THE SYNTHESIS AND REACTIONS OF HYDROXYALKYL SUBSTITUTED CYCLOOCTATETRAENES

By

Donald Frederick Rugen

B.S. Northeastern University, 1947

M.S. Tufts College, 1949

Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy
at the
Massachusetts Institute of Technology
1952

Signature of Author.. Signature redacted ....
Department of Chemistry, June 6, 1952

Signature of Professor
in Charge of Research.... Signature redacted ....

Signature of Chairman of
Departmental Committee
on Graduate Students.... Signature redacted ....

Chem
Thesis
1952

This doctoral thesis
has been examined by a committee
of the Department of Chemistry
as follows:

John C. Sheehan, Chairman........ Signature redacted

Arthur C. Cope, Research Supervisor........ Signature redacted

Richard C. Lord........ Signature redacted

Avery A. Ashdown........ Signature redacted

Lockhart B. Rogers........ Signature redacted

ACKNOWLEDGMENT

The author wishes to express his appreciation of the opportunity and priviledge of working with Dr. Cope and for the advice and encouragement which he patiently and generously gave.

TABLE OF CONTENTS

Page

Part A. The copolymerization of acetylene with substituted acetylenes.

Experimental

Part B. Proof of structure of phenylcyclooctadiene

Experimental

PART A

THE COPOLYMERIZATION OF ACETYLENE WITH SUBSTITUTED ACETYLENES

SUMMARY

Cyclooctatetraenylmethyl alcohol, β-cyclooctatetraenylethyl alcohol, and β-cyclooctatetraenylethyldimethylamine have been prepared by allowing the appropriately substituted acetylene to copolymerize with acetylene in a ratio of one to three. Cyclooctatetraenylmethyl alcohol and β-cyclooctatetraenylethyl alcohol were transformed into a variety of products possessing amino, dimethylamino, cyano, carboxyl, and halogen groups. Several compounds containing the cyclooctatetraene nucleus that may possess sympathomimetic activity have been prepared as well as others which will be of interest to test for plant hormone activity. An attempt to separate stereoisomers of β-cyclooctatetraenylpropionic acid by resolution of its quinine salt was not successful.

INTRODUCTION

The preparation of cyclooctatetraene from acetylene was first investigated by Reppe and coworkers in Germany.[1] By treating acetylene with various catalysts under moderate pressure it was possible to prepare cyclooctatetraene in reasonable yield. Various other organic compounds were also isolated as by-products depending on the conditions and catalyst employed. Reppe's discovery of a relatively easy synthesis of cyclooctatetraene has led to renewed interest in the general field of eight-membered cyclic compounds. In this country, A. C. Cope and coworkers became interested in finding convenient methods of preparing substituted cyclooctatetraenes and several synthetic procedures were developed by which eight-membered rings could be formed. These synthetic methods possessed the inherent disadvantage of being quite lengthy and expensive in time and materials, and consequently it was desirable to find an easier method of synthesizing substituted cyclooctatetraenes so that the fundamental chemistry of these compounds could be studied.

Although Reppe mentioned that phenylacetylene and vinylacetylene failed to polymerize he apparently did not consider the possibility of copolymerizing a sub-

---

1. W. Reppe, O. Schlichting, K. Klager, T. Toepel, Ann., 560, 1(1948)

stituted acetylene with acetylene to obtain substituted cyclooctatetraenes. H. C. Campbell[2] was able to prepare several substituted cyclooctatetraenes by such a copolymerization procedure, but the products were of limited utility since the substituent groups were all hydrocarbon radicals such as phenyl, methyl, ethyl, n-propyl, and n-butyl.

In order to determine the generality of the copolymerization reaction and at the same time prepare useful substituted cyclooctatetraenes, a series of copolymerizations of acetylene with acetylenic alcohols has been undertaken. In addition to the preparation and proofs of structure of two hydroxyalkyl substituted cyclooctatetraenes, the preparation of a number of substituted cyclooctatetraenes having amino, carboxyl, cyano, and halogen groups derived from the original hydroxyalkyl substituted cyclooctatetraene has been accomplished.

The selection of a substituted acetylene for copolymerization with acetylene was influenced primarily by (a) the probable utility of the substituted cyclooctatetraene, (b) the availability of the substituted acetylene, and (c) the probable effect, or lack thereof, on the catalyst. From these considerations 2-butyn-1-ol (propargyl alcohol) and 3-butyn-1-ol were considered as promising compounds for copolymerization with acetylene. The resulting

[2] H.C.Campbell, Ph.D. Thesis, M.I.T., 1951

hydroxyalkylcyclooctatetraenes would be especially useful for preparing substituted cyclooctatetraenes having other functional groups, such as amines, which might be of interest as possible sympathomimetic agents by analogy with the phenylethylamines and related compounds. The carboxylic acids available from the original cyclooctatetraenyl alcohols might possibly have plant hormone activity by analogy with naphthaleneacetic acid and related compounds. Further, the substituted cyclooctatetraenes having basic or acidic functions would be useful in determining whether the resolution of substituted cyclooctatetraenes is possible.

DISCUSSION

Campbell was able to prepare a number of substituted cyclooctatetraenes by allowing alkyl or aryl substituted acetylenes to copolymerize with acetylene. The alkyl and aryl substituted cyclooctatetraenes were prepared in the same general manner previously described for the preparation of cyclooctatetraene itself.[3] The importance of Campbell's work lies in the fact that it established a feasible experimental procedure by which substituted cyclooctatetraenes could be obtained.

In order to extend the copolymerization reaction in a logical manner, propargyl alcohol was selected as a substituted acetylene for the reasons outlined in the introduction. Propargyl alcohol was mixed with nickel acetylacetonate catalyst, calcium carbide and tetrahydrofuran in a 1-l. stirred autoclave. The usual copolymerization procedure was followed, and resulted in an uptake of acetylene which varied in different runs from 500 to 1200 p.s.i. After separation and purification of the products of the copolymerization, it was found that, in addition to 30-69 g. of cyclooctatetraene, cyclooctatetraenylmethyl alcohol (I) was obtained as a yellow liquid, b.p. 65-75°(0.5 mm.). Purification of I was accomplished

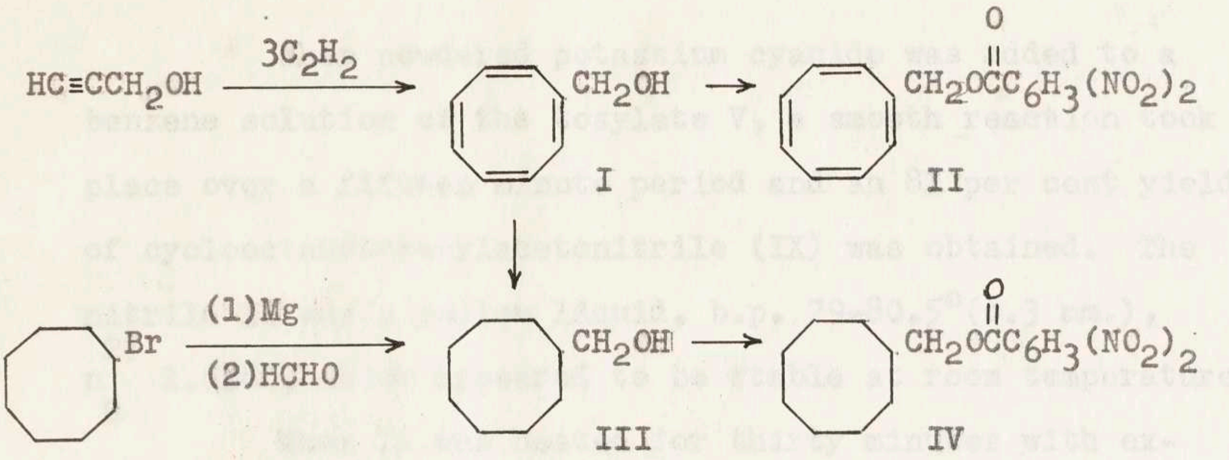
---

[3] A.C. Cope and L.L. Estes, Jr., J.Amer.Chem.Soc., 72, 1129(1950).

by chromatography using silica gel as the absorbent. When a pentane solution of I was passed through a column of silica gel, the bulk of the yellow liquid was absorbed on the silica gel while less polar impurities passed through the column with the solvent. When no further material could be brought through the column with pentane, a 5 per cent ether-pentane solution was used to displace I from the absorbent. In this manner it was possible to obtain pure I which analyzed correctly for cyclooctatetraenylmethyl alcohol, b.p. 65-66°(0.12 mm.), n_D^{25} 1.5612.

Preliminary evidence for the structure of I consisted of formation of a solid 3,5-dinitrobenzoate (II), m.p. 69-69.8°, and hydrogenation of I over platinum catalyst, resulting in an uptake equivalent to 98 per cent of four moles of hydrogen and forming cyclooctylmethyl alcohol (III) which also formed a solid 3,5-dinitrobenzoate (IV), m.p. 68.6-69.7°. Although the two esters (II and IV) had similar melting points, their mixed melting point was depressed.

Final proof for the structure of I was obtained by synthesizing cyclooctylmethyl alcohol from cyclooctylmagnesium bromide and formaldehyde. A 3,5-dinitrobenzoate (m.p. 68.5-69.6°) of the alcohol prepared by the Grignard synthesis did not depress the melting point of IV prepared by the sequence $I \rightarrow III \rightarrow IV$.



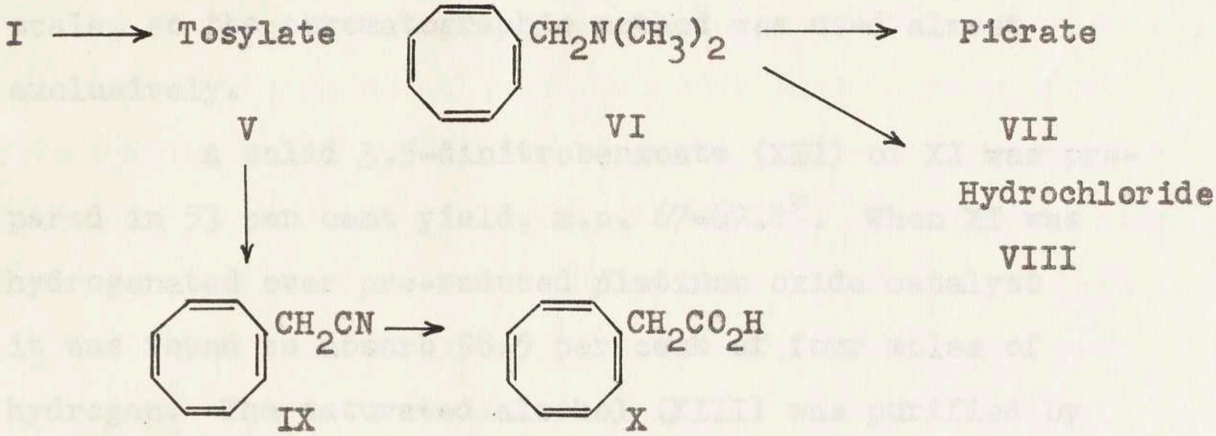
The tosylate V of I was prepared in good yield by allowing one mole of p-toluenesulfonyl chloride to react with one mole of I in the presence of pyridine. Purification of V by distillation was not possible since it decomposed upon heating and repeated attempts to induce V to crystallize from a variety of solvents were unsuccessful. Therefore, V was used without further purification in subsequent synthetic steps.

Cyclooctatetraenylmethyldimethylamine (VI) was prepared in 36 per cent yield by passing dimethylamine through a solution of V in benzene. Although VI was found to decompose very rapidly after distillation, a pure sample, b.p. 51-52° (0.2 mm.), n_D^{25} 1.5220, was obtained by distillation and analyzed immediately. The picrate (VII), m.p. 143.5-144.2°, and hydrochloride (VIII), m.p. 208.7-209.3°, were prepared in high yield. Both of these salts were stable at room temperature.

When powdered potassium cyanide was added to a benzene solution of the tosylate V, a smooth reaction took place over a fifteen minute period and an 81 per cent yield of cyclooctatetraenylacetonitrile (IX) was obtained. The nitrile IX was a yellow liquid, b.p. 79-80.5°(0.3 mm.), n_D^{25} 1.6260, which appeared to be stable at room temperature.

When IX was heated for thirty minutes with excess 10 per cent sodium hydroxide solution, the nitrile was hydrolyzed to cyclooctatetraenylacetic acid (X) in 68 per cent yield. Recrystallization of X from pentane afforded a white solid which rapidly turned to a gum upon exposure to air. It was not possible to obtain a pure sample of X for analysis.

