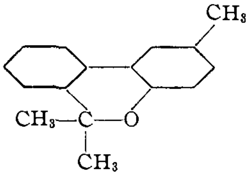
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF QUEENS COLLEGE]

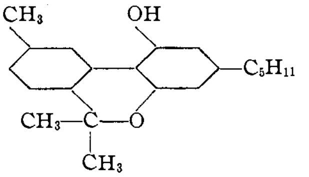
The Cyclic Dehydration of Biphenyl Derivatives to Fluorenes

BY MARJORIE ANCHEL AND A. H. BLATT

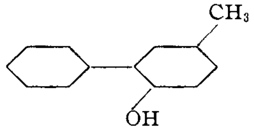
In 1933 Cahn,[1] while studying the pyran (I) in connection with his investigation of the structure of cannabinol (II), reported that the pyran on heating with hydrochloric and acetic acids underwent ring opening and loss of acetone to furnish a product which he formulated as 2-hydroxy-5-methylbiphenyl (III). Cahn was apparently unaware that only a few months earlier Sherwood, Short and Stansfield[2] had reported a synthesis of 2-hydroxy-5-methylbiphenyl and that their product, melting at 68°, was different from his which melted at 110°. We have determined the structure of Cahn's product and the course of the reactions by which it is formed and, in so doing, have found two new cyclic dehydration reactions which furnish, respectively, 9,9-dialkylfluorenes and 4-hydroxy-9,9-dialkylfluorenes.



I

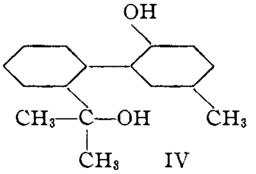


II[3]

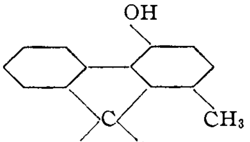


III

The direct comparison of Cahn's product with authentic specimens of 2-hydroxy-5-methylbiphenyl made it certain that these two substances were not identical. The oxidation of Cahn's product, which furnished an acid different from benzoic acid, the toluic acids or the phthalic acids, made it certain that this product was not a hydroxymethylbiphenyl, isomeric with III, formed as a result of a rearrangement. Analyses of Cahn's product made it clear that Cahn had been misled by faulty analytical data and showed that the product did not have the composition of a hydroxymethylbiphenyl but was, instead, isomeric with the pyran (I). The ultraviolet absorption spectrum of Cahn's product (Fig. 1), and comparisons of this spectrum with those of the biphenyl (III) (Fig. 2) and various polynuclear aromatic compounds, suggested that the product might be a fluorene derivative. Finally, the observation that Cahn's product could be obtained directly from the carbinol (IV) suggested that this product was the hydroxyfluorenol (V) formed by loss of the carbinol hydroxyl group and the *o'*-hydrogen atom in (IV).



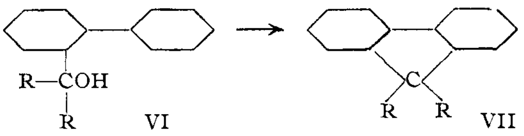
IV



V

It has been possible to show both that the dehydration of dialkyl-*o*-xenylcarbinols to form 9,9-dialkylfluorenes (the reaction postulated going from IV → V) does take place and that Cahn's product is 4-hydroxy-1,9,9-trimethylfluorene (V).

The evidence that dialkyl-*o*-xenylcarbinols undergo dehydration to 9,9-dialkylfluorenes comes from an examination of the behavior of dimethyl-*o*-xenylcarbinol (VI, $R = CH_3$) and dibenzyl-*o*-xenylcarbinol (VI, $R = C_6H_5CH_2$). Both carbinols on treatment with sulfuric acid furnish the corresponding 9,9-dialkylfluorenes (VII). 9,9-Dimethylfluorene (VII, $R = CH_3$) is also formed by heating the carbinol (VI, $R = CH_3$) with hydrochloric and acetic acids. These reactions run very smoothly and furnish 9,9-dialkylfluorenes in excellent yields.



The evidence that Cahn's product is the fluorenol (V) is as follows. This product contains a phenolic hydroxyl group for it can be methylated with methyl sulfate and alkali to furnish the methyl ether (VIII). It contains one unsubstituted position *ortho* to the hydroxyl group for it furnishes a monobromo and a mononitro derivative and couples with benzenediazonium chloride

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[1] Cahn, *J. Chem. Soc.*, 1400 (1933).

