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.[12c] 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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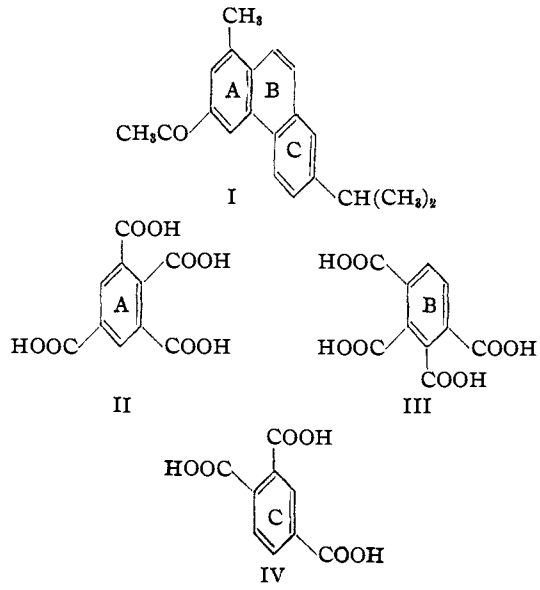
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Some Observations on the Oxidation and Determination of the Molecular Weight of Polynuclear Aromatic Compounds

BY WILLIAM P. CAMPBELL,[1] MILTON D. SOFFER[2] AND THOMAS R. STEADMAN[3]

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



(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

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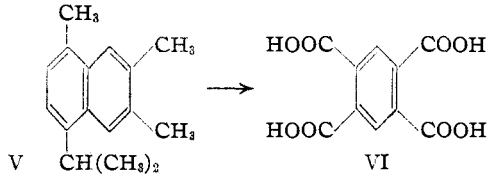
(3) Present address, The B. F. Goodrich Co., Akron, Ohio.

(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).

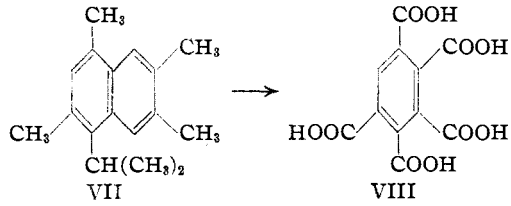
because of the relative ease of attack by oxidizing agents at the 9,10-positions.

We have obtained further evidence along these lines in the present work. The oxidation of 4,6,7-trimethyl-1-isopropylnaphthalene (V) by this re-



V VI

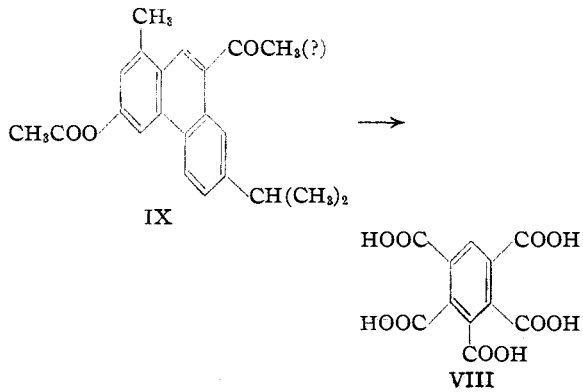
agent gave pyromellitic acid (VI). This result was a little surprising since it was expected that oxidation would occur most readily at the open 5,8-positions. In this connection it may be recalled that 2,3-dimethylnaphthalene is oxidized to the corresponding 1,4-quinone in good yield by chromic acid. When 2,4,6,7-tetramethyl-1-isopropylnaphthalene (VII) was oxidized the product



VII VIII

was benzene pentacarboxylic acid (VIII). In this case the ring which was previously destroyed contains an additional substituent and remained intact.

Another interesting example was found in the retene series. By a Friedel and Crafts condensation of the acetate or methyl ether of 3-retenol, an acetyl derivative (IX) was obtained which, on oxidation with nitric acid, gave benzene pentacarboxylic acid. This proves that the acetyl group entered the 9- or 10-position. We favor the 9-position since it has been shown[6] that the 1-alkyl

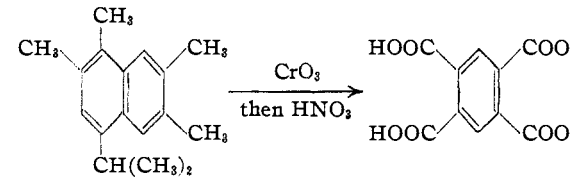


IX VIII

group offers hindrance to groups entering the 10-position. That the 9,10-positions were not attacked in this oxidation may be due to an initial reaction in which the ring containing the phenolic hydroxyl group was opened, with the resultant formation of a naphthalene ring system.