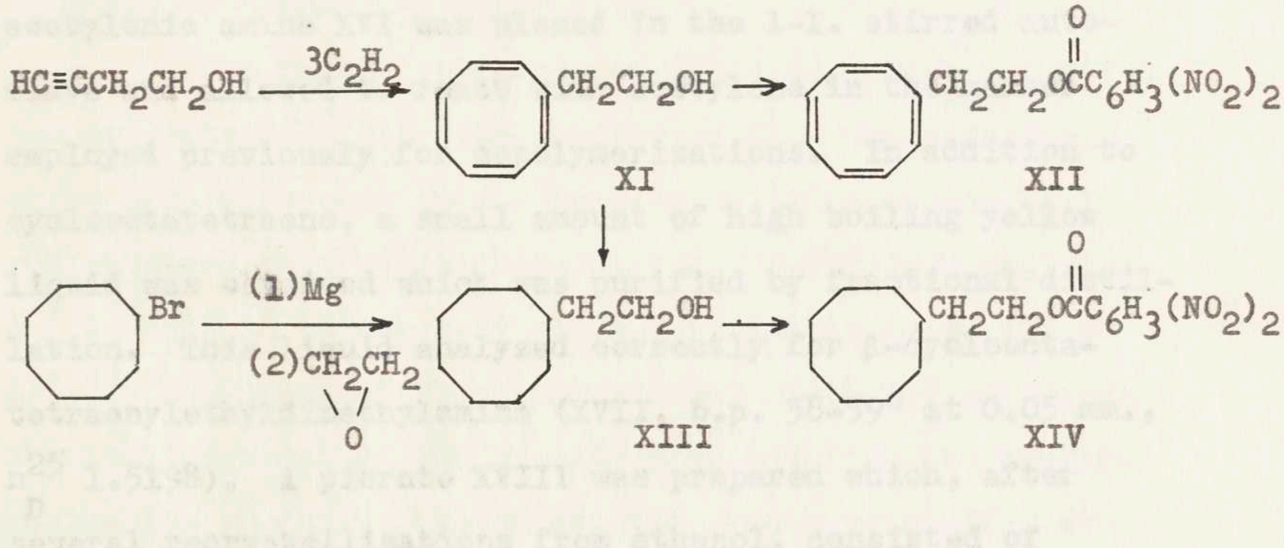
The structure of the tosylate V probably can be assumed to be correct since only the O-H bond of the alcohol I is broken in its formation. However, in the displacement reactions of V leading to the dimethylamine compound VI and the nitrile IX, allylic rearrangements could occur, leading to the formation of allylic isomers of VI and IX. A further possibility, particularly for the nitrile IX and the acid X derived from it, is migration of a double bond from the ring into conjugation with the nitrile or carboxyl group. These possibilities are being investigated at present.



The next higher homolog of I, β-cyclooctatetraenylethyl alcohol (XI) was prepared by copolymerizing 3-butyn-1-ol with acetylene in the manner previously described for I. Purification of XI was accomplished by passing a pentane solution of the impure alcohol through a column of silica gel. The non-polar impurities which came through with the pentane were discarded and then a 5 per cent ether-pentane solution was passed through the column to displace XI from the silica gel. In this manner a pure sample of XI, b.p. 77-78°(0.2 mm.), n_D^{25} 1.5480, was obtained which analyzed correctly.

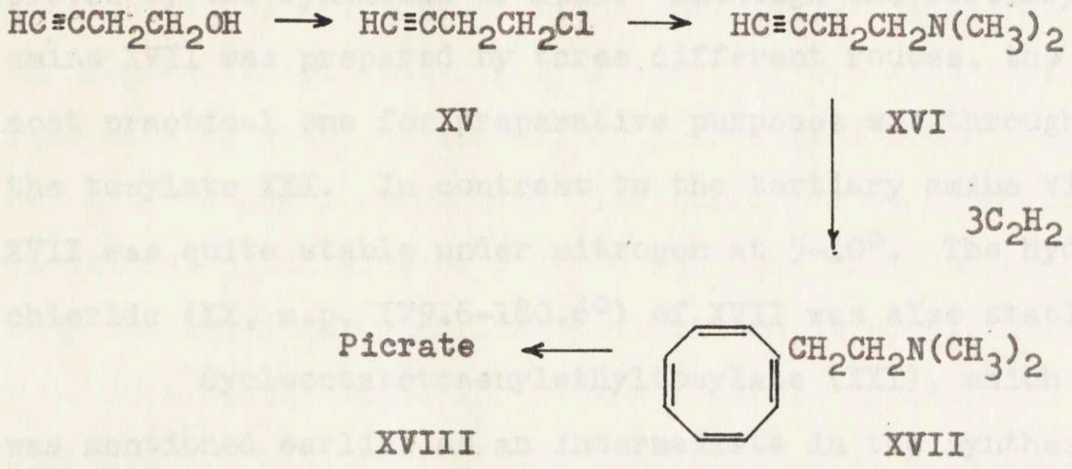
Purification of XI was also possible by extraction with concentrated phosphoric acid or 20 per cent aqueous silver nitrate solution. Regeneration of XI from the water-soluble complexes formed with phosphoric acid and silver nitrate followed by distillation afforded pure samples of XI, but both of these methods were impractical on a large scale, so the chromatographic method was used almost exclusively.

A solid 3,5-dinitrobenzoate (XII) of XI was prepared in 53 per cent yield, m.p. 67-67.8°. When XI was hydrogenated over pre-reduced platinum oxide catalyst it was found to absorb 98.5 per cent of four moles of hydrogen. The saturated alcohol (XIII) was purified by distillation, b.p. 78-79°(0.2 mm.), n_D^{25} 1.4825, and a solid 3,5-dinitrobenzoate (XIV), m.p. 46.5-47.8°, was prepared from the reduction product in 54 per cent yield. Final proof for the structure of XIII was obtained when β-cyclooctylethyl alcohol (XIII) was synthesized from cyclooctylmagnesium bromide and ethylene oxide. A solid 3,5-dinitrobenzoate of this product did not depress the melting point of the 3,5-dinitrobenzoate prepared from the alcohol XIII obtained by reduction of XI.



Since it had now been demonstrated that acetylenic alcohols were capable of copolymerizing with acetylene to form hydroxyalkyl substituted cyclooctatetraenes, it was desirable to determine if other substituted acetylenes, such as acetylenic amines, were capable of undergoing a similar type of reaction. 1-Dimethylamino-3-butyne (XVI) was selected as an acetylenic amine since the probable product, β-cyclooctatetraenylethyldimethylamine (XVII), should be available from XI in two steps so that a structure proof of XVII would be possible.

Preparation of a quantity of XVI suitable for a copolymerization reaction was accomplished by first converting 3-butyn-1-ol to 1-chloro-3-butyne (XV) in 58 per cent yield by treatment with thionyl chloride. When XV was stirred with an aqueous solution (25 per cent) of dimethylamine, a 69 per cent yield of XVI resulted. The acetylenic amine XVI was placed in the 1-l. stirred autoclave and allowed to react with acetylene in the manner employed previously for copolymerizations. In addition to cyclooctatetraene, a small amount of high boiling yellow liquid was obtained which was purified by fractional distillation. This liquid analyzed correctly for β-cyclooctatetraenylethyldimethylamine (XVII, b.p. 58-59° at 0.05 mm., n^{25}_{D} 1.5198). A picrate XVIII was prepared which, after several recrystallizations from ethanol, consisted of yellow needles, m.p. 117.8-118.5°.



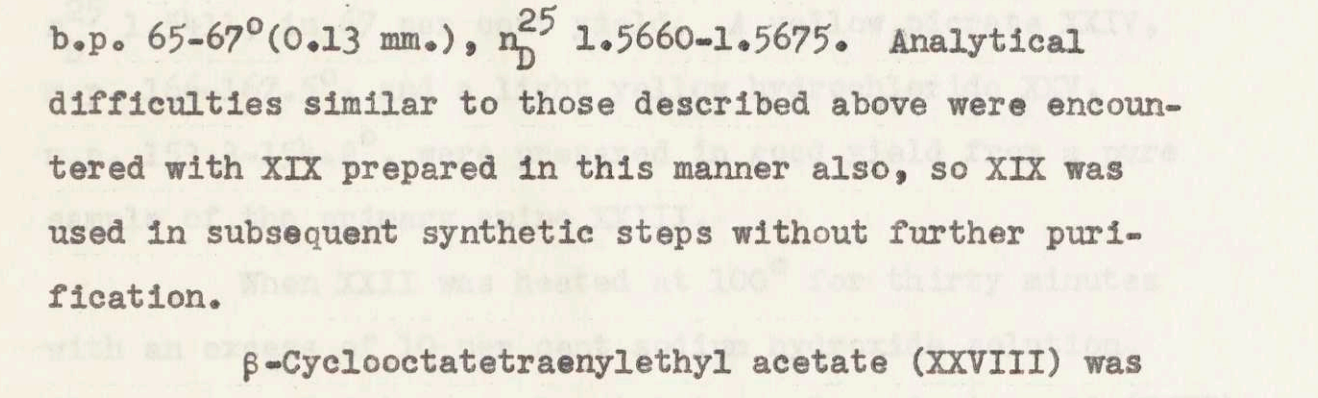
Alternate syntheses of XVII were accomplished by two different routes starting from XI. The first method involved the conversion of XI into β-cyclooctatetraenylethyl bromide (XIX, described below) followed by the displacement of the bromine atom in XIX by dimethylamine to form XVII. The picrate (m.p. 117.9-118.5°) prepared from this product did not depress the melting point of the picrate prepared from the copolymerization product.

The second synthesis of XVII was achieved through the tosylate XXI (described below) of XI. When dimethylamine was introduced into a benzene solution of XXI, XVII was obtained as a yellow liquid, b.p. 58-59° (0.08 mm.), n_D^{25} 1.6198, in 45 per cent yield. A picrate, m.p. 118.0-118.5°, was prepared from this product which did not depress the melting point of the picrate prepared from the copolymerization product. Therefore, the structure of XVII was established since the structure of XI had previously been proved by the synthesis of XIII. Although the tertiary amine XVII was prepared by three different routes, the most practical one for preparative purposes was through the tosylate XXI. In contrast to the tertiary amine VI, XVII was quite stable under nitrogen at 5-10°. The hydrochloride (XX, m.p. 179.6-180.6°) of XVII was also stable.

Cyclooctatetraenylethyltosylate (XXI), which was mentioned earlier as an intermediate in the synthesis of XVII, was prepared by adding XI to p-toluenesulfonyl chloride in pyridine. Pyridine hydrochloride precipitated as a white crystalline solid in 80-90 per cent of the theoretical amount. The liquid residue (XXI) was never obtained pure although many attempts were made to purify it by various means. Nevertheless, the tosylate XXI was used without further purification with good results in subsequent synthetic steps.

β-Cyclooctatetraenylethylbromide (XIX) was prepared in 40 per cent yield from the alcohol XI by treatment with phosphorus tribromide. Fractional distillation of crude XIX afforded a yellow liquid, n_D^{25} 1.5601 to 1.5639, which did not analyze correctly even though its infra-red spectrum showed the sample to be free of unreacted XI. Repurification of the bromide XIX by chromatography on silica gel followed by distillation changed the refractive index of a sample slightly but did not improve the analysis. It seems likely that partial dehydrobromination occurred upon distillation, thereby contaminating the sample with vinylcyclooctatetraene. The bromide XIX was also available through the tosylate XXI in 76 per cent yield (based on XI). When XXI was heated with anhydrous calcium bromide in dry methylcellosolve, a 70-80 per cent yield of calcium tosylate was formed and XIX was obtained as a yellow liquid, b.p. 65-67°(0.13 mm.), n_D^{25} 1.5660-1.5675. Analytical difficulties similar to those described above were encountered with XIX prepared in this manner also, so XIX was used in subsequent synthetic steps without further purification.

β-Cyclooctatetraenylethyl acetate (XXVIII) was prepared in 91 per cent yield from XI and acetic anhydride. The acetate XXVIII was a pleasant-smelling yellow liquid, b.p. 81-82°(0.15 mm), n_D^{25} 1.5130.

