B. A mixture of 1.4 g. of 1-benzyloxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran, 20 cc. of acetic acid and 3 cc. of concentrated hydrochloric acid was refluxed for three and one-half hours. At the end of the first and second hours, 2-cc. portions of concentrated hydrochloric acid were added. The solution was diluted with water, extracted with ether, the ether washed with water and then evaporated. The residue was steam distilled to remove volatile matter and the insoluble, non-volatile material taken up in petroleum ether. The latter was washed with water, evaporated and the residue distilled: viscous yellow liquid, b. p. 203–206° (3 mm.); yield 0.7 g. (64%).

1 - *p* - Nitrobenzoxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6-dibenzopyran.—This product was prepared from the corresponding hydroxy compound from methods A and B just described by the procedure followed for *p*-nitrobenzoylation of the 4-*n*-amyl derivative; yellow crystals from ethanol, m. p. 129–130° (cor.).

Anal. Calcd. for $C_{28}H_{29}O_5N$: C, 73.17; H, 6.36. Found: C, 73.06; H, 6.44.

Summary

Two isomeric cannabinols have been prepared, 1-hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran and 1-hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran. These compounds were synthesized through the condensation of 4-methyl-2-bromobenzoic acid with 4-*n*-amyldihydroresorcinol. The two isomeric lactones thus obtained were separated and dehydrogenated to the corresponding dibenzopyrones. Each dibenzopyrone was alkylated by a method which avoided as an intermediate the hydroxy acid, and then treated with methylmagnesium iodide to form the corresponding pyrans. The alkylated pyrans were then dealkylated to the cannabinol isomers.

It has been demonstrated experimentally that 4-alkyl-1,3-cyclohexanedione enolizes in two ways; that ring closure of a 2-carboxyl-2',6'-dihydroxy-5-alkylbiphenyl to a pyrone is preferably through the 6'-hydroxyl; that the dehydration of the phenolic alcohols to the pyrans of such molecules as 2-(α-methyl-α-hydroxyethyl)-2'-hydroxy-6'-alkoxy-5'-alkylbiphenyl and 2-(α-methyl-α-hydroxyethyl)-2'-hydroxyl-3'-alkyl-6'-alkoxybiphenyl takes place much more readily in the latter than in the former.

URBANA, ILLINOIS RECEIVED JUNE 17, 1940

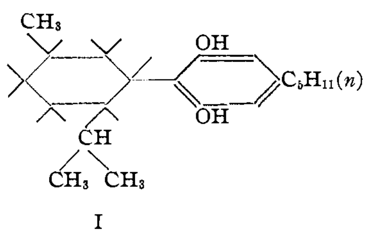
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. V.[1] Position of the Alicyclic Double Bonds

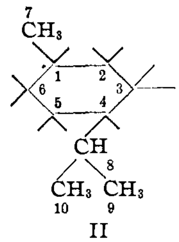
BY ROGER ADAMS, HANS WOLFF, C. K. CAIN AND J. H. CLARK[2]

IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.

The evidence submitted in previous communications[1] establishes for tetrahydrocannabidiol structure I. No attempt was made to determine the relative configuration of the asymmetric carbon atoms. As tetrahydrocannabidiol was made by catalytic reduction of cannabidiol with absorption of four atoms of hydrogen, this latter compound must have two double bonds in the left-hand residue (II). The possible combinations of two double bonds in such a radical (II) are very numerous (twenty or more) and merely the configurations for the two double bonds 6,1 and 3,4 or 1,2 and 3,4 are immediately excluded since the resulting structures would not allow the presence of optical activity in the molecule (cannabidiol $[\alpha]^{28}_{D}$ −125°). The cleavage of cannabidiol by pyrolysis with pyridine hydrochloride to *p*-cymene and olivetol is carried out under such conditions that, regardless of the mechanism involved, the double bonds in the molecule, wherever they may be placed, probably would migrate to complete the benzene nucleus.



