The Structure of Cadinene

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Cadinene is the most widely distributed sesquiterpene found in nature, but it is generally obtained from oil of cade or oil of cubebs. The oil is distilled at 12 mm., and the substance is isolated from the fraction boiling at 125–140° as the nicely crystalline and easily purified dihydrochloride melting at 119–120°. Cadinene is regenerated from the dihydrochloride by treatment with sodium acetate in acetic acid.

The structure of cadinene has been generally accepted as I, in which the only point of uncertainty was thought to be the position of the double bond in ring B. The carbon skeleton of this molecule has been established[2] by dehydrogenation
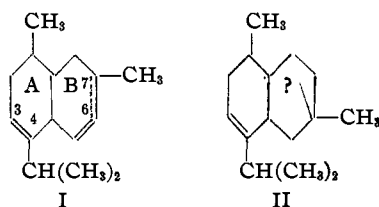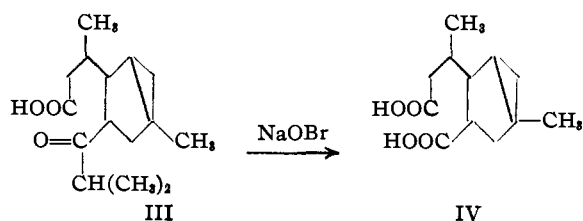

to 4-isopropyl-1,6-dimethylnaphthalene (or cadalene), identified by synthesis. The evidence upon which the positions of the double bonds is based is of a much less certain nature and in some cases is open to serious question.

Formula (I) is due to Ruzicka and Stoll[3] and to Semmler and Stenzel.[4] There is no direct evidence for the location of the double bond in ring A of cadinene, and the position adjacent to the isopropyl group was deduced from the relationship of cadinene to copaene (II). It was observed[4] that a copaene-containing fraction gave cadinene dihydrochloride in 30% yield when treated in ether solution with dry hydrogen chloride, and from this fact alone it was concluded that one of the double bonds of cadinene was in the same position as the copaene double bond.

The structure of copaene (II) is that of Semmler and Stenzel[4] and was arrived at by a study of the oxidation of the sequiterpene. With permanganate or ozone, an acidic product was ob-

tained which was esterified and distilled. Analysis of the main fraction agreed well with the methyl ester of the keto acid, III. The presence of a carbonyl group was indicated by the forma-

tion of a semicarbazone. Treatment of the keto acid with alkaline hypobromite at low temperatures apparently removed the isopropyl group as indicated by analysis of the distilled dimethyl ester of the product (IV). No yields were given for these products.

The double bond in ring B was placed at 5,6 or 6,7[5] by Ruzicka and Stoll.[3] Their conclusion was based on the analysis and properties of an impure ozonization product. However, they excluded from their list of possible formulas all of those which did not have one of the double bonds at 3,4, adjacent to the isopropyl group.

The present work was undertaken for the purpose of providing definite evidence for the positions of the cadinene double bonds. The method is similar to that used by Ruzicka and Sternbach[6] for the location of the nuclear double bond of dextropimaric acid. Cadinene was converted to the mono- and di-oxide by treatment with perbenzoic acid. In order to determine the conditions necessary to accomplish this, the reaction of the per acid with cadinene in different solvents was studied. The results, summarized in Table I, indicate that the rate is considerably greater

TABLE I

ATOMS OF OXYGEN ABSORBED PER MOLE OF CADINENE

0.276 g. of cadinene in 75 cc. of solvent and 25 cc. of 0.333 N perbenzoic acid in chloroform at 6°.

Solvent	0.5	1	Time, hours 4.5	9	65
Ether			1.31	1.49	1.78
Ethyl acetate			1.50	1.61	1.82
Chloroform	1.66	1.74	1.84	1.86	1.84

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(2) Ruzicka and Meyer, *Helv. Chim. Acta.*, **4**, 505 (1921); Ruzicka and Seidel, *ibid.*, **5**, 369 (1922).

(3) Ruzicka and Stoll, *ibid.*, **7**, 84 (1924).

(4) Semmler and Stenzel, *Ber.*, **47**, 2555 (1914).

(5) Ruzicka and Stoll[3] suggested in this paper that cadinene may be a mixture of isomers with double bonds in these positions.

(6) Ruzicka and Sternbach. *Helv. Chim. Acta*, **23**, 124 (1940).

in chloroform solution. At 15° the rates were nearly the same. In one run in chloroform using a nine-fold excess of the per acid, titration indicated the absorption of 2.5 atoms of oxygen after one hundred sixty-eight hours. In another experiment using only one mole of per acid per mole of cadinene in chloroform, the formation of the monoxide was complete in twenty minutes.
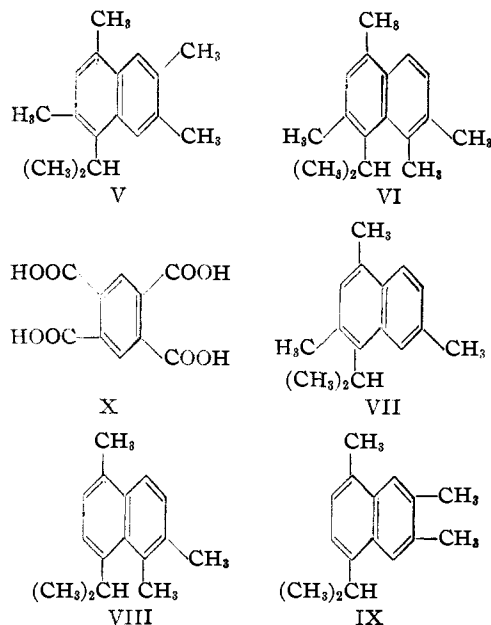
The cadinene mono- and di-oxide were prepared in chloroform solution and were obtained as oils which could not be completely purified. These products were treated with excess methyl magnesium chloride in ether, followed by dehydrogenation with selenium. Fractionation of the products of these reactions gave in each case only a small amount of material that was higher-boiling than cadalene. This indicates that the greater portion of the product consists of naphthalenes, less highly alkylated than cadalene, and that loss of the isopropyl group and perhaps some methyl groups must have occurred to considerable extent. The fraction, boiling above cadalene, from the dioxide crystallized in the condenser and purification gave a solid hydrocarbon melting at 102–103° which had the composition and molecular weight of a dimethylcadalene. Similarly from the monoxide was obtained the picrate of a liquid hydrocarbon which analytical data showed to be a monomethylcadalene. It should be pointed out that these are the only substances of a molecular weight greater than that of cadalene found in the reaction mixtures.

