

It is believed valid to compare the order of reactivity found for the hydrocarbons in this work with the order of k_e/k_s for the corresponding chlorides listed above. The variation in this ratio shows that, except for methylcyclohexyl chloride, the tendency for the carbonium ions to eject a proton is in the same sequence as the order of reactivity of the hydrocarbons observed in this work.

An explanation of the apparent discrepancy with regard to the relative unreactivity of methylcyclohexane in the alkylation reaction and the pronounced tendency of its carbonium ion to eliminate a proton as shown by the ratio k_e/k_s may be sought in the relatively small value of k_1 for the tertiary methylcyclohexyl halide. This indicates that methylcyclohexane forms a carbonium ion much more slowly than methylcyclopentane, for example; thus, for the hexahydroaromatic this step is probably rate-controlling and it behaves as a relatively inert solute in the experiments at hand.

The ratios k_e/k_s listed above are also evidence in support of the experimentally deduced conclusion that the methylcyclopentyl-*t*-carbonium ion loses a proton more readily than the carbonium ions of the isoparaffins studied.

Discussion of the Mechanism of Inhibition of Disproportionation in Aluminum Chloride-catalyzed Isomerizations of Pentane and Hexane.—The facts disclosed about the reactivity of methylcyclo-

pentane in this work offer a new insight into the problem of the mechanism of disproportionation of the higher hydrocarbons. It has been shown previously that isopentane and isohexane containing minor amounts of alkyl fluoride undergo extensive disproportionation on treatment with boron trifluoride.¹¹ It is believed that the same conditions apply in disproportionations during aluminum chloride-catalyzed isomerizations as exist during disproportionations initiated by alkyl fluoride-boron trifluoride, namely, the simultaneous presence of appreciable concentrations of both carbonium ion and olefin derived from the isoparaffin. The inclusion of from 5 to 10% of methylcyclopentane provides a very active substance which reacts rapidly with carbonium ions derived from the isoparaffin. This, however, is not sufficient, since the naphthenylcarbonium ions might be expected to undergo hydrogen transfer with more isoparaffin. Here, the pronounced tendency of the *t*-methylcyclopentyl ion to lose a proton influences the course of the reaction. The conversion of the naphthenylcarbonium ion to its olefin corresponds essentially to the irreversible saturation of an isoparaffinic carbonium ion. Thus, the action of the methylcyclopentane in suppressing disproportionation is postulated to be one of reducing the concentration of "free," isoparaffinic carbonium ions.

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Cyclic Polyolefins. XXXIII. Compounds Derived from Cyclooctatetraenylmethyl Alcohol. Isomerization of Cyclooctatetraenylacetonitrile¹

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N,N-Dimethylcyclooctatetraenylmethylamine (II) and cyclooctatetraenylacetonitrile (III) have been prepared by displacement reactions from cyclooctatetraenylmethyl bromide (I). The nitrile III was converted into an isomer (VIII or IX) by migration of one of the nuclear double bonds into conjugation with the nitrile group on heating with triethylamine, or on treatment with sodium hydroxide at room temperature. Both of the nitriles were converted to amides by treatment with alkaline hydrogen peroxide.

This paper reports an investigation of several cyclooctatetraene derivatives prepared from cyclooctatetraenylmethyl alcohol, an allylic-type alcohol obtained by copolymerization of acetylene with propargyl alcohol.²

Attempts to prepare the *p*-toluenesulfonate of cyclooctatetraenylmethyl alcohol under conditions used for other alcohols in the cyclooctatetraene series^{2,3} and to use the ester as an intermediate in displacement reactions gave erratic results, probably because of side reactions between the reactive allylic-type tosylate and the base (usually pyridine) employed in its preparation. It was possible to prepare cyclooctatetraenylmethyl bromide from the alcohol and phosphorus tribromide in hexane in the presence of pyridine, however, and the pure bromide I was isolated by distillation in 65% yield. Reaction of the bromide with dimethylamine in benzene

yielded N,N-dimethylcyclooctatetraenylmethylamine (II, 43%), which was characterized as the crystalline picrate and hydrochloride. Cyclooctatetraenylacetonitrile (III) also was prepared from the bromide by reaction with potassium cyanide in aqueous tetrahydrofuran in the presence of potassium iodide. The nitrile III was purified and isolated in 44% yield by conversion into a non-crystalline silver nitrate complex, followed by regeneration with ammonium hydroxide and chromatography on silica gel. Infrared spectra of the bromide, tertiary amine and nitrile contain the bands previously noted as characteristic of monosubstituted cyclooctatetraenes,² and accordingly provide evidence supporting the structures of these compounds. In addition, the spectrum of the nitrile III contains a sharp band at 4.4 μ characteristic of the (unconjugated) nitrile group.