I



II

It has been found that the possibility of either double bond being in positions 2,3 or 3,4 (structure II) is eliminated. This was accomplished by comparison of the absorption spectra of cannabidiol dimethyl ether and dihydrocannabidiol di-

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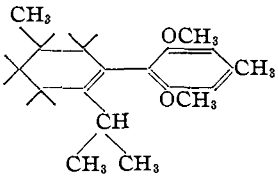
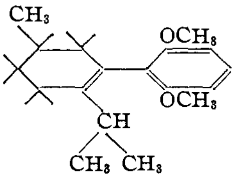
(1) For previous papers see (a) Adams, Hunt and Clark, THIS JOURNAL, **62**, 196 (1940); (b) Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940); (c) Adams, Hunt, and Clark, *ibid.*, **62**, 735 (1940); (d) Adams, Wolff, Cain and Clark, *ibid.*, **62**, 2215 (1940); (e) Adams, Pease and Clark, *ibid.*, **62**, 2194 (1940); (f) Adams, Baker, and Wearn, *ibid.*, **62**, 2204 (1940).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry. Solvay Process Company Fellow, 1939–1940.

methyl ether with various synthetic molecules of essentially unequivocal constitution. Thus, the compounds III and IV prepared by condensation of 2-lithium resorcinol dimethyl ether or 2-lithium



III



IV

orcinol dimethyl ether with menthone, followed by dehydration, must have the structures assigned or with the double bonds in the 2,3 positions; the former position for the double bond on general principles seems to be the more likely. The absorption spectra of compounds III and IV and those of the dimethyl ethers of cannabidiol and dihydrocannabidiol are compared in Fig. 1.

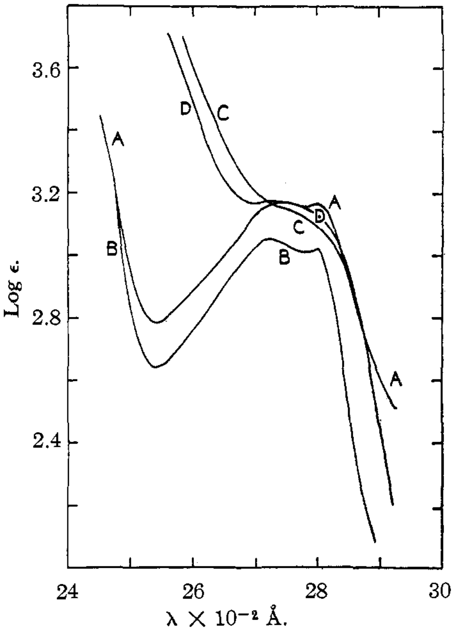


Fig. 1.—A, Cannabidiol dimethyl ether; B, dihydrocannabidiol dimethyl ether; C, 2-(3'-menthen-3',4'-yl)-1,3-dimethoxy-5-methylbenzene (III); D, 2-(3'-menthen-3',4'-yl)-1,3-dimethoxybenzene (IV).

It will be noticed that the absorption spectra of the synthetic compounds are entirely different from those of the natural products. Since it is certain that the synthetic compounds contain a double bond (either 2,3 or 3,4) conjugated to the resorcinol residue, it may be concluded that this conjugation may be the cause of the radical difference between their spectra and those of the cannabidiol derivatives. If such is the case, double bonds 2,3 or 3,4 (structure II) which would be conjugated to the olivetol residue in cannabidiol could not be present.

This assumption has now been confirmed experimentally. 2-Lithium resorcinol dimethyl ether and 2-lithium orcinol dimethyl ether were condensed with pulegone (V) to give dienes through dehydration of the intermediate tertiary alcohols. The structure of the primary addition product in the case of orcinol dimethyl ether is VI, which by dehydration leads to the introduction of a second double bond (VII). The corresponding product from resorcinol dimethyl ether presumably will have structure VIII. In both compounds VII and VIII the new double bonds must be in the 2,3 positions, unless by chance shifting of the original double bond in pulegone has occurred during the reaction and the second double bond would then probably conjugate with it. The absorption spectra of compounds VII and VIII (Fig. 2) resemble closely those of the synthetic substances III and IV (compare with Fig. 1) which contain only one double bond conjugated to the benzene nucleus. Compounds VII