In these reactions, the introduction of a methyl group into the molecule would take place according to the following series of reactions

$$H-\overset{|}{\underset{}{C}}=\overset{|}{\underset{}{C}}-R \longrightarrow H-\overset{|}{\underset{}{C}}\underset{\diagdown O\diagup}{\overset{|}{-}\overset{}{C}}-R \longrightarrow$$

$$H-\overset{|}{\underset{CH_3}{C}}\overset{|}{\underset{OH}{-}}\overset{|}{\underset{}{C}}-R \longrightarrow -\overset{}{\underset{CH_3}{C}}=\overset{|}{\underset{}{C}}-R$$
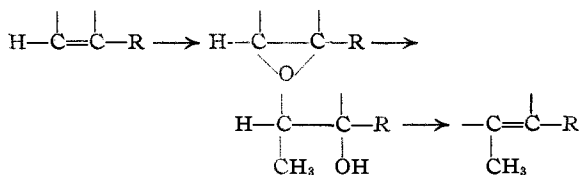
Thus the position of the additional methyl groups in the dimethyl- and monomethyl-cadalenes reveals the location of the double bonds in the cadinene molecule.

On the basis of the Ruzicka and Stoll formula for cadinene the dimethylcadalene would be represented by formula V or VI and the monomethyl derivative by VII, VIII or IX. Oxidation of the dimethylcadalene by chromic acid followed by nitric acid gave pyromellitic acid (X). This evidence definitely eliminates formula VI for di-

methylcadalene and proves that the ring which does not contain the isopropyl group must have methyl groups at 6 and 7 and must be unsubstituted at 5 and 8. On this evidence, alone, the double bond in ring B of cadinene is located at the 6,7 position. Therefore, by this evidence also, formula VIII for monomethylcadalene is eliminated.
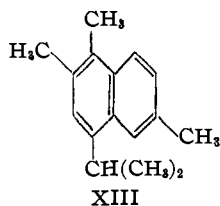
With the position of the ring B double bond of cadinene established, and on the assumption that the conclusions[3] regarding the position of the other double bond (formula I) are valid, the formula for dimethylcadalene is V and monomethylcadalene, either VII or IX. Accordingly the synthesis of compounds V and IX was undertaken. The synthetic 4-isopropyl-1,3,6,7-tetramethylnaphthalene (V) is a nicely crystalline solid melting at 96.5–97° but the mixed melting point with dimethylcadalene (m. p. 102–103°) was 71–78°. The melting point of the picrate also was depressed by admixture with dimethylcadalene picrate. Similarly synthetic 4-isopropyl-1,6,7-trimethyl naphthalene (IX) is a solid melting at 39.5–40° whereas monomethylcadalene is liquid at room temperature. The picrate of the synthetic hydrocarbon melts sharply 20° lower than monomethylcadalene picrate.

Thus with formula V eliminated there is only one isopropyl-tetramethylnaphthalene that is consistent with the observed oxidation to pyromellitic acid, namely, the 4-isopropyl-1,2,6,7-tetramethyl derivative (XII). Synthesis of this

XI → XII
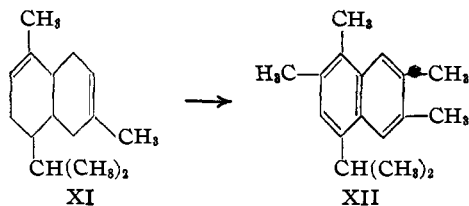
hydrocarbon gave a product shown to be identical with dimethylcadalene by the mixed melting points of the hydrocarbons and their picrates. The structure of cadinene is therefore represented by formula XI.

Of the two possible formulas for monomethylcadalene, one (IX) has been shown to be different from the hydrocarbon from cadinene monoxide. Monomethylcadalene therefore, must be 4-isopropyl-1,2,6-trimethylnaphthalene (XIII). Synthesis of this substance gave a hydrocarbon identical, by mixed melting points of the picrate, styphnate, and trinitrobenzene derivative, with monomethylcadalene. The identification of this hydrocarbon gives added proof of the 1,2 rather than the 3,4 position for the double bond in ring A of cadinene.

XIII

We think that the isolation of these two hydrocarbons provides definite proof that at least the great preponderance of the material in cadinene is represented by formula XI. As we have pointed out, the mono- and di-methylcadalenes are the only products of molecular weight greater than cadalene that were found. The ease with which the solid dimethylcadalene was isolated in pure form from the higher boiling fractions of the distillate precludes the possibility of the presence of appreciable amounts of isomeric dimethylcadalenes. This is supported by the observation that our synthetic isomer of dimethylcadalene (V) and its picrate have about the same solubility as the natural derivative, and a separation of these substances, therefore, would be difficult.

That the yield of these hydrocarbons from the cadinene oxides is low, is not surprising since the reactions involved would not be expected to go entirely in one direction or to give good yields of a

single product. In the previously mentioned application of this method to dextropimaric acid[6] the yield of hydrocarbon isolated was quite low. That one of the reasons for the low yields from cadinene was the loss of the isopropyl group during dehydrogenation, was shown by the isolation of 1,6-dimethylnaphthalene from one of the low-boiling fractions. When one atom of oxygen was absorbed by cadinene, the product must have been a mixture of some dioxide and some unchanged cadinene with a larger quantity of cadinene monoxide since cadalene picrate was isolated from one fraction of the final product. None of this substance was found in the hydrocarbon mixture from the dioxide.

With the double bonds of cadinene in the 1,2 and 6,7 positions the conversion of copaene (II) to cadinene and dihydrochloride [4] (XIV) is difficult to explain. It can only be pointed out that Semmler and Stenzel[4] worked with a "copaene-


XIV
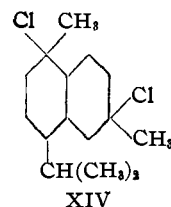
containing fraction," and, although they state that their fraction was nearly pure and gave a good yield of the dihydrochloride, the only yield reported was that of other workers who obtained 30% of the product. On the basis of the information available, the possibility that some substance other than that represented by the copaene formula II, gives rise to the cadinene dihydrochloride, cannot be completely excluded.