[2] Sherwood, Short and Stansfield, *ibid.*, 1832 (1932).

[3] The structural formula given for cannabinol is that established by Adams, Baker and Wearn, THIS JOURNAL, **62**, 2204 (1940), and differs from the formula proposed by Cahn, *cf.* Ref. 1.

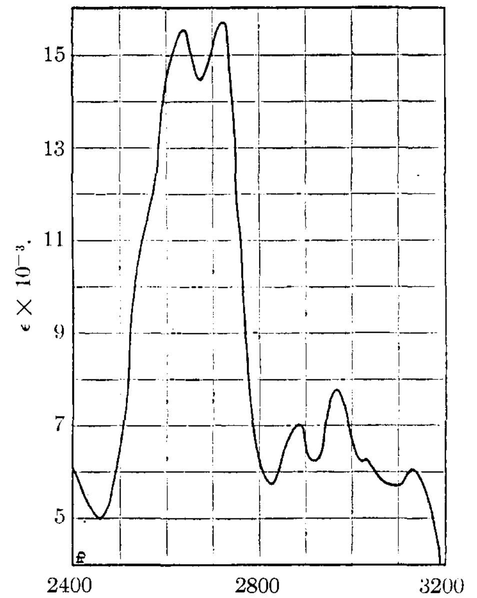
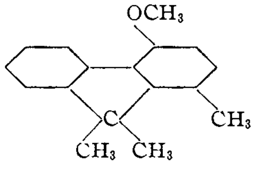
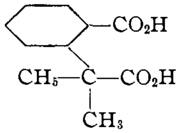


Fig. 1.—4-Hydroxy-1,9,9-trimethylfluorene in 95% alcohol.

to yield a monobenzeneazo compound. On oxidation with permanganate the fluorenol (V) and its methyl ether (VIII) furnish the same product, identified by analysis and conversion to its anhydride, as α,α-dimethylhomophthalic acid (IX).

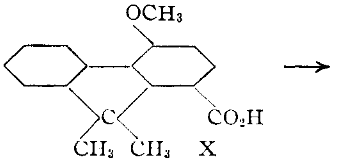


VIII

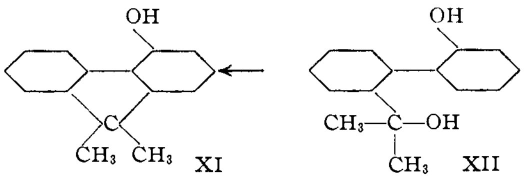


IX

These oxidation reactions locate two methyl groups and the points of attachment of the rings. Oxidation of the methyl ether (VIII) with permanganate also shows that still a third methyl group is present, for this oxidation furnishes in addition to α,α-dimethylhomophthalic acid (IX) the methoxy acid (X). The latter acid serves to relate the fluorenol (V) to the corresponding fluorenol (XI) obtained by dehydration of the carbinol (XII): when the methoxy acid (X) is heated with hydriodic acid it is demethylated and decarboxylated and yields 4-hydroxy-9,9-dimethylfluorene (XI).



X



XI XII

This evidence establishes the structure of Cahn's product as the fluorenol (V). This fluorenol can be obtained by heating either the carbinol (IV) or the pyran (I) with hydrochloric and acetic acids. The formation of the fluorenol from the carbinol is a straightforward cyclic dehydration, perhaps involving the chloride rather than the carbinol. The formation of the fluorenol from the pyran is more involved and is best interpreted as ring opening of the pyran to form the carbinol or its chloride followed by ring closure to the fluorenol. All our evidence is consistent with the view that the carbinol undergoes a rela-

