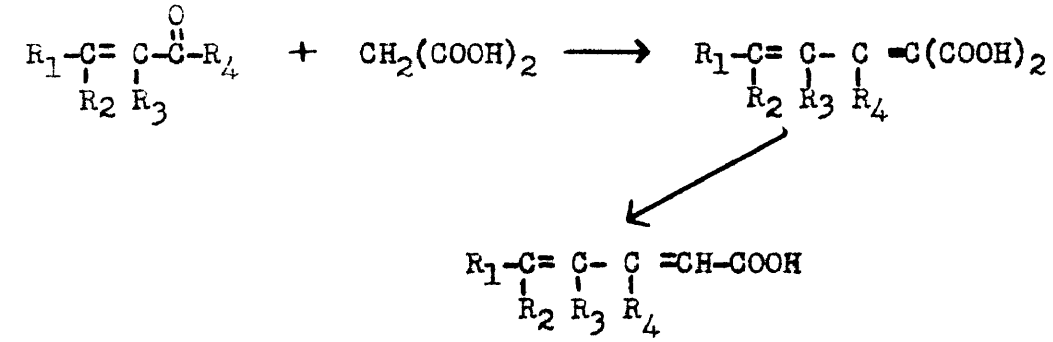
Bromohexatriene (XX) proved to be an unstable liquid, which decomposed rapidly on standing. While the dehydrohalogenation of 2-ethoxy-3,4-dibromotetrahydropyran (XVI) possibly also could have resulted in 4-bromo-2-ethoxy- Δ^3-dihydropyran, the subsequent course of the reaction nevertheless would have resulted in 3-bromohexatriene (XX). Thus the position of the bromine in the latter compound was definitely established.

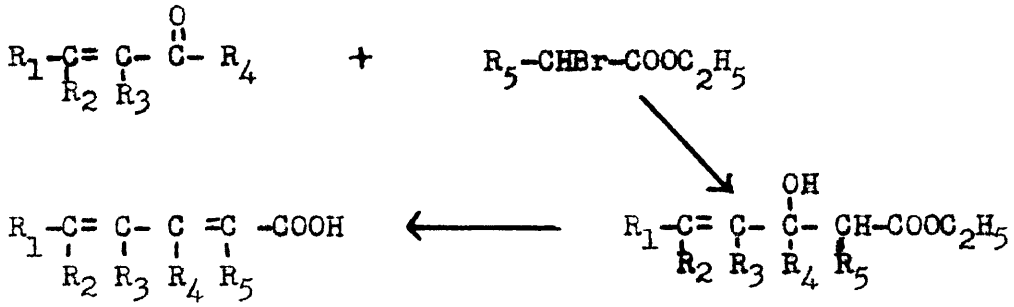
The previously reported synthesis of bromohexatriene (XX) was due to Farmer and coworkers.[27] They obtained it from the bromination of hexatriene, followed by dehydrohalogenation. They claimed to have synthesized both the cis and the trans isomer, but the position of the bromine atom was uncertain. Their samples for which no other data than the boiling point have been reported, also were very unstable and polymerized completely in one day.

The interest in the 2,4-dienoic acids has been of a twofold nature. Prior to 1930, most work concerned itself with the theoretical aspects of 1,2 and 1,4 addition. In subsequent years, the prime

interest shifted to the production of synthetic polymers from the acids themselves, or from their various esters.

Examination of the literature showed that two general methods have been used for the synthesis of the 2,4-dienoic acids. The Dobner modification of the Knovenagel reaction, followed by decarboxylation has found extensive use. The other method involved the Reformatsky reaction, and subsequent dehydration and saponification of the product:





2,4-Pentadienoic Acid (vinylacrylic acid) (XXI) was synthesized from acrolein and malonic acid, the condensation being followed by decarboxylation.[47] Various modifications of Dobners original synthesis subsequently were used by other workers.[48,49,50,51,52] Coffman obtained 2,4-pentadienoic acid from 1-cyanobutadiene by hydrolysis.[53] Carothers and Berchet also used derivatives of butadiene as intermediates for their synthesis.[54] A recent patent by Geyer, Bradford, Ballard and Seaver described the condensation of α-methylene alkanals with ketene as source of 2,4-dienoic acids.[55] 2,4-Pentadienoic acid for example

was obtained by the reaction of ketene with acrolein in the presence of a basic catalyst.

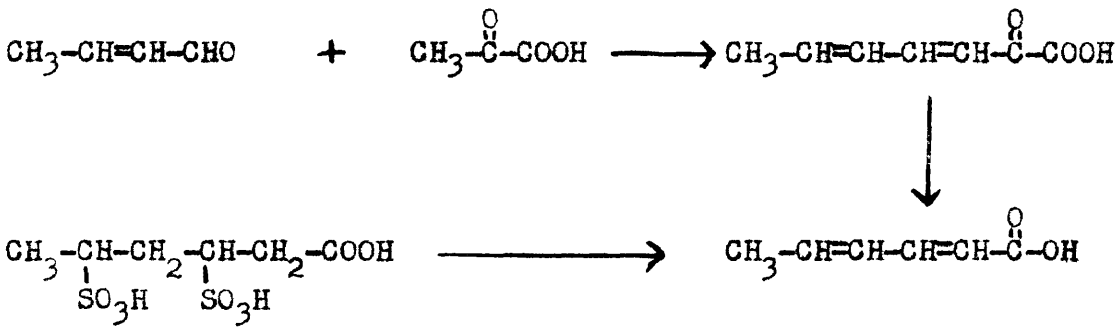
2,4-Pentadienoic acid has been studied extensively. Consequently only a brief summary, emphasizing the more unusual reactions will be given here. The acid is hygroscopic and polymerizes easily. It has a characteristic unpleasant odor, resembling that of its saturated analogues. The alkali salts are very soluble and hygroscopic; the silver salt however, doesn't show these latter properties.

Fischer and coworkers reported that a saturated diamino acid is the product of a reaction of a dienoic acid with concentrated ammonia at elevated temperatures.[56,57] Dobner[58] claimed to have synthesized tricyclooctane by heating the acid with barium hydroxide; but Kuhn and Deutsch[59] showed that Dobner's product probably was ethylbenzene.

The methyl ester of 2,4-pentadienoic acid has been reported by Kohler and Butler,[49] as well as by Farmer and Healy;[50] the ethyl ester of the acid is also known.[49,60] Both these esters are reportedly unstable. Gudgeon and Hill prepared the n-butyl ester, from which they obtained an elastic polymer.[61] The methyl and ethyl esters also were used for that purpose, as well as for improving the drying qualities of paints and varnishes.[62]

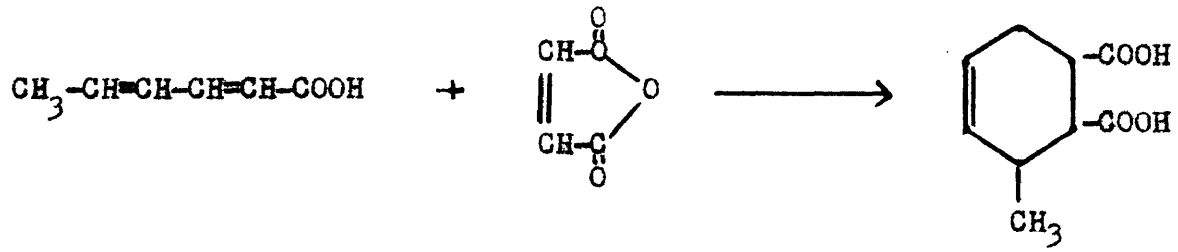
Sorbic acid (2,4-hexadienoic acid) has been isolated from various natural sources. It is one of the constituents of the berry of the mountain ash. Cram has recently isolated the acid from sorbicillin, a pigment produced by the mold Penicillium Notatum.[63] Dobner reported a laboratory synthesis from crotonaldehyde and malonic acid, followed by decarboxylation.[58] Jaworsky synthesized the acid from aldol and malonic acid by treatment with base.[64] The acid was obtained also from its five or six membered ring lactone by reacting the same with concentrated

sulfuric acid, or by bubbling hydrogen chloride through the reaction mixture.[65,66] The condensation of pyruvic acid with crotonaldehyde[67], as well as the reaction of β,δ-disulfo-n-caproic acid with potassium hydroxide[68] has been used as a source of sorbic acid:



Sorbic acid has been obtained also from the corresponding aldehyde or from γ-bromosorbic acid by removal of the bromine atom with zinc dust.[69]

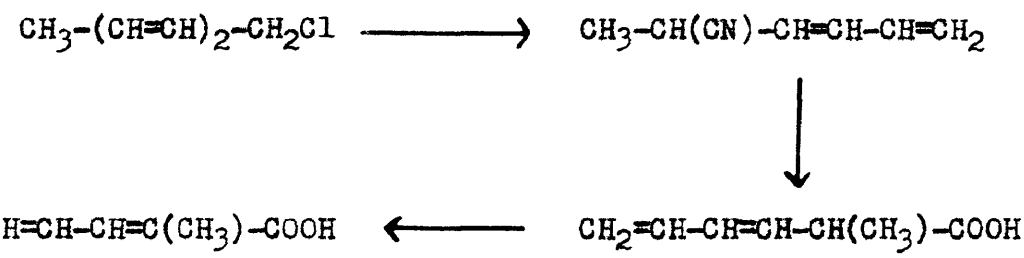
Smyth and Carpenter have tested sorbic acid for possible toxicity,[70] while McGowan, Brian and Hemmingway tested its fungistatic potentialities.[71] Rheinboldt and coworkers showed that sorbic acid forms coordination compounds with desoxycholic acid and apocholic acid.[72] When sorbic acid was fed to rabbits, Kuhn and coworkers were able to isolate trans muconic acid from their urine in small amounts.[73] Talomethylose was obtained by Hamada and Huzida in several steps from sorbic acid.[74] With peracetic acid, Hamade was able to hydroxylate the 4,5 double bond, so that Δ^2-4,5-dihydroxyhexenoic acid was the product.[75] Nystrom and Brown recently have reduced the acid to sorbyl alcohol in 92% yield.[76] When sorbic acid was heated to 100° with hydroxylamine in methanol solvent, Feist isolated the dioxime of acetylacetone.[77] Wickers, Daly and Lack obtained 3-methyl-1,2,3,6-tetrahydrophthalic acid, when sorbic acid underwent a Diels-Alder reaction with maleic anhydride:[78]



The use of sorbic acid in the diene synthesis previously had been reported by Diels and Alder.[79]

Various workers reported the methyl ester of sorbic acid.[80,81] Its ethyl ester is also known.[60,65,66,80,82,83] Other esters which have been synthesized are the esters of n-amyl alcohol, ethylene glycol propylene glycol, glycerol, pentaerythritol and l-menthol.[84,85] As with the esters of 2,4-pentadienoic acid, the primary interest in the esters of sorbic acid rests in the possibility of obtaining industrially useful polymers.

α-Methylsorbic acid was obtained by dehydration of 2-methyl-3-hydroxy-Δ^4-hexenoic acid with either acid or base. Jaworsky who synthesized it in such a manner reported that it was unstable, forming a yellow gummy mass on standing in the desiccator.[64] Von Auwers and Heyna prepared the compound by the Reformatsky reaction of ethyl α-bromopropionate on crotonaldehyde, followed by heating with dilute sulfuric acid. The same authors also reported the ester of α-methylsorbic acid.[86] α-Methylsorbic acid also has been prepared from sorbyl chloride.[87] When this substance was treated with potassium cyanide a double allylic shift resulted in a rearranged product, hydrolysis of which yielded α-methylsorbic acid:



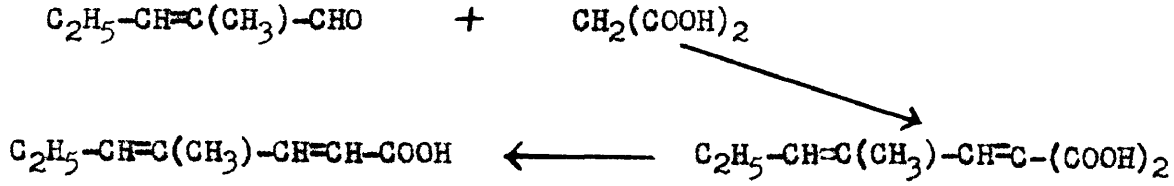
Burton and Ingold reported two forms of β-methylsorbic acid, which they obtained from 2-hydroxy-2-methyl-Δ^3-hexenoic acid by dehydration with potassium acid sulfate. One form melted at 120°, the other at 98-99°.[88]

γ-Methylsorbic acid was prepared by the Reformatsky reaction of ethyl bromoacetate on tiglic aldehyde (α,β-dimethylacrolein), followed by dehydration and saponification of the ester. Von Auwers and Heyna also prepared the ethyl ester of this acid.[86] They reported that the acid polymerized very easily.

Using ethyl α-bromopropionate and Δ^2-pentenal as the reagents in a Reformatsky reaction, Kuhn and Grundmann obtained α,ε-dimethylsorbic acid, in several steps.[89]

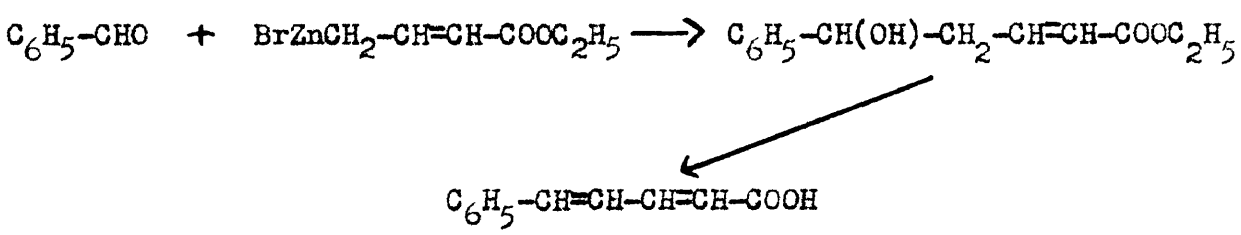
Similarly, when the reagents were ethyl bromoacetate and mesityl oxide, Rupe and Lotz obtained β,δ-dimethylsorbic acid.[90] They reported that the acid was unstable and lost water when stored in the desiccator.[91] The ethyl ester of this acid, a liquid of pleasant odor, was reported by Von Auwers and Eisenlohr.[83]

Dobner and Weissenhorn prepared γ,ε-dimethylsorbic acid from α-methyl-β-ethylacrolein and malonic acid, followed by decarboxylation:[90]

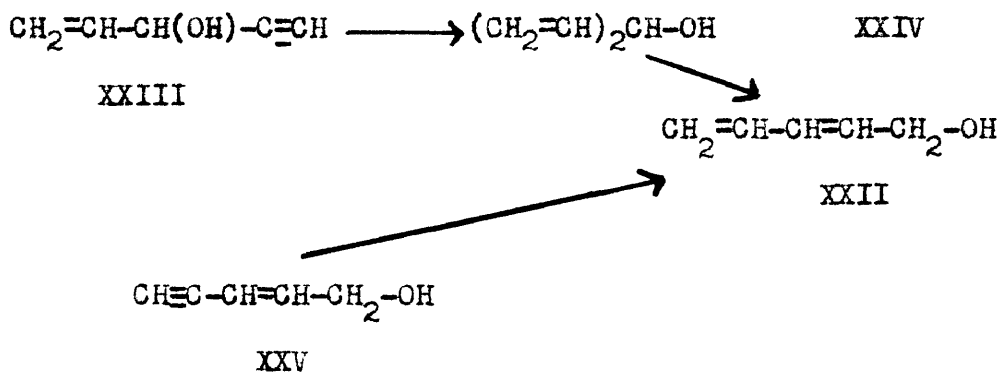


The Reformatsky reaction was again used in the preparation of α-ethylsorbic acid.[93,94]

When cinnamaldehyde was condensed with malonic acid, Bansal and Pandya obtained 5-phenyl-2,4-pentadienoic acid.[95] The same product was also obtained by English and Delafield, who used ethyl γ-bromocrotonate and benzaldehyde in an abnormal Reformatsky reaction, followed by dehydration and hydrolysis of the ester:[96]

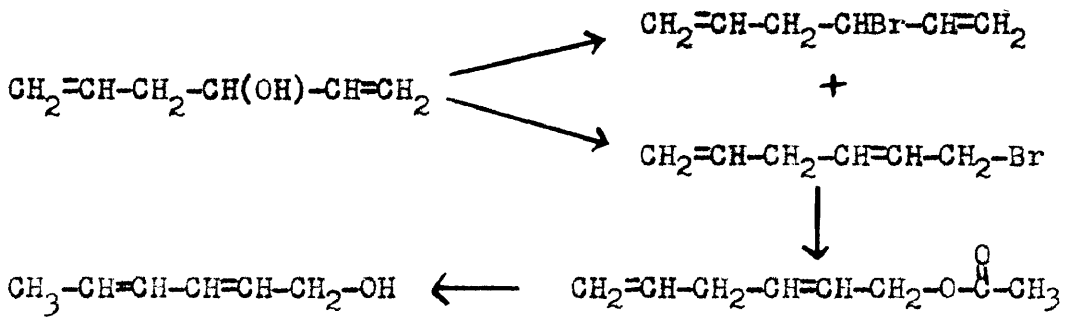


The next portion of the historical concerns the synthesis and the chemical properties of some 2,4-dien-1-ols. The simplest member of this series 2,4-pentadien-1-ol (XXII) was first characterized by Heilbron and coworkers, who obtained the compound by two closely related methods, both ultimately based on intermediates derived from acetylene.[24,97] The first method involved the partial hydrogenation of vinylethynylcarbinol (XXIII) to divinylcarbinol (XXIV), which upon treatment with dilute sulfuric acid underwent an allylic rearrangement to 2,4-pentadien-1-ol (XXII). Alternatively, 2-penten-4-yn-1-ol (XXV) could be hydrogenated partially to yield the same product:



Similarly, when 2-methyl-1,4-hexadien-3-ol was treated with dilute sulfuric acid, the product was 2-methyl-2,4-pentadien-1-ol. Jones and McCombie reported the maleic anhydride addition products of both 2,4-pentadien-1-ol (XXII) and 2-methyl-2,4-pentadien-1-ol.[98] Heilbron and coworkers stated that 2,4-pentadien-1-ol formed a clear, transparent polymer on standing.

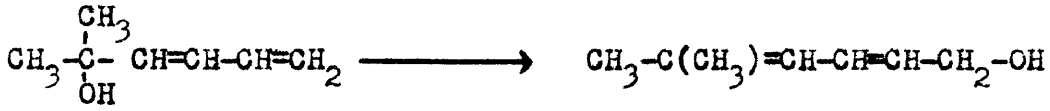
Reichstein and coworkers synthesized 2,4-hexadien-1-ol (XXVI), as well as their higher homologues, 2,4,6-octatrien-1-ol and 2,4,6,8-decatetraen-1-ol.[99] They reduced the corresponding unsaturated aldehydes with aluminum isopropoxide. Kuhn and Hoffer previously had prepared these aldehydes by condensation of crotonaldehyde and acetaldehyde.[100,101] A more recent synthesis of 2,4-hexadien-1-ol (sorbyl alcohol) (XXVI) was reported by Nystrom and Brown, who reduced sorbic acid with lithium aluminum hydride.[76] Kium Houo treated 1,5-hexadien-3-ol with phosphorus tribromide and obtained a desmotropic mixture of 3-bromohexadien-1,5 and 1-bromohexadien-2,5. When this desmotropic mixture was treated with sodium acetate in acetic acid, 2,4-hexadienyl acetate was obtained. Saponification of the latter substance yielded 2,4-hexadien-1-ol (XXVI):[32,33]



XXVI

Fischer and Wiedemann reported that sorbyl alcohol is slowly reduced to an alcohol containing one double bond, by the action of fermenting yeast.[102] Later they established its structure as Δ^4-hexen-1-ol.[103]

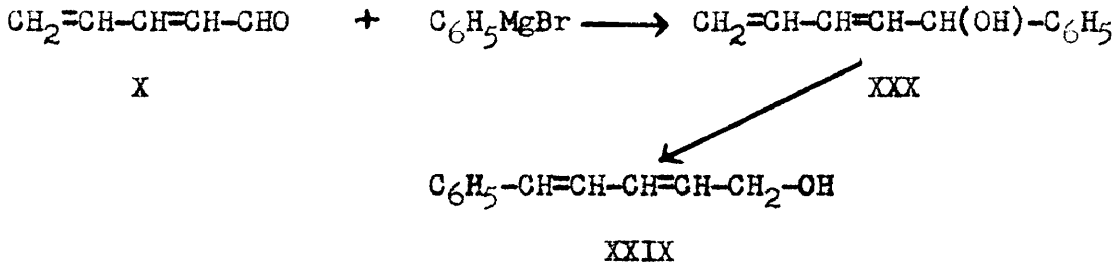
Nazarov and Fisher isomerized 2-methyl-3,5-hexadien-2-ol (XXVII) with dilute sulfuric acid, thereby obtaining 5-methyl-2,4-hexadien-1-ol (XXVIII):[104,105]



XXVII XXVIII

2,5-Dimethyl-2,4-hexadien-1-ol was synthesized by Prevost.[106,107] He refluxed 1-bromo-2,5-dimethylhexadien-2,4 with sodium acetate and saponified the ester so formed.

Woods and Sanders prepared 5-phenyl-2,4-pentadien-1-ol (XXIX) from 2,4-pentadienal (X) and phenylmagnesium bromide.[108] The resulting 1-phenyl-2,4-pentadien-1-ol rearranged immediately to 5-phenyl-2,4-pentadien-1-ol (XXIX):



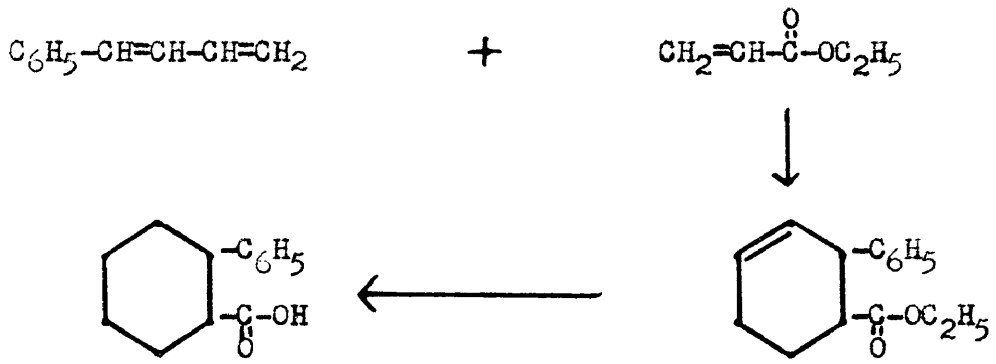
X XXX XXIX

The same compound (XXIX) also was prepared by Nazarov and Fisher, who isomerized 1-phenyl-2,4-pentadien-1-ol (XXX) with dilute sulfuric acid.[109] Zal'kind and Kulikov previously had prepared 5-phenyl-2-4-pentadien-1-ol (XXIX) but their compound was impure.[110]

II. THE CHEMISTRY OF COMPOUNDS RELATED TO MORPHINE

In our study of compounds related to morphine, 2-phenylcyclohexaneacetic acid (XXXI) and 4-phenylcyclohexaneacetic acid (XXXII) played a prominent role. This part of the historical therefore concerns itself with the chemistry of these acids, as well as with the corresponding cyclohexanecarboxylic acids, and with the chemistry of compounds obtainable from these acids by ring closure reactions.