Our syntheses of the polyalkylnaphthalenes were carried out by well-known methods and reactions. Most of the reactions have been described in the papers of Bachmann, Cole and Wilds[7] and of Kloetzel,[8] where they were used on more or less similar substances. Only a few of the compounds which we have prepared in these series of reactions have appeared previously in the literature. A few interesting observations in connection with this work are given below.

In several cases, substances such as compounds XV and XVI were obtained as solid or partially solid products and it was relatively easy to isolate one of the possible stereoisomeric forms. In

(7) Bachmann, Cole and Wilds, THIS JOURNAL, 62, 825 (1940).
(8) Kloetzel, ibid., 62, 1708 (1940).

XV   XVI
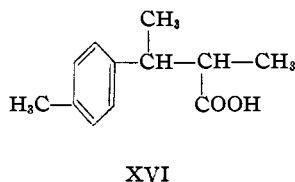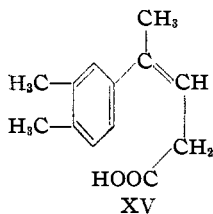
previous work[8] similar substances were liquid and were not separated. That the crude acid (XVI) was indeed a mixture of isomers was demonstrated by the determination of the neutral equivalent of the pure isomer, m. p. 133–133.5°, and the residual liquid mixture of isomers. The values were the same.

It was observed that the glyoxalate (XVII) obtained in 85% yield from 4,6,7-trimethyl-1-tetralone, appeared to be a single individual since

XVII

XVIII
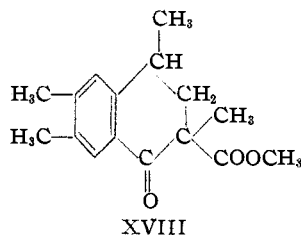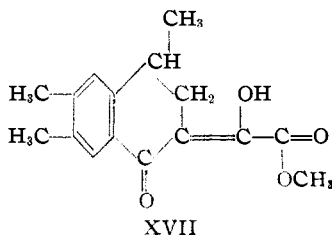
even the crude product (91% yield) melted rather sharply at 74.5–75°, and crystallization raised this melting point only one-half a degree. The substance may exist in the enol form in which there is no asymmetric center at carbon atom number two. An intense ferric chloride color reaction and a rapid absorption of bromine were noted. Support for this idea was found when the 2-methyl-2-carboxylate (XVIII) prepared from the glyoxalate was obtained as a mixture of isomers from which one pure form m. p. 86–87° was isolated. As would be expected, neither the pure isomer nor the liquid mixture of isomers gave a positive ferric chloride or bromine test.

In the Reformatsky reaction with p-methylacetophenone and α-bromopropionic ester, we found no evidence of dehydration of the hydroxy ester on distillation. A low-boiling neutral product was isolated from the reaction mixture. It is

thought that this substance may be the tetramethylstyrene formed by decarboxylation. Neutral products of this nature have been reported by others[9] in similar reactions.

Experimental[10]

Cadinene.—The cadinene used in this work was obtained from oil of cade by the method of Henderson and Robertson[11] with a few modifications. Distillation of cade oil gave 56% of a fraction b. p. 125–140° (12 mm.). The dihydrochloride was obtained by saturating a solution of this fraction in 0.6 volume of dry ether with hydrogen chloride gas. Additional crops were obtained by concentrating the mother liquor in vacuum and resaturating with hydrogen chloride. Crystallization of the dihydrochloride from ethyl acetate gave a pure product melting at 119–120°. Loss of hydrogen chloride from the molecule was observed when an alcohol solution was boiled. The cadinene was regenerated by treatment with sodium acetate in acetic acid and fractionation gave a product with the following constants, b. p. 136–138° (11 mm.), $[\alpha]^{25}D$ −113°, d^{20}_4 0.9199, $n^{20}D$ 1.5071, $[RL]^{20}D$ 66.11 (found), 66.16 (calcd.).

Perbenzoic Acid Titrations of Cadinene.—These titrations were run with 0.276 g. of cadinene in 75 cc. of the different solvents and 25 cc. of a 0.333 N perbenzoic acid solution in chloroform. This represents an excess of 1.1 moles of the acid. The values were determined by titrating 10-cc. aliquots at the intervals designated. Most of the results are summarized in Table I. In addition to these data, one run was made in chloroform with 9.1 moles of perbenzoic acid per mole of cadinene and titration after one hundred sixty-eight hours indicated the absorption of 2.5 atoms of oxygen.

The rate of addition of the first atom of oxygen was determined using molar quantities of perbenzoic acid and cadinene in chloroform. Titrations indicated 98% reaction in five minutes and 100% in twenty minutes.

Cadinene Dioxide.—A mixture of 5080 cc. of 0.331 N perbenzoic acid solution in chloroform and 45 g. of cadinene in 200 cc. of chloroform was allowed to stand at 5°. After forty-nine hours, titration of an aliquot indicated the absorption of two atoms of oxygen. The mixture was shaken with a solution of 106 g. of sodium thiosulfate and 95 g. of sodium carbonate in 2 liters of water. After washing with water and drying, the chloroform was removed by distillation through a column. On distillation of a sample of the residue at 0.2 mm., about two-thirds of the product was obtained which boiled at 106–131° and the rest remained in the distilling flask as a resin. A redistillation of this product gave the same results.

The whole product was distilled in a Hickman still at a bath temperature of 68–73°, and the following fractions were obtained: I, 2.0 g. at 0.2 mm. (discarded); II, 22.2 g. at 2 × 10⁻⁴ mm.; III, 13.3 g. at 2 × 10⁻⁴ mm.; and IV, 0.5 g. of residue (discarded). The second fraction was somewhat viscous and analyses (C, 75.63, 75.60; H, 10.10, 10.19) indicated that it was nearly pure dioxide (calcd.:

(9) Burton and Shoppee, *J. Chem. Soc.*, 1160 (1935).

(10) All melting points are corrected.

(11) Henderson and Robertson, *J. Chem. Soc.*, **125**, 1992 (1924).

C, 76.22; H, 10.24). The third fraction was still more viscous (*Anal.* C, 75.06, 75.03; H, 12.04, 12.22).

Cadinene Monoxide.—Cadinene (47 g.) was treated with 2475 cc. (2% excess) of a 0.190 N solution of perbenzoic acid in chloroform. One atom of oxygen was absorbed in one hour and the product was worked up as described above. Distillation at 0.3 mm. gave 44.5 g. (88%) of material boiling at 91–119°. The analyses of this product (C, 79.92; H, 10.76) as compared with the calculated value for the monoxide (C, 81.78; H, 10.98) gives some indication of its purity.