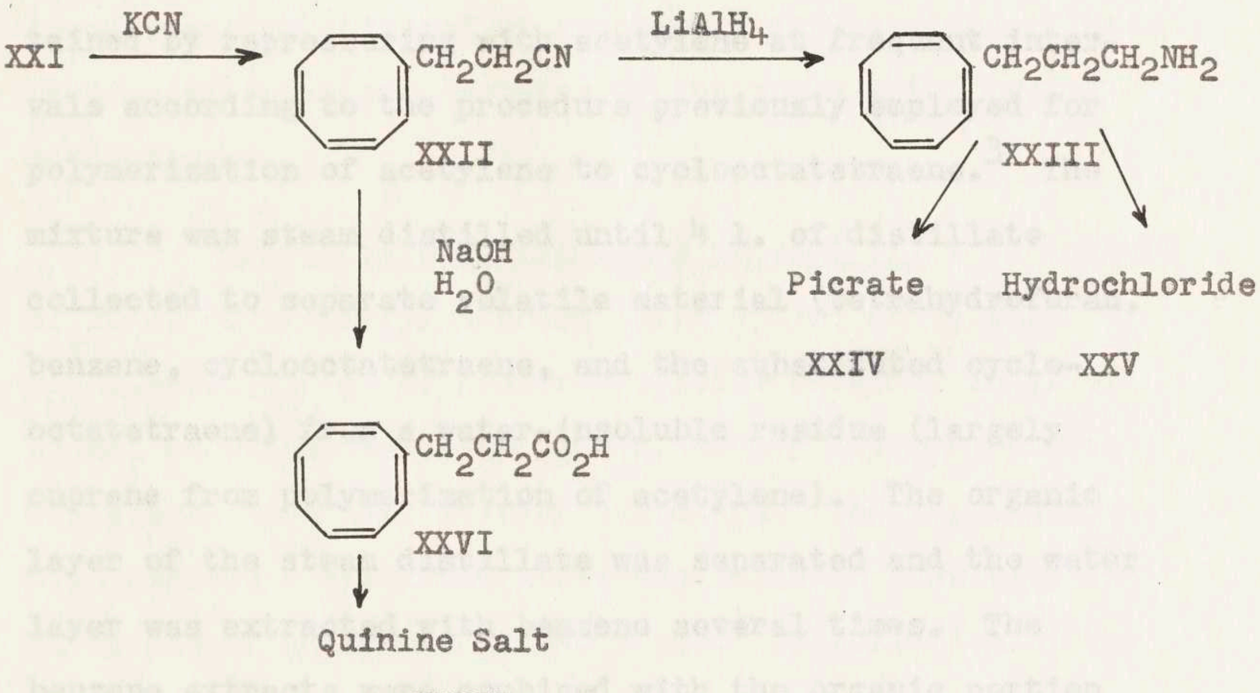


β-Cyclooctatetraenylethyl cyanide (XXII) was obtained in 78 per cent yield when XXI was heated with potassium cyanide in ethanol. Purification by fractional distillation afforded pure XXI as a light yellow liquid, b.p. 62-63°(0.25 mm.), n_D^{25} 1.5378.

Reduction of the nitrile XXI to the primary amine XXIII was accomplished by adding the nitrile to lithium aluminum hydride in dry ether. Purification by distillation afforded pure XXIII as a yellow liquid, b.p. 68-69°(0.1 mm.), n_D^{25} 1.5411, in 67 per cent yield. A yellow picrate XXIV, m.p. 166-167.5°, and a light yellow hydrochloride XXV, m.p. 153.3-154.2°, were prepared in good yield from a pure sample of the primary amine XXIII.

When XXII was heated at 100° for thirty minutes with an excess of 10 per cent sodium hydroxide solution, it was converted to β-cyclooctatetraenylpropionic acid (XXVI) in 77 per cent yield. The acid XXVI was a light greenish-yellow solid, m.p. 59.2-60.0°, obtainable in pure form by recrystallization from pentane. An attempt was made to prepare the brucine salt of XXVI but no crystalline product was obtained. The quinine salt (XXVII) of XXVI was prepared in 80 per cent yield and found to be a yellow solid, m.p. 119.6-120.6°, $[\alpha_D]^{25}$ 123.1°(l.=1, c=1.0 in 95 per cent ethanol). The melting point and optical rotation were unchanged after several recrystallizations from ether. When XXVII was dissolved in 1 per cent hydrochloric acid, pure XXVI was recovered and found to possess no optical activity. Therefore, if stereoisomers of XXVI exist, they either racemize too quickly to permit separation and isolation by this procedure or else no separation of isomers was effected through recrystallization of the quinine salt XXVII. A third possible explanation of these results is that the acid XXVI is not asymmetric.

The compounds which may possess sympathomimetic activity are the three amines previously described, namely VI, XVII, and XXIII, while the compound which will be of interest as a possible plant hormone is the acid XXVI.



Experimental+

Copolymerization and purification procedure - A mixture of 250-290 g. of dry tetrahydrofuran, 10-25 g. of a substituted acetylene, 10 g. of nickel acetylacetonate and 20 g. of powdered calcium carbide was placed in a 1-l. stirred autoclave. After displacing the air in the system with acetylene, the mixture was stirred and heated at 75-90° for 8-12 hours at a pressure of 300-170 p.s.i. maintained by repressuring with acetylene at frequent intervals according to the procedure previously employed for polymerization of acetylene to cyclooctatetraene.[3] The mixture was steam distilled until 4 l. of distillate collected to separate volatile material (tetrahydrofuran, benzene, cyclooctatetraene, and the substituted cyclooctatetraene) from a water-insoluble residue (largely cuprene from polymerization of acetylene). The organic layer of the steam distillate was separated and the water layer was extracted with benzene several times. The benzene extracts were combined with the organic portion of the steam distillate, and after the tetrahydrofuran, benzene, and cyclooctatetraene had been removed as low boiling fractions, the residue was distilled through a semi-micro column.[4] The crude product (containing

---

+All melting points are corrected. All boiling points are uncorrected.

[4] C.W.Gould, Jr., G.Holzmann and C.Niemann, Anal. Chem. 20, 361 (1948).

hydrocarbon impurities boiling in the same range) was dissolved in dry pentane and passed through a column (2.1 by 100 cm.) of silica gel (Davison, 20 to 200 mesh). The substituted cyclooctatetraene was adsorbed on the silica gel while hydrocarbon impurities passed through with the pentane. When an ether-pentane (10 per cent ether) solution was passed through the column, the substituted cyclooctatetraene was displaced from the silica gel and collected in the emerging solvent. Removal of the solvent under reduced pressure followed by fractional distillation of the residue afforded pure samples of the substituted cyclooctatetraene.

<u>Cyclooctatetraenylmethyl alcohol (I)</u> - A mixture of 20 g. of propargyl alcohol (b.p. 45-48° at 32 mm., n_D^{25} 1.4290), 20 g. of powdered calcium carbide, 10 g. of nickel acetylacetonate and 260 g. of dry tetrahydrofuran was placed in a 1-l. stirred autoclave. The copolymerization procedure described above was followed resulting in an uptake of acetylene of 950 p.s.i. Distillation of the high boiling residue obtained from the steam distillate (after removal of benzene and cyclooctatetraene) afforded 9.9 g. (20.5 per cent) of crude cyclooctatetraenylmethyl alcohol; b.p. 66-72° (0.5 mm.), n_D^{25} 1.5602-1.5620. A pure sample of I was obtained by passing the crude alcohol dissolved in pentane through a column of silica gel as described above. After 600 ml. of pentane had passed through

the column, no further material could be removed from the column and 3 l. of 10 per cent ether-pentane was passed through the column to remove the alcohol from the silica gel. Removal of the solvent followed by fractional distillation of the residue afforded 8.1 g. (17 per cent) of pure I; b.p. 65-66°(0.12 mm.), n_D^{25} 1.5612, d_4^{25} 1.0473.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.63; H, 7.66.

A solid 3,5-dinitrobenzoate of I was prepared by adding 0.39 g. (0.0019 mole) of freshly prepared 3,5-dinitrobenzoyl chloride to 0.25 g. (0.0019 mole) of pure I and heating the mixture on a steam bath for 1 minute. The mixture was dissolved in 10 ml. of dry hexane and cooled, whereupon yellow crystals formed. Several recrystallizations from hexane afforded 0.43 g. (73 per cent) of pure cyclooctatetraenylmethyl-3,5-dinitrobenzoate (II), m.p. 69.0-69.8°.

Anal. Calcd. for $C_{16}H_{12}O_6N_2$: C, 58.54; H, 3.69; N, 8.54. Found: C, 58.32; N, 3.78; N, 8.73.

Cyclooctylmethyl alcohol (III) - A solution of 0.11 g. of I in 10 ml. of 95 per cent ethanol was hydrogenated over 0.05 g. of platinum oxide catalyst which had previously been reduced. After 3 hours, 70.5 ml. (98.5 per cent) of the theoretical quantity of hydrogen had been absorbed and hydrogen uptake ceased. The reaction mixture was diluted with ethanol and the catalyst was removed through a filteraid. Removal of the ethanol under reduced pressure followed by distillation of the residue through a semi-micro column afforded 0.11 g. (94 per cent) of colorless III in three fractions, b.p. 66-68°(0.15 mm.), n_D^{25} 1.4802-1.4810. Fraction C (n_D^{25} 1.4810, d_4^{25} 0.9426) analyzed correctly for III.

Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 76.28; H, 12.82.

A solid 3,5-dinitrobenzoate of III was prepared by adding 0.27 g. (0.0014 mole) of 3,5-dinitrobenzoyl chloride to 0.20 g. (0.0014 mole) of III (n_D^{25} 1.4806) and heating the mixture on a steam bath for 1 hour. The mixture was dissolved in hexane and cooled. The white crystals which formed were collected and recrystallized twice from hexane to give 0.33 g. (69 per cent) of pure cyclooctylmethyl-3,5-dinitrobenzoate(IV), m.p. 68.6-69.7°.

Anal. Calcd. for $C_{16}H_{20}O_6N_2$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.21; H, 6.06; N, 8.37.

Cyclooctylmethyl alcohol (III) also was synthesized from cyclooctyl bromide. A solution of 5.3 g. (0.0027 mole) of cyclooctyl bromide in 25 ml. of dry ether was added slowly to 0.9 g. (0.038 gram atoms) of magnesium and 25 ml. of dry ether under nitrogen in a three-necked flask equipped with a condenser and mechanical stirrer. A vigorous reaction occurred and the mixture was stirred at room temperature for 30 minutes. Paraformaldehyde (1.8 g., 0.012 mole) was depolymerized by heating in an oil bath at 150-200° and the resulting gas was led into the cyclooctylmagnesium bromide with a stream of nitrogen. A white precipitate formed immediately, and after the addition of formaldehyde was complete (60 minutes), the mixture was stirred at room temperature for 30 minutes. About 20 g. of ice was added to the reaction mixture, followed by 100 ml. of 10 per cent sulfuric acid. After the mixture was extracted with ether several times, the combined ether layers were washed with water and then dried over anhydrous magnesium sulfate. After removal of the ether under reduced pressure, distillation of the residue through a semi-micro column afforded 1.2 g. of colorless liquid, n_D^{25} 1.4626-1.4801. Redistillation of three fractions afforded 0.58 g. (15.1 per cent) of cyclooctylmethyl alcohol, b.p. 67-68°(0.20 mm.), n_D^{25} 1.4801-1.4810. The last fraction, n_D^{25} 1.4810, analyzed correctly for III. A solid 3,5-dinitrobenzoate, m.p. 68.5-69-6°, was prepared from this product and did not depress the melting point of the ester IV prepared from III obtained by reduction of I.

<u>Cyclooctatetraenylmethyl tosylate (V)</u> - A mixture of 19.1 g. (0.1 mole) of pure p-toluenesulfonyl chloride and 7.0 g. (0.089 mole) of pyridine was added to 12.0 g. (0.089

mole) of I. The mixture became warm and after about 30 minutes pyridine hydrochloride separated as a white crystalline solid. After cooling, ether (200 ml.) was added and the pyridine hydrochloride was separated by filtration, washed with ether and dried at room temperature (yield 7.05 g., 68 per cent). After washing the ether solution with 10 per cent hydrochloric acid, the ether was removed by evaporation and the residue was placed under reduced pressure (0.2 mm.) to remove the remainder of the solvent. The light brown liquid residue weighed 17.0 g. (66.7 per cent). Repeated attempts to obtain a solid product by crystallizing the crude tosylate V from a variety of solvents were unsuccessful. When the tosylate V was dissolved in pentane and passed through a column of silica gel, it was rapidly decomposed. An attempt to distill V under reduced pressure (0.2 mm.) only decomposed the material in the pot. Therefore, the crude tosylate V was used in subsequent synthetic steps without further purification.

<u>Cyclooctatetraenylmethyldimethylamine (VI)</u> - Dimethylamine was passed through a solution of 4.0 g. (0.014 mole) of V in 20 ml. of dry benzene for 45 minutes with cooling and stirring. After 24 hours at room temperature, the reaction mixture was extracted with water and then with 100 ml. of 10 per cent hydrochloric acid. The acid layer was neutralized with 10 per cent sodium

hydroxide solution and then extracted several times with ether. The ether extracts were dried over anhydrous magnesium sulfate and, after removal of the ether under reduced pressure, distillation of the residue through a semi-micro column afforded 1.53 g. (37 per cent) of impure VI, b.p. 45-55°(0.2 mm.), n_D^{25} 1.5162-1.5219. All fractions were dissolved in dry ether and dry hydrogen chloride was passed into the ether solution. The light yellow crystalline salt was collected on a filter, washed with ether, and recrystallized twice from a methanol-ether solution, m.p. 208.7-209.3°. The free amine was obtained by dissolving the salt in excess 10 per cent sodium hydroxide solution and extracting the mixture with ether. After drying the ether solution over anhydrous magnesium sulfate and removing the ether under reduced pressure, fractional distillation of the residue through a semi-micro column afforded 1.45 g. (36.3 per cent) of pure VI, b.p. 51-52° (0.2 mm.), n_D^{25} 1.5220, d_4^{25} 0.9186.

<u>Anal</u>. Calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 82.11; H, 9.46.

<u>Cyclooctatetraenylmethyldimethylamine picrate (VII)</u> - Pure VI (0.10 g., 0.0062 mole) was dissolved in ether and picric acid in ether was added until no more precipitation occurred. The solid was collected on a filter, washed with ether and recrystallized from 95 per cent ethanol

several times to give 0.22 g. (91 per cent) of pure VII, m.p. 143.5-144.2°. The yellow crystals were quite stable at room temperature in contrast to the pure amine VI, which began to decompose in ten minutes.