It should be pointed out that the use of a different oxidizing agent will often change the course of the reaction. It is this fact which often makes available important evidence for the structure of these substances. For example, the oxidation of the quinone of the previously mentioned 3-acetylretene by potassium permanganate, followed by nitric acid and a trace of manganous nitrate,[7] gave trimellitic acid in 21% yield and no prehnitic acid was found. With this evidence to show that the acetyl group was not in ring C, the isolation of prehnitic acid by the other method provided conclusive proof that the group was in the 3-position.

We have carried out an oxidation of 3,4,6,7-tetramethyl-1-isopropylnaphthalene (X) by chromic acid followed by nitric acid.[4] This hydro-



X VI

carbon is very similar to the isomer, VII, which gave benzene pentacarboxylic acid when oxidized with dilute nitric acid alone. The product in this case, however, was pyromellitic acid, VI, a product which fortunately provided much more valuable evidence for the structure of this substance than could have been obtained if the penta-acid had been formed. Again, by analogy with the chromic acid oxidation of 2,3-dimethylnaphthalene to the 1,4-quinone, one would expect that this same reagent would attack X at the 5- and 8-positions. It appears that the presence of alkyl groups in the 1- and 4-positions in these substances renders this ring more susceptible to cleavage by oxidation.

In our work with the polyalkylnaphthalenes we encountered the problem of determining the molecular weights of these substances, when only small amounts were available, with sufficient precision to determine the number of carbon atoms in the

(6) Fieser and Young, THIS JOURNAL, **53**, 4120 (1931).

(7) Nyman, *Ann. Acad. Sci. Fennicae*, **A48**, No. 6 (1937) [*Chem. Abs.*, **33**, 8192 (1939)].

molecule. Since none of the conventional methods were satisfactory and no more useful methods could be found in the usual reference books in this field, it occurred to us that the direct titration of picrates of the hydrocarbons might provide a suitable solution to the problem. We attempted this using a mixture of benzene and water for the solvent, and phenolphthalein for the indicator. The results were very satisfactory.

Later we found that a very similar method had been described by Dermer and Dermer[8] in their paper dealing with the picrates of naphthyl ethers. We wish, therefore, only to report our results (Table I) and to point out the value of this method which, apparently, is little used. The neutral

TABLE I

NEUTRAL EQUIVALENTS OF PICRATES

Picrate of	Calcd.	Found
Naphthalene	357	357
β-Methylnaphthalene	371	370 371
Phenanthrene	407	407
1,6-Dimethylnaphthalene	385	382
Cadalene	427	431
3,4,7-Trimethyl-1-isopropylnaphthalene	441	447
4,6,7-Trimethyl-1-isopropylnaphthalene	441	440
3,4,6,7-Tetramethyl-1-isopropylnaphthalene	455	457
2,4,6,7-Tetramethyl-1-isopropylnaphthalene	455	458

equivalent of picrates can be determined with a precision better than 1%. This is much more precise than the elementary analysis for nitrogen and of course is much more rapidly and easily determined. As pointed out by Dermer and Dermer, the phenolphthalein end-point is easily discernible. This is especially true in the method that we used, since there is a very sharp and distinct change from a greenish yellow to yellow in the aqueous phase at the end-point.

Experimental Part[9]

The Nitric Acid Oxidations.—These oxidations were run on 75–500 mg. of compound by heating in a sealed tube with a mixture of 1 cc. of concentrated nitric acid and 2 cc. of water at 190–200°. The tube was opened after twelve to fifteen hours and, if the reaction mixture was not a clear pale yellow solution, an additional 1 cc. of concentrated nitric acid was added and the tube was sealed and reheated. The clear yellow solution was evaporated to dryness and the white solid residue was washed onto a filter with a small amount of fuming nitric acid. The white solid was esterified with excess diazomethane in ether and the ester was crystallized from methanol. In some cases, when the yield is low, more product can be obtained by esterification of the residue remaining on evaporation of the fuming nitric acid wash liquor.