4-Isopropyl-1,2,6,7-tetramethylnaphthalene (Dimethylcadalene)(XII) from Cadinene Dioxide.—The Grignard reagent was prepared from 36 g. of magnesium and excess methyl chloride in 1 l. of ether. To 625 cc. of this solution, the fraction II of the cadinene dioxide (22.2 g.) in 100 cc. of ether was added at a rate that maintained gentle refluxing. After the addition, the mixture was refluxed for seventy-two hours. After decomposition with ice and hydrochloric acid, and washing with sodium hydroxide solution, the solution was dried over anhydrous potassium carbonate and evaporated. The residue was heated with 35 g. of powdered selenium with nitrogen stirring. At 135° water was evolved. The temperature was slowly raised to 180–190° and maintained at this point for twenty-five hours. When no more gas was evolved the product was dissolved in ether, washed with alkali and water and dried. After removal of the solvent the product was distilled through a three-foot column and there was obtained 13.1 g. of distillate, b. p. 114–133° (6 mm.) and 1.6 g. of residue.

A similar treatment of fraction III of cadinene dioxide with 375 cc. of the methylmagnesium chloride solution and dehydrogenation as above using 21 g. of selenium gave 5.1 g. of distillate, b. p. 114–126° (6 mm.), and 3.0 g. of residue.

These two distillates were combined and, after filtration through an alumina column in petroleum ether solution, were fractionated at 12 mm. through a three-foot Podbielniak column. After removal of three fractions totaling 13.1 g. and boiling up to 162° [cadalene b. p. 154–158° (12 mm.)], 1.5 g. of product (b. p. 162–166°) was obtained. An additional 0.4 g. of material which partially solidified was forced through the still by raising the temperature. A further quantity of this partly crystalline material was obtained by distilling from a small flask the residue from this fractionation (1.24 g.) combined with the residues from the two previous distillations. The combined distillates, which contained solid material, gave 0.6 g. of crude dimethylcadalene (m. p. 93–95°) from methanol. Three crystallizations from methanol gave 0.25 g. of glistening plates melting constantly at 102–103°.

Material obtained by sublimation of the distillation residues combined with the mother liquors gave an additional 0.27 g. of pure hydrocarbon along with 0.17 g. of the picrate (m. p. 141.5–142.5°). *Anal.*[12a] Calcd. for C₁₇H₂₂: C, 90.20; H, 9.80. Found: C, 90.20, 90.22; H, 9.93, 9.96.

The *picrate* was obtained from equivalent quantities of the hydrocarbon and picric acid in methanol as deep red,

silky needles melting sharply at 145°. *Anal.*[12a] Calcd. for C₁₇H₂₂·C₆H₃O₇N₃: N, 9.23; mol. wt., 455. Found: N, 9.66; mol. wt. (by titration),[13] 457, 457.

By treatment of the fraction (1.5 g.) boiling at 162–166° with picric acid followed by seven recrystallizations of the product, 20 mg. of the above picrate (m. p. 144°) was obtained.

From the lower boiling fractions complex mixtures of picrates were obtained and no pure products could be separated. No cadalene picrate was found in any of these fractions.

The Oxidation of 4-Isopropyl-1,2,6,7-tetramethylnaphthalene (XII).—To a solution of 0.135 g. of the hydrocarbon in 1 cc. of glacial acetic acid at 65° was added a solution of 0.205 g. of chromic anhydride in 1 cc. of glacial acetic acid and three drops of water. A vigorous reaction began immediately and it was necessary to cool the reaction mixture to prevent boiling. After two hours at 45–50° and one hour at 60° the mixture was poured into water and extracted with ether. Evaporation of the washed ether extract gave 94 mg. of a yellow oil from which no crystalline material could be obtained. Oxidation of this oil with 1 cc. of concentrated nitric acid in 2 cc. of water in a sealed tube at 195° for twelve hours gave, after evaporation, a colorless crystalline solid. Treatment with excess diazomethane in ether gave, after one crystallization from methanol, 55 mg. of the tetramethyl ester of pyromellitic (1,2,4,5) acid (m. p. 139.5–142°). Recrystallization gave pure ester (m. p. 142–143.5°) which did not depress the melting point of an authentic sample.

4-Isopropyl-1,2,6-trimethylnaphthalene (Monomethylcadalene)(XIII) from Cadinene Monoxide.—In a manner similar to that described above for cadinene dioxide, 44.5 g. of the monoxide was treated with excess methylmagnesium chloride. Dehydrogenation of 29.3 g. of this product with 42 g. of powdered selenium was carried out at 180° until all of the water was removed and then at 310–330° for twenty-seven hours. Fractionation at 12 mm. in a thirty-inch Podbielniak column gave the following fractions: I, 1.49 g., b. p. 124–131°; II, 2.28 g., b. p. 131–139°; III, 2.88 g., b. p. 143–150°; IV, 3.54 g., b. p. 150–157°; V, 3.08 g., b. p. 157–162°; residue, 1.69 g.

Fraction V was converted to the **picrate** as previously described and after five recrystallizations of the product 0.23 g. of brilliant red needles melting constantly at 142.5–143° was obtained. A mixture of this picrate with that of the dimethylcadalene (m. p. 145°) melted at 130–132°.

Anal.[12b] Calcd. for C₁₆H₂₀·C₆H₃O₇N₃: N, 9.52; mol. wt., 441. Found: N, 9.90; mol. wt. (by titration),[13] 447.

The **trinitrobenzene derivative** crystallized in long, thin, golden needles from methanol, m. p. 167.5–168°.

The **styphnate,** orange needles from methanol, melted at 170–170.5°.

Other Hydrocarbons from Cadinene Monoxide.—(A) **Cadalene.** Fraction IV was converted to the picrate and, after five recrystallizations from methanol, 361 mg. of cadalene picrate m. p. 111.5–112° was obtained. This substance did not depress the melting point of authentic cadalene picrate. *Anal.*[12b] Calcd. for C₁₅H₁₈·C₆H₃O₇N₃: N, 9.84; mol. wt., 427. Found: N, 10.31; mol. wt. (by

(12) Analyses by (a) Lyon Southworth; (b) Arlington Laboratories, Chagrin Falls, Ohio; (c) Eleanor Werble.