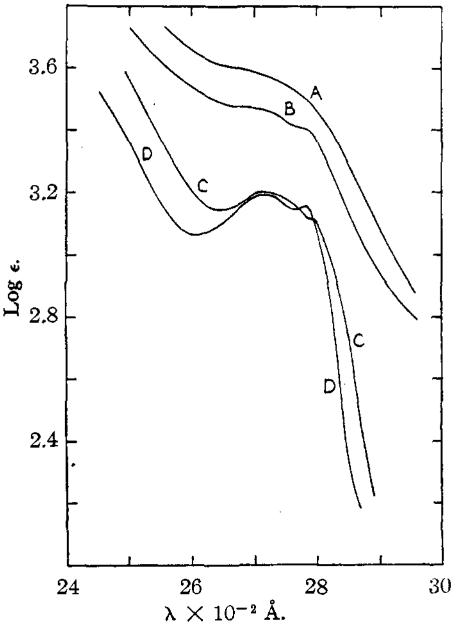
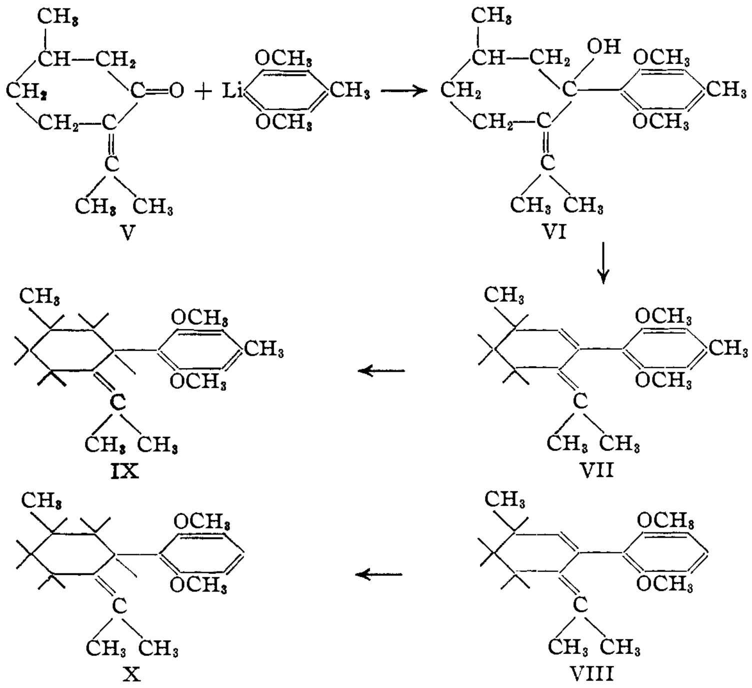


Fig. 2.—A, 2-(2'-Isopropylidene-5'-methyl-2',3',4',5'-tetrahydrophenyl)-orcinol dimethyl ether (VII); B, 2-(2'-isopropylidene-5'-methyl-2',3',4',5'-tetrahydrophenyl)-resorcinol dimethyl ether (VIII); C, 2-(2'-isopropylidene-5'-methylcyclohexyl)-orcinol dimethyl ether (IX); D, 2-(2'-isopropylidene-5'-methylcyclohexyl)-resorcinol dimethyl ether (X).



and VIII were then partially reduced. The first molecule of hydrogen was much more rapidly absorbed than the second and the absorption could be stopped readily so as to isolate the molecules with only one double bond whose structures are postulated as IX and X. It was assumed that the 2,3 double bonds which are only trisubstituted would be the first attacked. The absorption spectra of the resulting compounds IX and X (Fig. 2) proved to be strikingly similar to those of cannabidiol dimethyl ether and dihydrocannabidiol dimethyl ether; they were so different from those of the corresponding unreduced synthetics (VII and VIII) or the compounds III and IV, that the only logical deduction is the absence of the conjugation to the benzene ring in IX or X and also in the cannabidiol derivatives. Apparently, the loss of one double bond through hydrogenation in the cannabidiol dimethyl ether molecule has little effect upon the absorption spectrum. The assumption that one of the double bonds in cannabidiol is in the 4,8 position merely because of the spectra similarities of dihydrocannabidiol dimethyl ether and the synthetic dihydropulegone derivatives, is not justified.

A study of cannabidiol and its derivatives has indicated the presence of a methylene group. Doeuvre[3] reports that methylene groups may be determined quantitatively by ozonization, followed by decomposition and colorimetric determination with the Grosse–Bohle reagent of the formaldehyde evolved. Doeuvre's experiments could not be repeated on a quantitative basis; in fact, it is questionable whether theoretically one molecule of formaldehyde always may be expected from such a molecule. If Briner's[4] views on the decomposition of ozonized double bonds is accepted, then the amount of formaldehyde liberated from a molecule containing a methylene group will be dependent upon the substituents present and other factors. The procedure of Doeuvre with minor modifications described in the experimental part appears entirely satisfactory as a qualitative method of detection of a methylene group. The results of the comparison of a variety of compounds are shown in Table I.