Anal. Calcd. for $C_{17}H_{18}N_4O_7$: C, 52.31; H, 4.65; N, 14.35. Found: C, 52.42; H, 4.78; N, 14.17.

Cyclooctatetraenylmethyldimetylamine hydrochloride (VIII) - The hydrochloride VIII was prepared in essentially 100 per cent yield by dissolving pure VI in dry ether and passing hydrogen chloride gas into the solution. After collecting the solid on a filter, the light yellow crystals were washed with ether and recrystallized several times from a methanol-ether mixture to give pure VIII, m.p. 208.7-209.3°.

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16; N, 7.09. Found: C, 66.87; H, 8.28; N, 6.97.

Cyclooctatetraenylacetonitrile (IX) - A solution of impure V (9.0 g., 0.0311 mole) in 20 ml. of 95 per cent ethanol was added to 4.04 g. (0.062 mole) of potassium cyanide and the mixture was stirred vigorously for 25 minutes. During this time sufficient heat was liberated to cause the solvent to boil. After cooling, a quantity of light brown solid precipitated and was removed by filtration. The filtrate was added to 200 ml. of water and extracted with ether several times. After drying over anhydrous magnesium sulfate, the ether was removed through a packed column. Distillation of the residue through a packed column afforded 5.4 g. (81.5 per cent based on I) of impure IX. This yellow liquid was dissolved in 300 ml. of pentane and passed through a column of silica gel (1.5 by 75 cm.). A one per cent ether-pentane solution (500 ml.) was passed through the column and IX was partially displaced from the silica gel. A 2 per cent ether-pentane solution (800 ml.) brought through most of the remaining nitrile in the column. The combined ether-pentane solutions were distilled through a glass-helix packed column (1.5 by 25 cm.) to remove the solvent. Distillation of the residue through a semi-micro column afforded 3.5 g. of a yellow liquid, b.p. 70-87° (0.3 mm.), n_D^{25} 1.5321-1.6237. Redistillation of the fractions with higher refractive index afforded 2.7 g. (61 per cent) of cyclooctatetraenylacetonitrile, b.p. 79-80.5° (0.3 mm.), n_D^{25} 1.6240-1.6260. The last fraction, n_D^{25}1.6260, d_4^{25} 1.0127, analyzed correctly for IX.

Anal. Calcd. for $C_{10}H_9N$: C, 83.88; H, 6.34. Found: C, 84.01; H, 6.50.

Cyclooctatetraenylacetic acid (X) - A solution of 25 per cent sodium hydroxide (20 ml.) was added to 0.8 g. (0.056 mole) of IX and heated on a steam bath for 30 minutes with stirring. After cooling, the solution was extracted with ether to remove unreacted IX. The basic layer was neutralized with 10 per cent hydrochloric acid and extracted with ether several times. The ether layers were combined and evaporated to dryness under reduced pressure leaving a light yellow oily residue. Upon cooling and scratching the oil solidified to yellow crystals (0.62 g., 68 per cent), m.p. 76-77.6°. The crystals were dissolved in pentane with difficulty and when the pentane solution was cooled, white crystals, m.p. 76.5-78°, formed which did not analyze correctly for X. A second recrystallization from pentane afforded white crystals which became gummy shortly after being exposed to the air. Many attempts were made using different solvents to obtain X pure but all attempts resulted in the formation of the gummy material mentioned above.

β-Cyclooctatetraenylethyl alcohol (XI) - A mixture of 15.0 g. (0.22 mole) of 3-butyn-1-ol, 10.0 g. of nickel acetylacetonate, 20.0 g. of powdered calcium carbide and 216 g. of dry tetrahydrofuran was heated at 80-95° in a one liter stirred autoclave for 11 hours under 300 p.s.i. of acetylene. The total uptake of acetylene was 1200 p.s.i., which resulted in an increase in weight of 178 g. Following steam distillation of the mixture, the organic layer was separated and the water layer was extracted with benzene. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed through a packed column. Distillation of the residue under reduced pressure (90 mm) afforded 69.0 g. of cyclooctatetraene and 12.0 g. of a dark liquid, b.p. 63-75° (0.55 mm.). The high boiling dark liquid was dissolved in pentane (500 ml.) and passed through a column of silica gel (2.1 by 100 cm.). The material which came through with the pentane was discarded and then a 2 per cent ether-pentane solution (3 l.) was passed through the column to displace polar material from the silica gel. The ether-pentane fractions were combined and, after removal of the solvent under reduced pressure, distillation of the residue afforded 8.1 g. (24.2 per cent) of β-cyclooctatetraenylethyl alcohol (XI), b.p. 75-78° (0.2 mm.), n_D^{25} 1.5448-1.5480. Redistillation afforded pure XI, b.p. 77-78° (0.2 mm.), n_D^{25} 1.5480, d_4^{25} 1.0213.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.17. Found: C, 81.10; H, 8.39.

The alcohol XI also was obtained pure by dissolving the impure alcohol in concentrated phorphoric acid and extracting the mixture with ether (these extracts were discarded). Following neutralization of the acid layer with 10 per cent sodium hydroxide solution, the mixture was extracted with ether. After drying the extracts over anhydrous magnesium sulfate, the ether was removed through a packed column. Distillation of the residue afforded pure XI, but about 50 per cent of the starting material was polymerized by the acid treatment.

Fairly pure samples of XI were obtained by extracting the impure alcohol with 20 per cent aqueous silver nitrate solution. Regeneration of the alcohol-silver nitrate complex with concentrated ammonium hydroxide followed by distillation of the organic layer afforded samples of XI with refractive indices close to pure XI.

β-Cyclooctatetraenylethyl-3,5-dinitrobenzoate (XII) - A solution of 0.75 g. (0.0057 mole) of XI in 2.0 ml. of dry hexane was added to 1.1 g. (0.0057 mole) of freshly prepared 3,5-dinitrobenzoylchloride. After 2 minutes heating on a steam bath, the mixture was cooled overnight during which time 0.91 g. (53 per cent) of yellow crystals formed, m.p. 63-66.5°. Two recrystallizations from ethanol and water gave pure XII, m.p. 67.0-67.8°.

Anal. Calcd. for $C_{17}H_{14}O_6N_2$: C, 59.65; H, 4.12; N, 8.19. Found: C, 59.95; H, 4.27; N, 8.13.

β-Cyclooctylethyl alcohol (XIII) - A solution of 0.11 g. (0.00071 mole) of XI in 5.0 ml. of 95 per cent ethanol was hydrogenated over 0.05 g. of pre-reduced platinum oxide catalyst. After 150 minutes, 70.0 ml. (98.5 per cent) of four molar equivalents of hydrogen had been absorbed and hydrogen uptake ceased. The reaction mixture was diluted with ethanol and the catalyst was removed through a filteraid. Removal of the ethanol under reduced pressure followed by distillation of the residue through a semi-micro column afforded 0.098 g. (91 per cent) of colorless XIII, n_D^{25} 1.4820-1.4830. Redistillation afforded a pure sample of XIII, b.p. 78-79° (0.2 mm.), n_D^{25} 1.4825, d_4^{25} 0.9360.

<u>Anal</u>. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 77.15; H, 13.06.

<u>β-Cyclooctylethyl-3,5-dinitrobenzoate (XIV)</u> was prepared by adding 0.20 g. (0.0001 mole) of freshly prepared 3,5-dinitrobenzoyl chloride to 0.15 g. (0.0001 mole) of XIII in 5 ml. of dry hexane. The mixture was heated on a steam bath for 1 minute and then cooled in ice water. The light yellow crystals which formed were recrystallized twice from petroleum ether (0.19 g., 54 per cent), m.p. 46.5-47.8°.

<u>Anal</u>. Calcd. for $C_{17}H_{22}O_6N_2$: C, 58.27; H, 6.33; N, 8.02. Found: C, 58.04; H, 6.43; N, 8.17.

β-Cyclooctylethyl alcohol (XIII) was also prepared by adding a solution of 11.8 g. (0.062 mole) of cyclooctyl bromide (n_D^{25} 1.5032) in 25 ml. of dry ether to a mixture of 1.5 g. (0.062 gram atoms) of magnesium turnings in 125 ml. of dry ether under nitrogen in a three-necked flask equipped with a condenser and mechanical stirrer. A moderately vigorous reaction proceeded for 30 minutes at room temperature. After an additional 30 minutes of stirring, 3.1 g. (0.070 mole) of ethylene oxide in 20 ml. of cold ether was added slowly to the reaction mixture. A white precipitate formed at once which partially dissolved as more ethylene oxide was added. The mixture was heated at gentle reflux temperature for 1 hour, after which 50 ml. of dry benzene was added. The ether was gradually removed until the vapor temperature reached 65°, at which point the mixture was stirred for 1 hour at gentle reflux temperature.

Following addition of a small amount of ice, 50 ml. of 10 per cent sulfuric acid was added and the mixture was extracted several times with benzene. The benzene solution was washed with water and dried over anhydrous magnesium sulfate. Following removal of the benzene through a packed column, distillation of the residue through a semi-micro column afforded 2.43 g. (26 per cent) of a colorless liquid, b.p. 83-88°(0.5 mm.), n_D^{25} 1.4752-1.4858. Redistillation of several fractions afforded pure β-cyclooctylethyl alcohol (XIII), b.p. 77.5-78.5° (0.2 mm.), n_D^{25} 1.4821. The infrared absorption curve of this alcohol was practically identical with that of the alcohol obtained through reduction of XI. A solid 3,5-dinitrobenzoate (m.p. 46.2-47.5°) of the alcohol prepared via the Grignard synthesis did not depress the 3,5-dinitrobenzoate of XIII prepared from XI.

1-Chloro-3-butyne (XV) - A solution of 60.0 g. (0.50 mole) of thionyl chloride in 40 ml. of dry chloroform was added with stirring over a 2 hour period to a mixture of 28.0 g. (0.40 mole) of 3-butyn-1-ol and 15.0 g. (0.40 mole) of pyridine in 40 ml. of chloroform. The mixture was cooled in an ice bath during the addition of the thionyl chloride and then stirred at room temperature for 12 hours. The mixture was extracted twice with water and then with 5 per cent sodium bicarbonate solution. The chloroform solution was dried over anhydrous sodium sulfate and, following removal of the chloroform under reduced pressure, distillation of the residue afforded 20.6 g. (58.0 per cent) of impure XV, b.p. 75-85°. Redistillation of several fractions afforded 14.2 g. (40 per cent) of pure XV, b.p. 84-85°, n_D^{25} 1.4376.

Anal. Calcd. for $C_{11}H_5Cl$: C, 54.26; H, 5.69; Cl, 40.05. Found: C, 54.21; H, 5.92; Cl, 39.99.

1-Dimethylamino-3-butyne (XVI) - A mixture of 25.0 g. (0.28 mole) of XV and 180 g. (1.0 mole) of 25 per cent aqueous dimethylamine solution was stirred at room temperature for three days. The mixture was made basic with 10 per cent sodium hydroxide solution and extracted with ether several times. Following drying of the ether extracts over anhydrous magnesium sulfate, the ether was removed through a packed column. Distillation of the residue afforded 18.8 g. (69 per cent) of impure XVI, b.p. 89-106°. Redistillation of this material afforded 12.2 g. (44.6 per cent) of pure XVI, b.p. 104-106°, n_D^{25} 1.4294, d_4^{25} 0.8111.

Anal. Calcd. for $C_6H_{11}N$: C, 74.16; N, 11.43. Found: C, 73.88; N, 11.49.

β-Cyclooctatetraenylethyldimethylamine (XVII) - A mixture of 10.7 g. of XVI, 20.0 g. of powdered calcium carbide, 10.0 g. of nickel acetylacetonate and 286 g. of tetrahydrofuran was placed in a 1-l. stirred autoclave. The copolymerization procedure described above was followed and resulted in an uptake of acetylene of about 800 p.s.i. The purification procedure differed from the one described above in that the mixture was centrifuged and the clear liquid layer was distilled under reduced pressure to remove the tetrahydrofuran and benzene. Extraction of the residue with 3 per cent hydrochloric acid followed by distillation of the neutral fraction yielded 30.0 g. of cyclooctatetraene. The hydrochloric acid extract was made basic with 10 per cent sodium hydroxide solution and extracted with ether. Removal of the ether followed by distillation of the residue through a semi-micro column afforded 1.5 g. (7.8 per cent) of β-cyclooctatetraenylethyldimethylamine (XVII), b.p. 55-63° (0.05 mm.), n_D^{25} 1.5198. A pure sample of XVII was obtained by redistilling several fractions; b.p. 58-59° (0.05 mm.), n_D^{25} 1.5198, d_4^{25} 0.9186.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82,23; H, 9.78; N, 7.99. Found: C, 82.47; H, 9.73; N, 7.86.

β-Cyclooctatetraenylethyldimethylamine picrate (XVIII) - was prepared in good yield by adding an ether solution of XVII to a solution of picric acid in ether. After several recrystallizations from 95 per cent ethanol, the yellow crystals melted at 117.8-118.5°.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: C, 53,46; H, 4.98; N, 13.86. Found: C, 53.57; H, 4.99; N, 13.81.