2-Phenylcyclohexanecarboxylic acid has been prepared by a number of workers. Kipping and Perkin condensed diethylmalonate with 1-phenyl-1,5-dibromopentane.[111] Others obtained the acid (XXXIII) by reduction of 2-phenylbenzoic acid with sodium and amyl alcohol.[112,113,114,115] Cook and Hewett[115] and also Blumenfeld[116] have employed Diels-Alder reactions between phenylbutadiene and acrolein or ethyl acrylate:

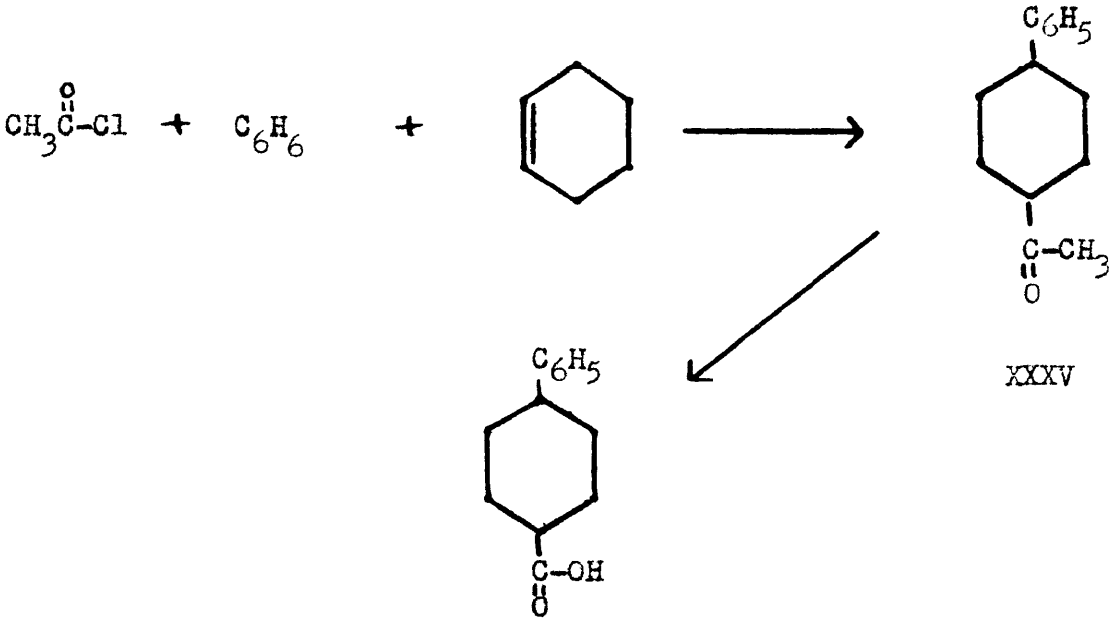


XXXIII

All these methods were shown to lead to the trans acid. Gutsche prepared the cis acid by degradation of cis-2-phenylcyclohexaneacetic acid.[117]

Rassow reported both forms of 4-phenylcyclohexanecarboxylic acid (XXXIV).[118] He reduced 4-phenylbenzoic acid with sodium and amyl alcohol. Equilibrium between the two forms was established on prolonged heating with concentrated hydrochloric acid. Ranedo and Leon obtained

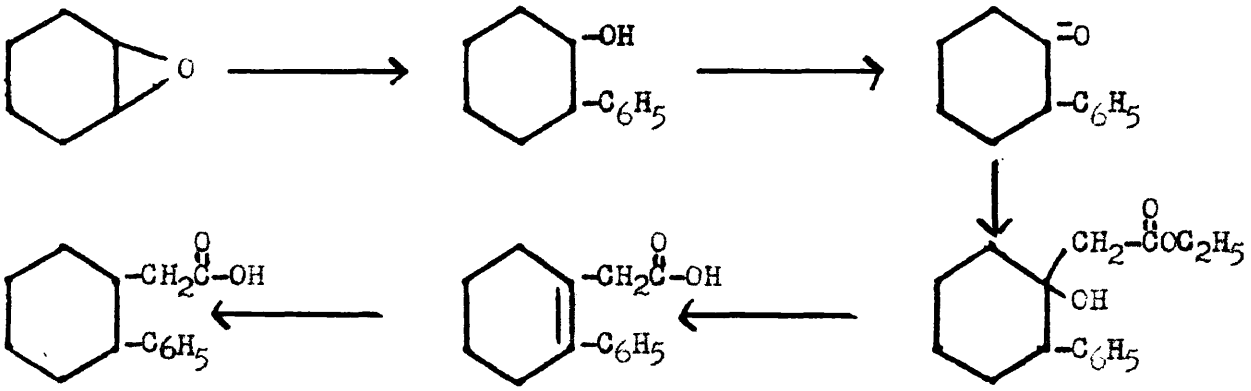
the same results.[119] A different and more recent synthesis is due to Johnson and Offenhauser.[120] Cyclohexene, acetyl chloride and benzene were treated under conditions of the Friedel-Crafts reaction, the product being 4-phenylhexahydroacetophenone (XXXV). This ketone was subjected to a haloform reaction, yielding the desired product (XXXIV):



XXXV

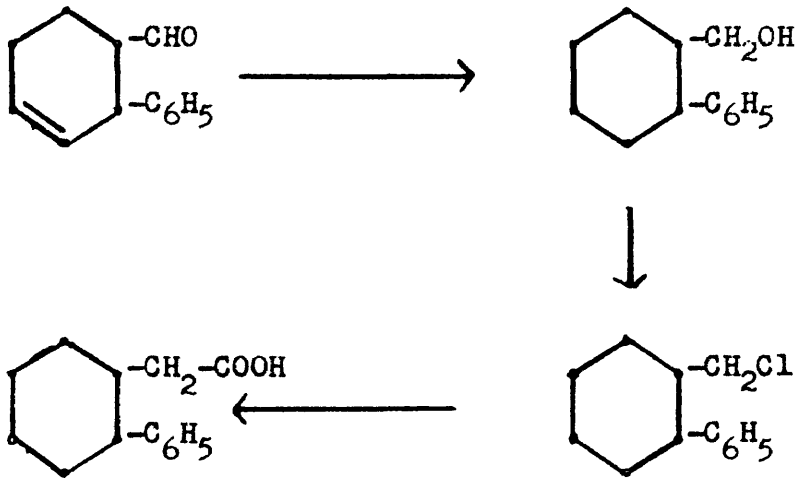
XXXIV

Cook, Hewett and Lawrence first synthesized cis and trans 2-phenylcyclohexaneacetic acid (XXXVI).[121] But the trans isomer was impure. They used the following method:



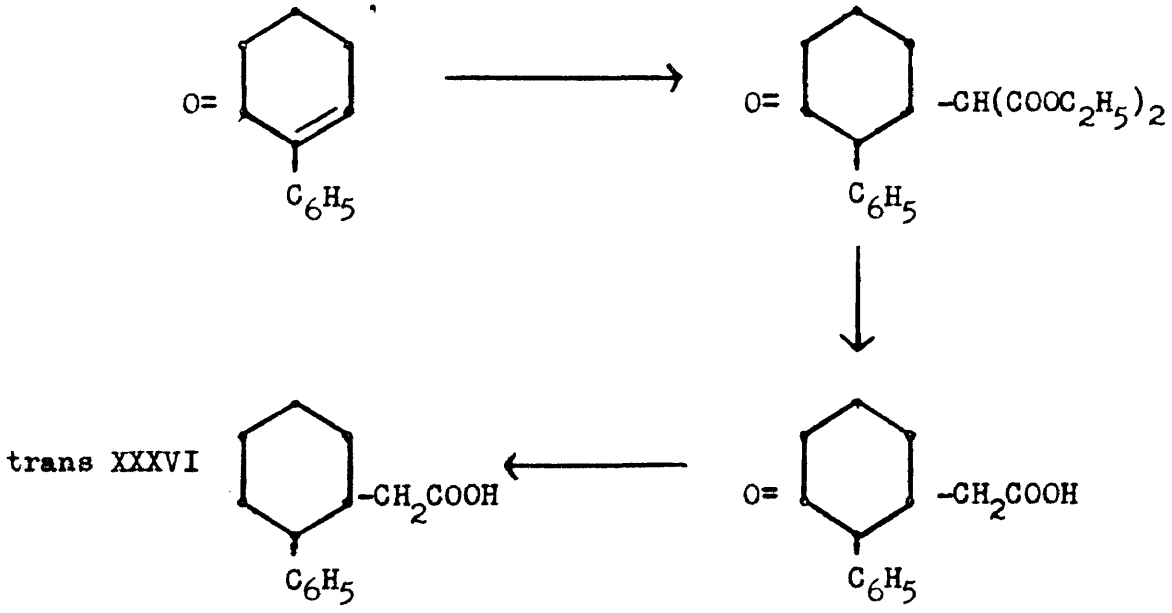
XXXVI

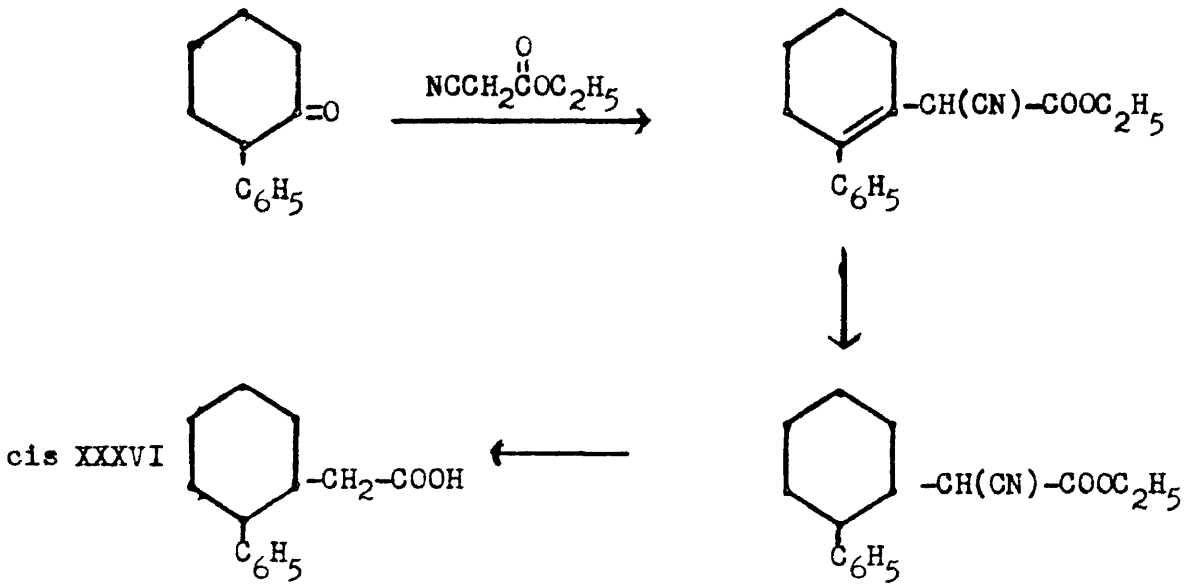
Chatterjee reported the ethyl ester of 2-phenylcyclohexaneacetic acid.[122] Linstead and coworkers obtained the trans acid in a pure state and also established the stereochemical configurations without doubt.[123] Blumenfeld obtained the cis acid, employing the following reactions:[116]



XXXVI

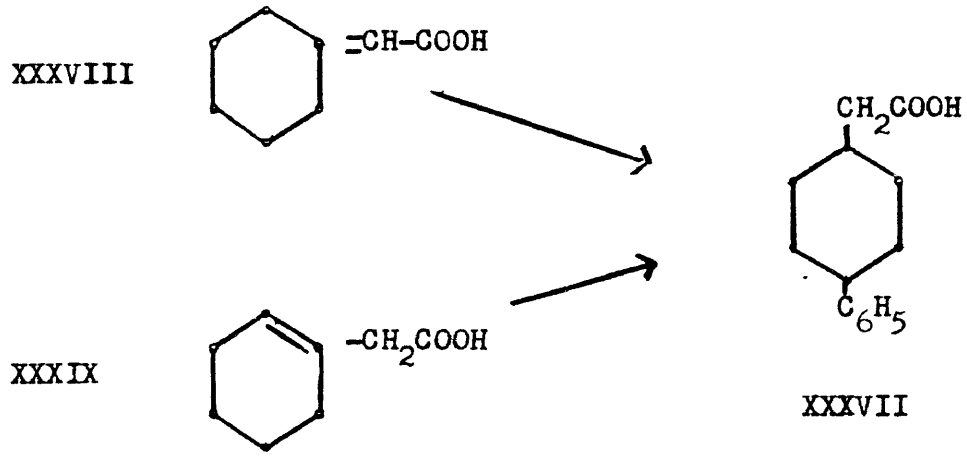
Bachmann and Fornefeld obtained both the cis and the trans isomer of 2-phenylcyclohexaneacetic acid (XXXVI).[124] They employed the following procedures:





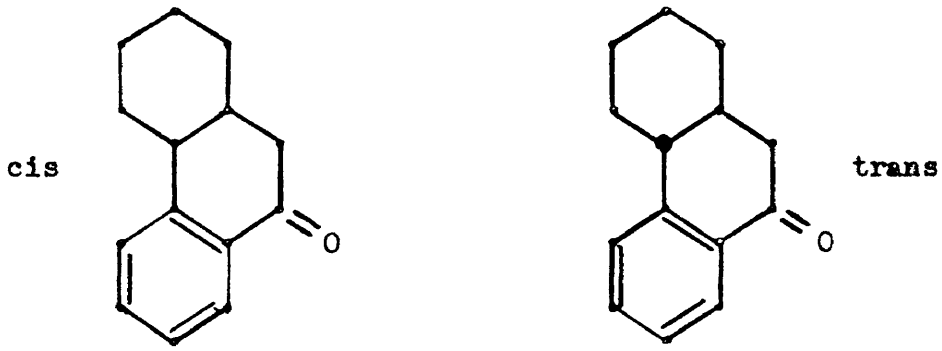
The latter reaction was essentially that employed by Linstead and coworkers,[123] except for the fact that Bachmann used the newer procedure of Alexander and Cope[125] which permitted both hydrogenation and condensation to proceed in one step.

Nenitzescu and Gavat reported the synthesis of 4-phenylcyclohexaneacetic acid (XXXVII) by the Friedel-Crafts reaction of cyclohexylideneacetic acid (XXXVIII) or cyclohexeneylacetic acid (XXXIX) in benzene:[126]



The authors proved the structure of their product by a Barbier-Wieland degradation to 4-phenylcyclohexanecarboxylic acid (XXXIV), the structure of which was known at that time. Cook and Goulden independently obtained 4-phenylcyclohexaneacetic acid (XXXVII) by a similar synthesis.[127] However they converted their acid to 4-methylbiphenyl for purposes of identification. Proper identification of the products obviously was very important in this instance, as the Friedel-Crafts reaction did not take the expected course. Only one isomer of 4-phenylcyclohexaneacetic acid (XXXVII) has been reported in the literature so far; it is believed that the other isomer was obtained during this research.

9-Keto-as-octahydrophenanthrene (XL, XLI)* has been identified in both the cis and the trans form. Both forms were obtained by Cook, Hewett and Lawrence, one form being a solid, the other a liquid.[121] Both ketones were synthesized by cyclization of the respective 2-phenylcyclohexaneacetic acids (XXXVI) with concentrated sulfuric acid.

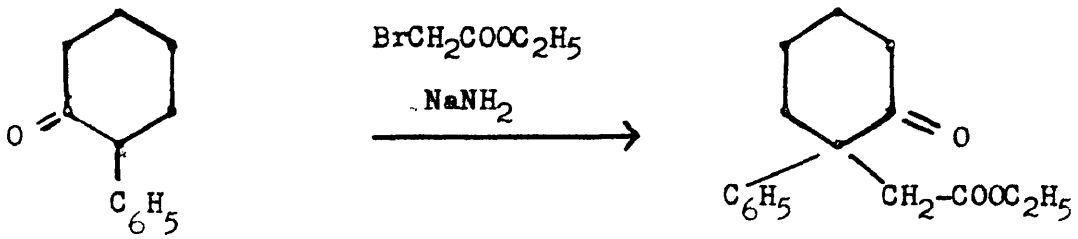


XLI XL

*This nomenclature was used by Linstead.[123] Other, more cumbersome names for this compound are 9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene,[124] and 9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene.[116]

Linstead and coworkers established both the configuration of the ketones (XL) and (XLI) as well as that of the acids (XXXIV) from which the ketones were derived, showing that the solid ketone was the trans form.[123] Both Blumenfeld[116] and Bachmann[124] obtained the trans ketone (XL) by dehydration of trans-2-phenylcyclohexaneacetic acid (XXXIV).

1-Phenylcyclohexaneacetic acid has not been synthesized to date. However, Boekelheide and Schilling reported the closely related keto ester, 2-carbethoxymethyl-2-phenylcyclohexanone (XLI). Their method of preparation is shown below:[128]

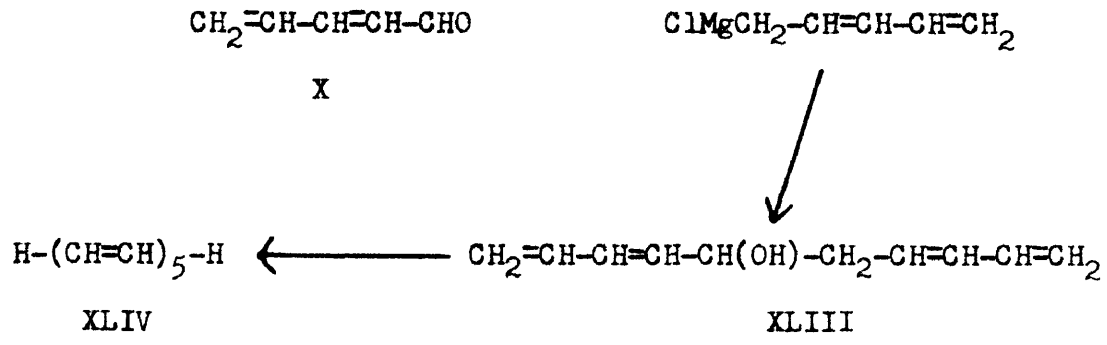


XLII

DISCUSSION

I. The first part of this research was an extension of the chemistry of 2,4-pentadienal (X). It dealt with the attempted synthesis of the conjugated straight chain decapentaene (XLIV), the synthesis of unsaturated alcohols, and the synthesis of unsaturated esters.

The synthesis of 1,3,5-hexatriene (XII) and 1,3,5,7-octatetraene (XIV) has been reported by Woods and Schwartzman.[23,35] They employed Grignard reactions on 2,4-pentadienal (X), followed by dehydration of the alcohols by passing them over activated alumina in the vapor phase. When methylmagnesium bromide was the Grignard reagent, they obtained hexatriene (XII); in similar fashion they isolated octatetraene (XIV) when the Grignard reagent was allylmagnesium bromide. Hence, the synthesis of 1,3,5,7,9-decapentaene (XLIV) seemed possible, provided the corresponding pentadienylmagnesium halide could be synthesized. The proposed scheme of reactions is shown below:



The project seemed especially promising, since two cyclic homologues of the proposed compound (XLIV) apparently had been prepared by Reppe and coworkers.[45]

To obtain the 1-chloro-2,4-pentadiene required in the proposed Grignard reaction, 2,4-pentadienal was reduced with aluminum isopropoxide using Lund's procedure.[129] The reaction was forced to completion by removal of the acetone from the reaction mixture by distillation. Decomposition could be brought about by acid or base; but in each instance the extraction of the organic layer was complicated somewhat by the formation of an aluminum hydroxide gel. Evaporation of the solvent yielded 2,4-pentadien-1-ol, but to obtain a sample of analytical purity special methods described in the experimental section had to be used. The melting point of the α-naphthylurethan of our pentadienol (XLV) is in excellent agreement with that reported by Heilbron and coworkers, who prepared this compound independently by two procedures, both different from the procedure used in this research.[24,97] That no allylic rearrangement during the formation of 2,4-pentadien-1-ol had taken place was shown by the compound's reduction to n-amyl alcohol, and identification of the latter substance by means of its derivatives.

$$CH_2{=}CH{-}CH{=}CH{-}CH_2OH$$

XLV

A pentadienyl chloride (XLVI) of undetermined structure was obtained by treatment of 2,4-pentadien-1-ol (XLV) with thionyl chloride. It had a characteristic, sharp odor and immediately formed a precipitate with silver nitrate solution. Depending on the type of reaction it undergoes, pentadienyl chloride may react as either divinylchloromethane (XLVI A) or 1-chloro-2,4-pentadiene (XLVI B):

$(CH_2{=}CH)_2{-}CH{-}Cl$ $\qquad\qquad$ $CH_2{=}CH{-}CH{=}CH{-}CH_2Cl$

A XLVI B

Our findings are not unique. Reichstein and coworkers reported a similar situation in the case of sorbyl chloride.[87] Kium Houo obtained a desmotropic mixture when 1,5-hexadien-3-ol was treated with phosphorus tribromide.[32,33] When the Grignard reagent of divinylbromomethane was treated with carbon dioxide, the normally expected product was obtained. But Paul and Tchelitcheff reported that the sodio derivative of the same bromide, treated with carbon dioxide, rearranged to 3,5-hexadienoic acid:[130]

$$(CH_2{=}CH)_2CHMgBr + CO_2 \longrightarrow (CH_2{=}CH)_2CH{-}COOH$$

$$(CH_2{=}CH)_2CHNa + CO_2 \longrightarrow CH_2{=}CH{-}CH{=}CH{-}CH_2{-}COOH$$

A large number of allylic shifts involving only one double bond is known; but they are too numerous to be reported here. The ultraviolet absorption spectrum of pentadienyl chloride (XLVI) may be found in the experimental section.

In the proposed Grignard reaction of pentadienylmagnesium chloride with 2,4-pentadienal (X), the possibility of 1,4 and 1,6 addition had to be taken into account. Grignard reacted a series of alkylmagnesium halides with unsaturated aldehydes, obtaining only carbinols as products, indicating 1,2 addition only.[131] Kohler[132] confirmed Grignard's report. But Kohler also showed that Grignard reagents may react by both 1,2 and 1,4 addition when the carbonyl compounds were α,β-unsaturated ketones. Fuson and McKusick have

reported a 1,6 addition.[133] Stevens reacted various Grignard reagents with crotonaldehyde.[134] He found that when the Grignard reagents were t-butyl or t-amylmagnesium halides a considerable amount of 1,4 addition products were isolated. These results could be attributed to the "bulkyness" of the t-butyl or t-amyl groups, but the interpretation of these results is probably considerably more complex. This is shown by the large amount of "complex products" isolated in the latter instances. But, barring a few examples of the type mentioned above, it can be stated that the Grignard reaction with unsaturated aldehydes takes place in 1,2 fashion. In addition to these considerations, the possibility of allylic rearrangement after the alcohol had been formed had to be taken into account. Several such reactions have been described in the historical portion of this thesis.

To prepare the Grignard reagent from pentadienyl chloride (XLVI), Gilman's procedure was modified somewhat by making the ether solution of the halide more dilute.[135] By this means the accompanying Wurtz reaction was suppressed and stirring was facilitated, as the reaction led to an insoluble complex, the mixture becoming a thick pasty mass, which however became fluid again on addition of the carbonyl compound. Despite these precautions, a considerable amount of low boiling forerun was obtained in most instances. The composition of this forerun was not investigated, but it may have contained a considerable amount of the Wurtz reaction product. The decatetraenol isolated from this reaction was a viscous liquid, which on prolonged standing formed a transparent polymer. Dehydration of this alcohol over alumina led to a few drops of material, which was insufficient for proper identification.

Since the possibility of the various rearrangements was recognized, it became highly desirable at this point, to obtain some proof of structure for the decatetraenol whose preparation was described above. For this purpose, the decatetraenol was hydrogenated catalytically to the corresponding decanol. The decanol yielded only one derivative, an α-naphthylurethan of melting point 79-80°. This derivative of the decanol of unknown structure was compared with a series of α-naphthylurethans of decanols of known structure, which were prepared by standard Grignard reactions from saturated reagents. For further identification, some of these decanols subsequently were oxidized to the corresponding ketones.

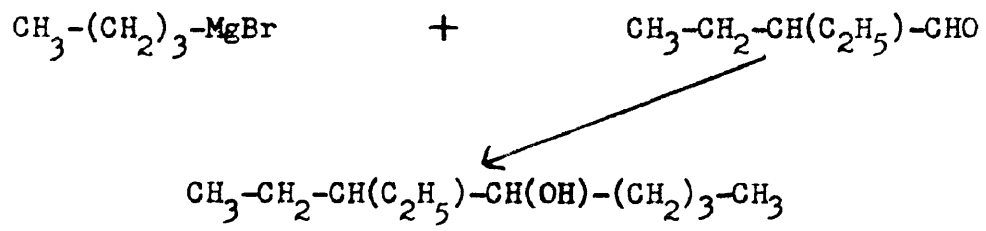
5-Decanol (XLVII) was prepared from n-amylmagnesium bromide and n-valeraldehyde. Its α-naphthylurethan melted at 55-56°, and hence was excluded as a possibility. Since n-valeraldehyde was not available commercially, it had to be prepared in this laboratory. The most convenient method was a modification of the procedure given for n-hexaldehyde in "Organic Syntheses".[136] n-Butylmagnesium bromide was treated with ethyl orthoformate and the resulting acetal was hydrolyzed. Isolation through the bisulfite addition product yielded n-valeraldehyde, which was stabilized by adding a pinch of hydroquinone.

4-Decanol (XLVIII) was obtained by the Grignard reaction of n-propylmagnesium bromide with n-heptaldehyde. Repeated attempts to prepare its α-naphthylurethan failed. This fact served to exclude 4-decanol as a possibility.

3-Decanol (XLIX) resulted when n-heptylmagnesium bromide was reacted with n-propionaldehyde. Its α-naphthylurethan was not identical with that of the unknown decanol.

1-Decanol was commercially available. Its α-naphthylurethan melted at 72°, but a melting point depression with the sample of doubtful structure was obtained.