(13) Campbell, Soffer and Steadman, THIS JOURNAL, **64,** 425 (1942).

titration),[13] 431. (B) **1,6-Dimethylnaphthalene.** From fractions I and II, picrates melting constantly at 112.5–113.5° were obtained (total yield 0.95 g.). The melting points of these samples were not depressed on mixing with each other or with 1,6-dimethylnaphthalene picrate (m. p. 112.5–113.5°), whereas a mixture with cadalene picrate (m. p. 111.5–112°) melted at 85–90°.

Anal.[12b] Calcd. for $C_{12}H_{12} \cdot C_6H_3O_7N_3$: N, 10.91; mol. wt., 385. Found: N, 11.09, 11.34; mol. wt. (by titration),[13] 378, 382.

Similarly the **trinitrobenzene** derivative, m. p. 134–135° was identical with the derivative of the 1,6-dimethyl compound. The styphnates could not be obtained from either sample as well-defined, sharp-melting crystals.

The Synthesis of 4-Isopropyl-1,3,6,7-tetramethylnaphthalene (V)

3-(3,4-Dimethylbenzoyl)-propionic Acid.—Following the procedure of Barnett and Sanders[14] the reaction was carried out with 80 g. of succinic anhydride and 93 g. of *o*-xylene. The recrystallized product (145 g., m. p. 129–129.5°) was obtained in 88% yield.

The **methyl ester** was prepared by refluxing, for six hours, a mixture of 120 g. of the acid, 160 cc. of absolute methanol and 10 cc. of concentrated sulfuric acid. After working up the reaction mixture in the usual way, 115 g. (90%) of the ester b. p. 161–162° (1.5 mm.) was obtained. From the alkaline washings 3.7 g. of starting material (m. p. 128–129°) was recovered.

The **methyl ester semicarbazone**, prepared from a small sample in the usual manner, melted at 157–157.5° after crystallization from aqueous ethanol.

4-(3,4-Dimethylphenyl)-pentene-3-oic Acid (XV).—Following the method used by Kloetzel[8] for a similar preparation, the Grignard reagent from 16.1 g. of magnesium and 93.6 g. of methyl iodide in 325 cc. of ether was added to a stirred and cooled (−5°) solution of 105 g. of the keto ester in 475 cc. of ether over a two and one-half hour period. After thirty minutes more at −5°, the solution was allowed to come to room temperature and then refluxed for three hours. Decomposition was accomplished with ice and hydrochloric acid. The color was removed from the ether layer by shaking with water containing a little sodium thiosulfate and the acidic product was extracted with sodium carbonate solution. The aqueous extract was heated to remove the ether and acidified at 0° with stirring. The product weighed 60.5 g. (62%), m. p. 55.5–58°, and consists of a mixture of geometric isomers (see similar product below). Recrystallization from 30–60° petroleum ether gave one pure isomer, m. p. 78–80°, and an oily residue.

Anal. Calcd. for $C_{13}H_{16}O_2$: neut. equiv., 204. Found: neut. equiv., 205.

4-(3,4-Dimethylphenyl)-pentanoic Acid.—The crude unsaturated acid above (53 g.) was hydrogenated in 140 cc. of acetic acid with 0.26 g. of Adams catalyst. Distillation of the product gave 46 g. of a colorless viscous oil, b. p. 146–147° (1 mm.), and 3.9 g., b. p. 147–152° (1 mm.). The total yield was 86%. This product gives no test for unsaturation with alkaline potassium permanganate or with bromine.

Anal. Calcd. for $C_{13}H_{18}O_2$: neut. equiv., 206. Found: neut. equiv., 207.

4,6,7-Trimethyl-1-tetralone.—Cyclization was brought about by treating 5.1 g. of the dimethylphenylvaleric acid with 105 g. of anhydrous hydrogen fluoride for sixteen hours at room temperature. The product was washed and dried in ether solution and distilled, yielding 3.12 g. (69%) b. p. 111.5° (0.4 mm.). The ketone crystallized on immersion in a dry-ice-bath and melted at 28.5–30°.

In another run the acid was cyclized by heating for two hours on the steam-bath with 80% sulfuric acid; yield 65%, m. p. 28–29°. Recrystallization from 20–40° petroleum ether gave a product melting sharply at 30°.

Anal.[12c] Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.44, 82.82; H, 8.51, 8.23.

The **semicarbazone**, prepared in the usual manner, and crystallized from absolute ethanol, melted at 238° with decomposition.

For proof of structure 0.33 g. of the ketone was oxidized with 1.5 cc. of concentrated nitric acid and 3 cc. of water at 180° for fourteen hours, followed by heating with an additional 1 cc. of nitric acid at 190° for thirty-six hours. The acid product was isolated and esterified as previously described. Crystallization from methanol gave pyromellitic (1,2,4,5) ester (m. p. 139.5–142°) which did not depress the melting point of an authentic sample.

Methyl 4,6,7-Trimethyl-1-tetralone-2-glyoxalate (XVII). —By the procedure of Bachmann, Cole and Wilds,[7] 6.0 g. of the trimethyltetralone was condensed with the sodium derivative of dimethyl oxalate prepared from 1.54 g. of sodium, 25 cc. of absolute methanol, and 7.55 g. of the ester. The crude glyoxalate (m. p. 74.5–75°) was obtained in 91% yield. One crystallization from methanol gave 7.4 g. (85%) of nearly pure material (m. p. 75–75.5°). A sample recrystallized for analysis melted sharply at 77°.

Anal.[12c] Calcd. for $C_{17}H_{18}O_4$: C, 70.05; H, 6.62. Found: C, 70.23; H, 6.97.

The glyoxalate gives a deep red color with ferric chloride in aqueous ethanol, it readily absorbs bromine in carbon tetrachloride solution, and it reduces an alkaline solution of potassium permanganate.

2,4,6,7-Tetramethyl-2-carbomethoxy-1-tetralone(XVIII). —By known[7,8] methods 6.85 g. of the glyoxalate (m. p. 175–175.5°) was converted into **4,6,7-trimethyl-2-carbomethoxy-1-tetralone** with powdered glass at 180°. The distilled product weighed 5.1 g. (83%) and boiled at 153–155° (1 mm.). The ester gives an intense violet color with ferric nitrate in aqueous ethanol and absorbs bromine in carbon tetrachloride solution readily.