The synthesis of XVII from XIX (described below) was accomplished by passing dimethylamine through a solution of 1.2 g. (0.0057 mole) of XIX in 50 ml. of benzene at room temperature for 2 hours. After heating on a steam bath for 2 hours the mixture was extracted with 10 per cent hydrochloric acid. The acid layer was neutralized with 10 per cent sodium hydroxide solution and then extracted with ether several times. The ether extracts were combined and dried over anhydrous magnesium sulfate. Following removal of the ether under reduced pressure, distillation of the residue through a semi-micro column afforded 0.37 g. (38 per cent) of impure XVII which upon redistillation yielded a fairly pure sample, b.p. 67.5-68° (0.45 mm.), n_D^{25} 1.5185. A picrate (m.p. 117.9-118.5°) prepared from this compound (in the manner previously described for XVIII) did not depress the melting point of the picrate prepared from XVII obtained by copolymerization.

A third synthesis of XVII was accomplished through the tosylate XXI (described below). A solution of XXI (3.0 g., 0.0099 mole) in 15 ml. of benzene was saturated with dimethylamine and then kept at room temperature overnight. The mixture was washed with water and then the benzene was removed through a packed column. Distillation of the residue through a semi-micro column afforded 0.94 g. (53 per cent) of impure XVII, b.p. 70-74° (13 mm.). Redistillation of this material afforded 0.80 g. (45 per cent) of pure XVII, b.p. 58-59° (0.07 mm.), n_D^{25} 1.5198. A picrate (m.p. 118.0-118.5°) was prepared which did not depress the melting point of the picrate prepared from XVII obtained by copolymerization.

β-Cyclooctatetraenylethyldimethylamine hydrochloride (XX) was prepared by passing dry hydrogen chloride through a solution of 0.63 g. (0.0036 mole) of XVII in 10 ml. of dry ether. The white solid was collected on a filter, washed with ether, and recrystallized twice from a methanol-ether solution. Pure XX was obtained as white needles, m.p. 179.6-180.6°, in a yield of 0.62 g. (82 per cent).

Anal. Calcd. for $C_{12}H_{18}NCl$: C, 68.07; H, 8.57; N, 6.62. Found: C, 68.02; H, 8.72; N, 6.50.

β-Cyclooctatetraenylethyl tosylate (XXI). - A mixture of 14.5 g. (0.074 mole) of p-toluene-sulfonyl chloride and 5.4 g. (0.069 mole) of pyridine was added with cooling to 10.0 g. (0.068 mole) of XI. The mixture became warm and in a few minutes a thick mass of pyridine hydrochloride crystals separated out. After the mixture stood for 12 hours at room temperature, it was added to 150 ml. of 10 per cent hydrochloric acid and then extracted with ether several times. The ether extracts were dried over anhydrous magnesium sulfate and, following removal of the ether by evaporation, the residue was placed under reduced pressure (0.2 mm.) at room temperature for 15 minutes to remove the last traces of solvent. The weight of crude XXI was 20.2 g. (91.5 per cent). Although many attempts were made to purify XXI by crystallization from various solvents, all such attempts were unsuccessful. The tosylate was used without further purification in subsequent synthetic steps.

β-Cyclooctatetraenylethyl bromide (XIX).- A solution of 4.50 g. (0.017 mole) of phosphorus tribromide in 25 ml. of dry hexane was added slowly to a mixture of 6.25 g. (0.042 mole) of XI and 1.30 g. (0.016 mole) of pyridine in 50 ml. of dry hexane at 5-10°. A white precipitate formed at once and the reaction mixture was stirred for 4 hours at room temperature. After carefully washing with water, the hexane solution was dried over anhydrous magnesium sulfate and the hexane was removed under reduced pressure. Distillation of the residue afforded 3.55 g. (40.2 per cent) of a yellow liquid, b.p. 58-67° (0.13 mm.), n_D^{25} 1.5601-1.5639. Redistillation of a fraction (n_D^{25} 1.5639) did not yield material having a constant refractive index between fractions. A typical analysis of a fraction (n_D^{25} 1.5629) is given.

Anal. Calcd. for $C_{10}H_{11}Br$: C, 56.89; H, 5.25. Found: C, 57.92; H, 5.48.

β-Cyclooctatetraenylethyl bromide was also prepared from XXI by adding 9.4 g. (0.047 mole) of anhydrous calcium bromide to 14.4 g. (0.047 mole) of XXI in 25 ml. of dry methylcellosolve. After heating for 15 minutes on an oil bath at 50°, a precipitate of calcium tosylate formed. The mixture was cooled and added to 200 ml. of ether. The calcium tosylate was collected on a filter, washed with ether, and dried at room temperature; yield 8.8 g. (96 per cent). After washing with water several times to remove methylcellosolve, the ether layer was dried over anhydrous magnesium sulfate and the ether was removed under reduced pressure. Distillation of the residue (9.4 g.) through a semi-micro column afforded 7.1 g. (72 per cent) of XIX, b.p. 61-67° (0.12 mm.), n_D^{25} 1.5580-1.5650. This material was dissolved in 300 ml. of dry pentane and put through a column of silica gel (1.5 by 75 cm.). The emerging solvent was collected in three fractions (100 ml. each) and each fraction was distilled through a semi-micro column after the solvent had been removed under reduced pressure. Fraction A was found to have the narrowest range of refractive indices (n_d^{25} 1.5612-1.5674) of the three fractions but several fractions (from A) that were analyzed (n_D^{25} 1.5648, 1.5661, 1.5674) did not analyze correctly. It was observed that XIX, after a short period of time (6 hours) at 5-10°, was partially insoluble in pentane. The insoluble portion, a white amorphous solid, could not be distilled. Examination of the infrared absorption curve of XIX did not reveal the nature of the foreign material present in the samples which were analyzed. A typical analysis of XIX, b.p. 65-67° (0.13 mm.), n_D^{25} 1.5686, d_4^{25} 1.2550, is given.

<u>Anal</u>. Calcd. for $C_{10}H_{11}Br$: C, 56.89; H, 5.25. Found: C, 57.80; H, 5.47.

<u>β-Cyclooctatetraenylethyl cyanide (XXII)</u>. - A solution if impure XXI (20.0 g., 0.0694 mole) and 7.3 g. (0.112 mole) of potassium cyanide in 50 ml. of 90 per cent ethanol was heated at the reflux temperature for 14 hours. After cooling, 100 ml. of water was added and the mixture was extracted with ether several times. The ether extracts were combined and dried over anhydrous magnesium sulfate. Following removal of the ether by evaporation, distillation

of the residue through a semi-micro column afforded 8.3 g. (78 per cent based on XI) of β-cyclooctatetraenylethyl cyanide, b.p. 55-65° (0.25 mm.), n_D^{25} 1.5374-1.5385. Redistillation of this material afforded a pure sample of XXII, b.p. 62-63° (0.25 mm.), n_D^{25} 1.5378, d_4^{25} 0.9853.

Anal. Calcd. for $C_{11}H_{11}N$; C, 84.04; H, 7.05; N, 8.91. Found: C, 84.06; H, 7.11; N, 8.61.

γ-Cyclooctatetraenylpropylamine (XXIII). - A solution of 2.0 g. (0.0127 mole) of XXII in 15 ml. of dry ether was slowly added with stirring to 0.48 g. (0.0127 mole) of lithium aluminum hydride in 20 ml. of dry ether. The reaction was carried out under nitrogen in a 100 ml. three-necked flask equipped with a condenser and mechanical stirrer. During the addition of XXII the reaction mixture became cloudy and after the addition was completed the mixture was heated for one hour on a steam bath. After cooling, a small amount of water was added very cautiously to the flask to decompose unreacted lithium aluminum hydride. Then 35 ml. of 10 per cent hydrochloric acid was added to the mixture, which was then extracted with ether. The acid layer was neutralized with 10 per cent sodium hydroxide solution and the free amine was extracted with ether. After drying the ether extracts over anhydrous magnesium sulfate the ether was removed through a packed column. Distillation of the residue through a semi-micro column afforded 1.37 g. (67 per cent) of impure XXIII, b.p. 64-68.5° (0.1 mm.), n_D^{25} 1.5388-1.5412. Redistillation afforded 1.15 g. (56 per cent) of pure XXIII, b.p. 68.0-68.5° (0.1 mm.), n_D^{25} 1.5411, d_4^{25} 0.9613.

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38. Found: C, 82.01; H, 9.51.

γ-Cyclooctatetraenylpropylamine picrate (XXIV) - was prepared by adding XXIII to a saturated solution of picric acid in ethanol. Several recrystallizations of the yellow solid which formed gave pure XXIV, m.p. 166-167.5°.

Anal. Calcd. for $C_{17}H_{18}O_7N_4$: C, 52.31; H, 4.65; N, 14.35. Found: C, 52.30; H, 4.93; N, 14.08.

γ-Cyclooctatetraenylpropylamine hydrochloride (XXV) was prepared by passing dry hydrogen chloride through a solution of 0.63 g. (0.0039 mole) of XXIII in dry ether. The white solid which formed was collected on a filter, washed with ether, and recrystallized twice from a methanol-ether solution to give 0.65 g. (84 per cent) of pure XXV, m.p. 153.3-154.2°.

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16; N, 7.09. Found: C, 66.57; H, 8.15; N, 7.04.

β-Cyclooctatetraenylpropionic acid (XXVI) - The nitrile XXII (2.0 g., 0.013 mole) was added to a solution of 2.0 g. of sodium hydroxide in 50 ml. of water and heated in an oil bath at reflux temperature for 4 hours. The mixture became homogeneous during this time. The mixture was cooled and then extracted with ether to recover any unreacted XXII. The basic solution was made strongly acidic with 10 per cent hydrochloric acid and then extracted several times with ether. The ether extracts were combined and the ether was removed by evaporation. The yellow oil residue upon cooling and scratching solidified to a solid mass of light yellow crystals (2.01 g., 90 per cent) which after three recrystallizations from hexane weighed 1.7 g. (77 per cent); m.p. 59.2-60.0°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.98; H, 6.98.

Quinine β-cyclooctatetraenylpropionate (XXVII) - A solution of 0.5 g. (0.0028 mole) of XXVI in 5 ml. of dry ether was added to 1.06 g. (0.0028 mole) of quinine hydrate in 200 ml. of ether. After evaporating the solution to a volume of about 50 ml., it was cooled overnight at 5-10°. The yellow crystals which formed were recrystallized three times from ether but the physical constants, m.p. 119.6-120.6°, $[\alpha]_D^{25}$ 123.1° (l.=1, c=1.0), remained unchanged. Regeneration of the free acid by treatment of XXVII with 1 per cent hydrochloric acid followed by extraction with ether afforded pure XXVI which was optically inactive.

Anal. Calcd. for $C_{31}H_{36}O_2N_4$: C, 74.37; H, 7.25; N, 5.60. Found: C, 74.21; H, 7.25; N, 5.70.

β-Cyclooctatetraenylethyl acetate (XXVIII). - A mixture of 3.0 g. of XI and 4.1 g. of acetic anhydride was heated on a steam bath for twenty minutes. The mixture was added to 100 ml. of water and the resulting solution was extracted with benzene several times. The combined benzene extracts were dried over anhydrous magnesium sulfate and the benzene was removed under reduced pressure. Distillation of the residue through a semi-micro column afforded 3.5 g. (91 per cent) of a yellow liquid (XXVIII), b.p. 81-82° (0.15 mm.), n_D^{25} 1.5130, d_4^{25} 1.0260. Saponification of XXVIII with excess 25 per cent hydroxide solution followed by titration of the unused base with standard hydrochloric acid showed a saponification equivalent for XXVIII of 181.5 (theory 190.2).

Anal. Calc. for $C_{12}H_{14}O_2$: C, 75.65; H, 7.42. Found: C, 75.56; H, 7.58.