All of the methyl esters of the benzene tetracarboxylic acids and of the pentacarboxylic acid are nicely crystalline, sharp melting compounds, and the mixed-melting points are considerably depressed.

(a) **2,4,6,7-Tetramethyl-1-isopropylnaphthalene.**[4]—By this method 70 mg. of 2,4,6,7-tetramethyl-1-isopropylnaphthalene was oxidized to benzene pentacarboxylic acid. The pentamethyl ester melted at 143.5–145°. Mixed with the tetramethyl ester of pyromellitic acid (m. p. 142.5–143.5°) the melting point was about 120°. Mixed with an authentic sample of the pentamethyl ester of benzene pentacarboxylic acid (m. p. 149–150°) the melting point was 144–147°.

(b) **4,6,7-Trimethyl-1-isopropylnaphthalene.**[4]—The oxidation of 110 mg. of this hydrocarbon gave pyromellitic tetramethyl ester, m. p. 142.5–144°, identified by a mixed-melting point.

(c) **9(?)-Acetyl-3-acetoxyretene.**—The oxidation of 0.53 g. of this substance gave 0.085 g. of crystalline acids which yielded the pentamethyl ester of benzene pentacarboxylic acid, melting at 149–150° after several crystallizations from methanol. When mixed with an authentic sample the melting point was the same.

9(?)-Acetyl-3-acetoxyretene.—To an ice-cold solution of 6.3 g. of 3-acetoxyretene and 3.0 cc. of acetyl chloride in 50 cc. of nitrobenzene was added 6.7 g. of aluminum chloride. After ninety hours at room temperature the mixture was poured into 250 g. of ice and 25 cc. of concentrated hydrochloric acid. The solvent was removed by steam distillation and the black residue was taken up in ether. After treatment with Nuchar XXX, crystallization from ethanol gave 1.0 g. of product, m. p. 164–167°. Recrystallization from ethanol gave 0.4 g. of pure material, m. p. 169–170°. From the mother liquors 0.75 g. more of the pure compound was obtained.

Anal.[10] Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63. Found: C, 79.12; H, 6.80.

The corresponding phenol was obtained by alkaline hydrolysis. On crystallization from methanol it melted constantly at 247–248°.

9(?)-Acetyl-3-methoxyretene.—In a manner similar to that described above, the reaction of 0.8 g. of 3-methoxyretene, 0.5 cc. of acetyl chloride, and 0.8 g. of aluminum chloride was carried out in 10 cc. of nitrobenzene for forty-two hours. Crystallization from ether gave 0.43 g. of fine white needles which melted at 131.5–132.5°. Recrystallization from ethanol raised the melting point to 133–133.5°.

Anal.[10] Calcd. for $C_{21}H_{22}O_2$: C, 82.31; H, 7.24. Found: C, 82.04; H, 7.53.

The same product was obtained by treating 0.18 g. of 9-acetyl-3-retenol with 0.2 g. of dimethyl sulfate in 3 cc. of 50% aqueous methanol containing 0.065 g. of sodium hydroxide. The melting point was 133–134° and no depression occurred when melted, mixed with the above product.

The Titration of Picrates.—A sample of 100–200 mg. of the picrate was dissolved in 5 cc. of benzene, 50 cc. of water and four drops of 0.2% phenolphthalein solution added. The mixture was titrated with 0.05 *N* sodium

(8) Dermer and Dermer, *J. Org. Chem.*, **3**, 289 (1938–39).

(9) All melting points are corrected.

(10) Analyses by Lyon Southworth.

hydroxide solution to the end-point described above. The results are listed in Table I.

Summary

The nitric acid oxidation of some aromatic hydrocarbons and derivatives is described.

The titration of several hydrocarbon picrates is reported and the advantages of this method of analysis are pointed out.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Synthetic Mydriatics. I

BY F. F. BLICKE AND CHARLES E. MAXWELL[1,2]

The great majority of substances which exhibit marked mydriatic activity, and especially those which find practical application as mydriatics, are of two types: esters of a hydroxy acid such as tropic, $C_6H_5CH(CH_2OH)COOH$, or mandelic, $C_6H_5CH(OH)COOH$, and an amino alcohol; aryl-alkylamines similar to epinephrine or ephedrine in structure.