By methods which have appeared[7,15] in the literature, 4 g. of the keto ester was methylated using the sodium methylate from 1.65 g. of sodium and 5 cc. of methyl iodide. Distillation of the product gave 3.08 g. (76%) of a viscous oil, b. p. 149–153° (0.9 mm.). In a larger run the yield was 87%. On cooling in a dry-ice-bath in the presence of petroleum ether the oil solidified to a waxy mass. This is a mixture of isomeric forms from which one pure isomer was isolated in poor yield by crystallization from 30–60° petroleum ether. This isomer melted at 86–87°.

(14) Barnett and Sanders, *J. Chem. Soc.*, 434 (1937).

(15) Titley, *ibid.*, 2577 (1928).

Anal.[12c] Calcd. for $C_{15}H_{20}O_3$: C, 73.82; H, 7.75. Found: C, 73.69; H, 7.89.

In contrast to the unmethylated compound neither the crude distillate nor the purified isomer gives a color with ferric nitrate or absorbs bromine.

2,4,6,7-Tetramethyl-1-tetralone.—By previously described methods,[7,8,15] hydrolysis and decarboxylation of the crude tetramethyl keto ester (2.8 g.) was accomplished. After steam distillation the product was washed in ether solution. Evaporation of the solvent gave 1.96 g. (89%) of crude tetralone (m. p. 65–72°). This substance can exist in two diastereomeric forms. Crystallization from methanol gave one isomer m. p. 89–89.5° in low yield.

Anal.[12c] Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.16; H, 8.64.

4-Isopropyl-1,3,6,7-tetramethylnaphthalene (V).—To a Grignard solution prepared from 3.65 g. of magnesium and 14.5 cc. of isopropyl chloride in ether, was added 5.27 g. of 2,4,6,7-tetramethyl-1-tetralone in 50 cc. of ether at ice-bath temperature. After two hours at room temperature and twelve hours of refluxing the mixture was decomposed with ice and 50 cc. of concentrated hydrochloric acid. After washing and drying, the ether solution was evaporated and the residual yellow oil (5.29 g.) was heated at 35–40° for one-half hour with 25 cc. of 88% formic acid. Water was added and the hydrocarbon was dissolved in hexane. This solution was washed and dried and passed through a column of activated alumina. After washing the column with dry benzene, the combined solutions were evaporated and the oily residue (4.2 g.) was distilled. There was obtained 3.24 g. of product boiling at 101–117° at 1.2 mm., and a crystalline residue in the still. Further purification of the distillate was effected by freezing out more of the crystalline material from a 20–40° petroleum ether solution by immersion in a dry-ice mixture.

The solid thus removed (0.6 g.) was combined with the still residue above and recrystallized. There was obtained 0.24 g. of colorless crystals (m. p. 86–87°) identified as the starting ketone by a mixed melting point.

The liquid unsaturated hydrocarbon from the petroleum ether solution 2.58 g. (43%) was refluxed with 2.98 g. of chloranil[16] in 20 cc. of xylene for seventeen hours. After cooling, petroleum ether was added to precipitate the hydroquinone (2.7 g., 91%). The filtered solution was washed with alkali containing sodium hyposulfite and dried. After passing the solution through activated alumina, evaporation gave 2.0 g. (79% based on the unsaturated hydrocarbon) of crystalline product. Three recrystallizations gave 0.58 g. of colorless crystals (m. p. 94–95°). After two recrystallizations as the picrate (constant m. p.) the regenerated hydrocarbon was obtained as stout colorless needles melting at 96.5–97°. Mixed with the dimethylcadalene the m. p. was 71–78°.

Anal.[12c] Calcd. for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 90.37; H, 9.60.

The picrate crystallized in deep red needles from methanol (m. p. 156.5–157°). Mixed with the dimethylcadalene picrate (m. p. 145°) the melting point was 134–140°.

Anal. Calcd. for $C_{17}H_{22}\cdot C_6H_3O_7N_3$: mol. wt., 455. Found: mol. wt. (by titration), 458.

(16) Arnold and Collins, THIS JOURNAL, **61**, 1407 (1939).

The Synthesis of 4-Isopropyl-1,2,6,7-tetramethyl-naphthalene (XII)

4-Acetyl-o-xylene.[17]—To a mixture of 106 g. of o-xylene, 360 g. of powdered aluminum chloride and 570 cc. of carbon disulfide was added 112 g. of acetic anhydride at a rate that maintained a gentle reflux (one hour). After refluxing for one and one-half hours more and standing at room temperature for the same period, the decomposition was brought about with ice and hydrochloric acid and the product was washed and dried in ether solution. After evaporation of the solvent the product was distilled; yield 133 g. (90%) of yellow oil, b. p. 118–130° (21 mm.). Fractionation of the distillate gave 92.1 g. of product boiling at 123–126.5° (19 mm.).

2-Methyl-3-(3,4-dimethylphenyl)-n-butyric Acid.—The Reformatsky reaction[7] was run using 74 g. of the acetylxylene, 95 g. of ethyl α-bromopropionate, 38.8 g. of purified zinc and 125 cc. of thiophene-free benzene. A crystal of iodine was added and after two minutes of warming a vigorous reaction started and the mixture had to be cooled. After twenty minutes the spontaneous reaction had subsided and the mixture was refluxed for three hours and then let stand overnight. The product was isolated in the usual manner and separated into three portions by distillation at 0.8 mm., I, b. p. 60–108°, II, b. p. 108–138° and III, b. p. 138–184°.

Fractions I and II were combined (75 g.) and heated with 150 g. of potassium acid sulfate at 155°.[18] The product was distilled yielding 25.8 g., b. p. 56–67° (1 mm.) and 43.9 g., b. p. 67–108° (0.2 mm.). The higher boiling material was hydrolyzed by refluxing for twenty-two hours with 25 g. of 85% potassium hydroxide in 150 cc. of water. When worked up as usual, 7 g. of neutral material and 28 g. (28% over-all yield from the ketone) of **2-methyl-3-(3,4-dimethylphenyl)-crotonic acid** was obtained as a pale yellow oil.

The low-boiling fraction [25.8 g., b. p. 56–67° (1 mm.)] from the dehydration was heated with aqueous potassium hydroxide as above. No acidic material was obtained. Distillation of the neutral material gave 18.2 g. of a colorless oil, b. p. 82–88° (1.2 mm.). This material is unsaturated and is probably the tetramethylstyrene formed by decarboxylation of the unsaturated ester although the analysis (C, 88.27; H, 9.52) indicates contamination with oxygen-containing material.