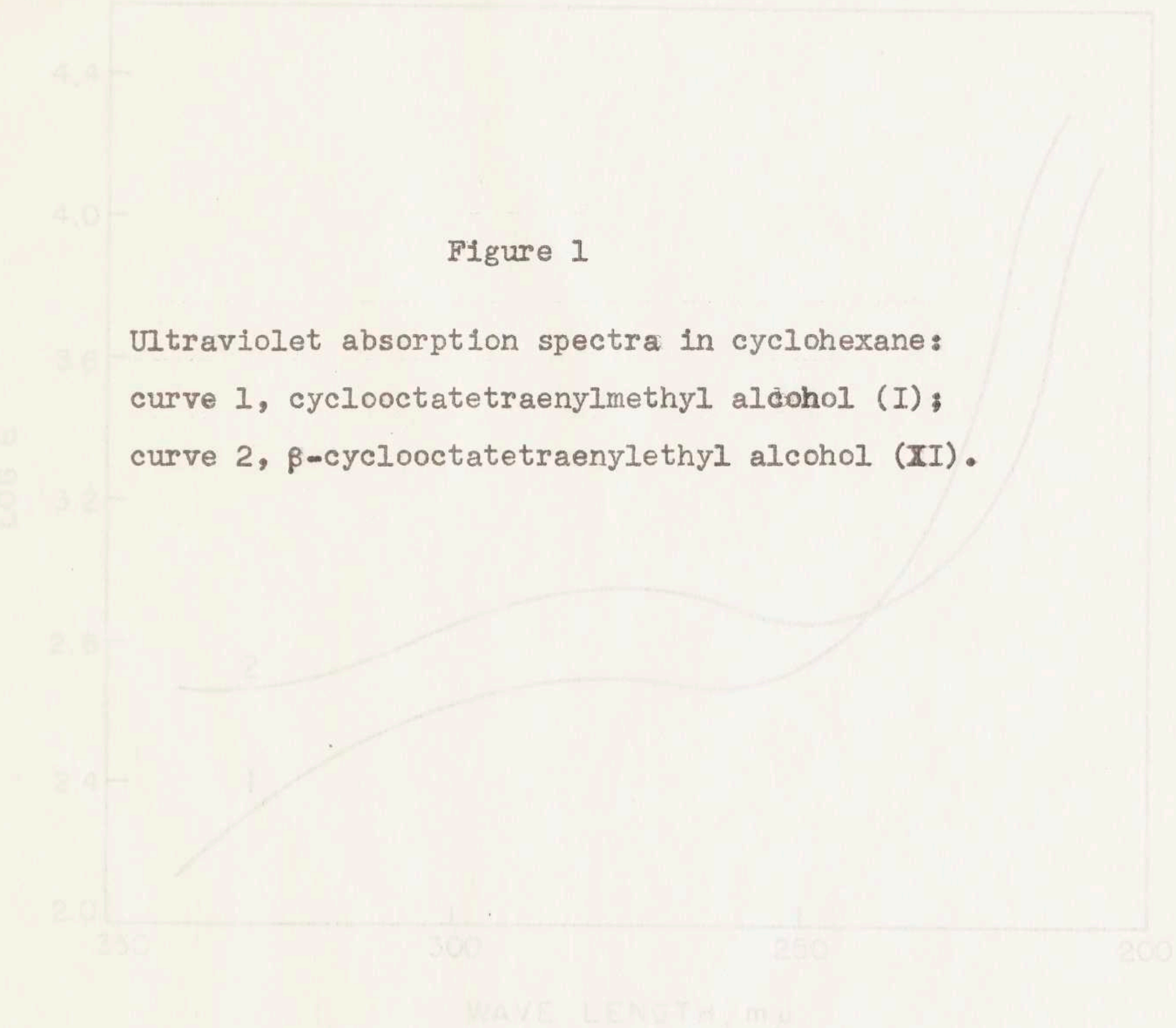


Figure 1

Ultraviolet absorption spectra in cyclohexane: curve 1, cyclooctatetraenylmethyl alcohol (I); curve 2, β-cyclooctatetraenylethyl alcohol (II).

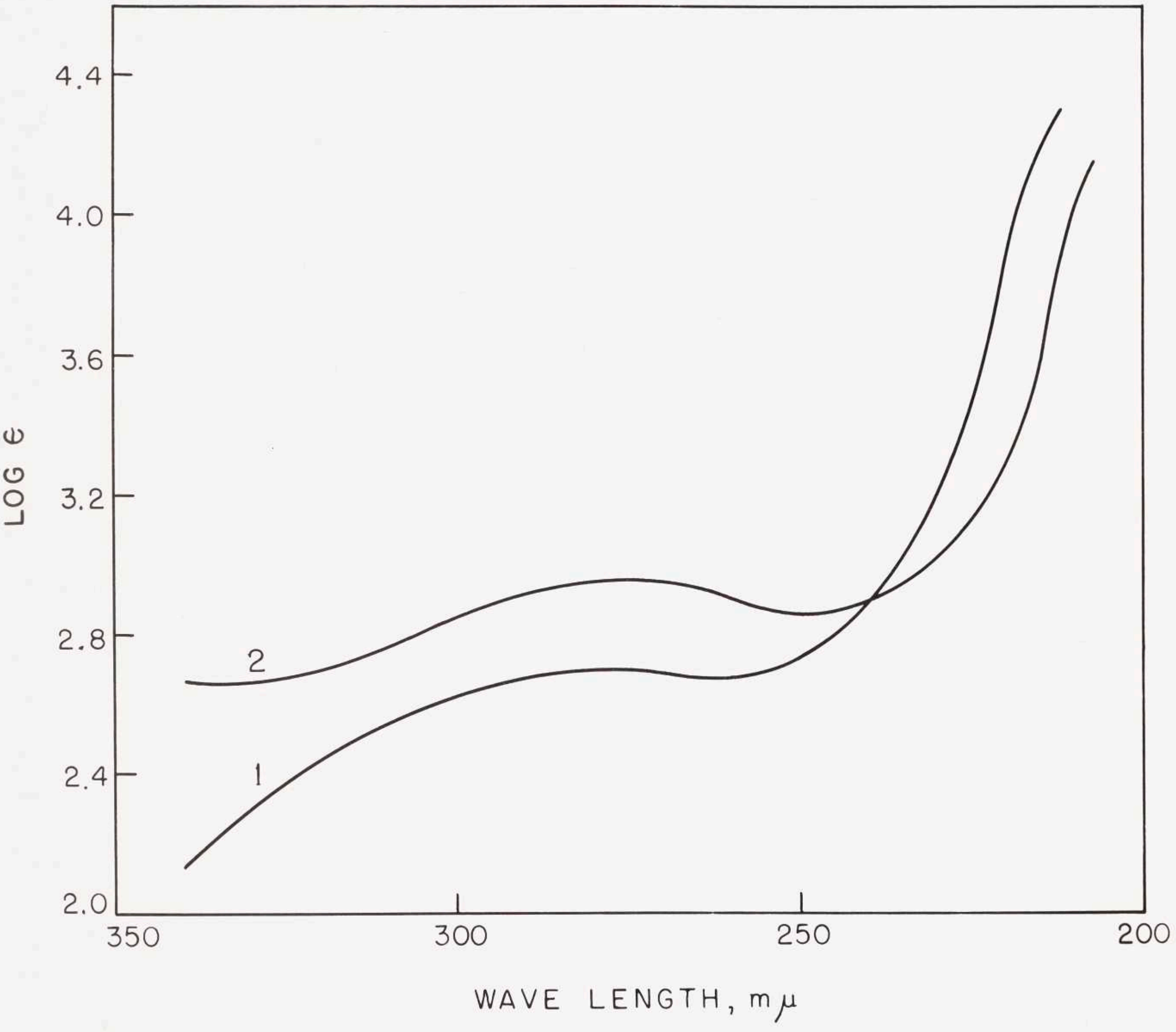
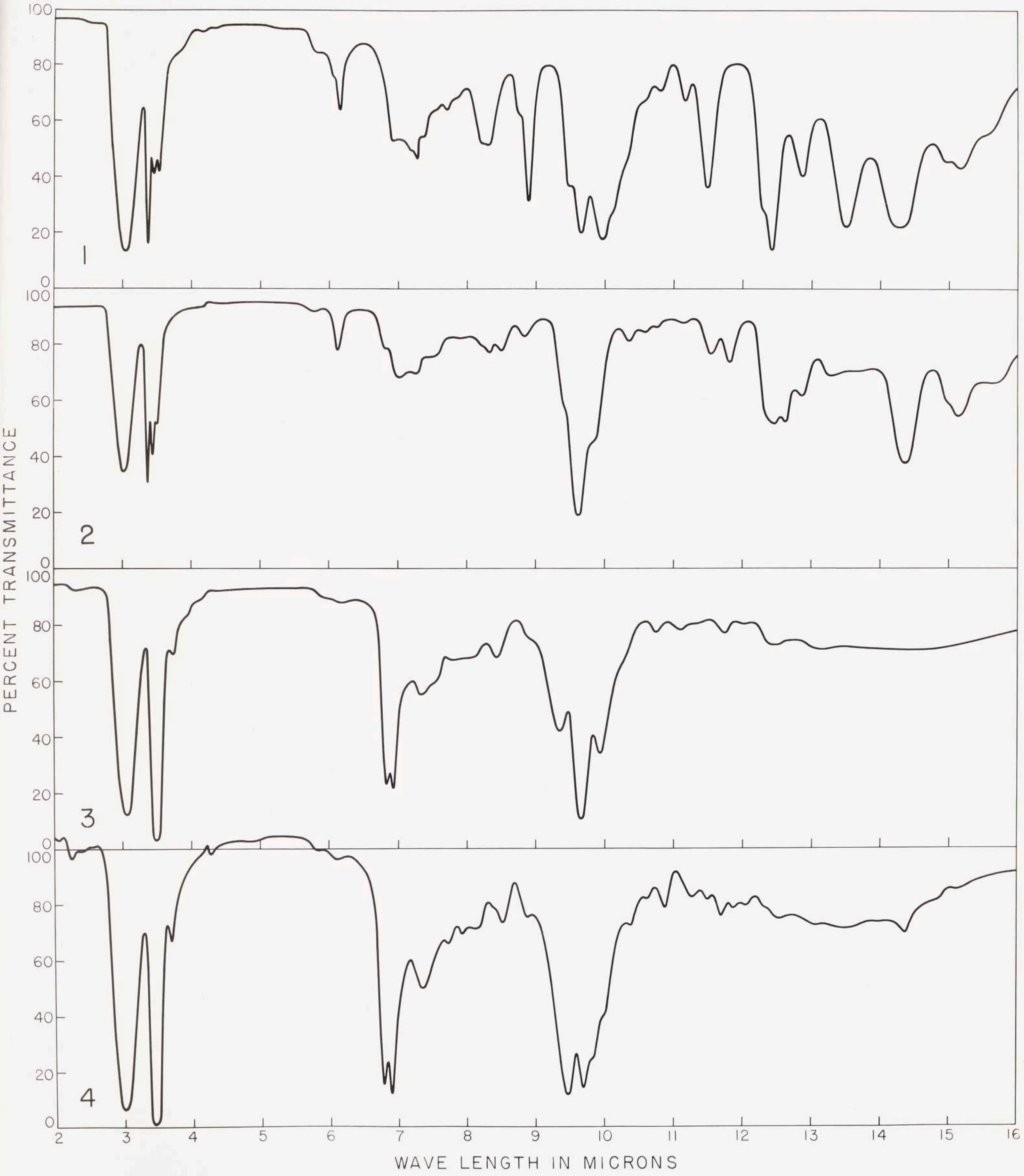

4.4
4.0
3.6
3.2
2.8
2.4
2.0
LOG ϵ
2
1
350
300
250
200
WAVE LENGTH, mμ

Figure 2

Infrared absorption spectra: curve 1, cyclooctatetraenylmethyl alcohol (I); curve 2, β-cyclooctatetraenylethyl alcohol (XI); curve 3, cyclooctylmethyl alcohol (III); curve 4, β-cyclooctylethyl alcohol (XIII). All samples were pure liquids.



PERCENT TRANSMITTANCE
100
80
60
40
20
0
1
2
3
4
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
WAVE LENGTH IN MICRONS

Figure 3

Infrared absorption spectra : curve 1, β-cyclooctatetraenylethyl cyanide (XXII) ; curve 2, β-cyclooctatetraenylpropionic acid (XXVI) ; curve 3, γ-cyclooctatetraenylpropylamine (XXIII). Curves 1 and 3 were on pure liquids; curve 2, 10 per cent solution of XXVI in carbon tetrachloride (2.0-7.9 microns) and carbon disulfide (7.9-16.0 microns).