TABLE I

COMPARISON OF COLOR INTENSITIES PRODUCED BY OZONIZED COMPOUNDS AND AN EQUIMOLAR QUANTITY OF FORMALDEHYDE AS 100

Formaldehyde	100
Eugenyl cinnamate	63
Cannabidiol	49
Cannabidiol dimethyl ether	41
Dihydrocannabidiol dimethyl ether	0
Tetrahydrocannabidiol dimethyl ether	0

These experiments lead to the conclusion that in cannabidiol a methylene group is present, which is assigned to the 8,9 or 8,10 positions (II) on the basis of the fact that by various acidic reagents it is possible to convert cannabidiol to a pyran derivative with consequent elimination of one of the hydroxyl groups and one double bond; the resulting molecule, tetrahydrocannabinol, containing the second double bond no longer gives a test for a methylene group. The formation of a pyran excludes the possibility of a methylene in the 1,7 positions. A detailed discussion of the transformation of cannabidiol to tetrahydrocannabinol and a description of its interesting properties and chemical reactions will be the subject of the next paper in this series.

With these facts available the structure of can-

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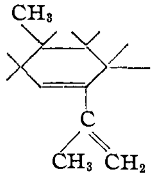
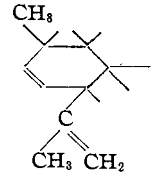
(3) Doeuvre, *Bull. soc. chim.*, [5] **3**, 612 (1936); *ibid.*, **45**, 146 (1929).

(4) Briner and de Nemitz, *Helv. Chim. Acta*, **21**, 748 (1938); Briner and Frank, *ibid.*, **22**, 587 (1938); Briner, *ibid.*, **22**, 591 (1939).

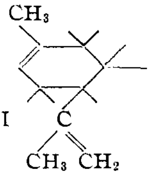
nabidiol is limited to one of four; the left-hand rings are shown in formulas XI–XIV.



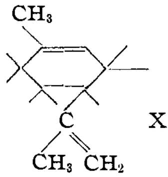
XI



XII



XIII



XIV

Experimental

Cannabidiol dimethyl ether and tetrahydrocannabidiol dimethyl ether were prepared as described in previous work.[1d] The dihydrocannabidiol dimethyl ether is described here for the first time.

Dihydrocannabidiol Dimethyl Ether.—A solution of 6.78 g. of cannabidiol dimethyl ether in 50 cc. of 95% ethanol was reduced at atmospheric pressure in a quantitative hydrogenation machine using platinum oxide catalyst. Hydrogen was absorbed corresponding to 1.02 moles per mole of starting material. The catalyst was filtered, the solvent evaporated, and the dihydrocannabidiol dimethyl ether, a colorless viscous oil, was distilled, b. p. 158–161° (2 mm.) (bath temperature 175°), $n^{20}\text{D}$ 1.5188; yield 5.53 g.

Anal. Calcd. for $C_{21}H_{30}(OCH_3)_2$: C, 80.17; H, 10.53; OCH_3, 18.02. Found: C, 80.40; H, 10.55; OCH_3, 18.38. *Rotation.* 0.0587 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −1.56°; *l*, 1; $[\alpha]^{28}\text{D}$ −133°.

The condensation of lithium orcinol dimethyl ether and lithium resorcinol dimethyl ether with menthone to give carbinols which were dehydrated to the corresponding unsaturated compounds (III and IV) was described in a previous paper.[1d] The condensation with pulegone is given below.