Hydrogenation of 28 g. of the unsaturated acid in 100 cc. of acetic acid using 350 mg. of Adams catalyst, was complete in two hours. The solvent was removed in vacuum and the product was distilled yielding 25.9 g. (92%) boiling at 156–161° at 0.5 mm.

Anal. Calcd. for $C_{13}H_{18}O_2$: neut. equiv., 206. Found: neut. equiv., 207.

3-Methyl-4-(3,4-dimethylphenyl)-n-valeric Acid.—The acid chloride was prepared from 10.3 g. of the above butyric acid by treatment with 17.9 g. of thionyl chloride and four drops of pyridine in 25 cc. of anhydrous ether. The solvent was removed at water-pump vacuum, two portions of benzene were added and removed in a similar manner. A solution of the acid chloride in 60 cc. of dry ether was

(17) Claus, *J. prakt. Chem.*, **41**, 409 (1890).
(18) Fraction III, b. p. 138–184°, (14.1 g.) gave none of the desired product on similar treatment.

added dropwise through a filter to a vigorously stirred solution of diazomethane (from 45 cc. of nitrosomethylurethan by the method of Meerwein and Burneleit[19] in 300 cc. of dry ether at −10 to −5°. After standing for two and one-half hours at room temperature, the solvent was removed in vacuum. The resulting yellow liquid diazoketone in 75 cc. of dioxane was added dropwise to a solution of 9.5 g. of sodium thiosulfate in 350 cc. of water at 65–70°, and, at the same time, the silver oxide from 9.5 g. of silver nitrate was added in small portions. After the addition of sodium hydroxide, the product was obtained in the usual way. Distillation at 0.2 mm. gave 0.6 g., b. p. 142–146°, and 5.1 g., b. p. 146–147°. The total yield is 52%.

Anal. Calcd. for $C_{14}H_{20}O_2$: neut. equiv., 220. Found: neut. equiv., 224.

3,4,6,7-Tetramethyl-1-tetralone.—The above acid (5.5 g.) was cyclized with 25 cc. of 80% sulfuric acid as previously described. Distillation at 1.2 mm. gave 0.35 g., b. p. 130–137°, and 3.31 g., b. p. 137–139°; total yield, 71%.

For proof of structure, 0.25 g. was oxidized with 1.5 cc. of concentrated nitric acid and 3 cc. of water at 180° for nine hours. The methyl ester of the product (m. p. 135–136°) was obtained in an amount too small to permit further purification. The melting point mixed with pyromellitic (1,2,4,5) methyl ester (m. p. 142.5–143.5°) was 138–141°. With mellophanic (1,2,3,4) ester (m. p. 129–130°) the melting point was 108–115°. The oxidation product is thus identified as the former.

4-Isopropyl-1,2,6,7-tetramethylnaphthalene (XII).—This reaction was carried out as previously described using 3.4 g. of the above tetralone and isopropylmagnesium chloride from 9.1 cc. of isopropyl chloride and 2.43 g. of magnesium in 75 cc. of ether. The product was hydrolyzed with ammonium chloride solution and dehydrated by heating at 50–65° for two hours with 25 cc. of 88% formic acid. Since no starting material could be removed, as in the previous preparation, by cooling a petroleum ether solution of the crude hydrocarbon in dry-ice, the solution was passed through an activated alumina tower and the product was distilled over sodium; yield, 1.14 g. (28%), b. p. 95–102° (0.6 mm.). The dehydrogenation with chloranil (1.4 g.) was run as before and the resulting pale yellow oil was converted into the picrate. Three crystallizations of the picrate from methanol gave pure material (0.5 g., 22%) (m. p. 143–144°); mixed with the dimethylcadalene picrate (m. p. 145°) from cadinene dioxide, the melting point was 143.5–144.5°.

The pure hydrocarbon obtained from this picrate and crystallized once from methanol melted at 101.5–103°. Mixed with the dimethylcadalene (m. p. 102–103°) from cadinene dioxide, the melting point was 102–103°.

The Synthesis of 4-Isopropyl-1,6,7-trimethylnaphthalene (IX).—The reactions used in this synthesis were carried out in the manner already described in this paper for similar preparations. The reaction of 3.35 g. of 4,6,7-trimethyl-1-tetralone with excess isopropylmagnesium bromide gave a crude product which was dehydrated by treatment with 11 cc. of anhydrous formic acid at room temperature for two and one-half hours and at 40° for five minutes. Distillation of the crude dihydronaphthalene derivative gave 1.47 g. (38%) of a colorless mobile oil boiling at 110–111° (1.5

(19) Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).

mm.). Dehydrogenation of 1.2 g. of this product by refluxing for twenty-three hours with 1.5 g. of chloranil in 7 cc. of xylene gave 0.93 g. (78%) of crude product boiling at 135–137° (2.5 mm.). The picrate after two recrystallizations melted at 122–123°.

Anal. Calcd. for $C_{16}H_{20} \cdot C_6H_3O_7N_3$: mol. wt., 441. Found: mol. wt. (by titration), 440.

The hydrocarbon was regenerated from the picrate and crystallized from methanol (m. p. 39.5–40°).

Anal.[12c] Calcd. for $C_{16}H_{20}$: C, 90.50; H, 9.50. Found: C, 90.44; H, 9.44.

The Synthesis of 4-Isopropyl-1,2,6-trimethylnaphthalene (XIII).—The reactions used in this synthesis were run as described for similar reactions above.

2-Methyl-3-(p-methylphenyl)-n-butyric Acid (XVI).—For the Reformatsky reaction 83 g. of p-methylacetophenone, 111.5 g. of ethyl α-bromopropionate and 44.3 g. of zinc in 150 cc. of pure benzene were used. The crude product was dehydrated without previous distillation by heating with 300 g. of powdered potassium acid sulfate. Distillation of the crude unsaturated ester at 2 mm. gave 22.5 g., b. p. 85–105°; 78.0 g., b. p. 105–130°; and 3.1 g., b. p. 130–170°.