When n-butylmagnesium bromide and 2-ethylbutyraldehyde were the reagents, 3-ethyloctan-4-ol (L) was produced. The α-naphthylurethan derived from it melted at 78-80°, and no melting point depression upon mixing with the sample of unknown structure was observed:

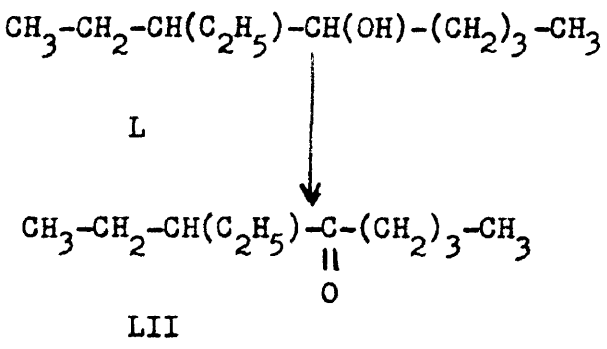


$CH_3-(CH_2)_3-MgBr$ + $CH_3-CH_2-CH(C_2H_5)-CHO$

$CH_3-CH_2-CH(C_2H_5)-CH(OH)-(CH_2)_3-CH_3$

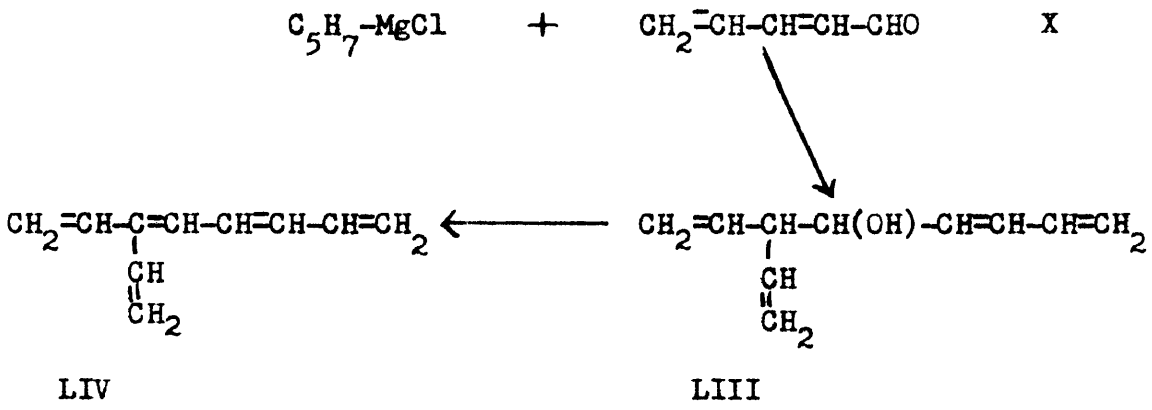
L

Hence it seemed very probable at this stage, that the unknown decanol was 3-ethyl-octan-4-ol (L). But since the alcohol yielded only one derivative, it seemed best to oxidize the known 3-ethyloctan-4-ol and the unknown decanol to their respective ketones, and to prove the identity of the two ketones through their derivatives. But here an unexpected difficulty ensued, for the carbonyl function of these compounds proved very unreactive. These findings are supported by Bried and Hennion, who stated that the closely related 5-decanone (LI) formed none of the common carbonyl derivatives.[137] 3-Ethyloctan-4-one (LII) formed no solid 2,4-dinitrophenylhydrazone; the semicarbazone formed extremely slowly, requiring ten days to two weeks in the ice box. By means of the semicarbazones the ketones from the known and unknown source were proven to be identical, no depression being observed, when a mixed melting point was taken:



L LII

The Grignard reaction of pentadienyl chloride (XLVI) with 2,4-pentadienal (X) and the subsequent dehydration therefore must have taken the following course:

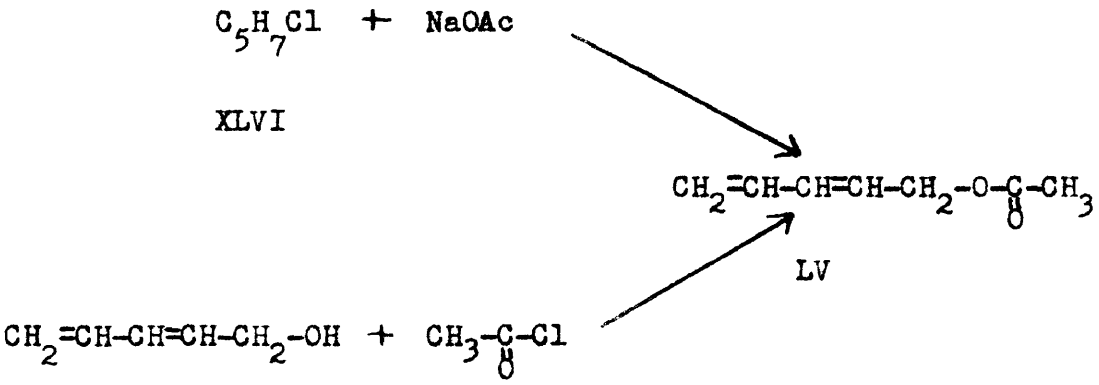


LIV LIII

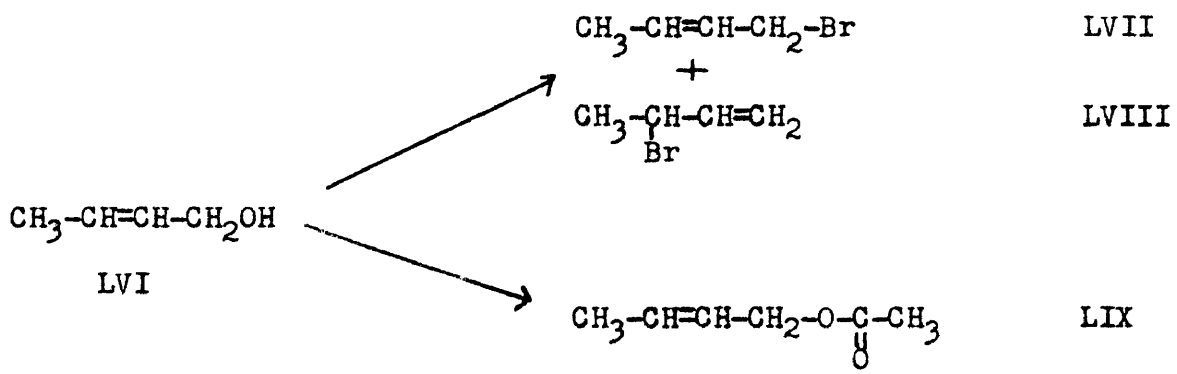
Dehydration of 3-vinyl-$\Delta^{1,5,7}$-octatrien-4-ol (LIII) probably resulted in 3-vinyl-$\Delta^{1,3,5,7}$-octatetraene (LIV). Obviously, the synthesis of the straight chain, conjugated decapentaene (XLIV) had become impossible by this method, and hence no further efforts along these lines were made.

Since a rearranged product was obtained when pentadienyl chloride (XLVI) underwent the Grignard reaction with 2,4-pentadienal (X), it seemed desirable to explore the reactions of this interesting halide toward other reagents. When pentadienyl chloride (XLVI) was treated with sodium acetate in acetic acid and refluxed for short periods, pentadienyl acetate (LV) was isolated. The same product was obtained from the

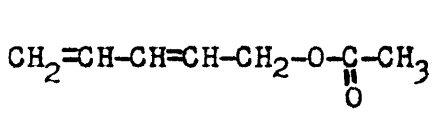
reaction of 2,4-pentadien-1-ol (XLV) with acetyl chloride. The ester proved to be unstable, and polymerized on standing for several weeks. The structure of the ester was established by catalytic hydrogenation to the corresponding saturated ester which was hydrolyzed by refluxing with base. n-Amyl alcohol was isolated from the reaction mixture, which showed that in this case, pentadienyl chloride had reacted as the 1-chloro-2,4-pentadiene (XLVI B). The reaction therefore took the following course:



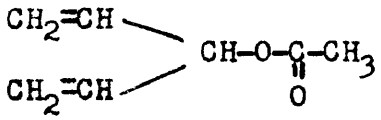
In treating the theory of esterification of allylic alcohols, Wheland reported that crotyl alcohol (LVI) gave a mixture of bromides (LVII, LVIII), one of which was the rearranged product, when the alcohol was treated with hydrogen bromide. But the normally expected, unrearranged acetate (LIX) was the only product in the esterification reaction of the same alcohol with acetic acid:[138]



The fact that in one instance one of the products was rearranged, while in the other reaction only the unrearranged acetate (LIX) was isolated, was interpreted as being due to the different bonds which were broken during the reaction. In the case of the bromide formation, a carbon-oxygen bond was obviously involved, while in the esterification, the oxygen-hydrogen bond was broken. That this is not the complete explanation in the case of pentadienyl chloride (XLVI), can be seen from the two independent syntheses of pentadienyl acetate (LV). While the structure of pentadienyl chloride (XLVI) itself may be uncertain, Wheland's interpretation would lead one to believe, that in the reaction of pentadienyl chloride (XLVI) with sodium acetate, a mixture of products should have resulted, since the carbon-chloride bond was affected. No such mixture has been observed in this research, the product appearing to be only one entity. This may be explained by the fact that in the reaction of pentadienyl chloride with sodium acetate, a doubly allylic system was involved, so that the factor of possible conjugation in the product might become an important factor:



Conjugated



Not conjugated

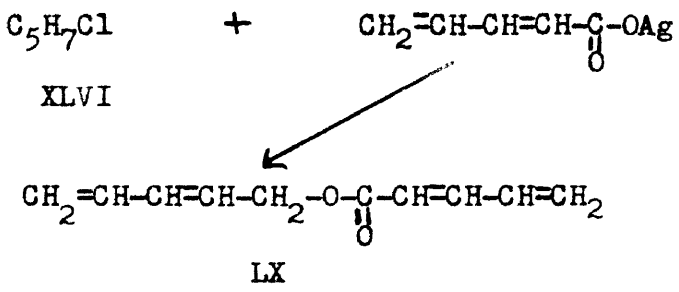
LV

The fact that a conjugated system has the higher stability when compared with a system of two isolated bonds, leads one to believe that the unrearranged ester should be the preferred form. This actually has been observed in this case.

The synthesis of the 2,4-pentadienyl ester of 2,4-pentadienoic acid was next attempted. Pentadienoic (XXI) acid was prepared by both the procedures of Kohler and Butler,[48] and by that of Muskat, Becker and

Lowenstein.[47] The former method proved more satisfactory both from the standpoint of convenience and time. Reliable workers reported a considerable variation of melting points for this compound, the values varying between 72 and 80°. These discrepancies may have been due to the presence of different stereoisomers, or mixtures thereof, depending on the individual modes of synthesis employed. In this work, no attempt to prepare an acid of extraordinary purity was made, except in the instance where the sample was used for the ultraviolet absorption spectrum. This sample had a melting point of 70.5-71.5°. Kohler and Butler, whose procedure was used in this case, reported a melting point of 72° for their product. The silver salt of 2,4-pentadienoic acid was prepared, and reacted with pentadienyl chloride (XLVI). This reaction yielded pentadienyl pentadienoate (LX). To prevent polymerization, this compound had to be distilled very rapidly. Even when distilled very rapidly, the majority of the compound polymerized. Due to this fact, no acceptable analytical data could be obtained for this compound. The polymer from this ester seemed very stable, and could not be broken down by prolonged refluxing with either acid or base.

To prove the structure of this highly unsaturated ester (LX), it was reduced catalytically to its saturated analogue, which was hydrolyzed, and the acid and alcohol components identified. The former proved to be n-valeric acid, the latter n-amyl alcohol. The reaction therefore must have taken the following course:

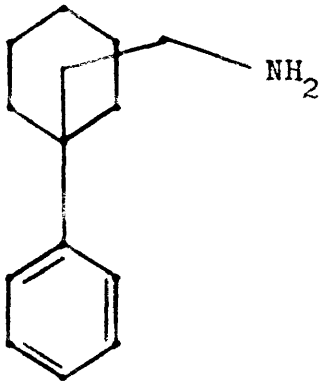


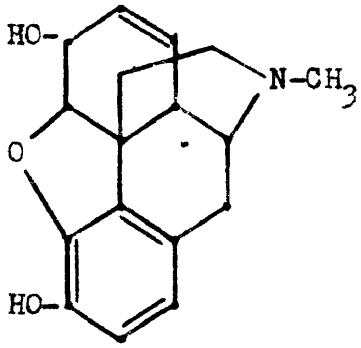
As in the case of pentadienyl acetate (LV), no rearrangement in the alcohol portion had taken place.

The direct synthesis of pentadienyl pentadienoate by means of the Tischenko reaction was not attempted. However, it was proposed originally to prepare both pentadienol (XLV) and pentadienoic acid (XXI) by means of the Cannizzaro reaction on 2,4-pentadienal (X). But this attempt was not successful, the reaction leading to polymerization.

II. The second portion of this discussion concerns itself with the attempt to prepare 1-phenylcyclohexaneethylamine (LXI). The synthesis of this compound was desirable, as it had some of the structural features of morphine (LXII):

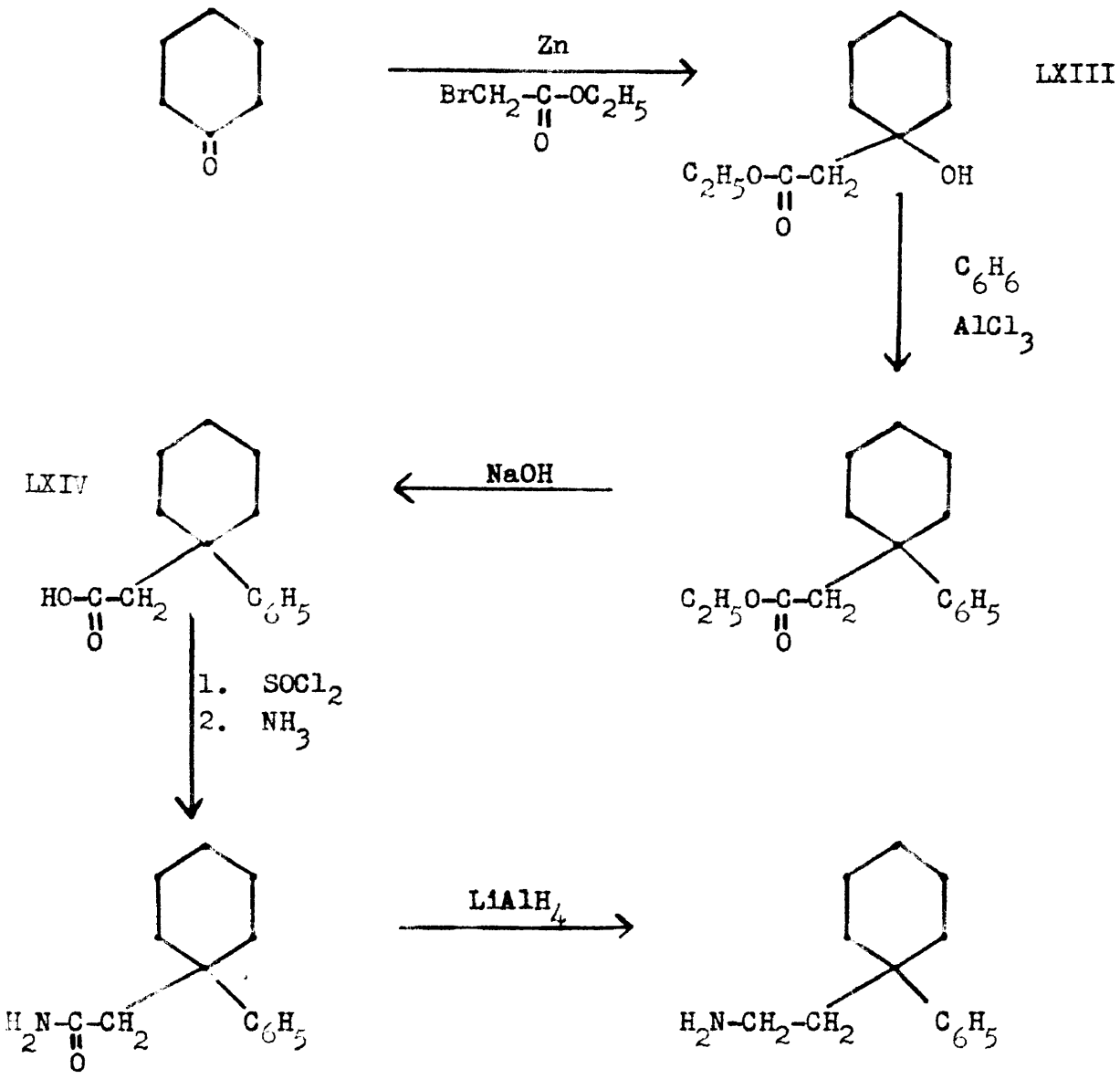
LXI





LXII

In the meantime, Bachmann and Fornefeld have synthesized this compound by a Curtius degradation of 1-phenylcyclohexanepropionic acid.[139] Our proposed scheme of reactions follows:

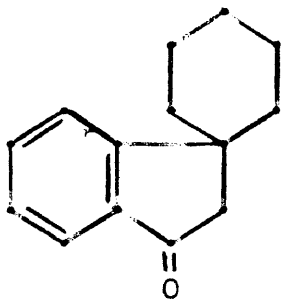


The Reformatsky reaction of ethyl bromoacetate on cyclohexanone was performed according to the procedure of Natelson and Gottfried.[140]

The Friedel-Crafts reaction of ethyl-1-hydroxycyclohexylacetate (LXIII) went smoothly. The ester obtained from this reaction was isolated and then hydrolyzed. Depending on how the Friedel-Crafts reaction was carried out, two different acids were obtained. One form, (melting point 112-114°) was obtained when the Friedel-Crafts reaction was carried out at room temperature. Another form, melting at 86-88°,

resulted from a Friedel-Crafts reaction in a mixture of boiling benzene and nitrobenzene. But both of these acids yielded the same amide, the melting point of which was 197-198°. Treatment of this amide with nitrous acid according to Gattermann's procedure, exclusively resulted in the acid of melting point 112-114°.[141] This series of reactions strongly suggests that the two acids are stereoisomers, one of them being the cis form, the other the trans form.

If either of the acids had the structure expected of it (LXIV), cyclization should have led to the known spiro (cyclohexane-1,1'-indanone-3') (LXV), but neither cyclization by means of sulfuric acid, nor through the acid chloride in a Friedel-Crafts reaction led to that compound.

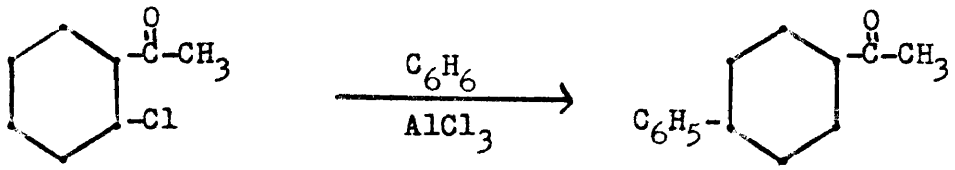


LXV

The former reaction resulted nearly quantitatively in sulfonation, the latter led to a mixture of complex reaction products. However, in either instance a small amount of a ketonic constituent not identical with spiro (cyclohexane-1,1'-indanone-3') (LXV) was obtained. The apparent failure of the acids to cyclize, showed that the Friedel-Crafts reaction had taken an abnormal course, so that in place of the expected 1-phenylcyclohexaneacetic acid (LXIV), its isomer, 4-phenylcyclohexaneacetic acid (XXXVII) was the product. Similar results were reported by

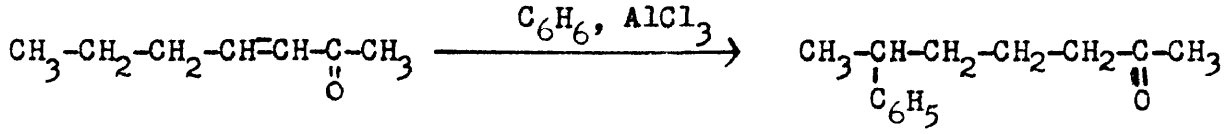
Nenitzescu and Gavat[126] and by Cook and Goulden[127], each of whom employed the unsaturated acid (XXXVIII) in place of the hydroxyeester (LXIII). Nenitzescu proved the structure of his product by the Barbier-Wieland degradation to the known 4-phenylcyclohexanecarboxylic acid (XXXIV), while Cook and Goulden aromatized their compound to 4-methylbiphenyl in several steps.

A number of rearrangements of this type during the Friedel-Crafts reaction have been reported in the literature, but they have received comparatively little attention. Hence, it seemed appropriate to present them in some detail here. Nenitzescu and coworkers have studied this type of rearrangement with considerable detail.[142,143,144,145] For example, when 2-chlorohexahydroacetophenone (LXVI) underwent a Friedel-Crafts reaction, none of the expected 2-phenylhexahydroacetophenone was isolated. They obtained instead the 4-phenylhexahydroacetophenone (LXVII):

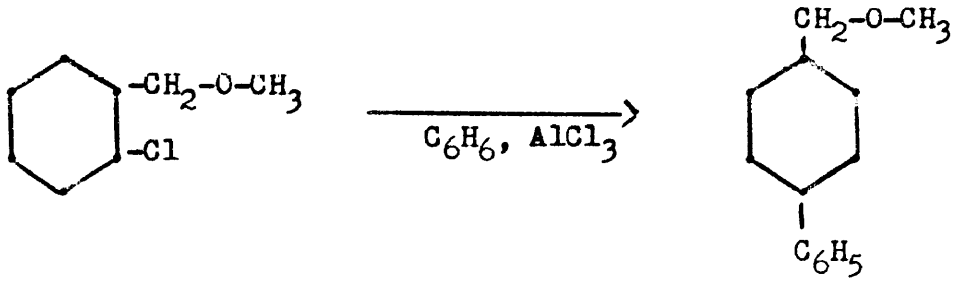


LXVI LXVII

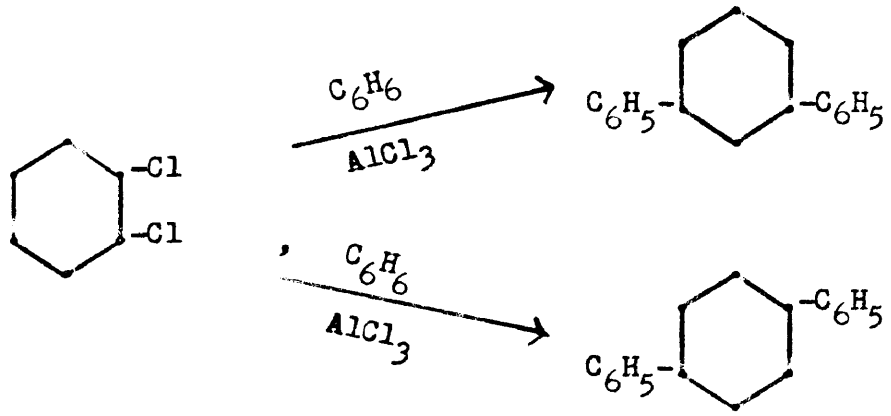
A similar reaction took place when the ring had a cyclopentane skeleton. The ketone need not have a cyclic structure; in this case substitution will proceed at the carbon next to the terminal carbon in the chain. In place of chloro ketones, unsaturated ketones may be used with the same results:



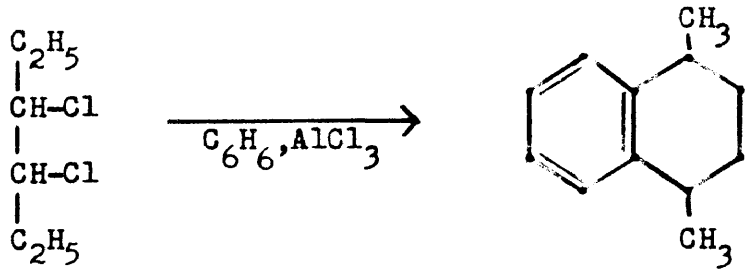
A related reaction took place in the ether series:



The product was identified by converting it in several steps to 4-phenylbenzoic acid. When 1,2-dichlorocyclohexane reacted under conditions of the Friedel-Crafts reaction, two products, both rearranged were isolated:



Sisido and Nozaki reported the open chain analogue of this reaction:[146]



Open chain unsaturated acids behaved like alicyclic unsaturated acids, with the notable exception that substitution was shown to proceed not at the position furthest removed from the polar group, but rather at the carbon atom one removed from the terminal carbon. In this respect unsaturated acids resembled the unsaturated ketones and the chloro ketones:

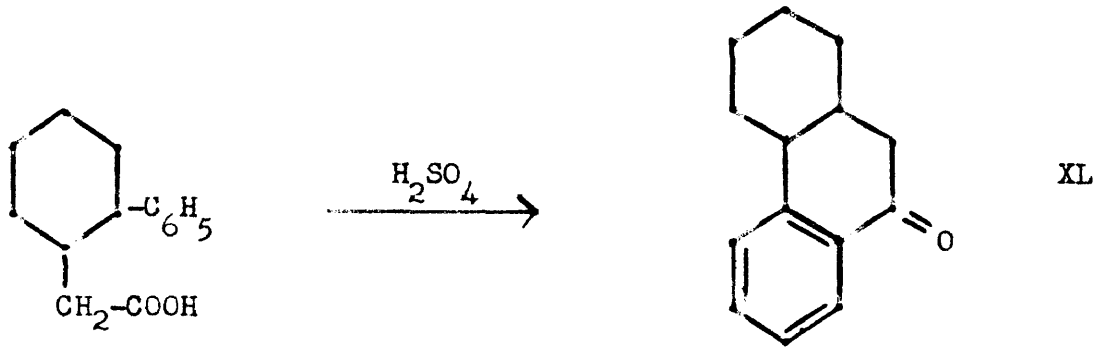
$$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH{=}CH\text{-}COOH \xrightarrow{C_6H_6,\ AlCl_3} CH_3\text{-}\underset{\displaystyle C_6H_5}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}COOH$$

A side chain apparently did not interfere with this reaction:

$$CH_3\text{-}CH_2\text{-}CH_2\text{-}\underset{\displaystyle CH_3}{C}{=}CH\text{-}COOH \xrightarrow{C_6H_6,\ AlCl_3} CH_3\text{-}\overset{\displaystyle C_6H_5}{CH}\text{-}CH_2\text{-}\underset{\displaystyle CH_3}{CH}\text{-}CH_2\text{-}COOH$$

The small amount of ketonic material isolated in the ring closure attempts on 4-phenylcyclohexaneacetic acid was identified as trans-9-keto-as-octahydrophenanthrene (XL). This compound previously had been synthesized and its structure was identified by reliable workers.[115,116,121,123] The presence of this material in the reaction mixture indicated that at least some small amount of the 2-phenylcyclohexaneacetic acid (XXXVI) must have been present. The relatively easy isolation of the ketone (XL) made this compound readily accessible in small amounts by procedures described in the experimental portion of this thesis. The yield varied depending on the conditions employed in the Friedel-Crafts reaction used for the synthesis of the ethyl ester of 4-phenylcyclohexaneacetic acid (XXXVII). The most convenient method for cyclization of the acid (XXXVI) was found to be the reaction with concentrated sulfuric acid, under which conditions 4-phenylcyclohexaneacetic acid (XXXVII) was completely sulfonated.[127] Thus an easy

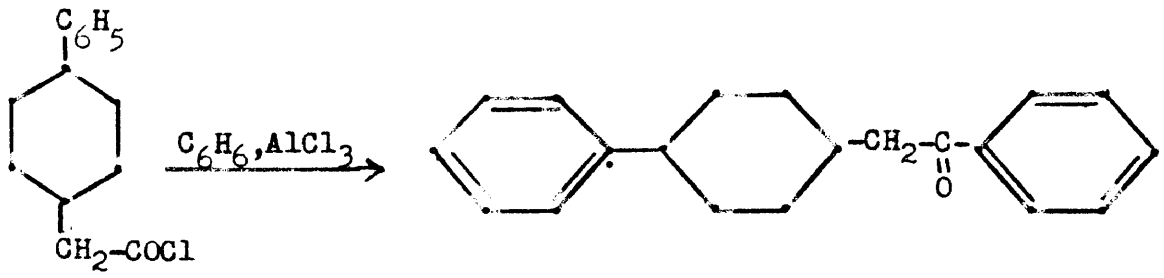
separation could be affected, so that even small amounts of the ketone were readily isolated:



XXXVI XL

When the Friedel-Crafts reaction took place at room temperature, roughly 5% of the ketone (XL) could be obtained; in boiling benzene, the yield was about 10%, while in a boiling nitrobenzene-benzene mixture the yield was in the vicinity of 1%. It will be remembered that it was the latter conditions, which also led to the other isomer of 4-phenylcyclohexaneacetic acid (XXXVII), which had a melting point of 86-88°. Whether the difference in the latter Friedel-Crafts reaction was due to a difference in temperature, or due to a difference in the solvent properties was not determined.