Reaction of cyclooctatetraenylacetonitrile with aqueous sodium hydroxide at room temperature did not yield the carboxylic acid, but resulted in partial isomerization forming a nitrile with an infrared ab-

(1) Supported in part by the Office of Naval Research under contract N5ori-07822, Project Designation NR356-096.

(2) A. C. Cope and D. F. Rugen, *THIS JOURNAL*, **75**, 3215 (1953).

(3) A. C. Cope and R. M. Pike, *ibid.*, **75**, 3220 (1953).

sorption band at 4.48μ , indicating that the nitrile group was conjugated. Isomerization of the nitrile III was most readily accomplished by heating under reflux with triethylamine in a nitrogen atmosphere for 70 hours, at which time the nitrile band of III at 4.4μ had disappeared completely and the pure isomer with a nitrile band at 4.48μ was isolated in 87% yield. In the isomerization, migration of an α -hydrogen occurs and a double bond shifts from the cyclooctatetraene nucleus of III into conjugation with the nitrile group. Formula VIII represents the structure that would be formed by a three-carbon tautomeric shift, while the cross-conjugated structure IX could be formed by a second three-carbon shift. In addition to differences between the infrared spectra of the isomeric nitriles (Fig. 1), the conjugated isomer has two strong maxima at 314 and $242.5 \text{ m}\mu$ in the ultraviolet

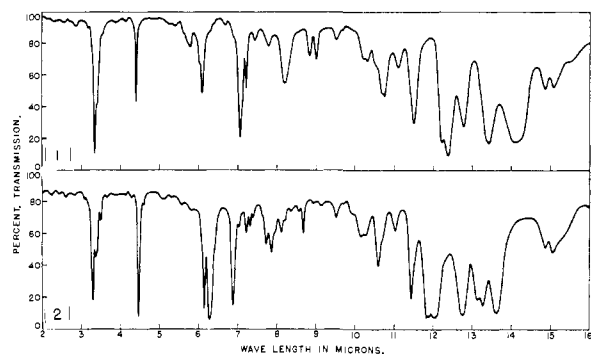
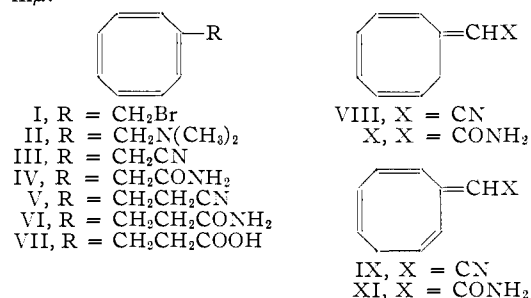


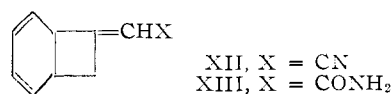
Fig. 1.—Infrared absorption spectra: curve 1, cyclooctatetraenylacetoneitrile (III); curve 2, 2,4,6(or 2,4,7)-cyclooctatrienyldeneacetoneitrile (VIII or IX), both as pure liquids in a 0.025-mm. cell.

spectrum, while cyclooctatetraenylacetoneitrile, like other cyclooctatetraene derivatives,² shows weak ultraviolet absorption becoming strong near $230 \text{ m}\mu$.



