[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

SYNTHESIS AND PROPERTIES OF 1,4,9-FLUORENETRIONE AND OTHER FLUORENONE DERIVATIVES[1]

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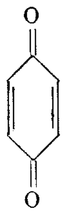
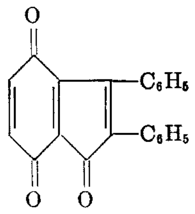
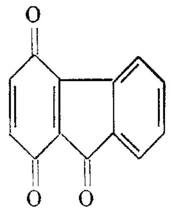
In a previous study (1), it was found that fusion of a 2,3-diphenylcyclopentenone ring directly on a benzoquinone nucleus raised the oxidation-reduction potential of the latter by 0.185 v. On indirect evidence, it was concluded that the same effect would be caused by a benzocyclopentenone ring. Measurement of the oxidation-reduction potential of 1,4,9-fluorenetrione (III) now indicates that this conclusion is approximately true; fusion with the benzocyclopentenone ring raises the potential of benzoquinone 0.169 v. Increases in potential by such fusions are to be expected (2), but more detailed interpretation of the results will have to wait until benzoylbenzoquinone (3) is investigated.



I. $E'_0 = 0.650$ v.

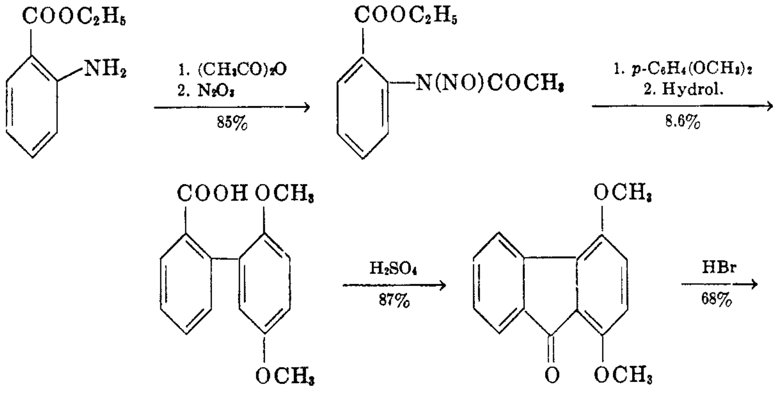


II. $E'_0 = 0.835$ v.



III. $E'_0 = 0.819$ v.

The synthesis of 1,4,9-fluorenetrione is diagrammed in the following formulas:



IV

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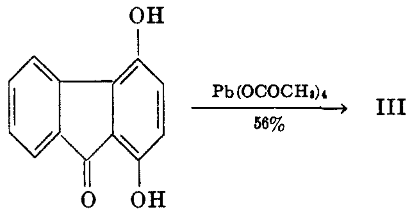
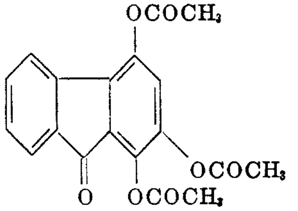
[1] From the Ph.D. Thesis of Robert Neil Flesch, August 1950.



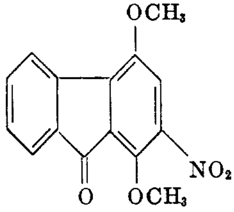
V

Some reactions of III were studied. The quinone reacted with cyclopentadiene to form a yellow 1:1 addition product. With acetic anhydride and a little sulfuric acid, III yielded 1,2(or 3),4-triacetoxy-9-fluorenone (VI). In this Thiele acetylation, an acetoxyl group probably entered position 2 as formulated (VI), but direct proof could not be obtained, for: (a) the triacetate was unchanged in an attempted Friess rearrangement, where a successful reaction might have led eventually to a known ethylfluorene; and (b) the derived trihydroxyfluorenone could not be converted into a cyclic diphenylmethylene ether (4), where the product of a successful reaction might have been distinctively an *o*- or a *m*-hydroxyketone.

Nitration of IV gave a mononitro derivative, probably a 2-nitro compound (VII).