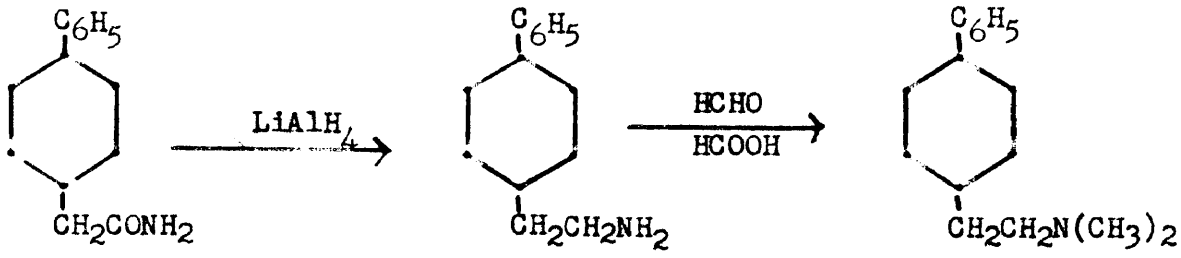
When the ring closure reaction of the crude acid mixture containing both 2-phenylcyclohexaneacetic acid (XXXVI) and 4-phenylcyclohexaneacetic acid (XXXVII) was attempted by means of a Friedel-Crafts reaction on the acid chloride, another ketonic entity was isolated. Its structure was not established with certainty, but analytical data indicated that it probably was α-(4-phenylcyclohexyl) acetophenone (LXVIII). This ketone presumably was formed by the following reaction:



LXVIII

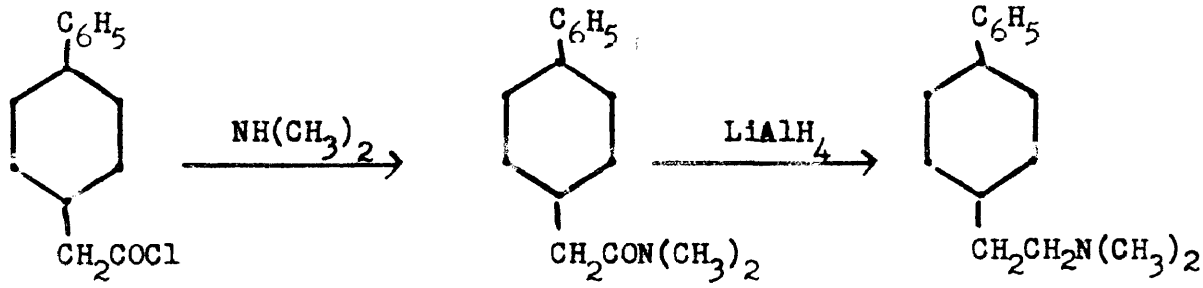
Attempts to separate 2-phenylcyclohexaneacetic acid (XXXVI) and 4-phenylcyclohexaneacetic acid (XXXVII) from the crude mixture of acids were not successful; only the latter substance could be obtained pure. Attempts to separate these acids through their amides were therefore made. The crude acid mixture was converted to the acid chlorides (LXIX) by means of thionyl chloride. When the acid chloride was reacted with concentrated aqueous ammonia, a solid amide (LXX) was isolated. But despite considerable difference in melting point between the two amides in question, only the one present in excess could be obtained in a pure state.

The amide (LXX) was reduced to the amine (LXXI) according to the procedure of Uffer and Schletter,[147] and then converted to the N,N-dimethylamine (LXXII) by refluxing with formalin and formic acid:



LXX LXXI LXXII

The same N,N-dimethylamine (LXXII) also was obtained when the acid chloride (LXIX) was reacted with a concentrated solution of dimethylamine, and the N,N-dimethylamide (LXXIII) was reduced with lithium aluminum hydride:

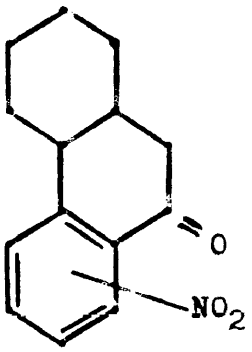


LXIX LXXIII LXXII

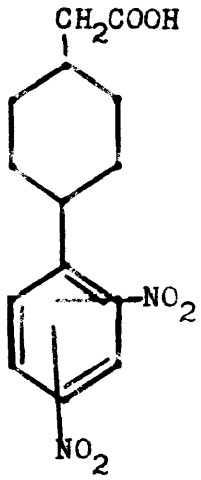
Nitration of N,N-dimethyl-4-phenylcyclohexaneethylamine (LXXII) according to the procedure of Ingold and Piggot led to complex reaction products which were difficult to handle and could not be identified with certainty.[148]

When 4-phenylcyclohexaneacetic acid (melting point 112-114° when pure) was nitrated, a small amount of a ketonic substance was obtained. Analytical data on its 2,4-dinitrophenylhydrazone indicated that it was an isomer of nitro-9-keto-as-octahydrophenanthrene (LXXIV). This ketone obviously resulted from a combined cyclization and nitration of the 2-phenylcyclohexaneacetic acid (XXXVI) present as an impurity. The bulk of the reaction mixture, presumably containing the nitrated acid, exploded when distillation under reduced pressure was attempted.

In another experiment some of the isomeric acid of melting point 86-88° (XXXVII) was nitrated. In this instance, a crystalline, light sensitive material was the product. Analyses showed that it was a dinitrated 4-phenylcyclohexaneacetic acid (LXXV). The position of the nitro groups however is uncertain.

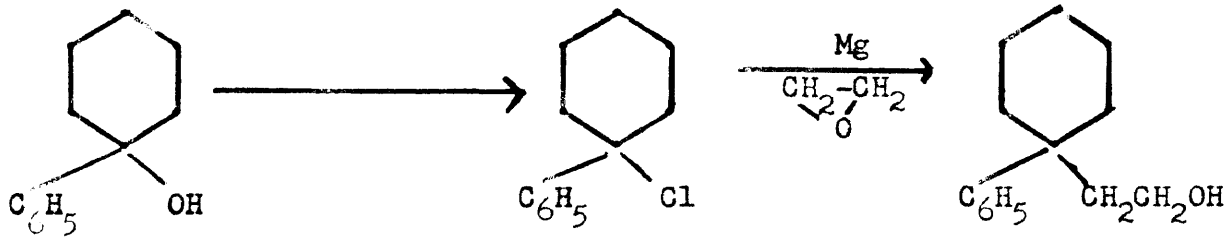


LXXIV



LXXV

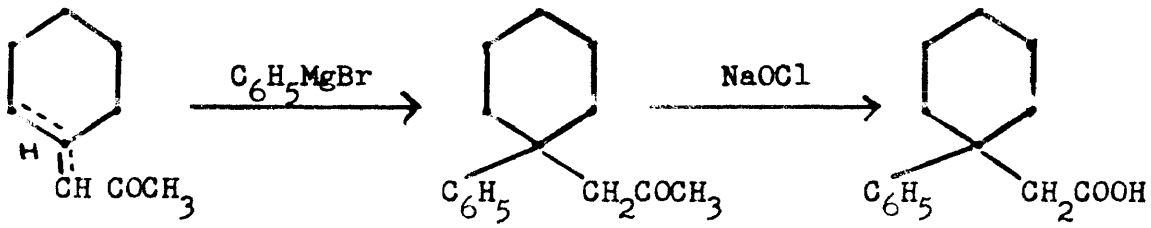
In an effort to obtain the originally desired product, 1-phenylcyclohexaneethylamine (LXI), the reactions of 1-phenylcyclohexanol (LXXVI) with phosphorus pentachloride and then with thionyl chloride were investigated. It was proposed to react the halide in an ethylene oxide Grignard reaction, and to convert the alcohol to the desired amine. However, these studies were not successful, the difficulty apparently being the extreme ease with which the tertiary alcohol (LXXVI) dehydrated. Actually, the chloride of this compound was never isolated. The proposed reaction scheme is given below:



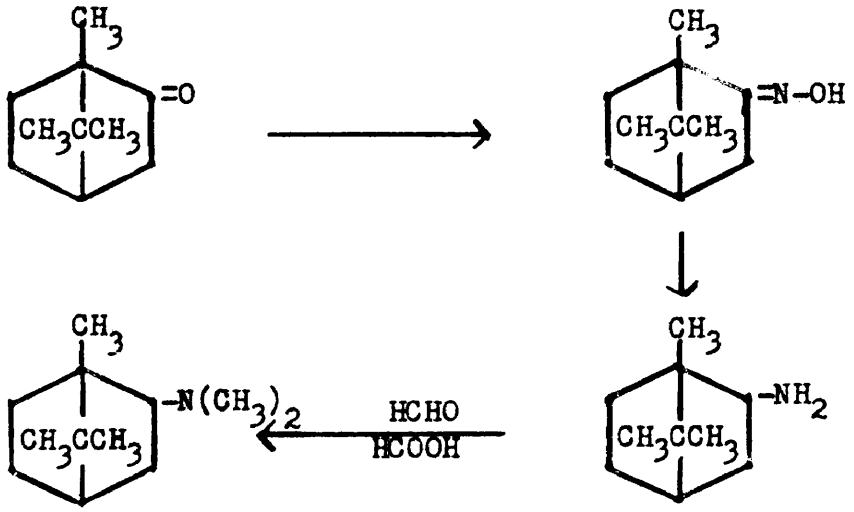
LXXVI

Another attempt along these lines involved the possibility of 1,4 addition of phenylmagnesium bromide to an equilibrium mixture of

cyclohexenylacetone and cyclohexylideneacetone, prepared according to the procedure of Jupp and coworkers.[149] It was proposed to react the methyl ketone resulting from the 1,4 addition with hypochlorite, and thus to isolate the desired product (LXIV). However, our experiments showed that no 1,4 addition took place, so that the desired acid (LXIV) could not be obtained. We had hoped to obtain the following reaction:



Another molecule which possesses some structural similarity to morphine (LXII) is N,N-dimethylbornylamine (LXXVII). This substance was synthesized from d,l-camphor. The oxime (LXXVIII) was prepared and in turn catalytically reduced to bornylamine (LXXIX), using Raney Nickel catalyst.[150,151,152,153] Along with bornylamine, some neo-bornylamine probably also was obtained. The bornylamine hydrochloride was refluxed with formaldehyde and formic acid. From this mixture N,N-dimethylbornylamine (LXXVII) was isolated in the usual fashion:



LXXVIII

LXXIX

LXXVII

EXPERIMENTAL

2-Ethoxy-Δ^3-Dihydropyran (VI). Dihydropyran (294 g., 3.5 mols) dissolved in 300 ml. of 60-80° petroleum ether was placed into a one liter three neck flask, fitted with an efficient stirrer, a dropping funnel, and a low temperature thermometer. A dry ice-acetone cooling bath was provided for immersion of the flask.

When the solution had been cooled to below -30°, a solution of bromine (560 g., 180 ml.) in 75 ml. of petroleum ether was added by means of the dropping funnel at such a rate that the temperature of the reaction was maintained between -20 and -40°. Just before the endpoint was reached, a white suspension was formed, in which the color of excessive bromine could be seen clearly. Not all of the theoretical amount of bromine was absorbed; a small residue usually was left behind.

The cooling bath was removed, the thermometer replaced with a condenser, and a capillary substituted for the stirrer. The third neck of the flask was plugged. The flask was heated by means of a water bath to 60-70°, and the greater portion of the solvent removed under the pressure obtainable with a water aspirator. Removal of the solvent was considered complete, when the vacuum distillation had become a slow, dropwise process.

The residue remaining in the flask was added immediately with caution, by means of a separatory funnel to a mechanically stirred solution of 95% ethanol (1500 ml.) which was saturated with ammonia, and which was cooled by means of an ice bath. The solution was allowed to stand an additional half hour in the ice bath during which time a

more complete precipitation of ammonium bromide occurred. The solution was filtered, and the precipitate was washed three times with 75 ml. portions of ethanol.

The filtrate was added in 500 ml. portions to an alcoholic solution of potassium hydroxide (400 g., dissolved in about two liters of 95% ethanol) contained in a 5 liter flask, which was cooled in an ice bath. After the initial reaction had subsided, the ice bath was replaced by a Glas-Col heater and the flask was fitted with a take off, on top of which a reflux condenser was placed. The contents of the flask were heated for twelve hours, during which time about 2½ liters of the solvent were removed by means of the take off. The solution was cooled to room temperature and without prior filtration, one liter of water containing 300 g. of ice was added to the reaction mixture.

This solution was transferred to a 6 liter separatory funnel containing one liter of peroxide free ether, and the reaction flask was rinsed with an additional 600 ml. of water. The washings were added to the contents of the separatory funnel. Without shaking, the ether layer was withdrawn into a second separatory funnel containing one liter of peroxide free ether. In this funnel, the aqueous layer was now extracted two successive times in the usual fashion. This unusual extraction procedure was required to prevent formation of emulsions. At times it became difficult to notice the interface, as both layers had the same color. This difficulty could be overcome by placing a strong light source directly behind the funnel, prior to withdrawing the water layer.

The combined ether layers were washed with one liter of cold water, using only mild stirring. The water layer was rejected and the ether layer was now extracted with four one liter portions of water,

shaking in the usual manner.

The ether layer was dried, filtered, and concentrated to a volume of about 600 ml. The solution was transferred to a one liter Claisen flask, to which a solution of sodium ethylate (2 g. of sodium in the minimum of anhydrous ethanol) was added. The solution was distilled to dryness under the pressure of the water aspirator, and the fraction boiling above 40°/20 mm. was collected. After adding another portion of sodium ethylate (quantities as above) to the distillate, it was distilled at atmospheric pressure. 2-Ethoxy-Δ^3-dihydropyran of boiling point 150-160° was collected. Yield: 175-200 g., 40-46%.

If required, the substance could be purified further by refluxing over sodium until free from bromine. A sample so prepared boiled at 153°. Woods and Sanders reported a boiling point of 153-155° for this compound.[16]

2,4-Pentadienal (X). 2-Ethoxy-Δ^3-dihydropyran, 80 g., was added to a solution of 80 ml. of concentrated phosphoric acid and 400 ml. of water. Within a few minutes the solution became homogeneous. This solution was added dropwise to a solution of 160 ml. of concentrated phosphoric acid and 800 ml. of water, which already was undergoing steam distillation. Distillation was continued until the distillate no longer had the characteristic, biting, lachrymatory odor of pentadienal. The steam distillate was saturated with sodium chloride and extracted three times with peroxide free ether. The ether layer was dried, concentrated and distilled under reduced pressure in a nitrogen atmosphere. Yield: 25 g. (50%), boiling at 36-37°/20 mm. Woods and Sanders reported a boiling point of 38-40°/20 mm. for this compound.[108]

The ultraviolet absorption spectrum of 2,4-pentadienal is shown in Figure 1. A Beckman spectrophotometer, with cells of 1.000 cm. length was used. The concentration was 5.17×10^{-5} mols/liter, the solvent being 95% ethanol distilled from sodium hydroxide. The experimental data are recorded in Table 1.

TABLE 1. Ultraviolet Absorption Spectrum of 2,4-Pentadienal.

mμ	% T	E	mμ	% T	E
229	54.8	$5.06 \times 10^{+3}$	269	11.1	1.85
230	52.3	5.44	270	13.1	1.71
231	50.1	5.83	271	15.3	$1.58 \times 10^{+4}$
232	47.2	6.32	272	18.3	1.43
233	44.2	6.85	273	21.7	1.29
234	41.8	7.33	274	25.4	1.15
235	39.0	7.90	275	30.1	1.01
236	46.4	8.48	276	34.3	$9.00 \times 10^{+3}$
237	33.0	9.28	277	38.8	7.96
238	30.4	$1.00 \times 10^{+4}$	278	44.2	6.85
239	27.6	1.08	279	49.7	5.86
240	24.8	1.17	280	54.9	5.03
241	22.8	1.24	281	60.0	4.32
242	20.8	1.32	282	64.3	3.72
243	18.2	1.43	283	70.5	2.94
244	16.0	1.54	284	73.4	2.58
245	14.2	1.64	285	76.8	2.21
246	12.7	1.73	286	80.0	1.88
247	11.1	1.85	287	82.8	1.61
248	9.92	1.94	288	85.3	1.32
249	8.93	2.03	289	87.6	1.10
250	7.90	2.13	290	90.0	$8.77 \times 10^{+2}$
251	7.19	2.21	291	91.1	8.02
251.5	6.97	2.24	292	92.5	6.46
252	6.89	2.25	293	93.5	5.69
252.5	6.55	2.29	294	94.5	4.90
253	6.43	2.31	295	94.7	4.90
254	5.44	2.45	296	94.8	4.11
255	4.99	2.52	297	96.1	3.29
256	5.60	2.43	298	96.3	3.29
257	5.27	2.47	299	97.3	2.48
258	4.85	2.54	300	96.8	2.48
259	4.85	2.54	301	97.4	2.48
260	5.03	2.51	302	97.0	2.48
261	4.91	2.52	303	97.3	2.48
262	5.31	2.47	304	97.8	1.66
263	5.61	2.42	305	97.8	1.66
264	6.04	2.36	306	98.0	1.66
265	6.73	2.27	307	97.6	1.66
266	7.20	2.21	308	97.8	1.66
267	8.53	2.07	309	97.8	1.66
268	10.1	1.93	310	98.0	1.66

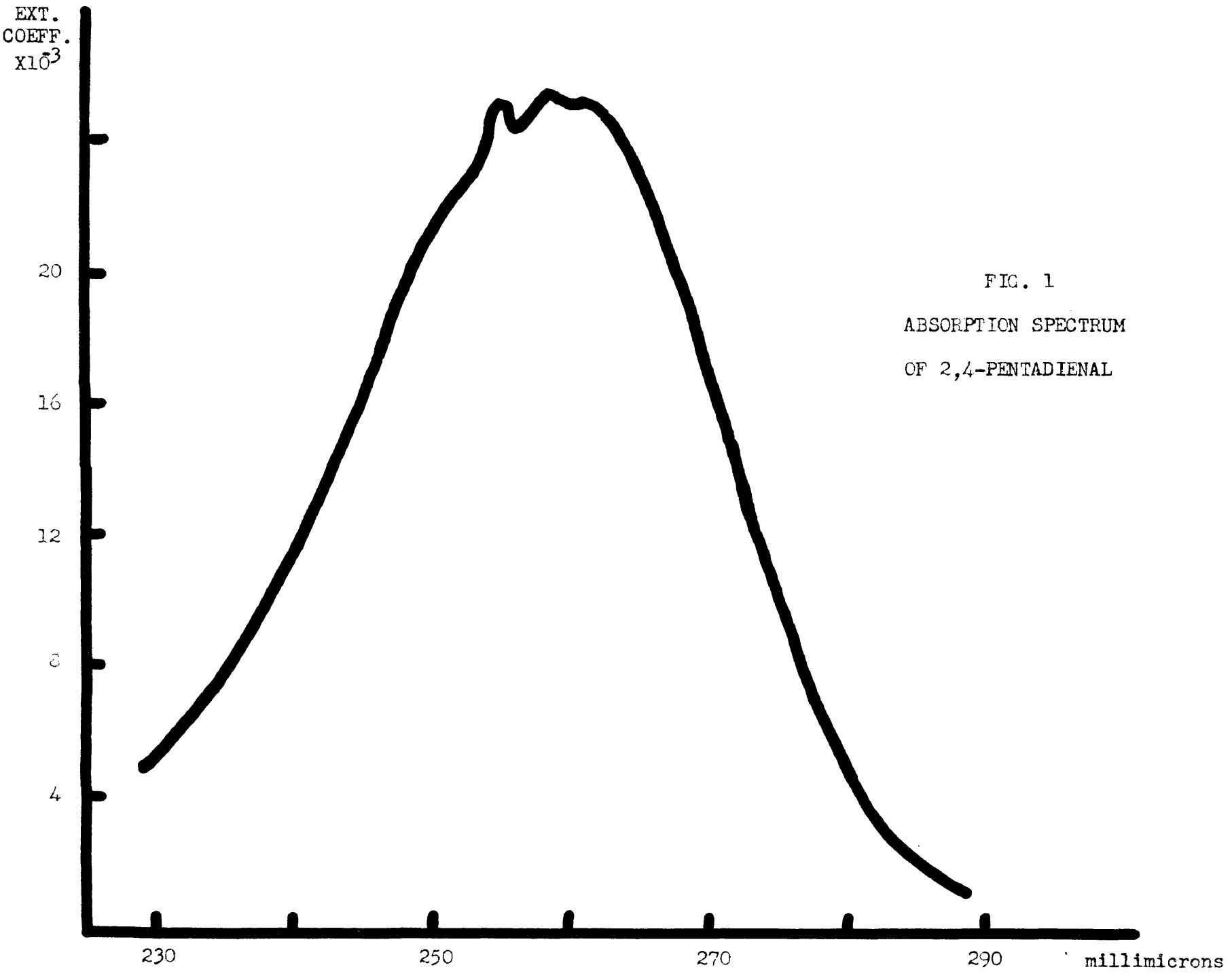


FIG. 1

ABSORPTION SPECTRUM

OF 2,4-PENTADIENAL

Reaction of 2,4-Pentadienal With Concentrated Base. To 60 ml. of a 60% aqueous solution of potassium hydroxide, 16 g. of pentadienal was added slowly. Considerable heat was evolved during the reaction. The mixture was cooled in ice, stoppered, vigorously shaken, and then put aside overnight to complete the reaction.