Since bases isomerized the nitrile III to VIII or IX, an attempt was made using β -cyclooctatetraenylethyl cyanide² (V) as a model compound to find milder conditions of hydrolysis. Reaction of V with dilute hydrogen peroxide in acetone containing a small amount of sodium carbonate yielded the crystalline amide, β -cyclooctatetraenylpropionamide (VI, 36%), which reacted with nitrous acid to form the known β -cyclooctatetraenylpropionic acid (VII). Under these conditions cyclooctatetraenylacetoneitrile was converted to cyclooctatetraenylacetamide (IV, 74%), and the isomeric nitrile (VIII or IX) also yielded the corresponding amide (X or XI), which was rather unstable but could be

isolated as a crystalline solid. The ultraviolet spectrum of cyclooctatetraenylacetamide is very similar to the spectrum of cyclooctatetraenylacetoneitrile and indicates that the cyclooctatetraene nucleus is present in the amide (formula IV). The spectrum of the isomeric amide (X or XI), like the corresponding nitrile, contains two maxima (at 243 and $314 \text{ m}\mu$). The ultraviolet spectra do not rule out bridged structures (XII and XIII) for the conjugated nitrile and amide, since 1,3,5-cyclooctatriene and the bridged isomer into which it is partially converted on heating, bicyclo[4.2.0]octa-2,4-diene, have very similar ultraviolet absorption spectra.⁴



Preliminary attempts to convert cyclooctatetraenylacetamide to cyclooctatetraenylacetic acid with nitrous acid under the conditions used for conversion of VI to VII were unsuccessful, for the product failed to crystallize and was converted to neutral, polymeric material on attempted short path distillation under reduced pressure.

Pharmacological

We are indebted to Dr. Karl H. Beyer and Mr. C. A. Ross of the Sharp and Dohme Division, Merck and Co., Inc., for preliminary pharmacological study of the hydrochloride of the amine II and of N,N-dimethyl- β -cyclooctatetraenylethylamine (V, ref. 2) and δ -cyclooctatetraenyl-*n*-butylamine (VI, ref. 3). Each compound was injected in the femoral vein of a dog under barbiturate anesthesia with both vagus nerves severed at the cervical level, and carotid blood pressure, respiration and heart rate were recorded, and electrocardiograms were taken. All three compounds produced weak vasopressor responses of moderate duration, but had less than one-thousandth of the vasopressor activity of epinephrine. The phenyl analogs of two of the amines (N,N-dimethylbenzylamine and N,N-dimethyl- β -phenylethylamine) also were tested as the hydrochlorides, and each produced a larger vasopressor response than the corresponding cyclooctatetraene derivative.

Experimental⁵

Cyclooctatetraenylmethyl Bromide (I).—Cyclooctatetraenylmethyl alcohol was prepared by copolymerization of propargyl alcohol and acetylene and purified by chromatography on silica gel by procedures described previously.² A solution of 0.95 g. of phosphorus tribromide in 15 ml. of dry hexane was added dropwise with stirring to a mixture of 1.34 g. of cyclooctatetraenylmethyl alcohol, 0.27 g. of pyridine and 10 ml. of dry hexane in an atmosphere of nitrogen at 0° . After the addition was complete, the ice-bath was removed, and the mixture was stirred for 6 hours at room temperature. The hexane solution was removed by decantation, washed twice with 25-ml. portions of water and dried over sodium sulfate. After filtration and concentration, distillation of the residue through a semi-micro column yielded 1.28 g.

(4) A. C. Cope, A. C. Haven, Jr., F. L. Ramp and E. R. Trumbull, *THIS JOURNAL*, **74**, 4867 (1952).

(5) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses, for the infrared spectra, which were determined with a Baird double beam infrared recording spectrometer, model B, fitted with a sodium chloride prism, and for the ultraviolet spectra, which were determined with a Cary ultraviolet recording spectrophotometer, model 11 MS.

(65%) of I, b.p. 75–77.5° (1.6 mm.), n_D^{25} 1.5849–1.5874. A redistilled analytical sample had b.p. 78° (1.6 mm.), n_D^{25} 1.5893, d_4^{25} 1.3634.

Anal. Calcd. for C_8H_9Br : C, 54.88; H, 4.60; Br, 40.57. Found: C, 55.03; H, 4.73; Br, 40.31.