2 - (2′ - Isopropylidene - 5′ - methyl - 2′,3′,4′,5′ - tetrahydrophenyl)-resorcinol Dimethyl Ether (VIII).—To butyllithium prepared from 2.5 g. of lithium and 20.5 g. of *n*-butyl chloride, 20 g. of resorcinol dimethyl ether was introduced. The reaction was carried out under nitrogen in the apparatus previously described.[1d] After shaking for three hours, 25 g. of pulegone in 50 cc. of dry ether was added and fifteen minutes later the mixture was decomposed with ice water. The two layers were separated, the water layer extracted with ether and the combined ether extracts washed with water containing 3 cc. of glacial acetic acid and then with pure water. After drying over anhydrous magnesium sulfate, the ether was evaporated and the oily residue distilled. The mixture of the carbinol and the dehydrated compound distilled at 138–180° (1 mm.). It was found impossible to isolate the pure carbinol from the mixture and, therefore, the whole distillate was treated with approximately 2 g. of fused potassium acid sulfate at 140°. Dehydration of the carbinol occurred readily. After heating for one hour, the product was taken up in ether, filtered and the ether dried: colorless oil, b. p. 138–141° (1 mm.); yield 7 g. Solution in methanol followed by dropwise addition of water, prolonged cooling in a salt–ice-bath and scratching caused crystals to deposit (about 2 g.). After three recrystallizations from 90% methanol, purity was obtained, m. p. 75–76° (cor.). From the combined mother liquors, more crystalline material could be obtained by redistillation and crystallization as described.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.36; H, 8.88. Found: C, 79.12; H, 8.82. *Rotation.* 0.0355 g. made up to 5 cc. with 95% ethanol at 27° gave α_D +0.40; *l*, 1; $[\alpha]^{27}\text{D}$ +56°.

2 - (2′ - Isopropylidene - 5′ - methylcyclohexyl) - resorcinol Dimethyl Ether (X).—The reduction of 2-(2′-isopropylidene - 5′ - methyl - 2′,3′,4′,5′ - tetrahydrophenyl)-resorcinol dimethyl ether was carried out with platinum oxide catalyst in 95% ethanol at atmospheric pressure, in which case only 1 mole of hydrogen could be introduced. In glacial acetic acid, under similar conditions, the reduction occurred much more rapidly but if not stopped after introduction of 1 mole of hydrogen it continued to reduce.

To a solution of 0.272 g. of the diene in 50 cc. of 95% ethanol, 30 mg. of previously reduced platinum oxide was added and the reduction carried out at atmospheric pressure. After three hours no more hydrogen was absorbed (1.08 mole). After evaporation of the solvent, the remaining oil was dissolved in ethanol and water added dropwise under cooling in a salt–ice-bath until crystallization occurred; white crystals, m. p. 53–54° (cor.).

Reduction in glacial acetic acid solution yielded the same compound when hydrogenation was stopped after 1 mole of hydrogen was absorbed (about twenty minutes). On further reduction a second mole of hydrogen could be introduced but no crystalline product could be obtained.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.77; H, 9.55. Found: C, 78.93; H, 9.51. *Rotation.* 0.0350 g. made up to 5 cc. with 95% ethanol at 32° gave α_D +0.42°; *l*, 1; $[\alpha]^{32}\text{D}$ +60°.

Determination of Methylene Groups.—The procedure used was a modification of that of Doeuvre.[3] A solution of 10^{-4} mole of the compound in 5 cc. of a 3:2 mixture of ethyl acetate and acetic acid was treated for ten minutes with ozone (about 1.5–2%) at −20° and 0.5 cc. was then added to a solution of fuchsin-aldehyde reagent. The excess sulfur dioxide present in the reagent brought about reductive cleavage of the ozonide and the resulting formaldehyde gave a color with the reagent. Addition of hydrochloric acid desensitized the reagent to aldehydes other than formaldehyde. The color was compared with that produced by the ozonization of eugenyl cinnamate, which is known to contain a methylene group, and also with the color produced by an equimolar amount of standard formaldehyde. Quantitative comparisons were obtained through the use of a colorimeter (see Table I).

The ethyl acetate used in the ozonization solvent was refluxed over phosphorus pentoxide before use and the acetic acid distilled from chromic acid (2 g. per 100 g. of acetic acid). The fuchsin–aldehyde reagent was prepared by dissolving 0.5 g. of fuchsin in 500 cc. of water, filtering any undissolved material, and passing in sulfur dioxide until the solution was practically colorless. Excess sulfur dioxide was then removed by evacuating the vessel by means of the water pump for thirty minutes. The solution to which the ozonized solution was added was made up of 30 cc. of the above fuchsin reagent, 15 cc. of hydrochloric acid (sp. gr. 1.12; 100 cc. of concentrated hydrochloric acid diluted with 70 cc. of distilled water), and 45 cc. of water. Readings were taken after three to six hours, the time usually required for full development of the color.