The first two fractions were hydrolyzed separately by refluxing with aqueous potassium hydroxide whereupon all of the second fraction and a small part of the first dissolved in the alkali. The acidic products were combined and isolated by extraction of the acidified solution. Evaporation of the solvent gave 58.9 g. (41% over-all yield from the ketone) of **2-methyl-3-(p-methylphenyl)-crotonic acid.**

Hydrogenation of the unsaturated acid in 225 cc. of acetic acid with 730 mg. of Adams catalyst was complete in three hours. On removal of the solvent, the residual oil partially crystallized. That this product is a mixture of isomeric forms[7] was demonstrated as follows. Crystallization from 70–90° ligroin gave 26.2 g. of solid material. After five recrystallizations from the same solvent the acid melted sharply at 133–133.5°.[20] From the mother liquor of the first crystallization an oil was obtained. Distillation at 3.5 mm. gave 32.3 g. of mixed isomeric forms, b. p. 155–157°.

Anal.[12c] Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; neut. equiv., 192. Found for the isomer, m. p. 133–133.5°: C, 74.88; H, 7.88; neut. equiv., 192, 192. Found for the liquid mixture, b. p. 155–157° at 3.5 mm.: neut. equiv., 193.

The total yield was 58.5 g. (97%). The unsaponifiable material weighed 14.6 g.

3,4,7-Trimethyl-1-tetralone.—The Arndt–Eistert reaction was run using the acid chloride from 9.6 g. of the acid. The yield of acid was increased over that obtained in the previous preparations by carrying out the hydrolysis of the diazoketone in the presence of a large amount of silver oxide (from 20 g. of silver nitrate) added in small portions along with the diazoketone solution to 20 g. of sodium thiosulfate in 300 cc. of water. After the addition of these substances the temperature was raised to 80° for one hour. The addition of 120 cc. of 5% sodium hydroxide to the hot solution brought about complete solution of the diazoketone ac-

(20) Rupe, Stieger and Fiedler, *ibid.*, **47**, 75 (1914), have reported only one form melting at 113–114°.

companied by a vigorous evolution of nitrogen. The 3-methyl-4-(p-methylphenyl)-n-butyric acid isolated as before weighed 8.9 g. (87%).

This acid (8.9 g.) was cyclized by treating with 80% sulfuric acid; yield, 5.9 g. (72%), b. p. 107–109° (0.4 mm.).[21]

Anal.[12o] Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.83; H, 8.30.

4-Isopropyl-1,2,6-trimethylnaphthalene (XIII).—The Grignard reaction was run on 5.4 g. of the trimethyltetralone using the isopropylmagnesium chloride from 0.15 mole each of magnesium and isopropyl chloride. Dehydration of the product was accomplished by heating with 50 cc. of 88% formic acid for one and one-half hours at 50° and for one-half hour at 65°. Distillation of the product over sodium gave 2.35 g. (39%) of a colorless oil boiling at 101–103° (1.2 mm.). This hydrocarbon was dehydrogenated by refluxing with 3.0 g. of chloranil in xylene for eighteen hours. After purification by passing through a column of alumina, 1.23 g.[22] of a colorless oil was obtained.

(21) Ruzicka and Ehrmann, *Helv. Chim. Acta*, **15**, 147 (1932), have prepared this ketone and the preceding acid by a different method.
(22) The yield is low as the result of loss of material through an accident.

The **picrate**, after three crystallizations from methanol, was obtained as brilliant red needles melting at 143.5–144°. Mixed with the picrate of the monomethylcadalene (m. p. 142.5–143°) from cadinene monoxide, the melting point was 143–144°.

The **styphnate** crystallized from methanol in orange needles (m. p. 170.5–171°). Mixed with the monomethylcadalene styphnate (m. p. 170–170.5°) the melting point was 170–170.5°.

The **trinitrobenzene derivative** was obtained as golden-yellow needles from methanol and melted at 168.5–169°. Mixed with the trinitrobenzene derivative of monomethylcadalene (m. p. 167.5–168°), the melting point was 168–168.5°.

Summary

From cadinene by way of the reaction of methyl magnesium chloride on the mono- and di-oxides, 2-methyl- and 2,7-dimethyl-cadalene were obtained. These substances, identified by synthesis, indicate that the double bonds of cadinene are in the 1,2 and 6,7 positions.
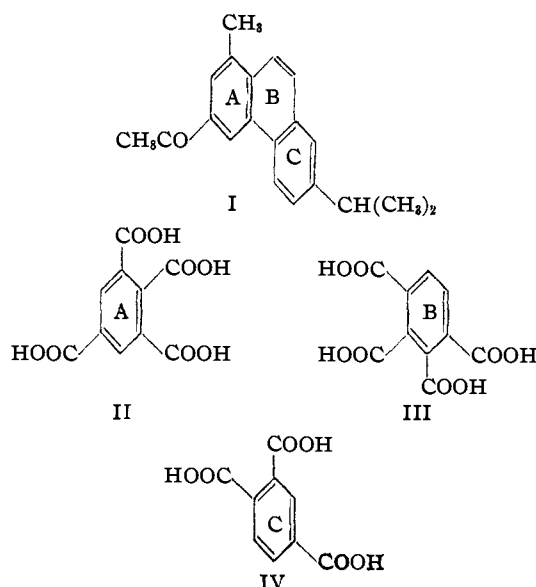
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Some Observations on the Oxidation and Determination of the Molecular Weight of Polynuclear Aromatic Compounds

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In connection with some recent work involving the identification and synthesis of polyalkylnaphthalenes[4] and other substances, we have collected some data which may be of interest to other workers in this field. Since this work must be discontinued, we are reporting the results available at this time.

In the oxidation of polynuclear aromatic hydrocarbons with dilute nitric acid at 190–200°,[5] it is generally assumed that the ring which is most highly substituted will be the least susceptible to cleavage by oxidation, and that the product will be the benzene polycarboxylic acid derived from this ring. When the extent of substitution is the same, the ring which is most easily oxidized will be destroyed. This point can be illustrated by the oxidation, by this method, of 3-acetylretene (I), which theoretically could lead to prehnitic acid

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(4) Campbell and Soffer, THIS JOURNAL, **64**, 417 (1942).
(5) Campbell and Todd, *ibid.*, **62**, 1287 (1940); see also Fieser and Campbell, *ibid.*, **60**, 2631 (1938); **61**, 2528 (1939).

(II) from ring A, mellophanic acid (III) from ring B, or trimellitic acid (IV) from ring C. The product of this reaction is prehnitic acid[5] and it is assumed that ring C was destroyed because it is least highly substituted and ring B was cleaved