N,N-Dimethylcyclooctatetraenylmethylamine (II).—A solution of 2.43 g. of the bromide I in 30 ml. of benzene was saturated with gaseous dimethylamine and allowed to stand overnight at room temperature. Water (20 ml.) was added, and the benzene was washed with a second 20-ml. portion of water and concentrated under reduced pressure at room temperature. Dry hydrogen chloride was passed through the resulting dry solution of II in a small volume of benzene, and the precipitate of the hydrochloride was separated by filtration. Recrystallization from a mixture of methanol and ether yielded 1.45 g. of the hydrochloride of II, m.p. 209–210.2°. The hydrochloride was added to 15 ml. of 10% sodium hydroxide and the amine II was extracted with two 20-ml. portions of ether. The extracts were diluted with benzene, concentrated under reduced pressure and the residue was fractionated through a semi-micro column. The yield of II was 0.85 g. (43%), b.p. 34–35° (0.1 mm.), n_D^{25} 1.5216–1.5222. An analytical sample had b.p. 35° (0.1 mm.), n_D^{25} 1.5222, d_4^{25} 0.9169.

Anal. Calcd. for $C_{11}H_{13}N$: C, 81.94; H, 9.38; N, 8.68. Found: C, 82.24; H, 9.34; N, 8.77.

N,N-Dimethylcyclooctatetraenylmethylamine picrate was prepared by adding 0.05 g. of the amine II to a saturated solution of picric acid in ether, and was washed with ether; the yield was 0.06 g., m.p. 145.7–146.2° (capillary inserted at 130°).

Anal. Calcd. for $C_{17}H_{19}N_4O_7$: C, 52.31; H, 4.65; N, 14.35. Found: C, 52.02; H, 4.87; N, 14.52.

N,N-Dimethylcyclooctatetraenylmethylamine hydrochloride was prepared by passing dry hydrogen chloride through a solution of 0.60 g. of II in dry ether. The precipitate was treated with activated charcoal in a mixture of methanol and ether and crystallized from that solvent; yield 0.41 g., m.p. 209–209.5° (dec., capillary inserted at 195°).

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16; N, 7.09. Found: C, 67.12; H, 8.21; N, 7.09.

Cyclooctatetraenylacetonitrile (III).—A solution of 5.42 g. of potassium cyanide and 1.5 g. of potassium iodide in 20 ml. of water was added to a solution of 6.76 g. of the bromide I in 50 ml. of tetrahydrofuran, and the mixture was heated under reflux on a steam-bath for 6 hours. The cooled solution was poured into 40 ml. of water, and then extracted with two 30-ml. portions of ether. The extracts were washed with two 25-ml. portions of water, dried over sodium sulfate and concentrated under reduced pressure. Fractionation through a semi-micro column yielded 5.34 g. of the crude nitrile III, b.p. 53–90° (0.06 mm.). A solution of the crude nitrile in 150 ml. of absolute ethanol was heated to boiling, 20.4 g. of powdered silver nitrate was added, and the mixture was heated under reflux until a clear solution was obtained. The excess silver nitrate was separated by filtering the hot solution, and the filtrate was cooled in an ice-bath. The solvent was decanted from the gummy, yellowish-green solid that separated, and the solid residue was dissolved in 20 ml. of water. The solution was added to 100 ml. of ice-cold concentrated ammonium hydroxide, which was extracted immediately with two 50-ml. portions of ether. The combined extracts were washed with water, dried over sodium sulfate and concentrated under reduced pressure, yielding 2.8 g. of a light-yellow liquid residue. This residue was chromatographed on a 13 × 2-cm. column of silica gel,² and the nitrile III was eluted with 200 ml. of a 10% solution of ether in pentane. Concentration and fractionation of the residue through a semi-micro column yielded 2.16 g. (44%) of III, b.p. 78–79° (0.10 mm.), n_D^{25} 1.5434–1.5442. An analytical sample had b.p. 79° (0.10 mm.), n_D^{25} 1.5442, d_4^{25} 1.0167.

Anal. Calcd. for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.84; H, 6.16; N, 9.84.

Cyclooctatetraenylacetamide (IV).—The nitrile III (0.30 g.) was added to 3 ml. of 10% hydrogen peroxide, and acetone was added until a homogeneous solution was obtained, followed by 0.5 ml. of 10% sodium carbonate solution.⁶

(6) Conditions adapted from a procedure described by J. V. Murray and J. B. Cloke, *THIS JOURNAL*, **56**, 2749 (1934).