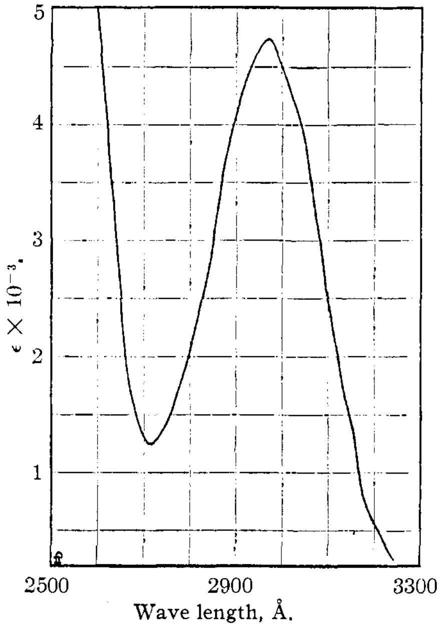
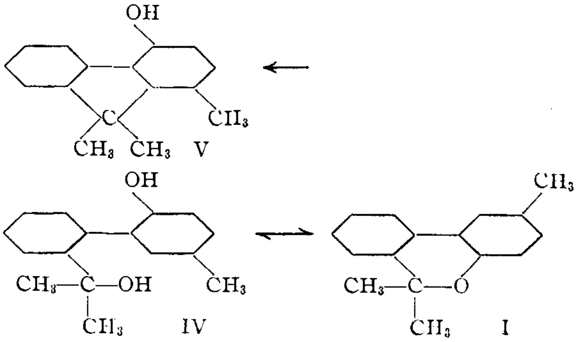


Fig. 2.—2-Hydroxy-5-methylbiphenyl in 95% alcohol.



V IV I

tively rapid, reversible dehydration to the pyran and a comparatively slow, irreversible dehydration to the fluorenol. Thus, on short heating with hydrochloric and acetic acids, the carbinol furnishes the pyran in excellent yield, while on prolonged heating with the same reagent both the carbinol and the pyran give the fluorenol in about the same yield.

We are indebted to Dr. Hugh H. Darby, of the Department of Biochemistry, College of Physicians and Surgeons, Columbia University, for advice and assistance in connection with the absorption spectra, and to an anonymous donor for a grant of funds.

Experimental

Synthesis of 2-Hydroxy-5-methylbiphenyl (III).—We prepared this material by two independent methods, both different from the original synthesis of Sherwood, *et al.*,[2] which involved a high temperature dehydrogenation. A.[4] When 120 cc. of 1:1 hydrochloric acid was added slowly and with vigorous stirring to an iced solution of 41.1 g. (0.3 mole) of cresidine in 234 g. of benzene, cresidine hydrochloride precipitated as a spongy mass. The benzene–acid suspension of the hydrochloride was kept between 10–15° and a solution of 20.7 g. (0.3 mole) of sodium nitrite in 30 cc. of water was added dropwise. This was followed by the dropwise addition of 120 cc. of a 25% solution of sodium hydroxide. Stirring was maintained during the additions and until the reaction mixture came to room temperature.

After the reaction mixture had stood overnight, the benzene layer was separated and washed with water until free from alkali. Most of the benzene was removed by distillation and ether was added to the residue to precipitate the dye which had been formed in the reaction. After filtration the ether and benzene were distilled from the filtrate and the residual liquid was fractionally distilled. The fraction which boiled at 140–165° (16 mm.) was separated by redistillation into a low-boiling portion, identified as cresidine, and a main portion of 4.0 g. of 2-methoxy-5-methylbiphenyl boiling at 150–155° (16 mm.); yield, 7% (*Anal.* Calcd. for $C_{14}H_{14}O$: OCH_3, 15.65. Found: OCH_3, 15.81).

For demethylation 6.8 cc. of 40% hydrobromic acid was added dropwise to a boiling solution of 1.0 g. of the ether in 8 cc. of glacial acetic acid. After refluxing for two hours, the solution was cooled, diluted, and extracted with ether. The extract was washed free of acid with water and with sodium carbonate solution, then extracted with 5% sodium hydroxide solution. Acidification of the alkaline extract, followed by extraction with ether, furnished 0.63 g. of an oil which crystallized on addition of ligroin. The yield of crude 2-hydroxy-5-methylbiphenyl, melting at about 67°, was 67%. After high-vacuum distillation, the pure product melted at 67–68°.

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.74; H, 6.57. Found: C, 84.44; H, 6.62.[5]

B. Benzenediazonium sulfate was prepared according to the directions of Knoevenagel[6] and 21 g. of the dry salt was added to 75 g. of *p*-cresol. On heating to 70° gas was evolved, and the reaction was completed by heating to 100° for ten minutes. After cooling, the reaction mixture was extracted with ether, the extract washed free of acid, the ether removed and the residual material distilled. The fraction which boiled at 105–140° (2 mm.) was redistilled and furnished 2.0 g. of material, boiling at 101–105° (2 mm.), which solidified on seeding with 2-hydroxy-5-methylbiphenyl prepared in A, above. Crystallization from ligroin gave 0.76 g. of pure material, melting at 67–68°, whose melting point was not depressed by admixture with the product from A.