We have discovered that the benzilic acid ester of β-piperidinoethyl alcohol,[3] $(C_6H_5)_2C(OH)CO\text{-}OCH_2CH_2NC_5H_{10}$, is a strong mydriatic. This observation shows that the alcoholic hydroxyl in the acid radical, which seems to be quite essential for strong mydriasis in the ester type, may be tertiary as well as secondary (mandelic acid) or primary (tropic acid).

Recently four other esters of benzilic acid—the tropyl,[4] the pseudotropyl,[5] the β-diethylamino-ethyl[6] and the γ-diethylamino-β,β-dimethylpropyl[7] ester—have been shown to be not only mydriatics but also local anesthetics and antispasmodics.[8]

The substituted ethyl and propyl esters of benzilic acid, which we prepared, are listed in Table II. Three compounds, β-piperidinoethyl benzilate hydrochloride, the ester methobromide and the methobromide of β-diethylaminoethyl benzilate, when tested on the rabbit's eye, were described by Dr. F. Bruce Fralick and Dr. Harold F. Falls, to whom we are indebted for all of the animal tests, as excellent mydriatics; the hydrochlorides of the β-diethylaminoethyl and the γ-piperidinopropyl ester of benzilic acid, as well as the methobromide of the latter, produced good mydriasis.

Some of the ester hydrochlorides were found to be so insoluble in water that satisfactory 1–2% solutions could not be prepared. In these instances the methobromides of the esters proved to be much more soluble. Furthermore, the quaternary compounds have been found to be much less irritant and are as active or even more active than the corresponding tertiary amine hydrochlorides.[9]

The esters were prepared by the methods of Horenstein and Pählicke,[10] according to which the potassium salt of the required acid was heated with the hydrochloride or hydrobromide of the basic-substituted alkyl halide, or the acid, dissolved in isopropyl alcohol, was allowed to react with the basic-substituted alkyl halide.

In view of the statement in the literature[11] that aminomethyl phenyl ketone produces mydriasis,[12] it seemed desirable to prepare and test a few amino ketones and some of the corresponding secondary alcohols. It was found that no, or only slight, mydriasis was obtained with 1–5% solutions of the hydrochlorides of the ketones and secondary alcohols listed below.

Ketones: aminomethyl phenyl,[13] diethylamino-

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by Charles E. Maxwell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Lilly Endowment Fellow.

(3) Von Brucke and Jesserer [*Arch. expil. Path. Pharmacol.*, **190**, 516 (1938)] stated that this ester is an antispasmodic but no description of its preparation seems to have been published.

(4) Kreitmair, *Klin. Wschr.*, **15**, 676 (1936).

(5) Kroner, *ibid.*, **15**, 678 (1936).

(6) Halpern, *Arch. int. Pharmacodynam. Therap.*, **59**, 179 (1938).

(7) Fromherz, *Arch. expil. Path. Pharmacol.*, **173**, 113, 126 (1933).

(8) During the last few years a number of esters have been prepared primarily in the hope that they might be found to be antispasmodics; their mydriatic activity was discovered more or less incidentally during routine pharmacological tests. Among the very few studies which deal with the relationship between chemical structure and mydriatic activity those of Pyman [*J. Chem. Soc.*, **111**, 1109 (1917)] and of von Braun, Braunsdorf and Räth [*Ber.*, **55**, 1666 (1922)] deserve mention.

(9) As early as 1868, Crum, Brown and Fraser [*Trans. Roy. Soc. Edinburgh*, **25**, 708 (1868)] discovered that the mydriatic action of methylatropinium sulfate is about the same as that of atropine sulfate.

(10) Horenstein and Pählicke, *Ber.*, **71**, 1654 (1938).

(11) Pitini, *Arch. internat. de pharmacodyn. et de Therapie*, **14**, 75 (1905).

(12) A 10% solution was required.

(13) Mannich and Hahn, *Ber.*, **44**, 1546 (1911). Used as hydrobromide.