2 - (2′ - Isopropylidene - 5′ - methyl - 2′,3′,4′,5′ - tetrahydrophenyl)-orcinol Dimethyl Ether (VII).—This compound was prepared in a manner similar to the corresponding resorcinol dimethyl ether derivative; white crystals, m. p. 81–82° (cor.).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.60; H, 9.16. Found: C, 79.70; H, 9.16. *Rotation.* 0.0325 g. made up to 5 cc. with 95% ethanol at 27° gave α_D +0.24°; *l*, 1; $[\alpha]^{27}{}_D$ +37°.

2 - (2′ - Isopropylidene - 5′ - methylcyclohexyl) - orcinol Dimethyl Ether (IX).—The reduction of 0.286 g. of the diene was carried out in 30 cc. of glacial acetic acid with platinum oxide catalyst and stopped after introduction of 1 mole of hydrogen. The solvent was evaporated *in vacuo* and the product recrystallized from ethanol; m. p. 114–115° (cor.).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.09; H, 9.79. Found: C, 79.13; H, 9.57. *Rotation.* 0.0309 g. made up to 5 cc. with 95% ethanol at 30° gave α_D +0.27°; *l*, 1; $[\alpha]^{30}{}_D$ +44°.

Summary

Experimental evidence is submitted which limits the positions of the two double bonds in cannabidiol to one of the four following combinations, 8,9 and 4,5, 8,9 and 5,6, 8,9 and 6,7 or 8,9 and 1,2.

Comparison of the absorption spectra of cannabidiol dimethyl ether with various synthetics of unequivocal constitution which had one double bond conjugated with the benzene residue, showed a marked difference. Two analogous synthetic compounds with a double bond not conjugated to the benzene residue, gave absorption spectra very similar to cannabidiol dimethyl ether. Exclusion of double bonds in the 2,3 or 3,4 positions was thus deduced.

Formation of formaldehyde by decomposition of ozonized cannabidiol dimethyl ether indicated presence of a methylene group. Ease of isomerization of cannabidiol to tetrahydrocannabinol, a molecule with one hydroxyl and one double bond eliminated and no methylene group, excludes the possibility of a 1,7 double bond and proves the presence of an 8,9 double bond.

URBANA, ILLINOIS RECEIVED JUNE 26, 1940

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Phenanthrene Derivatives. X. Acetylation of 4-Methylphenanthrene

BY W. E. BACHMANN AND R. O. EDGERTON[1]

As part of a program concerned with the study of the orienting effect of the methyl group in the methylphenanthrenes, we have investigated the Friedel–Crafts reaction of 4-methylphenanthrene with acetyl chloride. In this reaction 4-methylphenanthrene yielded a mixture of acetyl derivatives from which two crystalline compounds were isolated fairly easily. One of these, isolated to the extent of 50%, proved to be 1-acetyl-4-methylphenanthrene (I); the other, isolated in about 15% yield, was shown to be 3-acetyl-5-methylphenanthrene (II), the 6-acetyl derivative of 4-methylphenanthrene.

The formation of 3-acetyl-5-methylphenanthrene corresponds to the reaction of phenanthrene itself, which yields chiefly the 3-derivative and some of the 2-isomer in a similar reaction. In the substituted ring, however, the methyl group exerts its para-directing influence, and judging from the proportions of the isomers its influence is the strongest operating in this reaction.

The structures of the acetyl derivatives were determined by reducing them to 1-ethyl-4-methylphenanthrene and 3-ethyl-5-methylphenanthrene, respectively, the structures of the hydrocarbons being definitely established by synthesis. In the synthesis of 1-ethyl-4-methylphenanthrene, β-(1-naphthyl)-butyric acid (III) was converted to γ-(1-naphthyl)-valeric acid (IV) by means of the Arndt–Eistert reaction. This acid was cyclized through its acid chloride to 1-keto-4-methyl-1,2,-3,4-tetrahydrophenanthrene (V). Proof of the structure of this new cyclic ketone was obtained by converting it to 1,4-dimethylphenanthrene through reaction with methylmagnesium iodide and subsequent dehydration and dehydrogenation of the carbinol. Furthermore, the ketone was reduced to 4-methyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrogenated smoothly by

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[1] From part of the Ph.D. dissertation of R. O. Edgerton.