The reaction produced an amber solid. The mixture was diluted with water and steam distilled. Hardly any organic material was present in the distillate. The residue was acidified with sulfuric acid. The solid material did not dissolve, but its color became somewhat lighter. Again, no organic material could be isolated by steam distillation.

The solid residue was filtered, washed, and dried. The yield of this material was 16 g., so that all the pentadienal appeared to have reacted to give this substance. The solid was insoluble in carbon tetrachloride, ethanol, methanol, acetone, diethylketone, petroleum ether and acetic acid. The material melted above the range of the melting point apparatus (above 300°), and presumably was polymerized starting material.

2,4-Pentadien-1-ol (XLV). To a boiling solution of 122 g. of aluminum isopropoxide in 600 ml. of isopropanol, 81 g. of 2,4-pentadienal was added slowly. The solution was distilled slowly through a fractionating column for three hours. The aluminum isopropoxide solution was decomposed by pouring it into 2 liters of 10% sulfuric acid (by volume) containing crushed ice. The mixture was extracted several times with ether. The combined ether extracts were washed with sodium bicarbonate solution, followed by several washings with water. Distillation of the ether solution in a nitrogen atmosphere yielded 46 g. (55.2%) of 2,4-pentadien-1-ol of boiling point 55°/8 mm: n_D^{26} 1.4857.

Crude pentadienol contained small amounts of 2-ethoxy-Δ^3-dihydropyran, which could not be removed by repeated distillations. This difficulty was overcome by extracting the phosphoric acid solution of 2-ethoxy-Δ^3-dihydropyran with ether prior to steam distillation, as described in the section on 2,4-pentadienal. Analysis: Calculated for C_5H_8O: C 71.39, H 9.59. Found: C 71.39, 71.42, H 9.73, 9.70.

Heilbron and coworkers reported the following data for this compound:[24,97] Boiling points: 95-97°/100 mm; 34-40°/1.5 mm. Refractive index: n_D^{18} 1.4902.

A phenylurethan was prepared from pentadienol in the usual manner, It melted at 62.5-63.5°. Analysis: Calculated for $C_{12}H_{13}O_2N$: C 70.91, H 6.45. Found: C 71.09, 71.17; H 6.64, 6.64.

An α-naphthylurethan was prepared also. Melting point: 96.5-97.5°. Heilbron reported a melting point of 97.5° for this compound. Analysis: Calculated for $C_{16}H_{15}O_2N$: C 75.86, H 5.97. Found: C 75.84, 76.20; H 6.01, 5.99.

Pentadienol formed a clear, transparent polymer on prolonged standing.

The ultraviolet absorption spectrum of 2,4-pentadien-1-ol is shown in Figure 2. Table 2 contains the experimental data. A Beckman spectrophotometer with cells of 1.000 cm. thickness was used. The solvent was spectro grade isooctane; the concentration was 8.16×10^{-4} mols/liter.

Reduction of 2,4-Pentadien-1-ol to n-Amyl Alcohol. Twelve g. of pentadienol in methanol solvent was hydrogenated, using palladium-charcoal catalyst. When absorption of hydrogen had ceased, the solution was filtered and the solvent was evaporated. Distillation yielded 5.7 g. of n-amyl alcohol (44%), which boiled at 137°. Scheuble and

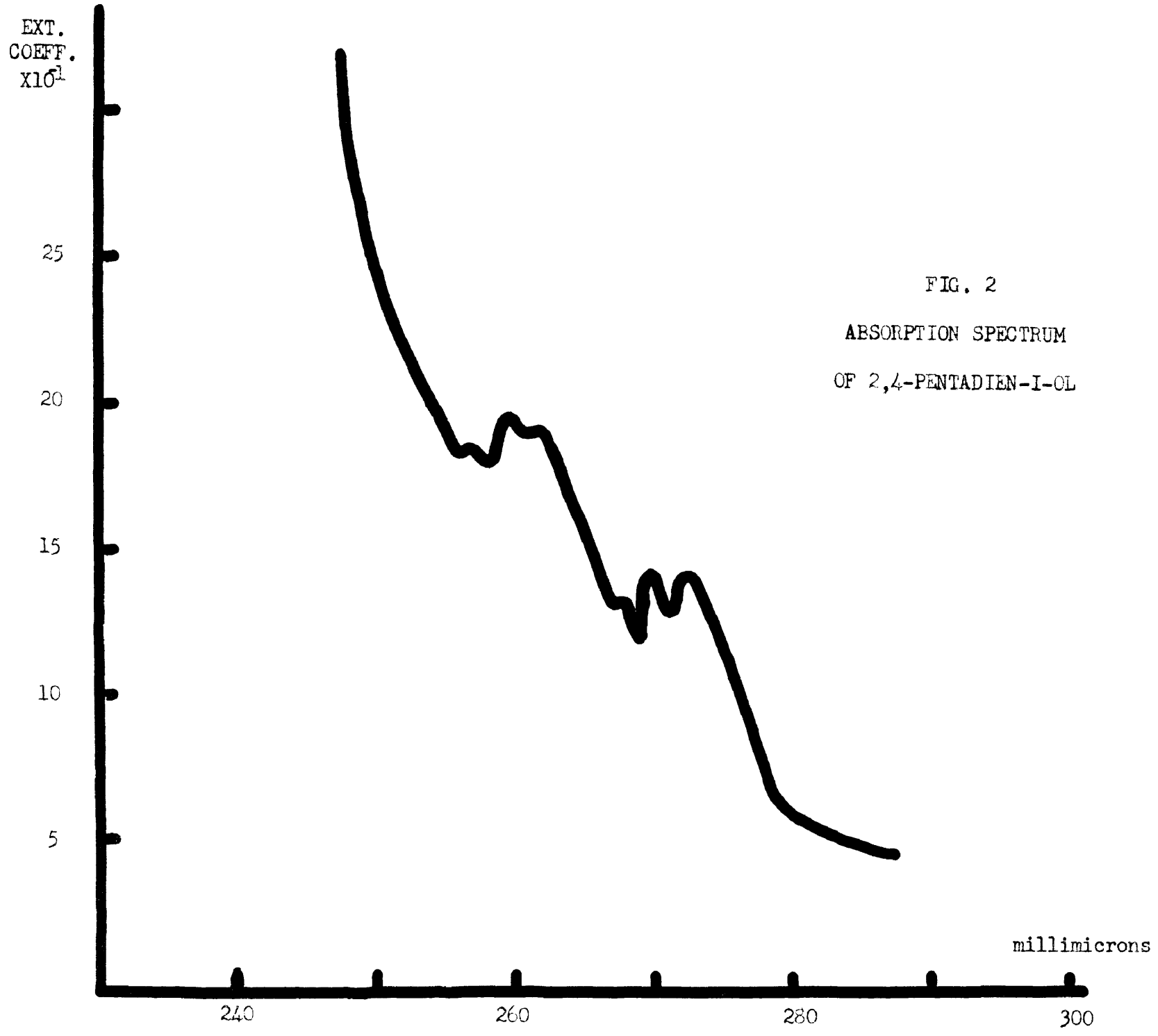


FIG. 2

ABSORPTION SPECTRUM

OF 2,4-PENTADIEN-I-OL

TABLE 2. Ultraviolet Absorption Spectrum of 2,4-Pentadien-1-ol.

mμ	% T	E	mμ	% T	E
235	.45	$2.88X10^{+3}$	262	69.8	$1.90X10^{+2}$
236	.58	2.74	263	72.0	1.75
237	.05	4.04	264	73.4	1.64
238	.60	2.72	265	75.6	1.48
239	3.84	1.74	266	77.1	1.40
240	4.27	1.68	267	78.8	1.28
241	7.80	1.36	268	78.2	1.31
242	15.3	1.01	269	80.0	1.19
243	23.0	$7.82X10^{+2}$	269.5	77.2	1.40
244	32.8	5.93	270	78.2	1.31
245	41.0	4.74	271	77.5	1.36
246	48.2	3.88	272	76.5	1.40
247	55.2	3.16	273	76.8	1.40
248	58.8	2.82	274	77.8	1.31
249	61.7	2.57	275	79.8	1.19
250	62.8	2.46	276	81.9	1.06
251	65.3	2.27	277	84.0	$9.27X10^{+1}$
252	66.8	2.16	278	87.3	6.98
253	68.2	2.05	279	89.0	6.03
254	68.9	1.97	280	89.4	6.03
255	70.2	1.86	282	91.2	5.08
256	70.9	1.83	283	91.0	5.08
257	71.1	1.83	284	90.8	5.08
258	71.3	1.79	285	91.1	5.08
258.5	70.7	1.83	286	91.1	5.03
259	69.5	1.94	288	91.9	4.58
260	69.9	1.90	290	91.5	4.58
261	69.8	1.90	295	92.7	4.10
			300	93.3	3.61

Lobl reported a boiling point of 137°/740 mm. for this alcohol.[154]

An α-naphthylurethan of the n-amyl alcohol was prepared in the usual fashion. It melted at 64-66° (literature value 68° [155]). A mixed melting point with an authentic sample gave no depression. Analysis: Calculated for $C_{16}H_{19}O_2N$: C 74.68, H 7.44. Found: C 74.81, 74.92; H 7.31, 7.44.

The 3,5-dinitrobenzoate melted at 45°. The value reported for this compound is 46°.[156] Analysis: Calculated for $C_{12}H_{14}O_6N_2$: C 51.06, H 5.00. Found: C 51.16, 51.14; H 5.00, 5.07.

Pentadienyl Chloride (XLVI). A three neck flask was fitted with a condenser, a dropping funnel and a connection to the aspirator.

The flask was equipped with a magnetic stirring bar, and the condensor was fitted with a drying tube. Thionyl chloride (65 g.) was placed inside the flask, and while the magnetic stirrer was in operation, 42 g. of 2,4-pentadien-1-ol was added slowly through the dropping funnel. The gaseous reaction products were swept out of the flask by means of a slight vacuum applied by means of the water aspirator. Stirring and vacuum were continued for ten minutes after all the pentadienol had been added. The solution was distilled in a nitrogen atmosphere under reduced pressure. After a few milliliters of forerun were collected, pentadienyl chloride was obtained boiling at 24°/13 mm. Yield 30 g. (58.2%). Refractive indices showed considerable variation the values lying between 1.4696 and 1.4919. One sample, after four redistillations had a refractive index of $n_D^{25.4}$ 1.4701. Analysis: Calculated for C_5H_7Cl: C 58.55, H 6.83. Found: C 58.51, 58.38; H 7.18, 7.04.

The ultraviolet absorption spectrum of pentadienyl chloride in spectro grade isooctane was taken. A Beckman spectrophotometer with cells of 1.000 cm. thickness was used. Two different concentrations were used; since the extinction coefficients for the two concentrations did not agree, both of the curves are given in this thesis. The data are collected in Table 3 and Table 4; the corresponding curves are shown in Figures 3 and 4.

3-Vinyl-$\Delta^{1,5,7}$-Octatrien-4-ol (LIII). * A dry one liter three neck flask was fitted with a condenser, a dropping funnel and a powerful mechanical stirrer. Powdered magnesium (8.8 g.) in 25 ml. of dry ether

---

*For the sake of convenience, this compound is henceforth called decatetraenol.

TABLE 3. Ultraviolet Absorption Spectrum of Pentadienyl Chloride. (1.23×10^{-2} mols per liter)

mμ	% T	E	mμ	% T	E
242	1.03	162	273	81.8	7.11
242.5	1.65	145	274	83.1	6.72
243	.63	180	275	86.4	5.16
245	.63	180	276	86.6	5.14
250	1.40	151	277	86.8	5.02
252	.62	180	277.5	86.8	5.02
254	.55	184	278	88.9	4.18
256	1.08	160	278.5	88.6	4.30
258	1.58	147	279	88.2	4.46
260	5.52	103	279.5	87.9	4.58
261	8.11	89.0	280	88.6	4.11
262	14.2	69.2	281	88.9	4.18
262.5	17.3	62.2	282	87.8	4.61
263	21.4	54.7	282.5	90.2	3.66
263.5	25.3	48.7	283	89.4	3.98
264	29.4	43.4	283.5	89.1	4.08
264.5	32.8	39.5	284	89.0	4.14
265	39.5	32.9	285	89.8	3.83
265.5	42.3	30.5	286	90.1	3.70
266	45.6	27.8	287	90.5	3.54
266.5	49.7	24.7	288	90.5	3.54
267	52.5	22.8	289	90.0	3.73
267.5	57.7	19.4	290	90.1	3.70
268	60.5	17.8	292	90.4	3.57
268.5	63.9	15.9	294	90.8	3.41
269	67.8	13.7	296	91.3	3.22
270	72.3	11.4	298	92.8	2.65
271	76.1	9.62	300	93.4	2.42
272	79.2	8.28			

was placed inside the flask. Pentadienyl chloride (12 g. in 333 ml. of dry ether) was added slowly over a period of three to four hours, while stirring was in progress. The solution was stirred for ten minutes after the last pentadienyl chloride had been added, and 7.6 g. of pentadienal in 20 ml. of dry ether was added to the mixture. Stirring was continued for 15 minutes and then the solution was decanted from the excess magnesium into a concentrated solution of ammonium chloride. The ether layer was separated and the water layer once extracted with ether. The combined ether layers were washed with sodium bicarbonate solution, and with water. The dried solution was

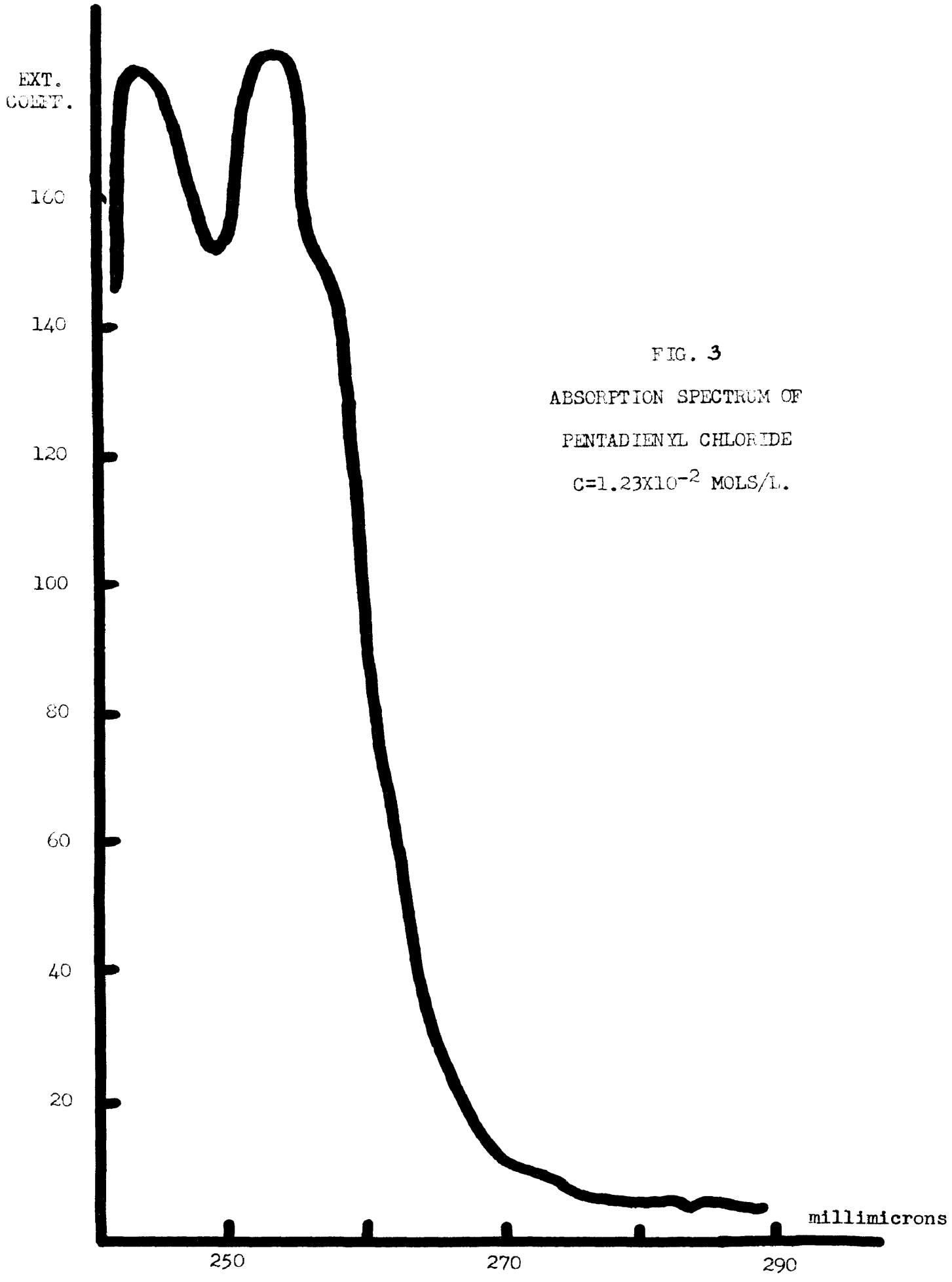


FIG. 3

ABSORPTION SPECTRUM OF

PENTADIENYL CHLORIDE

$C=1.23X10^{-2}$ MOLS/L.

TABLE 4. Ultraviolet Absorption Spectrum of Pentadienyl Chloride. ($1.23X10^{-5}$ mols per liter)

mμ	% T	E	mμ	% T	E
227	50.9	$2.36X10^{+4}$	247	88.4	4.32
228	49.2	2.50	248	88.9	4.12
229	50.3	2.43	249	89.9	$3.75X10^{+3}$
230	51.4	2.34	250	89.4	3.93
231	53.3	2.23	251	90.2	3.65
232	53.8	2.19	252	90.5	3.53
233	55.1	2.10	253	90.5	3.53
234	57.8	1.94	254	89.8	3.78
235	60.0	1.81	255	89.6	3.88
236	61.9	1.71	256	89.1	3.75
237	64.5	1.54	257	87.9	4.56
238	67.3	1.38	258	88.6	4.28
239	70.6	1.24	259	87.8	4.59
240	73.3	1.09	260	88.5	4.31
241	76.6	$9.51X10^{+3}$	261	86.9	4.97
242	78.7	8.29	262	89.6	3.88
243	82.1	7.02	263	86.3	5.24
244	83.5	6.44	264	86.2	5.24
245	85.9	5.24	265	87.7	5.02
246	86.6	4.94			

evaporated in a nitrogen atmosphere. The fraction boiling at 75-95°/8 mm. contained the decatetraenol. Nearly all this material distilled between 88 and 93°/8 mm. Yield: 10 g. (72%). A carefully purified sample had a boiling point of 90-92°/8 mm., and a refractive index of $n_D^{25.5}$ 1.5042. Analysis: Calculated for $C_{10}H_{14}O$: C 79.95, H 9.39. Found: C 80.04; H 9.34.

Reduction of 3-Vinyl-$\Delta^{1,5,7}$-Octatrien-4-ol to 3-Ethyloctan-4-ol (L). Decatetraenol, 15 g., was catalytically hydrogenated at room temperature using palladium-charcoal catalyst, and methanol solvent. Absorption of hydrogen was very rapid, 93% of the theoretical amount of hydrogen being absorbed. After no more hydrogen was absorbed, the catalyst was removed by filtration, and the solution was dried over magnesium sulfate. Evaporation of the solvent yielded 13 g. of 3-ethyloctan-4-ol, boiling at 92-95°/10 mm. The refractive index observed

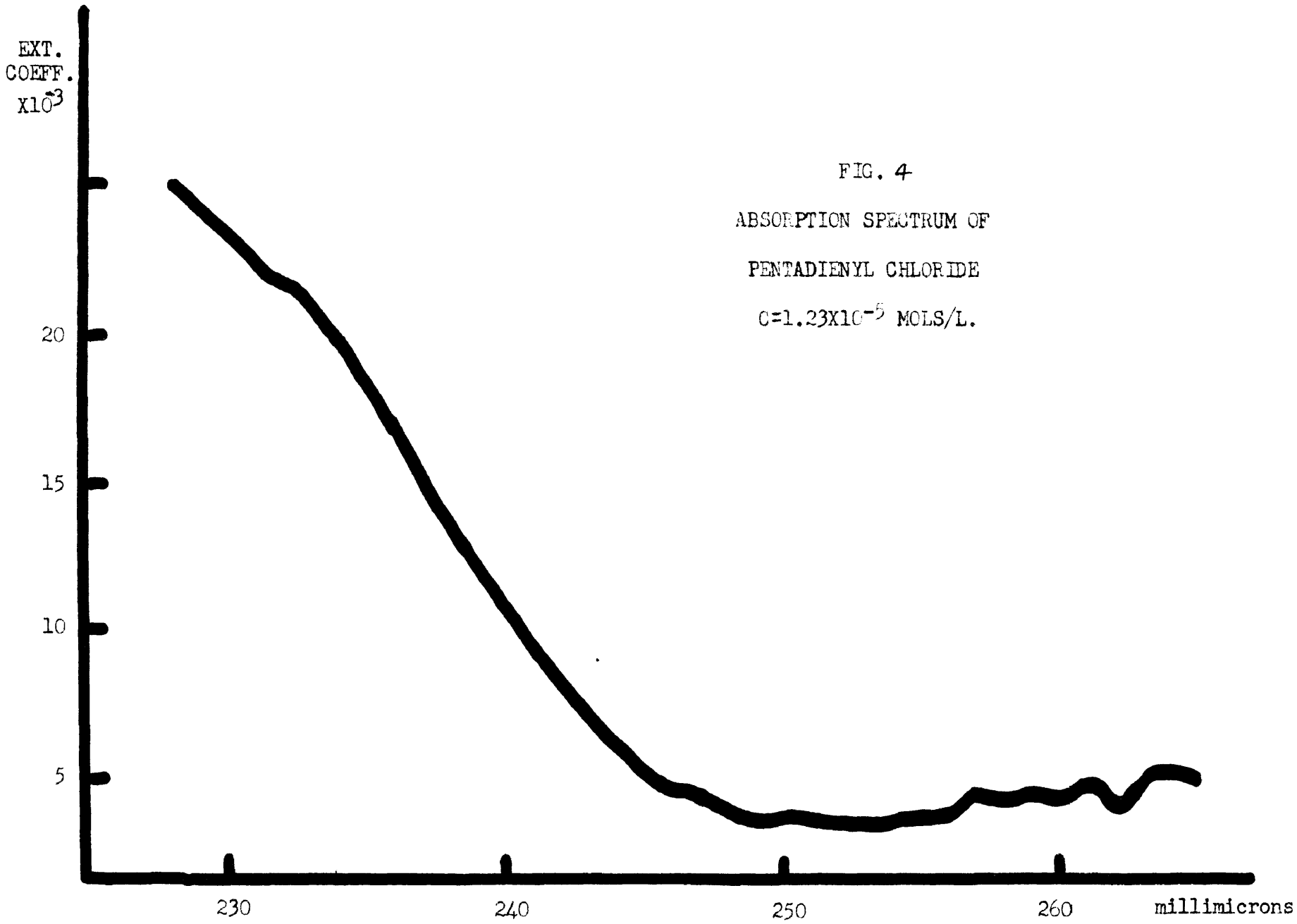


FIG. 4

ABSORPTION SPECTRUM OF

PENTADIENYL CHLORIDE

$C=1.23\times10^{-5}$ MOLS/L.

was $n_D^{26.0}$ 1.4385. Analysis: Calculated for $C_{10}H_{22}O$: C 75.88, H 14.01. Found: C 76.02, 75.86; H 13.26, 13.47.

The α-naphthylurethan of this decanol was prepared in the usual fashion. It melted at 79-80°. Analysis: Calculated for $C_{21}H_{29}O_2N$: C 77.02, H 8.93. Found: C 77.48, 77.35; H 9.20, 9.08.

3-Vinyl-$\Delta^{1,3,5,7}$-Octatetraene (LIV) ?. 3-Vinyl-$\Delta^{1,5,7}$-octatrien-4-ol (5.5 g.) was passed through a column of activated alumina, under the pressure obtainable with the water aspirator. The column was heated to 250° by means of resistance wire, which was wound around the column. The products were caught in two receivers, which were chilled by means of dry ice baths.

The distillate was dissolved in petroleum ether and chilled. This solidified the water which had come from the cracking of the alcohol molecule. The solution was decanted from the ice and distilled. Three drops of a viscous, yellow liquid, having a characteristic odor were isolated. The boiling point was roughly 70°/20 mm., n_D^{27} 1.5048.

The material obtained was insufficient for proper identification of this compound.

n-Valeraldehyde. Into a dry three liter three neck flask, fitted with mechanical stirrer, dropping funnel and a condenser equipped with a drying tube, was placed 45 g. (1.9 mols) of magnesium turnings, 75 ml. of dry ether and a few crystals of iodine.