The solution was allowed to stand at room temperature for 3 days, after which the acetone was removed with a stream of air and the aqueous suspension was cooled in an ice-bath. The pale yellow crystals of IV that separated were recrystallized from a mixture of benzene and 30–60° petroleum ether, yielding 0.25 g. (74%) of IV, m.p. 138.6–139.2°. An analytical sample that was recrystallized and sublimed at 0.03 mm. with a heating block temperature of 120–140° had m.p. 138.4–139°.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.79; H, 7.14; N, 8.74.

Attempts to convert the amide IV to cyclooctatetraenylacetic acid by treatment with sodium nitrite and hydrochloric acid under conditions described below for conversion of the next higher homolog VI into the acid VII were unsuccessful. The crude product was a viscous liquid which failed to crystallize and formed a dark, neutral, non-volatile solid on attempted short path distillation, apparently by decarboxylation and polymerization.

β -Cyclooctatetraenylpropionamide (VI).— β -Cyclooctatetraenylethyl cyanide² (0.30 g.) was treated with alkaline hydrogen peroxide in aqueous acetone for 4 days under the conditions described above for conversion of III to IV. The product was isolated in the same manner as IV, and purified by sublimation at 1.5 mm. with a heating block temperature of 110°. The yield of VI was 0.12 g. (36%), m.p. 61.8–63°. An analytical sample with the same melting point was recrystallized from a mixture of benzene and pentane.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.32; H, 7.49; N, 7.77.

β -Cyclooctatetraenylpropionic acid (VII) was prepared by adding 1 drop of concentrated hydrochloric acid to a solution of 56.8 mg. of the amide VI and 22.4 mg. of sodium nitrite in 4 ml. of water and 8 ml. of dioxane, and stirring the solution at room temperature for 10 hours. The solution was cooled with ice, made basic by addition of sodium hydroxide and extracted with benzene. The alkaline aqueous solution was acidified with hydrochloric acid and extracted with two 20-ml. portions of ether. The extracts were dried over sodium sulfate, concentrated and the residue was crystallized from hexane, yielding 20 mg. (35%) of the acid VII, m.p. and mixed m.p. with an authentic sample,² 58.9–59.8°.

2,4,6(or 2,4,7)-Cyclooctatrienylideneacetonitrile (VIII or IX).—A solution of 0.68 g. of the nitrile III in 10 ml. of freshly distilled triethylamine was heated under reflux in a nitrogen atmosphere for 70 hours. The solution was cooled, diluted with 20 ml. of ether, and extracted with four 25-ml. portions of 3% hydrochloric acid at 0°. The ether solution was dried over sodium sulfate, concentrated under reduced pressure, and the residue was fractionated through a semi-micro column. The yield of the isomeric nitrile VIII or IX was 0.59 g. (87%), b.p. 79° (0.3 mm.), n_D^{25} 1.6235–1.6255. An analytical sample had b.p. 79° (0.3 mm.), n_D^{25} 1.6255, d_4^{25} 1.0226; $\lambda_{max.1}$ 242.5 μ (log ϵ 4.31), $\lambda_{max.2}$ 314 μ (log ϵ 4.00) in 95% ethanol.

Anal. Calcd. for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.95; H, 6.38; N, 9.83.

The isomeric nitrile VIII or IX with an infrared spectrum essentially identical with the spectrum of the sample described above also was obtained by shaking the nitrile III with 20% sodium hydroxide at room temperature for 55 hours.

2,4,6(or 2,4,7)-Cyclooctatrienylideneacetamide (X or XI).—The nitrile VIII or IX was treated with hydrogen peroxide in alkaline aqueous acetone under the conditions described for conversion of III to IV. The extract of the amide was concentrated at a low temperature in a nitrogen atmosphere to avoid decomposition and the product was purified by sublimation at 0.1 mm. with a heating block temperature of 120–130°. The rather unstable amide X or XI was isolated as yellow crystals, m.p. 96–98° dec., in a yield of 0.11 g. (32%). An analytical sample prepared by resublimation and crystallization from a mixture of benzene and 30–60° petroleum ether had m.p. 99–100° dec.; $\lambda_{max.1}$ 243 μ (log ϵ 4.32), $\lambda_{max.2}$ 314 μ (log ϵ 3.95) in 95% ethanol.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.45; H, 7.05; N, 8.55.