2-Hydroxy-5-methylbiphenyl (III) as prepared above agrees in its properties with the material described by Sherwood, *et al.*[2] For further characterization, the acetate and benzoate were prepared. When the biphenyl (III) was warmed with acetic anhydride containing a drop of sulfuric acid, the reaction mixture on dilution with water furnished 2-acetoxy-5-methylbiphenyl which crystallized from dilute acetic acid in diamond-shaped plates melting at 28–29°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.26; H, 6.24. Found: C, 79.20; H, 6.38.

The benzoate, prepared by the Schotten–Baumann procedure, crystallized from alcohol in plates melting at 94–94.5°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.33; H, 5.56. Found: C, 83.08; H, 5.60.

The acetate and benzoate of 4-hydroxy-1,9,9-trimethylfluorene (V) melt at 63–65° and 109–110°, respectively.[1]

An attempt to prepare 2-hydroxy-5-methylbiphenyl from diazotized aniline and *p*-cresol in acid solution according to the procedure of Norris[7] did not furnish a crystalline product. However, from the oil which was obtained it was possible to prepare the benzoate in crystalline form.

2-Hydroxy-5-methylbiphenyl (III) was related to the known 2-methoxy-5-carboxybiphenyl[8] by the permanganate oxidation of its methyl ether, 2-methoxy-5-methylbiphenyl. The melting point, 215–218°, of the methoxy acid thus obtained was not depressed on admixture with the acid prepared by a Fries reaction on 2-acetoxybiphenyl, followed by methylation of the resulting 2-hydroxy-5-acetylbiphenyl and oxidation of the methoxy ketone.

Preparation of 4-Hydroxy-1,9,9-trimethylfluorene (V).—A mixture of one part of acetic acid and three parts of hydrochloric acid was saturated with hydrogen chloride at 0°. A suspension of 2.7 g. of the carbinol (IV) in 20 cc. of this "acetic–hydrochloric acid mixture" was heated in a sealed tube for twenty-four hours at 200°. When cold the contents of the tube were diluted with water and the oil was washed several times by decantation, then dissolved in acetone. The acetone solution was poured into an excess of 2 *N* sodium hydroxide solution which was then

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[4] These directions are based on the procedure of Gomberg and Bachmann, THIS JOURNAL, **46**, 2339 (1924).

[5] We are indebted to Mr. William Saschek for the analyses of the biphenyl derivatives.

[6] Knoevenagel, *Ber.*, **28**, 2048 (1895).

[7] Norris, Macintire and Corse, *Am. Chem. J.*, **29**, 120 (1903).

[8] Slotta and Nold, *Ber.*, **68**, 2226 (1935).

diluted with about twice its volume of water and filtered. The filtrate was acidified with hydrochloric acid, extracted with ether and the ether removed by distillation. The residual oil, when distilled on the oil pump, furnished 1.75 g. of the fluorenol (V), a yield of 71%. After crystallization from ligroin the fluorenol melted at 109–110°.

The yield of the fluorenol in the above reaction is a function of the time of heating. Experiments in which the reaction mixtures were heated for 8, 24, 31 and 48 hours gave yields of 35, 71, 68 and 51%, respectively, of distilled product. With short reaction times the carbinol (IV) furnishes the pyran (I). Thus when the carbinol was suspended in "acetic–hydrochloric acid mixture" and heated in a sealed tube to 200° during one-half hour then allowed to cool, the crude product solidified promptly on seeding with the pyran. On crystallization from methanol an 80% yield of the pyran was obtained.

The fluorenol can be prepared in approximately the same percentage yields starting with the pyran (I) and the product from the pyran is identical (mixed m. p. and mixed m. p. of the methyl ethers) with that obtained from the carbinol. Cahn prepared the fluorenol from the pyran, not from the carbinol. He reported a yield of 64% of crude product—as obtained by acidification of the alkaline solution.[1]

The fluorenol (V) is difficult to analyze and, unless precautions are taken to ensure complete combustion, the values for carbon and hydrogen run low enough to approximate values for the biphenyl derivative (III). The analysis cited below is representative of those in which it was made certain that complete combustion took place.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.20. Found: C, 85.84; H, 7.15.