After stirring had been started, 5 ml. of n-butyl bromide was added. As soon as the reaction had begun, 450 ml. of dry ether was added, and then more slowly, a solution of 253 g. of n-butyl bromide in 225 ml. of dry ether. All the halide was added within about half an hour, external cooling being provided during this process. The solution was refluxed gently for half an hour. Ethyl orthoformate, (225 g.,

1.5 mols) was added during an interval of about thirty minutes, a white precipitate being formed during this process. The mixture was refluxed for six hours.

The ether was removed completely on the steam bath, and the cooled mixture was decomposed with 1125 ml. of cold 6% hydrochloric acid. The contents of the flask were kept cool by means of an ice bath during this process. The upper layer of n-valeraldehyde acetal was separated and hydrolyzed by reacting it with a solution of 83 ml. of concentrated sulfuric acid in 1050 ml. of water. The free aldehyde was steam distilled, the distillation being considered complete when no more immiscible layer was obtained. The top layer was separated, and shaken vigorously for several minutes with a concentrated solution of sodium bisulfite (150 g. dissolved in 450 ml. of water). The remaining organic layer was discarded, and the bisulfite solution was steam distilled, to remove the remaining organic material.

The bisulfite addition product was decomposed by addition of a suspension of 120 g. of sodium bicarbonate in 300 ml. of water. The free aldehyde was removed by steam distillation. The organic layer in the distillate was washed three times with 75 ml. portions of water and dried over magnesium sulfate. For the sake of increasing the compound's stability, a pinch of hydroquinone was added. The solution was filtered from the drying agent and distilled through a fractionating column. Yield, 34 g. By redistillation of the combined fore and after-run, an additional 10 g. of the aldehyde was obtained. The combined yield of boiling point 98-102° was 44 g. (34.2%). The boiling point for this compound reported in the literature is 102.5-103°.[157,158,159]

5-Decanol (XLVII). A one liter three neck flask was fitted with a condenser, a dropping funnel and a mechanical stirrer. Inside the

flask were placed 14 g. of magnesium turnings and 50 ml. of anhydrous ether containing 5 g. of n-amyl bromide. When the reaction had started, an additional 150 ml. of dry ether was added, followed by 86 g. of n-amyl bromide in 50 ml. of dry ether. The latter solution was added slowly with cooling during a period of about half an hour. To this reagent, 43 g. of n-valeraldehyde was added cautiously. Stirring of the mixture was continued an additional 15 minutes. The reaction was decomposed by adding 150 ml. of a saturated solution of ammonium chloride, which was followed by sufficient hydrochloric acid to dissolve all the magnesium hydroxide. The ether layer was separated, washed with water, and with dilute base. After drying over magnesium sulfate, the solution was distilled, under the pressure obtainable with the water aspirator. The fraction boiling at 105-119°/26 mm. was collected, but nearly all this material distilled at 115-117°/26 mm. Yield: 70 g. (89%). A redistilled sample boiled at 118-120°/30 mm., n_D^{27} 1.4321. Analysis: Calculated for $C_{10}H_{22}O$: C 75.88, H 14.01. Found: C 75.93, 75.65; H 13.95, 14.05.

An α-naphthylurethan of 5-decanol was prepared in the conventional manner, the observed melting point being 55-56°. Analysis: Calculated for $C_{21}H_{29}O_2N$: C 77.02, H 8.93. Found: C 76.95, 77.01; H 9.06, 9.00.

A 3,5-dinitrobenzoate, prepared in the usual fashion melted at 42-43°. Analysis: Calculated for $C_{17}H_{24}O_6N_2$: C 57.94, H 6.87. Found: C 57.64, 57.79; H 6.75, 7.10.

Oxidation of 5-Decanol to 5-Decanone (LI). 5-Decanol (33 g.) was oxidized with a sodium dichromate-sulfuric acid mixture. The ketone was steam distilled from the reaction mixture, extracted with ether, and dried over magnesium sulfate. After removal of the drying agent,

the solution was fractionally distilled. Yield, 29 g. (92%) of boiling point 84-86°/8 mm., $n_D^{25.2}$ 1.4225. Analysis: Calculated for $C_{10}H_{20}O$: C 76.86, H 12.90. Found: C 77.20, 77.06; H 12.86, 12.96.

Bried and Hennion, who previously prepared this compound by a different method, reported the following data: Boiling point, 106-108°/27 mm., n_D^{24} 1.4225.[137]

The semicarbazone of 5-decanone was prepared by conventional methods, except that from ten days to two weeks in the ice box were required for formation of the derivative. Analysis: Calculated for $C_{11}H_{23}ON_3$: C 61.93, H 10.87. Found: C 62.13, 61.95; H 10.97, 10.92.

A substituted hydantoin, prepared by the method of Henze and Speer[160] melted at 143-145°. Analysis: Calculated for $C_{12}H_{22}O_2N_2$: C 63.68, H 9.80. Found: C 63.83, 63.90; H 9.84, 9.79.

4-Decanol (XLVIII). A dry one liter three neck flask was fitted with a mechanical stirrer, a dropping funnel and a condenser equipped with a drying tube. Into the flask were placed 12 g. of magnesium turnings and 50 ml. of dry ether. n-Propyl bromide, (65 g. in 75 ml. of dry ether) was slowly added, while the solution was being stirred. Stirring was continued for half an hour after addition was complete.

To this reagent was added 57 g. of n-heptaldehyde in 75 ml. of dry ether. The mixture was decomposed by pouring it into one liter of 10% sulfuric acid (by volume) which contained crushed ice. The ether layer was separated and the water layer once extracted with ether.

The combined ether layers were dried and distilled under reduced pressure. To remove the last traces of water, a small amount of calcium oxide was added prior to distillation. Yield: 70 g. (88%). A sample, redistilled three times, had a boiling point of 105-110°/16 mm., and a refractive index of $n_D^{28.5}$ 1.4300.

Wagner reported a boiling point of 210-211° at atmospheric pressure for this compound.[162]

Several attempts to prepare the α-naphthylurethan of this alcohol were unsuccessful.

3-Decanol (XLVIIII). Into a dry 500 ml. three neck flask, fitted with condenser, dropping funnel and mechanical stirrer, ~~were~~ was placed 8.8 g. of magnesium turnings and 50 ml. of dry ether. n-Heptyl bromide, (60 g. in 100 ml. of dry ether) ~~were~~ was slowly added and stirring continued for 15 minutes. To this reagent, 21 g. of propionaldehyde in 50 ml. of dry ether was added, stirring being continued for an additional 15 minutes. The solution was decomposed by pouring it into one liter of 10% sulfuric acid (by volume) containing crushed ice. The ether layer was separated, and the water layer once extracted with ether. The combined ether layers were washed with sodium bicarbonate, followed by water. The dried solution was fractionally distilled under reduced pressure. Yield, 43 g. (82%) of boiling point 105-107°/13 mm., $n_D^{22.5}$ 1.4338. Analysis: Calculated for $C_{10}H_{22}O$: C 75.88, H 14.01. Found: 75.99, 76.12; H 13.89, 14.06.

Pickard and Kenyon reported a boiling point of 108°/15 mm., and a refractive index of n_D^{20} 1.4336 for this compound.[161]

3-Decanol yielded an α-naphthylurethan of melting point 60-62°. Analysis: Calculated for $C_{21}H_{29}O_2N$: C 77.02, H 8.93. Found: C 77.11, 77.14; H 8.73, 8.83.

3-Ethyloctan-4-ol (L). A one liter three neck flask was fitted with a dropping funnel, a mechanical stirrer and a condenser equipped with a drying tube. Inside the flask ~~were~~ was placed 16 g. of magnesium turnings, which ~~were~~ was then covered with 100 ml. of dry ether. n-Butyl bromide (96 g.) ~~were~~ was added slowly through the dropping funnel. Stirring

was continued for 15 minutes, and 71 g. of 2-ethylbutyraldehyde in 100 ml. of dry ether ~~were~~ was added. Stirring was kept up for a short while, and the solution was decomposed with a saturated solution of ammonium chloride. The ether layer was separated and the water layer was once extracted with ether. The combined ether layers were washed with water and dried over magnesium sulfate. The drying agent was removed by filtration, and the solution was distilled under reduced pressure. Yield, 70 g. (64%) of boiling point 90-93°/ mm., $n_D^{25.3}$ 1.4362. Analysis: Calculated for $C_{10}H_{12}O$: C 75.88, H 14.01. Found: C 76.05, 75.97; H 14.07, 14.06.

The α-naphthylurethan of 3-ethyloctan-4-ol, obtained in the usual manner, melted at 78-80°. Analysis: Calculated for $C_{21}H_{29}O_2N$: C 77.02, H 8.93. Found 76.96, 76.91; H 9.15, 8.87.

A mixed melting point of this urethan with the urethan of the decanol derived from decatetraenol by catalytic hydrogenation, gave no depression.

Oxidation of 3-Ethyloctan-4-ol to 3-Ethyloctan-4-one.(LII). 3-Ethyloctan-4-ol (33 g.) was treated with dichromate-sulfuric acid mixture in the usual manner. The product was isolated by steam distillation, followed by extraction of the aqueous layer with ether. After drying, the solution was fractionally distilled, yielding 27 g. (86%) of the desired ketone, boiling at 77-79°/10 mm., n_D^{26} 1.4214. Neither redistillation nor treatment with charcoal was able to remove a slightly yellow to green tinge from the ketone. Analysis: Calculated for $C_{10}H_{20}O$: C 76.86, H 12.90. Found 76.82, 77.00; H 12.95, 13.05.

Bardan, who synthesized this ketone by a different method, reported a boiling point of 122-125°/38 mm., n_D^{20} 1.4287 for this compound.

The semicarbazone of the ketone was prepared in the usual manner, except that about two weeks in the ice box were required for formation of the derivative, which melted at 83.5-84°. Analysis: Calculated for $C_{11}H_{23}N_3O$: C 61.93, H 10.87. Found: C 61.99, 62.03; H 10.88, 10.83.

A mixed melting point of this derivative, with the semicarbazone of the decanone derived from decatetraenol gave no depression.

2,4-Pentadienyl Acetate (LV) from Pentadienyl Chloride and Sodium Acetate. To 12 g. of pentadienyl chloride was added anhydrous sodium acetate (12 g.) and an equal amount of glacial acetic acid. The mixture was refluxed for half an hour, poured onto ice, and extracted three times with ether. The combined ether layers were washed twice with water, twice with bicarbonate and again twice with water. The ether layer was dried and distilled, yielding 9 g. (58%) of pentadienyl acetate, boiling at 54-55°/8 mm. A sample, redistilled four times, had a refractive index of n_D^{26} 1.4698. Analysis: Calculated for $C_7H_{10}O_2$: C 66.64, H 7.99. Found: C 66.50, 66.54; H 8.18, 8.10.

2,4-Pentadienyl Acetate (LV) from 2,4-Pentadienol and Acetyl-Chloride. A three neck flask was fitted with a condenser, a dropping funnel and a connection to an aspirator. A magnetic stirring bar was placed inside the flask. Pentadienol (10 g.) was added slowly to 11 g. of acetyl chloride, while the magnetic stirrer was in operation. In order to remove the gases from the reaction, a slight vacuum was applied by means of an aspirator. After all the alcohol had been added, stirring was continued for ten minutes, the aspirator in the meantime being kept in operation. The mixture was poured into water, and twice extracted with ether. The combined ether extracts were washed with 5% potassium carbonate, and then with water. Distillation of the dried ether layer yielded 10 g. of pentadienyl acetate (70%), boiling at 68-69°/18 mm.

Reduction of 2,4-Pentadienyl Acetate to n-Amyl Acetate. 2,4-Pentadienyl acetate (10 g.) was catalytically hydrogenated at room temperature, using palladium-charcoal catalyst and methanol solvent. Absorption of hydrogen (99.6% of the theoretical amount) was very rapid. The catalyst was removed by filtration, and the solution poured into water, where a small top layer separated. The bottom layer was extracted twice with ether, and the combined top and ether layers were washed with water to remove as much of the methanol as possible. Distillation of the ether layer yielded 6.3 g. (62%) of n-amyl acetate, boiling at 146-149°. The value for the boiling point of this ester given in the literature is 148°/737 mm.[164]

Hydrolysis of n-Amyl Acetate. n-Amyl acetate (6.3 g.) was refluxed with an excess of a 25% sodium hydroxide solution for 21 hours. The top layer was separated and the bottom layer extracted with ether. The combined top layer and ether extract was washed twice with water and dried over magnesium sulfate. Distillation yielded 3.2 g. (76%) of n-amyl alcohol boiling at 137-139°.

Neither the 3,5-dinitrobenzoate of n-amyl alcohol from pentadienyl acetate prepared from pentadienyl chloride and sodium acetate, nor the 3,5-dinitrobenzoate of n-amyl alcohol prepared from pentadienyl acetate obtained via pentadienol and acetyl chloride, gave a melting point depression, when compared with an authentic sample of the same derivative.

Pentadienoic Acid (Vinylacrylic Acid) (XXI).[49] To a solution of 90 g. of malonic acid in 200 g. of pyridine, which was cooled in a freezing mixture, 60 g. of acrolein was added gradually, the solution being stirred during this process. A yellow color developed and a very viscous oil was deposited. After three hours, the temperature was raised to 45-50°, where it was kept for five hours, during which time

the oil dissolved with evolution of carbon dioxide.

The solution was poured into an excess of half concentrated hydrochloric acid containing crushed ice. The mixture was extracted three times with ether, and the combined extracts were washed with water and dried. The ether solution was concentrated in a nitrogen atmosphere, under the pressure obtainable with the water aspirator. When nearly all the solvent had been removed, the viscous material was cooled in an ice bath, which caused part of the mixture to solidify. The crystals were filtered and recrystallized from 60-80° petroleum ether. Additional amounts of the acid were obtained by concentrating the mother liquors two more times. Yield, first concentration, 19.5 g. of melting point 64-68°, second concentration 3.7 g. melting at 64-66°, third concentration 7.7 g. of melting point 57-65°. Combined yield, 31 g. (28.7%). Literature values for the melting point of this acid vary between 72 and 80°. Kohler and Butler, whose method was used, reported a melting point of 72°. A carefully purified sample of our acid melted at 70.5-71.5°.

The ultraviolet absorption spectrum of 2,4-pentadienoic acid (melting point 70.5-71.5°) was taken. A Beckman spectrophotometer, with cells of 1.000 cm. cross section was used. The solvent was 95% ethanol, distilled from sodium hydroxide. The data are recorded in Table 5, the results are plotted in Figure 5. A concentration of $9.47X10^{-5}$ mols per liter was used.

TABLE 5. Ultraviolet Absorption Spectrum of 2,4-Pentadienoic Acid.

mμ	% T	E	mμ	% T	E
229.5	4.63	$1.41X10^{+4}$	232.5	5.06	1.37
230	3.69	1.52	233	2.42	1.71
230.5	4.54	1.42	233.5	2.94	1.62
231	6.19	1.28	234	2.07	1.78
231.5	3.89	1.49	234.5	2.58	1.68
232	3.40	1.55	235	2.58	1.68

TABLE %. Ultraviolet Absorption Spectrum of 2,4-Pentadienoic Acid.

mμ	% T	E	mμ	% T	E
235.5	2.23	1.74	267	44.5	3.72
236	3.74	1.51	268	49.7	3.20
236.5	2.42	1.71	268.5	52.2	2.97
237	1.50	1.93	269	54.5	2.77
237.5	1.64	1.89	269.5	56.8	2.60
238	1.22	2.02	270	58.8	2.43
238.5	1.75	1.85	271	62.5	2.16
239	1.45	1.94	272	64.8	1.99
239.5	1.78	1.85	273	69.9	1.65
240	1.89	1.82	274	73.1	1.45
240.5	2.24	1.74	275	74.6	1.34
241	1.21	2.02	276	77.2	1.20
241.5	1.38	1.97	277	79.2	1.06
242	1.26	2.00	278	80.5	$9.85 \times 10^{+2}$
242.5	1.18	2.04	279	82.4	8.76
243	1.33	1.98	280	83.0	8.76
243.5	1.53	1.92	281	84.4	7.99
244	1.47	1.94	282	85.6	7.20
244.5	.98	2.12	283	86.5	$6.82 \times 10^{+2}$
245	1.25	2.01	284	87.3	6.41
245.5	1.58	1.91	285	87.6	6.01
246	1.18	2.04	286	88.6	5.61
246.5	1.00	2.11	287	88.8	5.61
247	1.52	1.92	288	89.6	5.19
247.5	1.43	1.95	289	90.4	4.63
248	1.55	1.91	290	90.5	4.58
248.5	1.55	1.91	291	90.8	4.42
249	1.46	1.94	292	91.4	4.12
249.5	1.78	1.85	293	92.1	3.78
250	1.95	1.81	294	92.2	3.78
250.5	1.90	1.82	295	92.6	3.53
251	2.06	$1.78 \times 10^{+4}$	296	93.3	3.19
251.5	2.34	1.72	297	93.6	3.02
252	2.43	1.71	298	94.0	2.84
252.5	2.65	1.67	299	94.4	2.63
253	2.86	1.63	300	94.5	2.59
253.5	3.19	1.58	301	94.8	2.46
254	3.81	1.50	302	94.8	2.46
254.5	4.24	1.45	303	95.0	$2.36 \times 10^{+2}$
255	4.57	1.42	304	95.1	2.32
255.5	5.22	1.36	305	95.5	2.10
256	5.58	1.32	306	95.8	1.98
256.5	6.38	1.26	307	96.5	1.63
257	7.18	1.21	308	96.5	1.63
257.5	8.03	1.16	309	97.3	1.27
258	8.49	1.13	310	97.0	1.40
258.5	10.0	1.05	311	96.7	1.53
259	11.3	1.00	312	96.2	1.75
259.5	12.8	$9.43 \times 10^{+3}$	313	96.8	1.49
260	15.4	8.57	314	97.4	1.22
261	16.2	8.35	315	96.4	1.67
262	20.0	7.38	316	97.2	1.31
263	24.5	6.46	317	96.8	1.49
264	29.8	5.54	318	97.1	1.35
265	34.6	4.87	319	97.2	1.31
266	39.3	4.30	320	97.4	1.22

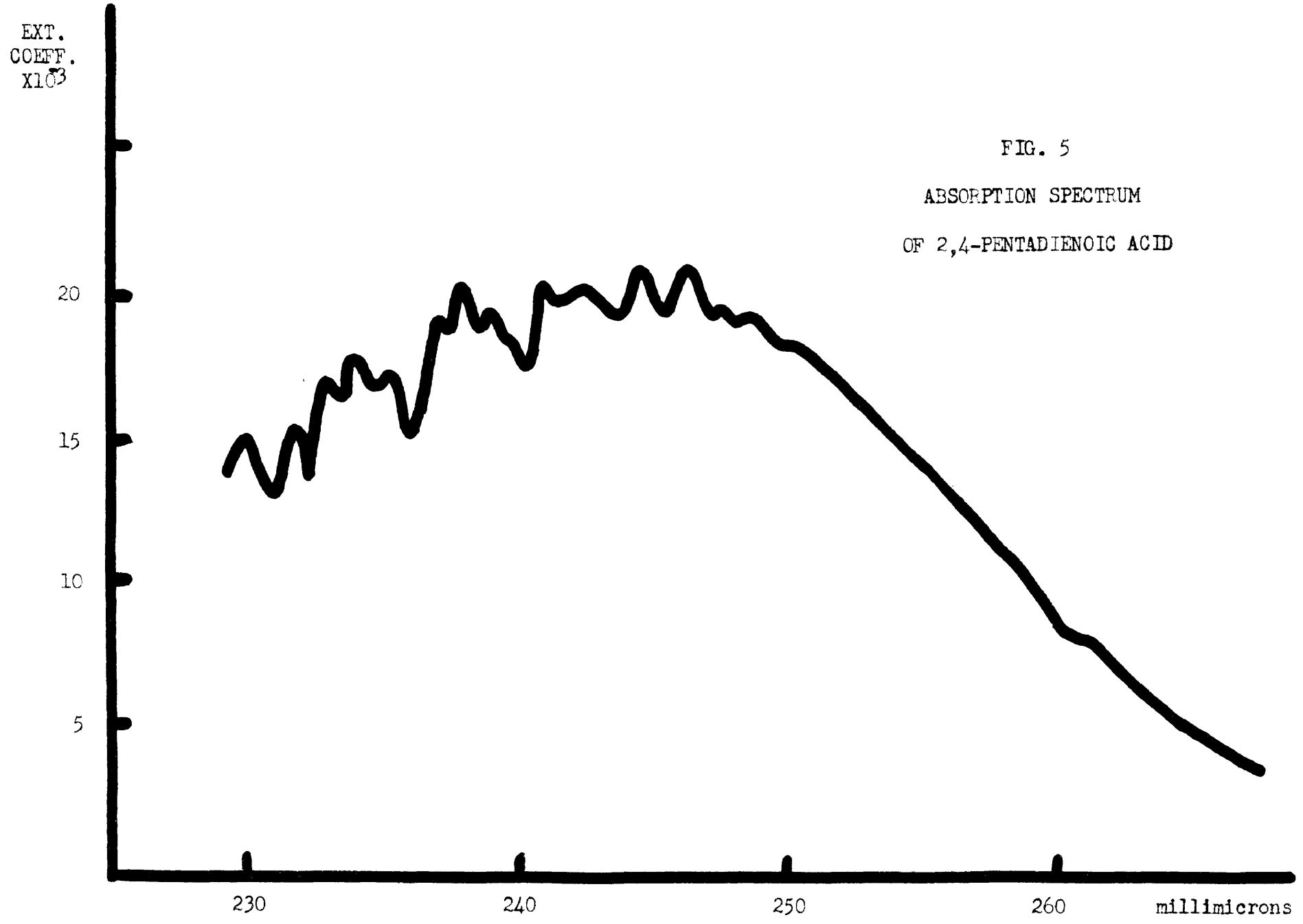


FIG. 5

ABSORPTION SPECTRUM

OF 2,4-PENTADIENOIC ACID

Silver Pentadienoate. 2,4-Pentadienoic acid (6.8 g.) was added slowly to 250 ml. of distilled water, while the solution was stirred vigorously. Any material not dissolved in ten minutes was removed. This material, comprising polymerized pentadienoic acid had a gummy consistency and was discarded. Silver nitrate (12 g.) in 100 ml. of distilled water was added to the solution while stirring was continued. The solution was carefully adjusted to a pH of 6 (indicator paper) by means of a dropwise addition of 3% sodium hydroxide. The silver salt was filtered and dried in a vacuum desiccator. The salt, though originally white, was changed to a brownish-grey color by exposure to air.

2,4-Pentadienyl Ester of 2,4-Pentadienoic Acid (LX).* A 500 ml. three neck flask was fitted with a mechanical stirrer and an azeotrope trap, on top of which a condenser was placed. Benzene, (250 ml.) was placed inside the flask. In order to remove the water from the benzene, the liquid was refluxed until no more water was collected in the azeotrope trap. Heating was discontinued and the contents of the flask were cooled. Silver pentadienoate, (18 g.) was introduced into the flask and the mixture again refluxed with stirring. An additional amount of water, coming from the incompletely dried silver salt was removed by means of the azeotrope trap. The amount depends on the dryness of the silver salt; in this instance, 1 ml. of water was collected so that the original weight of the silver salt in the dry state was 17 g. Nearly all the benzene was removed through the azeotrope trap. To the cooled mixture, 200 ml. of dry acetone was added. The azeotrope trap was removed, and the flask fitted with a condenser and a small

---

*Subsequently referred to as pentadienyl pentadienoate.

dropping funnel. Stirring was again started, and while the solution was heated under reflux, 8.5 g. of pentadienyl chloride was added slowly through the dropping funnel. After all the halide had been added, stirring and refluxing were continued for another 20 minutes.

The cooled mixture was filtered, and flask and precipitate were washed several times with small portions of peroxide free ether. The filtrate was poured into water, from which the organic material was extracted with peroxide free ether. The ether extracts were washed with water, then with bicarbonate solution, and again with water. A few crystals of hydroquinone were added to stabilize the solution, which was dried over magnesium sulfate.

The drying agent was filtered, and most of the solvent was evaporated in a nitrogen atmosphere under the pressure obtainable with a water aspirator. When about 50 ml. of solution remained, the material was transferred to a smaller flask, and again a few crystals of hydroquinone were added. The flask was fitted with a small electrically heated Vigreaux column. Distillation under reduced pressure in a nitrogen atmosphere was continued until nearly all the solvent had been removed. Then a high vacuum pump was connected, and the remainder was distilled as fast as possible, using a luminous flame. The boiling point was about 84°/.8 mm. Yield, 3.6 g. (26%), $n_D^{30.5}$ 1.5189. A quick distillation was found to be essential, as otherwise complete polymerization resulted. Even when isolated in the manner described, the major portion of the substance polymerized. Due to the extreme instability of the material at its boiling point, we were unable to obtain the material sufficiently pure for a satisfactory analysis.