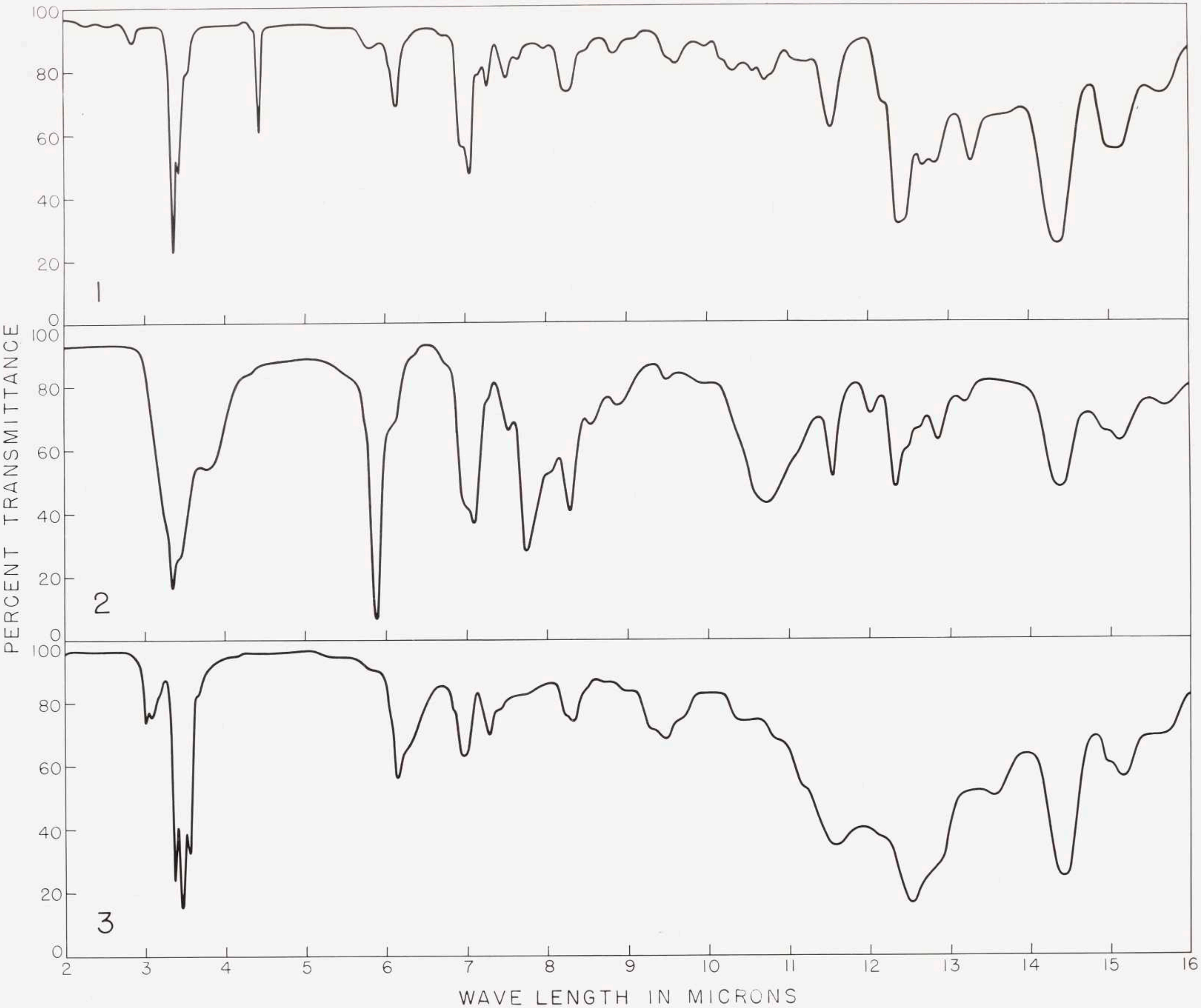
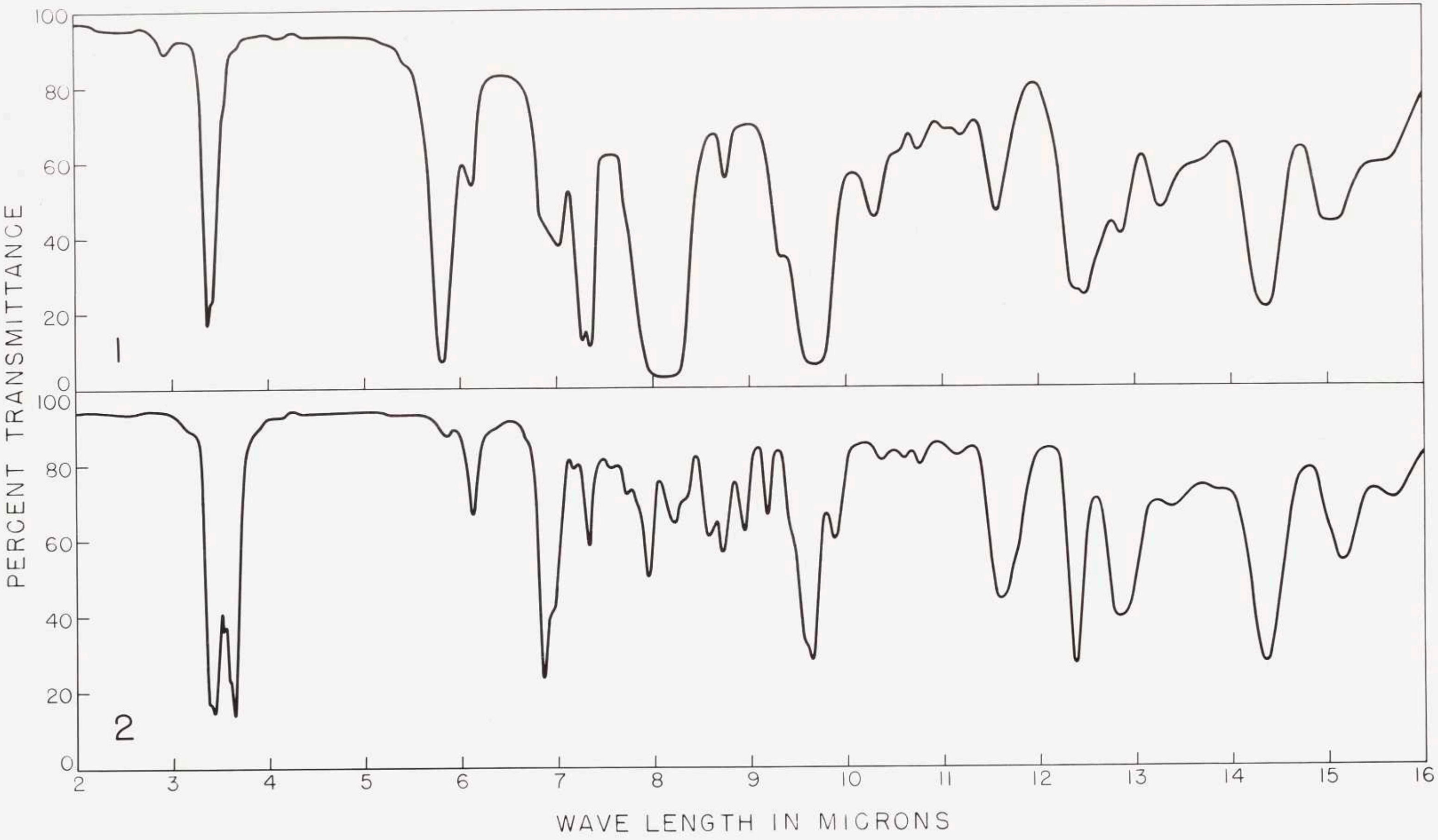

100
80
60
40
20
0
1
2
3
PERCENT TRANSMITTANCE
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
WAVE LENGTH IN MICRONS

Figure 4

Infrared absorption spectra: curve 1, β-cyclooctatetraenylethyl acetate (XXVIII); curve 2, β-cyclooctatetraenylethyldimethylamine (XVII). Both samples were pure liquids.

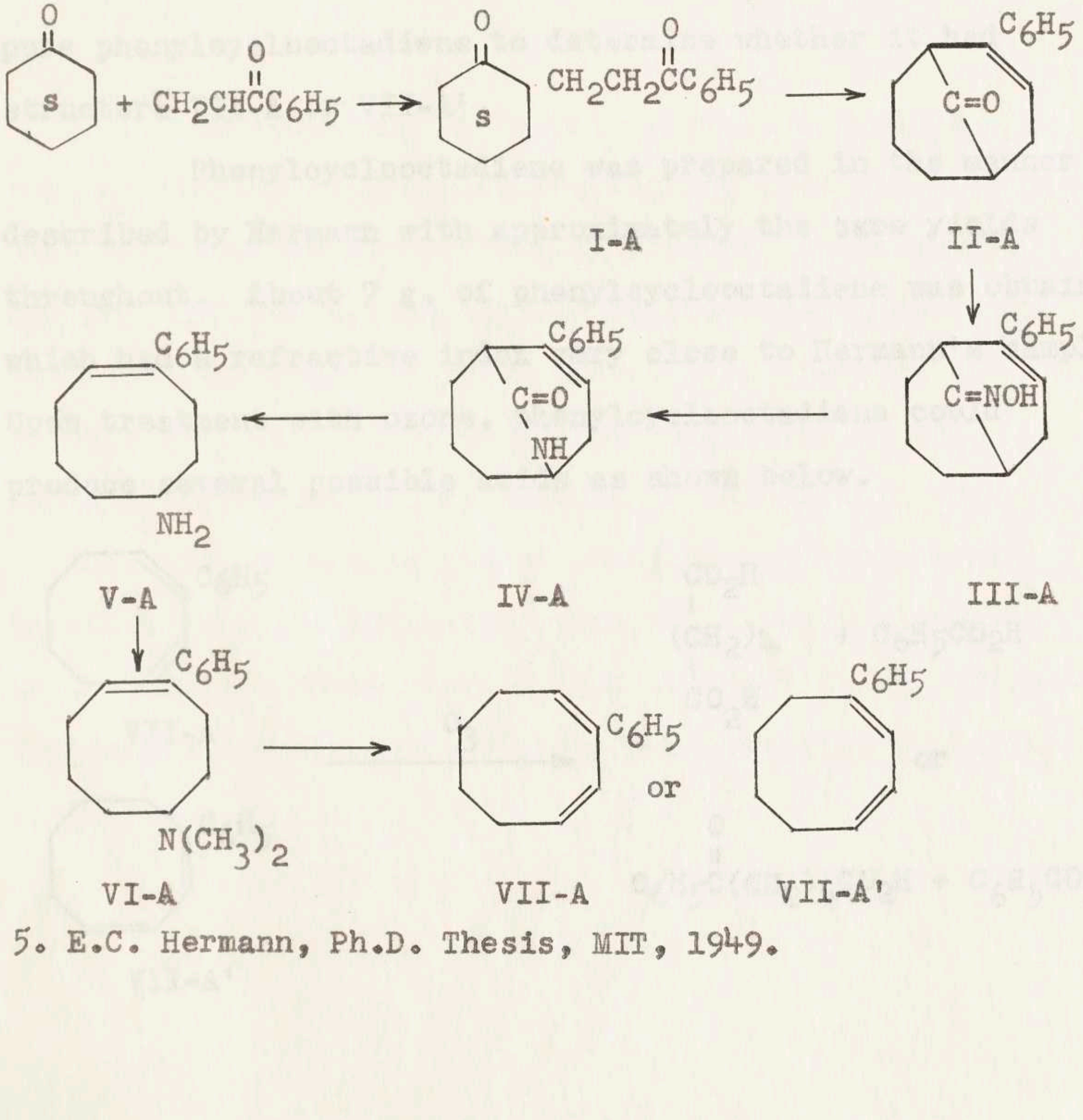

PERCENT TRANSMITTANCE
100
80
60
40
20
0
1
2
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
WAVE LENGTH IN MICRONS

PART B

PROOF OF STRUCTURE OF PHENYLCYCLOOCTADIENE

DISCUSSION

The seven step synthesis of 1-phenylcycloocta-1,3-diene (VII-A') from 2-phenylbicyclo 3.3.1 nonene-9-one (II-A) by the Beckmann rearrangement of the oxime of the cyclic ketone III-A, hydrolysis of the resulting lactam (IV-A) and a Hoffmann exhaustive methylation of the methylated amine has been carried out successfully by E. C. Hermann.[5]

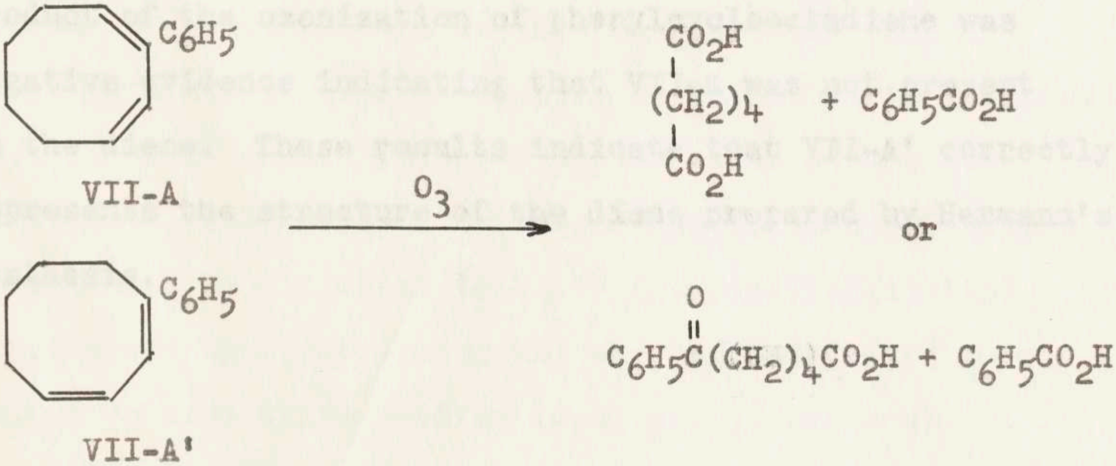


---

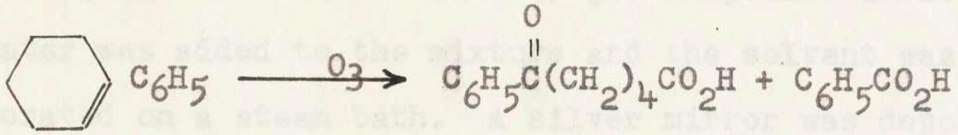
[5] E.C. Hermann, Ph.D. Thesis, MIT, 1949.