Derivatives of 4-Hydroxy-1,9,9-trimethylfluorene (V).—Because of the difficulties encountered in securing satisfactory analytical data with the fluorenol, a number of derivatives were prepared in which the differences in composition between the biphenyl (III) and the fluorenol (V) were more pronounced. A. The methyl ether (VIII) had been prepared by Cahn.[1] Our product agreed in properties with his description.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.71; H, 7.56; OCH_3, 13.04. Found: C, 85.51; H, 7.48; OCH_3, 12.59.

B. The monobromo derivative of the fluorenol was prepared by the dropwise addition of a slight excess of a 1% solution of bromine in acetic acid to a solution of the fluorenol in the same solvent. The product was precipitated by the addition of water and was purified by distillation followed by crystallization from alcohol, from which it was obtained as colorless, glistening rods melting at 123–124°.

Anal. Calcd. for $C_{16}H_{15}BrO$: C, 63.36; H, 4.92. Found: C, 63.40; H, 5.06.

C. The mononitro derivative of the fluorenol was prepared by the dropwise addition of concentrated nitric acid to an acetic acid solution of the fluorenol. The product was precipitated by the addition of water and purified by distillation, followed by crystallization from alcohol. The pure product was obtained as fine, yellow needles which melted at 136°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.34; H, 5.62. Found: C, 71.77; H, 5.8.

D. The benzeneazo derivative of the fluorenol was prepared by adding a solution of benzenediazonium chloride to a cold solution of the fluorenol in 10% sodium hydroxide. The product was precipitated by the addition of water and purified by crystallization from dilute alcohol. It was obtained as short, ruby red, prismatic rods which melted at 119.5–120.5°.

Anal. Calcd. for $C_{21}H_{18}N_2O$: C, 80.44; H, 6.14; N, 8.54. Found: C, 80.57; H, 6.20; N, 8.60.

Oxidation of 4-Hydroxy-1,9,9-trimethylfluorene (V).—A solution of 3.0 g. of potassium permanganate in 75 cc. of water was added to a suspension of 0.3 g. of the fluorenol in 50 cc. of hot water. The mixture was heated on the steam-bath for seven hours, then cooled and the excess permanganate removed with sulfurous acid. The solution was filtered from suspended impurities and thoroughly extracted with ether. On evaporation of the ether, a residue of 0.03 g. of partially crystalline material melting at about 100° was obtained. This was crystallized from water for analysis.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.43; H, 5.81. Found: C, 63.42; H, 5.76.

α,α-Dimethylhomophthalic acid (IX), the product of the above oxidation, is obtained more readily by oxidation of the methyl ether (VIII), below. The products from both oxidations are identical and agree with the description given by Gabriel.[9] On slow heating the acid melts at about 114°, on rapid heating it melts at 123°. Melting is accompanied by the evolution of gas due to anhydride formation and the melt, on cooling, solidifies and remelts at 81–82°, the melting point of α,α-dimethylhomophthalic anhydride.[9] A small amount of the acid was melted, then distilled at 2 mm. and the anhydride thus formed, which melted at 81–82°, was analyzed.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.44; H, 5.30. Found: C, 69.57; H, 5.14.

Oxidation of 4-Methoxy-1,9,9-trimethylfluorene (VIII).—A solution of 5.6 g. of potassium permanganate in 350 cc. of water was added to a suspension of 3.5 g. of the ether (VIII) in 50 cc. of boiling water. The mixture was boiled for twelve hours, during which time all the permanganate was reduced, then cooled and filtered from the manganese dioxide. The manganese dioxide was washed with water and extracted with ether. From the ether, 2.5 g. of slightly impure starting material was recovered.

The filtrate and water washings were combined and acidified with hydrochloric acid. The white, flocculent precipitate of the methoxy acid (X) was filtered and dried. It melted at 229–233°, and weighed 0.25 g. For analysis the material was crystallized from acetic acid. The pure product melted at 233–234°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.12; H, 5.97; OCH_3, 11.57. Found: C, 75.84; H, 5.90; OCH_3, 11.36.

The acidified filtrate from the methoxy acid (X) was evaporated to dryness and the residue extracted with ether. On evaporation, the ether left 0.5 g. of a mixture of oil and solid which was dissolved in a small volume of warm water, filtered from a little undissolved material, and concentrated at room temperature. The solid which crystallized from this concentrated solution was recrystallized in the same

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(9) Gabriel, *Ber.*, **20**, 1198 (1887).

way and proved to be identical with the α,α-dimethylhomophthalic acid (IX) obtained from the oxidation of the fluorenol (V), above.