Figure 6 illustrates the ultraviolet absorption spectrum of pentadienyl pentadienoate. It should be born in mind however, that this

substance in all probability contained considerable amounts of impurities. A Beckman spectrophotometer was used, the cells having a length of 1.000 cm. The solvent was spectro grade isooctane, the concentration being $1.72X10^{-5}$ mols/liter. The experimental data are collected in Table 6.

TABLE 6. Ultraviolet Absorption Spectrum of Pentadienyl Pentadienoate.

mμ	% T	E	mμ	% T	E
225	33.3	$2.77X10^{+4}$	247	35.0	2.65
226	33.8	2.74	248	36.0	$2.58X10^{+4}$
227	33.8	2.74	249	37.4	2.44
228	34.4	2.70	250	39.5	2.34
229	35.0	2.65	251	41.0	2.25
230	34.5	2.69	252	42.9	2.14
231	34.5	2.69	253	45.1	2.01
232	33.9	2.73	254	47.6	1.87
233	33.4	2.77	255	50.5	1.73
234	33.1	2.79	256	54.4	1.54
235	32.6	2.83	257	57.4	1.40
236	32.5	2.84	258	62.2	1.20
237	32.2	2.85	259	66.6	1.02
238	31.9	2.88	260	70.5	$8.85X10^{+3}$
239	32.0	2.87	261	75.4	7.19
240	31.5	2.91	262	80.2	5.64
241	31.7	2.90	263	85.6	3.97
242	31.7	2.90	264	89.1	2.86
243	31.9	2.88	265	93.0	1.82
244	32.4	2.85	266	96.9	$7.73X10^{+2}$
245	33.2	2.79	267	98.0	5.00
246	34.8	2.66	268	99.6	1.00

Reduction of Pentadienyl Pentadienoate to n-Amyl Valerate.

Pentadienyl Pentadienoate (6.0 g.) was hydrogenated at room temperature using methanol solvent and palladium-charcoal catalyst. The hydrogen absorbed was 103% of the theoretical amount. The solution from which the catalyst had been removed by filtration was poured into water, and extracted three times with ether. The combined ether extracts were washed twice with water and dried over magnesium sulfate. Fractional distillation yielded 4.6 g. (74%) of n-amyl valerate boiling at 198-208°, n_D^{34} 1.4095.

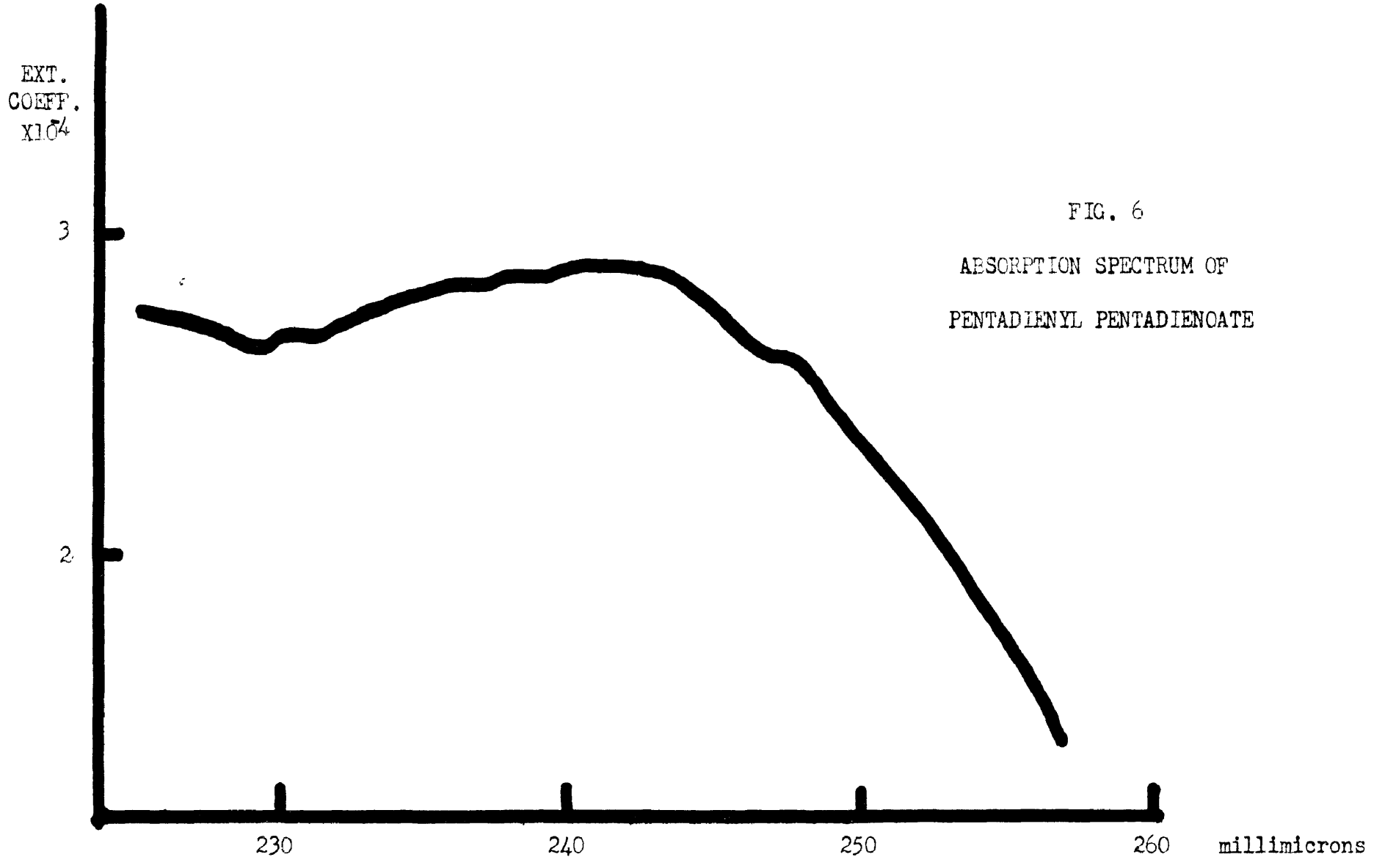


FIG. 6

ABSORPTION SPECTRUM OF

PENTADIENYL PENTADIENOATE

Gartenmeister reported a boiling point of 203.7 for this compound.[165]

Hydrolysis of n-Amyl Valerate. n-Amyl valerate (6.0 g.) was refluxed for 12 hours with 100 ml. of a 25% aqueous solution of sodium hydroxide. The alkaline solution from the hydrolysis was extracted three times with ether. The aqueous layer was kept for subsequent isolation of the n-valeric acid. Distillation of the dried ether extract yielded 2.4 g. of n-amyl alcohol (77%), n_D^{25} 1.3998.

The 3,5-dinitrobenzoate of n-amyl alcohol, prepared in the usual manner, melted at 44° (literature 46°). A mixed melting point with an authentic sample gave no depression.

The basic aqueous layer from which the n-amyl alcohol had been extracted with ether, was acidified with hydrochloric acid, and then extracted three times with ether. The combined ether extracts were washed with water and dried over magnesium sulfate. The drying agent was removed by filtration and the solution was distilled. n-Valeric acid (3.1 g., 87%) having a refractive index of n_D^{25} 1.4054 was isolated.

The p-bromophenacyl ester was prepared in the usual fashion. It melted at 72.5-73.0°. Moses and Reid reported a melting point of 75°[166] for this compound. A mixed melting point with an authentic sample gave no depression.

Ethyl-1-Hydroxycyclohexyl Acetate (LXIII). The procedure for Natelson and Gottfried was used.[140] To a mixture of 800 ml. of dry benzene and 700 ml. of dry toluene were added 334 g. (220 ml., 2 mols) of ethyl bromoacetate and 196 g. (207 ml., 2 mols) of cyclohexanone. Copper-zinc alloy (140 g.) containing 8% copper was placed into a dry 5 liter three neck flask, fitted with a mechanical stirrer, a condenser with drying tube, and a dropping funnel. Some of the reaction mixture

(300 ml.) and a few crystals of iodine were added. Stirring and heating by means of a steam bath were started. A vigorous reaction set in within 15 minutes. At times it became necessary to cool the mixture by means of an ice bath. Once the initial reaction had subsided, the rest of the reaction mixture was introduced at such a rate that gentle refluxing was obtained. Stirring on the steam bath was continued for two hours after addition was complete. Nearly all the zinc alloy had dissolved during that time.

The cooled mixture was decomposed by means of 10% sulfuric acid (by volume). The organic layer was separated, washed and dried. Distillation yielded 250 g. (67%) of the hydroxy ester, boiling at 126-129°/15 mm, $n_D^{19.5}$ 1.4610.

Ethyl-4-Phenylcyclohexyl Acetate. The attempted synthesis of ethyl-1-phenylcyclohexyl acetate by means of the Friedel-Crafts reaction led predominantly to ethyl-4-phenylcyclohexyl acetate, as described in the discussion section. Four methods of preparation for this latter compound were employed:

I. Reaction at room temperature. A dry one liter three neck flask was fitted with a dropping funnel, a mechanical stirrer and a condenser. The top of the condenser was fitted with a two hole rubber stopper, containing a drying tube in one of the openings, while the other hole was connected to the water aspirator. When slight suction was applied by means of the aspirator, the reaction gases were swept out of the flask, while only dry air was permitted to enter through the drying tube.

Dry benzene (260 ml.) was placed inside the flask, to which anhydrous aluminum chloride (160 g., 1.2 mols) was added, while stirring was in progress. The solution was cooled by means of an ice bath, while

94 g. of ethyl-1-hydroxycyclohexyl acetate was added over a period of about three hours. Cooling was continued for one hour, and stirring without cooling was continued for another six hours at room temperature. The stirrer was shut off overnight, but it was again started for one hour on the next day. The yield was increased substantially by permitting the material to stand overnight.

The mixture was decomposed by pouring it into 400 ml. of concentrated hydrochloric acid containing ice. The organic layer was separated, and the water layer was twice extracted with ether. The combined organic layers were washed, dried, and distilled. Yield, 75 g. (60%) boiling at 153-160°/3 mm. A carefully redistilled sample boiled at 171-172°/5.3 mm., its refractive index was $n_D^{24.5}$ 1.5101. Nenitzescu and Gavat reported a boiling point of 168°/5 mm. for this compound.[126] Analysis: Calculated for $C_{16}H_{22}O_2$: C 78.00, H 9.00. Found: C 77.98, 77.91; H 8.98, 9.10.

II. Reaction in boiling benzene. A dry 500 ml. three neck flask was fitted with a mechanical stirrer, a dropping funnel and a condenser, fitted with a gas outlet and drying tube as described in section I. Dry benzene (150 ml.) containing 90 g. of anhydrous aluminum chloride was placed inside the flask. While the mixture was stirred and refluxed, 50 g. of ethyl-1-hydroxycyclohexyl acetate was added slowly. Refluxing and stirring were continued for another 20 minutes. The cooled mixture was decomposed by pouring it into concentrated hydrochloric acid, containing crushed ice. The benzene layer was separated, and the aqueous layer was twice extracted with ether. The combined benzene and ether layers were washed, dried and distilled. Yield: 34 g. (52%).

III. Reaction in boiling benzene-nitrobenzene mixture. A dry one liter three neck flask was fitted with a mechanical stirrer, a dropping funnel and a condenser fitted with an outlet and drying tube, as described previously. Dry nitrobenzene (333 ml.) and dry benzene (100 ml.) were placed inside the flask. To this solution, 167 g. (1.25 mols) of anhydrous aluminum chloride was added. The mixture was stirred and refluxed, while 92 g. of ethyl-1-hydroxycyclohexyl acetate were introduced slowly. Stirring and refluxing were continued for 45 minutes after all the ester had been added. The cooled mixture was decomposed by pouring it into concentrated hydrochloric acid, containing ice shavings. The organic material was removed by several extractions with ether, and the ether layers were washed, dried and concentrated. Distillation yielded 44 g. (36%) of the ester, boiling at 172-175°/8 mm.

IV. Friedel-Crafts reaction of ethyl-Δ^1-cyclohexeneyl acetate at room temperature. Ethyl-1-hydroxycyclohexyl acetate (150 g.) was heated on a steam bath for three hours, while hydrogen chloride gas was bubbled through the substance. The mixture was distilled, two fractions being collected. The first boiled at 97-109°/8 mm.; its refractive index was $n_D^{24.5}$ 1.4615. The second fraction, boiling at 109-116°/8 mm., had a refractive index of n_D^{25} 1.4626. Because of the small difference in the refractive indices, the two fractions were combined. Total yield 107 g. (79%) of ethyl-1-phenylcyclohexeneyl acetate.

A dry 500 ml. three neck flask was fitted with a mechanical stirrer, a dropping funnel and a condenser equipped with a drying tube and gas outlet as described previously. Dry benzene (150 ml.) and 100 g. of anhydrous aluminum chloride were added. The mixture was chilled by means of an ice bath, while 53 g. (.3 mols) of ethyl-Δ^1-cyclohexenyl acetate was added dropwise during a period of about two

hours. Stirring with cooling was continued for another hour, after which time the ice bath was removed. After stirring for six hours at room temperature, the stirrer was shut off overnight. Stirring at room temperature was resumed for an additional 2½ hours, followed by decomposition of the mixture by pouring it into 400 ml. of concentrated hydrochloric acid, containing ice. The benzene layer was separated, and the aqueous layer was twice extracted with ether. The combined benzene and ether layers were washed, dried, and distilled. Yield, 41 g. (52%) boiling at 135-145°/.95 mm., n_D^{26} 1.5101.

4-Phenylcyclohexaneacetic Acid (XXXVII). Ethyl-4-phenylcyclohexyl acetate (41 g.) was hydrolyzed by refluxing it for 17 hours with a 100% excess of a 25% aqueous sodium hydroxide solution. The alkaline solution was poured into water and extracted with ether. The ether layer was discarded, and the water layer acidified in the cold. The precipitated acid was dried in a vacuum desiccator. Yield 36 g. (99%).

When the ester used in the hydrolysis was prepared by procedure I an acid was obtained which upon several recrystallizations from 40-60° petroleum ether melted at 112-114°. The purified acids derived from esters prepared by procedures II and IV had the same melting points, and gave no depression when a mixed melting point with the acid prepared by hydrolysis of the ester from procedure I was taken. The melting point reported in the literature for this acid is 113°.[126,127] Analysis: Calculated for $C_{14}H_{18}O_2$: C 77.03, H 8.31. Found: C 77.32, 77.35; H 7.98, 8.37.

When the ester used in the hydrolysis was prepared by procedure III and the acid recrystallized several times from 40-60° petroleum ether, a melting point of 86-88° was obtained. Another sample of the

same acid, was recrystallized in succession from petroleum ether, methanol-water, and toluene, but the observed melting point was still 87-89°. Subsequent reactions seemed to indicate that this compound is probably the hitherto unknown other stereoisomer of 4-phenylcyclohexaneacetic acid. Analysis: Calculated for $C_{14}H_{18}O_2$: C 77.03, H 8.38. Found: C 77.09, 76.98; H 8.38, 8.38.

4-Phenylcyclohexaneacetyl Chloride (LXIX). A dry 100 ml. three neck flask was fitted with a magnetic stirrer, a dropping funnel, and a condenser, which was equipped with a gas outlet and a drying tube as previously described. 4-Phenylcyclohexaneacetic acid from procedure I was dissolved in 25 ml. of dry benzene; to this solution 19 g. of thionyl chloride was added slowly, the solution being stirred by means of the magnetic stirrer in the meantime. The gases were swept out of the reaction mixture by applying slight suction at the aspirator. After all the thionyl chloride was added, the mixture was refluxed for 1½ hours, after which time no more vapors seemed to be given off by the reaction. Distillation yielded 22 g. (80%) of the acid chloride, boiling at 177-179°/9 mm. A redistilled sample boiled at 182-183°/14 mm., $n_D^{26.5}$ 1.5358.

The same method was used when the acid originated from the ester obtained by procedure III. Yield 71%, boiling at 158-173°/9 mm., n_D^{19} 1.5351.

4-Phenylcyclohexylacetamide (LXX). 4-Phenylcyclohexylacetyl chloride (18.1 g. derived from the acid of melting point 112-114°) was added slowly to 250 ml. of concentrated ammonia, which was stirred and chilled by means of an ice bath. Stirring was continued in the cold for several hours, after which time the amide was filtered and dried. Yield, after one recrystallization from ethanol, 12 g. (70%).

On several recrystallizations from ethanol, the amide melted at 197-199°. Analysis: Calculated for $C_{14}H_{19}ON$: C 77.38, H 8.81 Found: C 77.60, 77.39; H 9.09, 9.21.

An attempt to prepare the amide directly from the ester by shaking the latter with an excess of concentrated aqueous ammonia for three days, was not successful.

When the acid chloride (10.5 g.) of the 4-phenylcyclohexaneacetic acid of melting point 86-88° was used in the reaction described above, 6.7 g. (70%) of the amide was obtained. Three recrystallizations from methanol-water mixtures, gave a melting point of 197-198°. No melting point depression was obtained with the amide prepared from the higher melting acid. Nenitzescu and Gavat, and Cook and Goulden reported melting points of 195.5° and 196-197° respectively for this compound.[126,127]

Hydrolysis of 4-Phenylcyclohexylacetamide (LXX) Derived from Lower Melting Acid (XXXVII) by Means of Nitrous Acid. Since the mildest conditions possible were desirable, Gattermann's method was used.[141] The amide (9.2 g.) was suspended in 500 ml. of 5% sulfuric acid (by volume). The mixture was stirred and heated on the steam bath. An excess of a concentrated solution of sodium nitrite in water was added slowly, as deeply beneath the level of the solution as possible.

The solution was cooled and neutralized. Unreacted material was removed by means of an ether extraction. The aqueous solution was acidified in an ice bath, yielding 1.6 g. (17%) of a crude acid, which upon two recrystallizations melted at 112.5-115°. It is therefore possible to convert the lower melting isomer of 4-phenylcyclohexane-acetic acid to the higher melting substance through its amide by means of this reaction.

β-(4-Phenylcyclohexyl)ethylamine (LXXI). To a solution of 100 ml. of dry ether containing a 100% excess of lithium aluminum hydride, 12 g. of 4-phenylcyclohexylacetamide ~~were~~ was added slowly. The mixture was refluxed for 24 hours, and then decomposed by dropwise addition of water, until the reaction ceased. The ether solution was decanted from the solid and the solid twice washed with small amounts of ether. Then the ether solutions were dried over magnesium sulfate. The ether was replaced with absolute ether, and hydrogen chloride gas bubbled through the solution. This yielded 6.9 g. of the crude amine hydrochloride (54%).

A sample, several times recrystallized from ethanol-ether mixtures melted at 173-177°. Analysis: Calculated for $C_{14}H_{22}NCl$: C 70.12, H 9.25. Found: C 70.02, H 9.33.

N,N-Dimethyl-β-(4-Phenylcyclohexyl)ethylamine (LXXII). β-(4-Phenylcyclohexyl)ethylamine hydrochloride (5.0 g.) was mixed with 3.6 g. of formic acid and 5.2 g. of formalin. The solution was heated on the steam bath overnight. The solvent was evaporated and the crude amine salt was neutralized with ammonia. The amine was extracted with ether, and the ether dried and replaced by absolute ether. Hydrogen chloride gas was passed through this solution. Yield of the crude hydrochloride: 4.3 g. (77%).

After three recrystallizations from alcohol-ether mixtures, the compound melted at 177-180°. Analysis: Calculated for $C_{16}H_{26}NCl$: C 71.75, H 9.79. Found: C 71.68, H 9.88.

N,N-Dimethyl-4-Phenylcyclohexylacetamide (LXXIII). To a mixture of 25 ml. of dimethylamine in 50 ml. of water, vigorously stirred and cooled in an ice bath, 16 g. of 4-phenylcyclohexylacetyl chloride (from acid of melting point 112-114°) was added slowly. After prolonged

stirring in the cold, the mixture was still liquid. The organic material was extracted with ether, and the extracts were dried and distilled. Yield 15 g. (89%), boiling at 155-172°/.2-.25 mm.

A redistilled sample boiled at 170°/.5 mm., $n_D^{23.0}$ 1.5379. Analysis: Calculated for $C_{16}H_{23}ON$: C 78.32, H 9.45. Found: C 78.42, H 9.68.

N,N-Dimethyl-β-(4-Phenylcyclohexyl)ethylamine (LXXII) from N,N-Dimethyl-4-Phenylcyclohexylacetamide (LXXIII). N,N-Dimethyl-4-phenylcyclohexylacetamide (12 g.) was reduced with lithium aluminum hydride as described in the synthesis for β-(4-phenylcyclohexyl) ethylamine. Yield, 10 g. (90%) of N,N-dimethyl-β-(4-phenylcyclohexyl) ethylamine boiling at 102-114°/.14-.32 mm. A redistilled sample had the following refractive index: $n_D^{24.5}$ 1.5146. Analysis: Calculated for $C_{16}H_{25}N$: C 83.05, H 10.89. Found: C 82.78, H 11.12.

N,N-Dimethyl-β-[4(x-Nitrophenyl)cyclohexyl]ethylamine. N,N-Dimethyl-β-(4-phenylcyclohexyl)ethylamine (LXXII) (1.7 g.) was dissolved in concentrated sulfuric acid, which was stirred and maintained at 0° by means of an ice-salt bath. To this solution .75 g. of potassium nitrate was added gradually, the temperature being kept between -10 and 0°. The mixture was stirred for 15 minutes at room temperature, and subsequently decomposed by pouring it on ice. The neutralized solution was extracted with ether. Hydrogen chloride gas was passed through the dried ether extract, but little more than a slight opalescence was produced. After standing, a small amount of an oily material was deposited. Attempts to prepare a solid picrate from this material failed.

N,N-Dimethyl-β-[4(x-Aminophenyl)cyclohexyl]ethylamine. The nitro amine (1.5 g.) was dissolved in 25 ml. of 95% ethanol. While the

solution was gently refluxed, a mixture of 8.8 g. of stannous chloride dihydrate, 11 ml. of 95% ethanol, and 9 ml. of concentrated hydrochloric acid, was added slowly. Refluxing was continued for half an hour. The solvent was evaporated and the remaining solid material was washed out of the flask with water. The solution was neutralized, and the diamine extracted from it with ether. Hydrogen chloride gas was passed through the dried solution. However, even after two recrystallizations from ethanol-ether, the dihydrochloride was so hygroscopic, that it became extremely difficult to handle. Hence work on this material was discontinued.

x,x-Dinitro-4-Phenylcyclohexaneacetic Acid (LXXV). The synthesis of this compound was attempted by two methods.

I. 4-Phenylcyclohexaneacetic acid, (19 g. of the higher melting isomer) was nitrated according to the procedure of Ingold and Piggot.[148] The temperature during the nitration never exceeded 5°. After the addition of potassium nitrate was completed, stirring was continued for another hour. By that time most of the solid material had disappeared, and the solution had become dark brown. The mixture was poured onto ice, and neutralized with sodium hydroxide. The basic solution was extracted twice with ether, and the ether extracts were dried.

The ether extract gave a small amount of a dark brown liquid on concentration. A positive test with 2,4-dinitrophenylhydrazine reagent was obtained. Subsequent reactions pointed to the fact that this compound was the 2,4-dinitrophenylhydrazone of a nitro-9-keto-as-octahydrophenanthrene (LXXIV). The hydrazone, recrystallized once from ethanol-water, and once from toluene-ethanol, melted at 233-236°. Analysis: Calculated for $C_{20}H_{19}N_5O_6$: C 56.47, H 4.50. Found: C 56.97, 57.24; H 4.82, 5.09. The amount of material was insufficient for further purification.

The basic aqueous solution from which the nitro ketone (LXXIV) had been extracted, was acidified in the cold. This precipitated an oil, which was extracted with ether and dried. After removal of the solvent, a high vacuum distillation was attempted; but only a small amount of unreacted starting material was isolated. The bulk of the reaction mixture, presumably containing the nitro acid exploded.

II. 4-Phenylcyclohexaneacetic acid (1.6 g. of the lower melting isomer) was nitrated as described under procedure I, the reaction temperature being kept below 10°. The mixture was decomposed by pouring it onto ice. The organic material was extracted with ether, and the ether layer in turn extracted with base. The ether layer was concentrated; but the amount of neutral component obtained was too small for further study.

The base extract was acidified in the cold, yielding .4 g. (24%) of a crude dinitro acid. Recrystallized twice from methanol-water, the acid had a slightly yellow color which was intensified by light; it melted at 161-164°. Analysis: Calculated for $C_{14}H_{16}N_2O_6$: C 54.54, H 5.23. Found: C 54.81, 55.23; H 5.39, 5.59.

Products Isolated from the Friedel-Crafts Reaction of 4-Phenylcyclohexylacetyl Chloride, Derived from Higher Melting Acid (XXXVII). Two modifications of the Friedel-Crafts reaction were used.