It was found that phenylcyclooctadiene prepared by this method absorbed two moles of hydrogen to form phenylcyclooctane, which was compared with an authentic sample and found to be identical. The ultra-violet absorption spectrum of the phenylcyclooctadiene showed that the double bonds were conjugated with the phenyl group in either a terminal or cross-conjugated manner as represented by VII-A or VII-A'. However, the exact structure of the phenylcyclooctadiene was unknown. Part II of this thesis describes the oxonolysis of a sample of the pure phenylcyclooctadiene to determine whether it had structure VII-A or VII-A'.

Phenylcyclooctadiene was prepared in the manner described by Hermann with approximately the same yields throughout. About 7 g. of phenylcyclooctadiene was obtained, which had a refractive index very close to Hermann's sample. Upon treatment with ozone, phenylcyclooctadiene could produce several possible acids as shown below.



When the diene, VII-A or VII-A', was treated with ozone at 0° and the ozonide was decomposed in the presence of neutral silver oxide, two compounds, benzoylvaleric and benzoic acid were isolated. The benzoylvaleric acid was recrystallized from hexane several times (m.p. 75.5-76.5°) and it did not depress the melting point of an authentic sample obtained by ozonization of 1-phenylcyclohexene.



$$C_6H_5 \xrightarrow{O_3} C_6H_5\overset{O}{\overset{\|}{C}}(CH_2)_4CO_2H + C_6H_5CO_2H$$

The presence of benzoic acid as a product of the ozonization of phenylcyclooctadiene does not indicate that the isomeric diene VII-A is present in the sample, for 1-phenylcyclohexene yielded benzoic acid along with benzoylvaleric acid as shown above. The presence of benzoic acid may be due to further oxidation of the benzoylvaleric acid. The absence of adipic acid as a product of the ozonization of phenylcyclooctadiene was negative evidence indicating that VII-A was not present in the diene. These results indicate that VII-A' correctly represents the structure of the diene prepared by Hermann's synthesis.

EXPERIMENTAL

Ozonolysis of 1-phenylcyclooctadiene (VII-A') - A solution of 500 mg. (2.7 m.mole, n_D^{25} 1.5898) of phenylcyclooctadiene in 25 ml. of dry ethyl acetate was allowed to react at 0° with 260 mg. (5.4 m.mole) of ozone, introduced from an ozonizer during 25 minutes. Freshly prepared, neutral silver oxide (5 g.) suspended in 10 ml. of water was added to the mixture and the solvent was evaporated on a steam bath. A silver mirror was deposited on the wall of the vessel during the decomposition of the ozonide. The mixture was filtered, the filtrate was made basic and then extracted with ether (the ether extracts were discarded). The basic solution was acidified and extracted with ether several times. The ether extracts were combined and evaporated to dryness, and the solid residue was dissolved completely in hexane (adipic acid is insoluble in hexane). The hexane was removed under reduced pressure and the residue was sublimed in a short path still. White crystals of benzoic acid (0.11 g., m.p. 116-118° crude) appeared on the walls of the tube at 50-100° (1.0 mm.). A colorless liquid (benzoylvaleric acid) which distilled at 100-140° (1.0 mm.) solidified immediately upon scratching and was recrystallized from hexane to give white needles (0.25 g., 51 per cent, m.p. 75.5-76.5°).

<u>Anal</u>. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.91.

This acid did not depress the melting point of an authentic sample of benzoylvaleric acid.

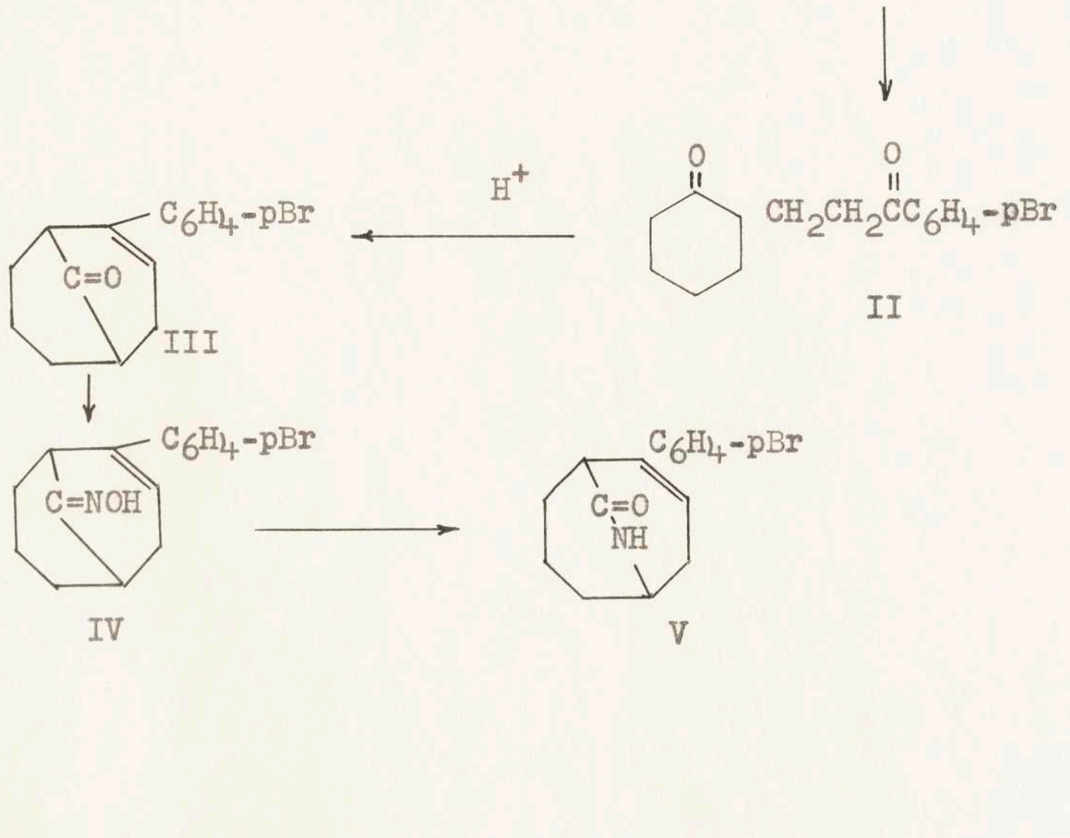
APPENDIX

THE SYNTHESIS OF EIGHT-MEMBERED CARBONYL BRIDGED COMPOUNDS HAVING A p-BROMOPHENYL SUBSTITUENT

The preparation of phenylcyclooctadiene from acetophenone, formaldehyde, and dimethylamine by a seven step synthesis has been described by E. C. Hermann.[5] At the time this work was in progress, it seemed desirable to duplicate Hermann's synthesis using p-bromoacetophenone instead of acetophenone with the eventual object of obtaining a p-bromophenyl substituted cyclooctatetraene. From such a compound a derivative suitable for attempted resolution might be prepared. Therefore, the synthesis shown below was undertaken as far as the lactam V at which point the work was abandoned as a result of the discovery of improved methods of obtaining substituted cyclooctatetraenes.

$$p\text{-}BrC_6H_4COCH_3 + HCHO + (CH_3)_2NH \cdot HCl \longrightarrow p\text{-}BrC_6H_4COCH_2CH_2N(CH_3)_2 \cdot HCl$$

I



This problem was not carried to completion, but compounds I, II, and IV were obtained analytically pure.

<u>β-Dimethylamine-p-bromopropiophenone hydrochloride (I)</u> - p-Bromoacetophenone (5.0 g., 0.025 mole) and dimethylamine hydrochloride (2.5 g., 0.031 mole) were dissolved in 25 ml. of absolute ethanol. To this solution 2.7 g. (0.033 mole) of 37 per cent formaldehyde solution and 0.1 ml. of concentrated hydrochloric acid were added. The solution was heated at reflux temperature in an oil bath for 6 hours and, after cooling, the alcohol was removed under reduced pressure. The residue was added to 100 ml. of acetone and, after cooling to 5°, white crystals formed at once. The crystals were collected on a filter and washed with ether, m.p. 191.5-193°. Two recrystallizations from methanol afforded 3.5 g. (48 per cent) of pure I, m.p. 195.2-196.2°.

<u>Anal</u>. Calcd. for $C_{11}H_{15}ONBrCl$: C, 45.15; H, 5.17; N, 4.79. Found: C, 45.06; H, 5.25; N, 4.63.

<u>2-(β-p-Bromobenzoylethyl)-cyclohexanone (II)</u> - A solution containing 1.4 g. (0.034 mole) of sodium hydroxide, 10 ml. of water and 6.7 g. (0.068 mole) of cyclohexanone was added to 5.0 g. (0.017 mole) of I in 35 ml. of 95 per cent ethanol. The solution was heated for

15 minutes at reflux temperature on a steam bath, and after cooling to room temperature, hydrochloric acid was added until the solution was neutral. After removal of the ethanol under reduced pressure, the residue was made strongly acidic with hydrochloric acid and then extracted with benzene. The benzene extract was shaken with sodium bicarbonate solution and then dried over anhydrous magnesium sulfate.

After removal of the benzene and cyclohexanone under reduced pressure, the residue was distilled in a short path still at 190-220°(0.3 mm.). The distillate was collected and then dissolved in cyclohexane. After cooling and scratching, pale yellow crystals, m.p. 70.2-70.6°, (1.1 g., 21 per cent) of II formed.

Anal. Calcd. for $C_{15}H_{17}O_2Br$: C, 58.26; H, 5.54; Br, 25.85. Found: C, 58.13; H, 5.31; Br, 25.78.

2-(p-Bromophenyl)-bicyclo[3.3.1]non-2-ene-9-one (III) - A solution of 31.0 g. (0.1 mole) of II in 21.0 ml. of glacial acetic acid and 4.8 ml. of concentrated hydrochloric acid was heated at reflux temperature in an oil bath for 24 hours. After removal of the acetic acid under reduced pressure, water (20.0 ml.) was added to the solution, which was then extracted with benzene. The benzene extract was washed with sodium bicarbonate solution and then dried over anhydrous magnesium sulfate. After removal of the benzene under reduced pressure, the residue was cooled causing brownish-white crystals to form. Two recrystallizations from methanol afforded 2.6 g. (89 per cent) of III, m.p. 88.1-89.1°.

Anal. Calcd. for $C_{15}H_{15}OBr$: C, 61.87; H, 5.19; Br, 27.45. Found: C, 61.50; H, 5.41; Br, 26.74.

2-(p-Bromophenyl)-bicyclo[3.3.1]non-2-ene-9-one oxime (IV) - A mixture of 1.0 g. (0.0034 mole) of III, 0.47 g. (0.0068 mole) of hydroxylamine hydrochloride, 1.5 ml. of pyridine and 1.5 ml. of ethyl alcohol was heated at reflux temperature for 24 hours on a steam bath. After removal of the alcohol and pyridine under reduced pressure, the residue was dissolved in benzene and extracted with 10 per cent hydrochloric acid. The benzene solution was then washed with sodium bicarbonate solution and the benzene was removed under reduced pressure. The solid residue was recrystallized twice from methanol to yield 0.53 g. (51 per cent) of IV, m.p. 143-144°.

Anal. Calc. for $C_{15}H_{16}ONBr$: C, 58.83; H, 5.27; N, 4.58; Br, 26.10. Found: C, 58.68; H, 5.50; N, 4.55; Br. 25.94.

5-Amino-2-(p-bromophenyl)-cyclooct-2-ene carboxylic acid lactam (V) - Benzenesulfonyl chloride (0.53 g., 0.003 mole) was added slowly to a mixture of 0.9 g. (0.003 mole) of IV and 10 ml. of pyridine with stirring and cooling.

The temperature of the reaction mixture was kept below 40°. The mixture was stirred for 30 minutes, after which 15 ml. of water was added. The mixture was extracted with chloroform and then the chloroform layer was washed with 10 per cent hydrochloric acid followed by sodium bicarbonate solution. The chloroform was removed under reduced pressure and the residue was recrystallized twice from methanol to yield 0.8 g. (86 per cent) of V, m.p. 173-185°.

Anal. Calcd. for $C_{15}H_{16}ONBr$: C, 58.83; H, 5.27. Found: C, 58.16; H, 5.40.

BIOGRAPHICAL NOTE

The author was born in Providence, Rhode Island, on October 6, 1923. He attended public schools in Needham, Massachusetts, and graduated from Needham High School in 1941. He entered Northeastern University in 1941 and attended there until July, 1943, at which time he entered the Marine Corps. During the following three years he served at various Naval and Marine Corps Posts in the United States and abroad. He was on Guam with the 3rd Marine Division and in North China with the 1st Marine Division. Following his discharge in 1946, he re-entered Northeastern University and graduated in June 1947. He was employed as a junior chemist by the Atlantic Refining Company from June 1947 to September, 1948, at which time he entered the graduate school at Tufts College, Medford, Massachusetts. He completed the requirements for an M.S. degree in June, 1949, having worked with Dr. Elmer Trumbull on the chemistry of camphene. He entered M.I.T. in July 1949 and was a Research Assistant for four semesters.