Conversion of 1-Carboxy-4-methoxy-9,9-dimethylfluorene (X) to 4-Hydroxy-9,9-dimethylfluorene (XI).—When 100 mg. of the methoxy acid (X) was boiled for seven hours with 3 cc. of constant-boiling hydriodic acid, a clear oil formed which solidified on cooling. The solid was crystallized twice from petroleum ether and then melted at 90–91°.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.67; H, 6.72. Found: C, 85.47; H, 6.81.

The fluorenol (XI) is identical with the material obtained by the fluorenol ring closure from 2-hydroxy-2′-α-hydroxyisopropylbiphenyl (XII). Two and one half grams of the carbinol (XII), prepared according to Cahn,[1] was heated in a sealed tube for twenty-four hours at 200° with 20 cc. of "acetic–hydrochloric acid mixture." The reaction was worked up as in the preparation of the fluorenol (V), and furnished 1.2 g. of distilled product. On crystallization from petroleum ether the fluorenol (XI) melted at 90° and did not depress the melting point of the product from the methoxy acid (X).

Formation of 9,9-Dialkylfluorenes from Dialkyl-*o*-xenylcarbinols.—Dimethyl-*o*-xenylcarbinol (VI, $R = CH_3$) and dibenzyl-*o*-xenylcarbinol (VI, $R = C_6H_5CH_2$) were prepared from 2-carbomethoxybiphenyl[10] and the corresponding Grignard reagents. Dimethyl-*o*-xenylcarbinol crystallizes from ligroin in fine needles melting at 73°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.85; H, 7.60. Found: C, 84.81; H, 7.32. Dibenzyl-*o*-xenylcarbinol crystallizes from methanol and melts at 98–98.5°. *Anal.* Calcd. for $C_{27}H_{24}O$: C, 88.96; H, 6.64. Found: C, 89.04; H, 6.61.

When 2.3 g. of dimethyl-*o*-xenylcarbinol was heated in a sealed tube at 200° for twenty-four hours with 20 cc. of "acetic–hydrochloric acid mixture," 2.2 g. of 9,9-dimethylfluorene (VII, $R = CH_3$) crystallized on addition of ligroin to the oily reaction product. The crude material was distilled, then crystallized from ligroin. It consisted then of needles which melted at 71°. Apparently this was an unstable form of the hydrocarbon for, on standing, the melting point rose to 94°. On further crystallization the melting point was raised to 95–96°, the value reported in the literature.[11]

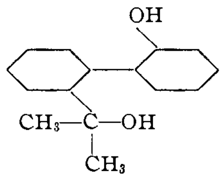
Anal. Calcd. for $C_{15}H_{14}$: C, 92.75; H, 7.25. Found: C, 92.81; H, 7.35.

9,9-Dimethylfluorene agrees in its properties with the description given by Lebeau and Picon.[11] It does not reduce permanganate nor is it affected by cold concentrated sulfuric acid. In fact the simplest way of preparing fluorene is by treating dimethyl-*o*-xenylcarbinol with sulfuric acid. On addition of concentrated sulfuric acid to the carbinol, the material became oily, then resolidified. The product, obtained in quantitative yield on diluting with water, was 9,9-dimethylfluorene, melting at 94–95°.

When dibenzyl-*o*-xenylcarbinol was treated with cold sulfuric acid no reaction took place. On warming, however, the carbinol became oily, then resolidified. The 9,9-dibenzylfluorene, obtained by diluting the reaction mixture with water, melted at 148–149°, and was identical (mixed m. p.) with a sample prepared from the potassium derivative of fluorene with benzyl chloride.[12] Dibenzyl-*o*-xenylcarbinol was not heated with "acetic–hydrochloric acid mixture."

Summary

When 2,6,6-trimethyldibenzopyran is heated with hydrochloric and acetic acids the product is 4-hydroxy-1,9,9-trimethylfluorene and not 2-hydroxy-5-methylbiphenyl. It is shown that dialkyl-*o*-xenylcarbinols can be dehydrated to form 9,9-dialkylfluorenes, that carbinols of the type can be dehydrated to form either dibenzopyrans or 4-hydroxy-9,9-dialkylfluorenes, and that the pyran ring closure is reversible.



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[10] Graebe and Rateanu, *Ann.*, **279**, 257 (1894).

[11] Lebeau and Picon, *Compt. rend.*, **173**, 84 (1921).

[12] Weissgerber, *Ber.*, **34**, 1660 (1901)