I. Reaction in carbon bisulfide. A dry 500 ml. three neck flask was fitted with a mechanical stirrer, a dropping funnel and a condenser fitted with a drying tube and a connection to the aspirator, for convenient removal of the gases generated during the reaction. Anhydrous aluminum chloride, (12.5 g.) and 100 ml. of carbon bisulfide were placed inside the flask. The solution was stirred and cooled by means of an ice bath. Then 4-phenylcyclohexylacetyl chloride was added slowly to

this mixture over a period of 50 minutes. The reaction was stirred at room temperature for an additional 5½ hours.

The solution was decomposed by pouring it into 100 ml. of concentrated hydrochloric acid, containing crushed ice. The reaction mixture was extracted with ether, and the ether in turn extracted with base to remove acidic constituents. The ether layer was dried and concentrated, but only a small yield was obtained, the majority of the material having polymerized. Distillation of the crude ketonic material gave two products, both boiling at about 120°/.5 mm.

The first fraction was a white solid, which was subsequently shown to be trans-9-keto-as-octahydrophenanthrene (XL). The ketone was obtained from cyclization of 2-phenylcyclohexylacetyl chloride, present in small amounts in the bulk of the 4-phenylcyclohexylacetyl chloride. The ketone (XL) was recrystallized from 20-40° petroleum ether, and then sublimed. It melted at 94-96°. Analysis: Calculated for $C_{14}H_{16}O$: C 83.96, H 8.05. Found: C 83.84, 83.99; H 8.42, 8.42.

A 2,4-dinitrophenylhydrazone of this compound was prepared in the usual fashion. Melting point, after several recrystallization from toluene: 263-265°. Analysis: Calculated for $C_{20}H_{20}O_4N_4$: C 63.15, H 5.30. Found: C 63.15, 63.00; H 5.70, 5.76.

II. Reaction in benzene. A dry 500 ml. three neck flask was fitted as described under I. Anhydrous aluminum chloride (14 g.) and 200 ml. of dry benzene were placed inside the flask, which was cooled by means of an ice bath. 4-Phenylcyclohexylacetyl chloride (25 g.) derived from the higher melting acid was slowly added during a period of one hour. The mixture was stirred an additional three hours at room temperature and then decomposed in the usual way.

The organic material was extracted with ether, and the ether in turn extracted with base. The ether extract was dried and distilled, yielding 4.0 g. of crude material, boiling at 187-192°/1.1 mm. This fraction gave a positive test with 2,4-dinitrophenylhydrazene, but it seemed that more than one ketonic substance was present, as the hydrazone did not have a uniform red color.

After storing the crude material in the refrigerator for four days, it had partially crystallized. The liquid portion was removed, and the solid was twice recrystallized from 20-40° petroleum ether. This material (.6 g.) was refluxed for three hours with .7 g. of hydroxylamine hydrochloride, 1.3 ml. of pyridine, and 5 ml. of absolute ethanol. The mixture was poured into water, from which the organic material was extracted with ether. The ether was dried and evaporated. Six recrystallizations of the residue from methanol water, yielded a substance of melting point 160-162°. Analytical data indicated that this compound probably was the oxime of α-(4-phenylcyclohexyl)acetophenone (LXVIII). Analysis: Calculated for $C_{20}H_{23}ON$: C 81.87, H 7.90. Found: C 81.59, 81.31; H 8.03, 8.05.

The liquid portion of the crude ketone, recrystallized four times from 20-40° petroleum ether had a melting point of 38-40°. Analytical data indicated that this compound was α-(4-phenylcyclohexyl) acetophenone. The preparation of the oxime of this compound was described in the preceding paragraph. Analysis: Calculated for $C_{20}H_{22}O$: C 86.09, H 8.00. Found: C 85.83, 85.88; H 8.07, 8.27.

An oxime prepared from this substance gave no melting point depression with the oxime prepared from the solid portion of the products isolated from the attempted Friedel-Crafts cyclization.

Trans-9-Keto-as-Octahydrophenanthrene (XL). The presence of small amounts of 2-phenylcyclohexaneacetic acid in the crude 4-phenylcyclohexaneacetic acid made the preparation of this ketone (XL) in small amounts feasible. Two methods could be used; the first, the Friedel-Crafts cyclization of the acid chloride, has been described in the previous section. The second method, involved the cyclization of the crude acid mixture with concentrated sulfuric acid. The isolation of the ketone was facilitated by the fact that the 4-phenylcyclohexaneacetic acid was sulfonated and hence became water soluble, under the same conditions which cyclized the 2-phenylcyclohexaneacetic acid.[127] A typical procedure follows:

The crude 4-phenylcyclohexaneacetic acid (9.5 g.) was dissolved in 48 ml. of concentrated sulfuric acid, and heated on the steam bath for 15 minutes. The cooled mixture was poured onto ice, and the mixture was extracted. The ether extract was washed with bicarbonate, and then dried and concentrated. A small amount of the ketone was obtained, the quantity depending on the preparation of the ethyl-4-phenylcyclohexylacetate, from which the acid was derived. When the ester was obtained by procedure I, about 5% of the ketone was the product; procedures II and III yielded roughly 10% and 1% respectively.

The ketone (XL) twice recrystallized, and once sublimed, melted at 95.5-97.5°. This sample gave no melting point depression with an authentic sample kindly supplied by Dr. W. E. Bachmann.

Other melting points reported for this ketone (XL) are 95-96°[121], 94-95°[123], 96°[116], 95.5-96.5°[129].

A 2,4-dinitrophenylhydrazone was prepared in the usual manner, and recrystallized several times from toluene-methanol mixtures. It

melted at 267-269° and gave no melting point depression on mixing with the 2,4-dinitrophenylhydrazone of the ketone isolated from the attempted Friedel-Crafts cyclization of the crude 4-phenylcyclohexylacetyl chloride. Analysis: Calculated for $C_{20}H_{20}O_4N_4$: C 63.15, H 5.30. Found: C 63.33, 63.21; H 5.31, 5.35.

1-Phenylcyclohexanol. A dry two liter three neck flask was fitted with a mechanical stirrer, a dropping funnel and a condenser with drying tube. Magnesium turnings (54 g.) were placed inside the flask and covered with 400 ml. of dry ether. While cooling and stirring were in progress, 345 ml. of bromobenzene in 600 ml. of dry ether ~~were~~ was added at such a rate, that gentle refluxing was obtained. Stirring was continued at room temperature for another hour. Cyclohexanone (98 g.) in 200 ml. of dry ether ~~were~~ was added slowly with cooling. Stirring was continued for a little longer, and then the mixture was decomposed by pouring it into a concentrated solution of ammonium chloride containing crushed ice. The aqueous layer was extracted once with ether, and the ether layers were dried and concentrated. When most of the solvent had distilled, the remainder of the material was poured into a large crystallizing dish, where evaporation was allowed to continue at a slow rate. Yield, 245 g. (72%). The melting point after one recrystallization from 20-40° petroleum ether was 61-63°.

V. Auwers and Treppmann reported a melting point of 61°, Kussarow a melting point of 62-63.5° for this compound.[167,168]

An attempt to isolate the alcohol by distillation resulted in its dehydration. Neither thionyl chloride, nor phosphorus pentachloride were able to convert the alcohol to its analogous chloride.

Grignard Reaction of Phenylmagnesium Bromide with Cyclohexylideneacetone*. A dry two liter three neck flask was equipped with a mechnical stirrer, a dropping funnel and a condenser with a drying tube. Inside the flask, were placed 22 g. of magnesium turnings and 100 ml. of dry ether. An ethereal solution of 141 g. of bromobenzene was added slowly with stirring, the solution being cooled during this addition. Stirring at room temperature was continued for 45 minutes.

To this mixture which was again cooled, was added slowly 115 g. of cyclohexylideneacetone in 100 ml. of dry ether. The mixture was stirred for another 45 minutes at room temperature, and decomposed with a saturated solution of ammonium chloride. The aqueous layer was extracted twice with ether, and the combined ether layers were washed and dried.

Distillation yielded three fractions; the first (11 g.) had a boiling point of 83-87°/8 mm., n_D^{25} 1.5328. The second fraction (9.4 g.) boiled at 87-122°/1.4 mm. and had a refractive index of n_D^{25} 1.5535. The main fraction (99 g.) had a boiling point of 126-132°/1.4 mm.; its refractive index was n_D^{25} 1.5477.

All this material was oxidized by permanganate, thereby showing that no 1,4 addition product was present.

Oxime of d,l-Camphor (LXXVIII). d,l Camphor (31 g.) was dissolved in a mixture of 80 ml. of pyridine and 175 ml. of absolute alcohol. Hydroxylamine hydrochloride (42 g.) was added and the mixture heated under reflux overnight. The mixture was diluted with water until cloudy and finally cooled. The precipitated oxime was recrystallized

---

*This substance was kindly prepared by Dr. Louis H. Schwartzman according to the procedure of Jupp, Kon and Lockton.[149]

from ethanol. Yield, 24 g. (72%), melting at 113-115°.

Wallach and Hartmann, and Bredt and Rosenberg reported melting points of 118° and 119° for this substance.[152,153]

Bornylamine Hydrochloride (LXXIX). A solution of 24 g. of camphor oxime in 100 ml. of absolute ethanol was saturated with ammonia, the mixture being chilled during this process. Raney Nickel catalyst was added, and the mixture was hydrogenated at 75°. After the theoretical pressure drop of 600 lbs. had been obtained, the catalyst was removed by filtration, and the solvent was evaporated. The residue was dissolved in ether, and the ether layer was extracted with dilute hydrochloric acid. The aqueous layer was neutralized, and the free amine was extracted with ether. Hydrogen chloride gas, passed through the solution precipitated 13 g. (46%) of the hydrochloride, which was purified by recrystallization from ethanol-ether mixtures, followed by sublimation.

N,N-Dimethylbornylamine (LXXVII). A solution of 4.1 g. of bornylamine hydrochloride in 7 ml. of formic acid and 10 ml. of formalin, was refluxed overnight on the steam bath. The mixture was neutralized, and the free amine extracted with ether. Evaporation of the dried solution yielded 3.3 g. of the crude amine (85%).

The crude amine was redistilled three times and the middle portion of the third distillation submitted for analysis. The observed boiling point was 80-108°/10 mm., the analytical sample boiling at about 90°/10 mm. This sample had a refractive index of $n_D^{25.0}$ 1.4747. Analysis: Calculated for $C_{12}H_{23}N$: C 79.49, H 12.78. Found: C 79.67, H 12.24.

The boiling point reported in the literature for this amine is 210-212° at atmospheric pressure.[169,170,171]

BIBLIOGRAPHY

1. Paul, Bull. soc. chim., 53, 1489 (1933).
2. Paul, Bull. soc. chim., 6, 1166 (1939).
3. Blanchard and Paul, Compt. rend., 200, 1414 (1935).
4. Mozingo and Adkins, J. Am. Chem. Soc., 60, 669 (1938).
5. Wilson, J. Am. Chem. Soc., 70, 1311 (1948).
6. Bremner, Jones and Taylor, British Patent #565,175, Oct. 31, 1944; C.A., 40, 5072 (1946)
7. Jurjew, J. Gen. Chem. (U.S.S.R.), 9, 590 (1939).
8. Paul, Bull. soc. chim., 2, 745 (1935).
9. Woods and Sanders, J. Am. Chem. Soc., 68, 2111 (1946).
10. Paul, Bull. soc. chim., 1, 971 (1945).
11. Schniepps and Geller, J. Am. Chem. Soc., 68, 1646 (1946).
12. Paul, Bull. soc. chim., 14, 158 (1947).
13. Paul, Bull soc. chim., 1, 973 (1934).
14. Woods and Kramer, J. Am. Chem. Soc., 69, 2246 (1947).
15. Paul, Bull. soc. chim., 1, 1397 (1934).
16. Woods and Sanders, J. Am. Chem. Soc., 68, 2483 (1946).
17. Branden, Derfer and Boord, J. Am. Chem. Soc., 72, 2120 (1950).
18. Paul and Tchelitcheff, Compt. rend., 224, 1722 (1947).
19. Paul, Compt. rend., 218, 122 (1944).
20. Jacobson, J. Am. Chem. Soc., 72, 1489 (1950).
21. Yur'ev, Dubrovina and Tregabow, J. Gen. Chem. (U.S.S.R.), 16, 843 (1946).
22. Wilson, J. Am. Chem. Soc., 69, 3004 (1947).
23. Woods and Schwartzman, J. Am. Chem. Soc., 70, 3394 (1948); Schwartzman, Ph.D. thesis, University of Maryland, 1949.

24. Heilbron, Jones, McCombie and Weedon, J. Chem. Soc., 1945, 84.

25. Griner, Ann. chim. phys., 26, 368 (1892).

26. Van Romburgh and Van Dorssen, Verslag Akad. Wetenschappen, Amsterdam, 8, 565 (1905).

27. Farmer Laroia, Switz and Thorpe, J. Chem. Soc., 1927, 2937.

28. Farmer and Warren, J. Chem. Soc., 1929, 897.

29. Klebansky, Popov and Tsukeiman, J. Gen. Chem. (U.S.S.R.), 16, 2083 (1946); C.A., 42, 857 (1948).

30. Butz, Butz and Gaddis, J. Org. Chem., 5, 171 (1940).

31. Butz, J. Am. Chem. Soc., 64, 1978 (1942).

32. Kium Houo, Ann. chim., 13, 175 (1940); C. A., 34, 4379 (1940).

33. Kium Houo, Compt. rend., 208, 40 (1939).

34. Kharasch and Sternfeld, J. Am. Chem. Soc., 61, 2318 (1938).

35. Woods and Schwartzman, J. Am. Chem. Soc., 71, 1396 (1949); Schwartzman, Ph. D. thesis, University of Maryland, 1949.

36. Willstatter and Waser, Ber., 44, 3423 (1911).

37. Willstatter and Heildelberger, Ber., 46, 517 (1913).

38. Reppe, Schlichting, Klager and Tolpel, Ann., 560, 1 (1948).

39. Seksena and Narain, Current Sci. (India), 17, 50 (1948).

40. Pink and Ubbelohde, Nature, 160, 502 (1947).

41. Pink and Ubbelohde, Trans. Faraday Soc., 44, 708 (1948).

42. Kaufmann, Fankuchen and Mark, Nature, 161, 165 (1948).

43. Cope and Overberger, J. Am. Chem. Soc., 70, 1433 (1948).

44. Cope and Bailey, J. Am. Chem. Soc., 70, 2305 (1948).

45. Reppe, Schlichting and Meister, Ann., 560, 93 (1948).

46. Woods and Temin, J. Am. Chem. Soc., 72, 139 (1950).

47. Dobner, Ber., 35, 1137 (1902).

48. Muskat, Becker and Lowenstein, J. Am. Chem. Soc., 52, 329 (1930).

49. Kohler and Butler, J. Am. Chem. Soc., 48, 1041 (1926).

50. Farmer and Healy, J. Chem. Soc., 1927, 1062.

51. Nottbohm, Ann., 412, 73 (1917).

52. Burton and Ingold, J. Chem. Soc., 1929, 2028.

53. Coffman, J. Am. Chem. Soc., 57, 1982 (1935).

54. Carothers and Berchet, U.S. Patent #2,073,363, March 9, 1937; C. A., 31, 3503 (1937).

55. Geyer, Bradford, Ballard and Seaver, U.S. Patent #2,515,595, July 18, 1950.

56. Fischer and Raske, Ber., 38, 3608 (1905).

57. Fischer and Schlotterbeck, Ber., 23, 2376 (1890).

58. Dobner, Ber., 35, 2129 (1902).

59. Kuhn and Deutsch, Ber., 65B, 43 (1932).

60. V. Auwers, J. prakt. Chem., 105, 374 (1922).

61. Gudgeon and Hill, U.S. Patent #2,395,812, March 5, 1946; C. A., 40, 3648 (1946).

62. Gudgeon and Hill, British Patent #570,326, July 4, 1945; C. A., 40, 5296 (1946).

63. Cram, J. Am. Chem. Soc., 70, 3467 (1948).

64. Jaworsky, J. Russ. Phys. Chem. Soc., 35, 274 (1903).

65. Hofmann, Ann., 110, 132 (1859).

66. Dobner, Ber., 27, 351 (1894).

67. Smedley and Lubrzynska, Biochem. J., 7, 370 (1913).

68. Nottbohm, Ann., 412, 77 (1917).

69. Baumgarten and Glatzel, Ber., 59, 2663 (1926).

70. Smyth and Carpenter, J. Ind. Hyg. Toxicol., 30, 63 (1948).

71. McGowan, Brian and Hemmingway, Ann. Appl. Biol., 35, 25 (1948).

72. Rheinboldt, Pieper and Zervas, Ann., 451, 226 (1927).

73. Kuhn, Kohler and Kohler, Z. physiol. Chem., 247, 197 (1937).

74. Hamada and Huzita, J. Agr. Soc. Jap., 15, 503 (1939); C. A., 33, 8572 (1939).

75. Hamada, J. Agr. Soc. Jap., 16, 181 (1940); C. A., 34, 5824 (1940).

76. Nystrom and Brown, J. Am. Chem. Soc., 67, 2548 (1947).

77. Feist, Ber., 37, 3316 (1904).

78. Wickers, Daly and Lack, J. Org. Chem., 12, 713 (1947).

79. Diels and Alder, Ann., 470, 92 (1929).

80. Dobner and Wolff Ber., 34, 2221 (1901).

81. Posner and Rohde, Ber., 43, 2670 (1910).

82. Vorlander, Weissheimer and Sponnagel, Ann., 345, 228 (1906).

83. V. Auwers and Eisenlohr, J. prakt, Chem., 84, 92 (1911).

84. Korolev and Mur, C. A., 42, 6776 (1948).

85. Drinkberg and Blagonravova, C. A., 35, 3966 (1941).

86. V. Auwers and Heyna, Ann., 434, 157 (1923).

87. Reichstein ann Trivelli, Helv. Chim. Acta, 15, 254 (1932).

88. Burton and Ingold, J. Chem. Soc., 1929, 2029.

89. Kuhn and Grundmann, Ber., 70B, 1894 (1937).

90. Rupe and Lotz, Ber., 36, 15 (1903).

91. Rupe and Lotz, Ann., 369, 344 (1909).

92. Dobner and Weissenhorn, Ber., 35, 1143 (1902).

93. Jaworsky and Reformatsky, Ber., 35, 3689 (1902).

94. Jaworsky, J. Russ. Phys. Chem. Soc., 35, 283 (1903).

95. Bansal and Pandya, J. Ind. Chem. Soc., 24, 443 (1947); C. A., 42, 8178 (1948).

96. English and Delafield, J. Am. Chem. Soc., 69, 2123 (1947).

97. Heilbron, Jones and Sondheimer, J. Chem. Soc., 1947, 1586.

98. Jones and McCombie, British Patent #571,777, Sept. 7, 1945; C. A., 41, 4507 (1947).

99. Reichstein, Ammann and Trivelli, Helv. Chim. Acta, 15, 261 (1932).

100. Kuhn and Hoffer, Ber., 63, 2164 (1930).

101. Kuhn and Hoffer, Ber., 64, 1977 (1931).

102. Fischer and Wiedemann, Ann., 513, 250 (1934).

103. Fischer and Wiedemann, Ann., 522, 1 (1936).

104. Nazarov and Fisher, C. A., 40, 4657 (1946).

105. Nazarov and Fisher, C. A., 43, 112 (1949).

106. Prevost, Compt. rend., 184, 1562 (1927).

107. Prevost, Ann. chim., 10, 431 (1928).

108. Woods and Sanders, J. Am. Chem. Soc., 69, 2926 (1947).

109. Nazarov and Fisher, C. A., 43, 2576 (1949).

110. Zal'kind and Kulikov, J. Gen. Chem. (U. S. S. R.), 15, 643 (1945); C. A., 40, 6061 (1946).

111. Kipping and Perkin, J. Chem. Soc., 1890, 304.

112. Gutsche and Johnson, J. Am. Chem. Soc., 68, 2239 (1946).

113. Ranedo and Leon, Chem. Zentr., 96, 2557 (1925).

114. Fujise, Ber., 71B, 2461 (1938).

115. Cook and Hewett, J. Chem. Soc., 1936, 62.

116. Blumenfeld, Ber., 74B, 524 (1941).

117. Gutsche, J. Am. Chem. Soc., 70, 4150 (1948).

118. Rossow, Ann., 282, 147 (1894).

119. Ranedo and Leon, Chem. Zentr., 95, 768 (1924).

120. Johnson and Offenhauser, J. Am. Chem. Soc., 67, 1045 (1945).

121. Cook, Hewett and Lawrence, J. Chem. Soc., 1936, 71.

122. Chatterjee, J. Ind. Chem. Soc., 13, 593 (1936); C. A., 31, 1791 (1937).

123. Linstead, Wheatstone and Levine, J. Am. Chem. Soc., 64, 2014 (1942).

124. Bachmann and Fornefeld, J. Am. Chem. Soc., 72, 5529 (1950).

125. Alexander and Cope, J. Am. Chem. Soc., 66, 886 (1944).

126. Nenitzescu and Gavat, Ber., 70, 1883 (1937).

127. Cook and Goulden, J. Chem. Soc., 1937, 1559.

128. Boekelheide and Schilling, J. Am. Chem. Soc., 72, 712 (1950).

129. Lund, Ber., 70, 1520 (1937).

130. Paul and Tchelitcheff, Compt. rend., 224,1118 (1947).

131. Grignard, Ann. chim. phys., 24, 433 (1901).

132. Kohler, Amer. Chem. J., 31, 642 (1904).

133. Fuson and McKusick, J. Am. Chem. Soc., 65, 60 (1943).

134. Stephens, J. Am. Chem. Soc., 57,1112 (1935).

135. Gilman and McGlumphy, Bull. soc. chim., 43, 1322 (1928).

136. Bachmann, "Organic Syntheses", coll. vol. II, p. 323.

137. Bried and Hennion, J. Am. Chem. Soc., 60, 1717 (1938).

138. Wheland, "Advanced Organic Chemistry", 2nd ed., 1949, pp. 280-281.

139. Bachmann and Fornefeld, J. Am. Chem. Soc., 73, 51 (1951).

140. Natelson and Gottfried, J. Am. Chem. Soc., 61, 970 (1939).

141. Gattermann, Ber., 30, 1279 (1897).

142. Neniztescu and Gavat, Ann., 519, 260 (1935).

143. Nenitzescu and Przemetzki, Ber., 69, 2706 (1936).

144. Nenitzescu and Corceanu, Ber., 70, 346 (1937).

145. Neniztescu, Gavat and Corcora, Ber., 73B, 233 (1940).

146. Sisido and Nozaki, J. Am. Chem. Soc., 70, 1288 (1948).

147. Uffer and Schletter, Helv. Chim. Acta, 31, 1397 (1948).

148. Ingold and Piggot, J. Chem. Soc., 1923, 1469.

149. Jupp, Kon and Lockton, J. Chem. Soc., 1928, 1638.

150. Semon and Damerell, J. Am. Chem. Soc., 46, 1290 (1924).

151. Houben and Pfannkuch, Ber., 60, 594 (1927).

152. Wallach and Hartmann, Ann., 259, 325 (1890).

153. Bredt and Rosenberg, Ann., 289, 6 (1896).

154. Scheuble and Lobl, Monatsh., 25, 1096 (1904).

155. Bickel and French, J. Am. Chem. Soc., 48, 747 (1926).

156. Malone and Reid, J. Am. Chem. Soc., 51, 3424 (1929).

157. Lieben and Rossi, Ann., 159, 70 (1871).

158. Bruylants and Ernould, C. A., 26, 3232 (1932).

159. Blaise, Compt. rend., 138, 689 (1904).

160. Henze and Speer, J. Am. Chem. Soc., 64, 522 (1942).

161. Pickard and Kenyon, J. Chem. Soc., 1913, 1945.

162. Wagner, J. Russ. Phys. Chem. Soc., 16, 1329 (1886).

163. Bardan, Bull. soc. chim., 1, 371 (1934).

164. Lieben and Rossi, Ann., 159, 74 (1871).

165. Cartenmeister, Ann., 233, 275 (1886).

166. Moses and Reid, J. Am. Chem. Soc., 54, 2101 (1931).

167. V. Auwers and Treppmann, Ber., 48, 1216 (1915).

168. Kussarow, Chem. Zentr., 78, 1744 (1907).

169. Forster and Attwell, J. Chem. Soc., 1904, 1088.

170. Forster, J. Chem. Soc., 1899, 945.

171. Ruzicka, Helv. Chim. Acta, 3, 750 (1920).

VITA

Name: Henry Frederick Lederle

Permanent Address: 646 Broadway, Paterson, New Jersey.

Date of Birth: December 31, 1921.

Place of Birth: Freiburg, Germany

Secondary Education: Seton Hall High School, South Orange, N. J.

Universities Attended:	Dates	Degree	Date
University of Freiburg, Germany	1940-1941		
University of Heidelberg, Germany	1941-1942		
St. Bonaventure College	1942-1943	B.S.	1943
Columbia University	1946-1947	A.M.	1947
University of Maryland	1947-1951	Ph. D.	1951

Positions Held:

U. S. Army, 1943-1946

Graduate Assistant, University of Maryland, 1948-1950

Research Fellow, University of Maryland, 1950-1951.