VI

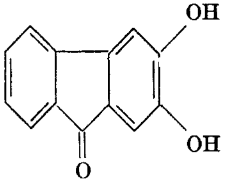


VII

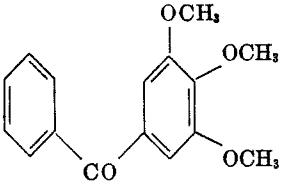
Reduction of VII gave an amine, and although diazotization of the amine was possible, attempts to replace the diazonium group by hydroxyl gave only tars. When diazotization was carried out using excess sodium nitrite, the diazonium group was replaced by a nitro group, and at the same time one methoxyl (probably at position 1) was replaced by hydroxyl. Demethylation of the amine from VII with hydrochloric or hydrobromic acid was partial. Again, the methoxyl affected was probably the one at position 1, since it is known that *o*-aminoethers are dealkylated three times as fast as their *m*-isomers (5), and that *o*-alkoxyketones are more easily dealkylated than their *m*-isomers (3).

A little work was done in an attempt to prepare a fluorenone-*o*-quinone. The known 2,3-dimethoxyfluorenone (6) was demethylated, yielding VIII. But this difficultly soluble substance was recovered unchanged when a suspension of it in benzene was shaken with silver oxide or with lead tetraacetate.

Incidentally, 2,3-dimethoxyfluorenone was converted into a mononitro derivative. The nitro group was shown not to be in position 1; it is likely that it was in position 4, but this was not proved. Neither the demethylated nitro compound, nor the amine derived from the nitro compound gave significant products with permanganate.



VIII



IX

A synthesis of trihydroxyfluorenone, patterned after that used for VIII, was abandoned when no conditions for nitrating IX in the desired way could be discovered. All methods tried gave 5-nitropyrogallol trimethyl ether, an acyl displacement of a known type (7) occurring.

EXPERIMENTAL

2′,5′-Dimethoxybiphenyl-2-carboxylic acid. A solution of 133 g. of ethyl anthranilate in 400 ml. of acetic acid and 200 ml. of acetic anhydride was kept at 90° for one hour and then cooled to 0°. Nitrous fumes (8) were passed in at below 5° until the solution became green. The mixture then was poured on ice and stirred until the nitroso derivative crystallized. (Methyl anthranilate gave a liquid nitrosoacetyl derivative and a somewhat smaller yield.) The yellow product, washed and dried 12 hours under reduced pressure, weighed 150 g.

In a one-liter three-necked flask, equipped with a stirrer, thermometer, and large bore rubber hose attached to a 250-ml. Erlenmeyer flask for adding the solid, there was placed 400 g. of *p*-dimethoxybenzene. The material was melted and kept at 57° for four hours, while 147 g. of the nitrosoacetyl derivative was added. Stirring at 55–60° was continued for 12 hours. Distillation then gave unchanged dimethoxybenzene, b.p. 93° at 13 mm., a little ethyl benzoate, and 65 g. of a red liquid, b.p. 165–200° at 13 mm.

The crude product (65 g.) was boiled for one hour with 40 g. of sodium hydroxide in 100 ml. of alcohol and 200 ml. of water. Insoluble material was removed with ether and discarded. Acidification gave a red oil (31 g.) which solidified but could not be purified by crystallization. It was dissolved in alcohol and passed through a column of alumina, giving 18 g. of colorless crystals m.p. 155–157°. [Cook and co-workers have recently prepared the acid using 1-*o*-carbethoxyphenyl-3,3-dimethyltriazene, reporting m.p. 155° (9)].

Anal. Calc'd for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5.
Found: C, 69.5; H, 5.4.

1,4-Dimethoxyfluorenone (IV). A solution of 2 g. of 2,5-dimethoxybiphenyl-2-carboxylic acid in 15 ml. of sulfuric acid was kept at 50° for one hour, then poured on ice. The product was washed with dil. sodium carbonate and dried, giving 1.65 g. m.p. 160–164°; recrystallization from alcohol and sublimation gave yellow needles m.p. 165–166°.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0.
Found: C, 74.9; H, 5.4.

1,4-Dihydroxyfluorenone (V). A mixture of 2 g. of IV with 25 ml. of acetic acid and 9 ml. of 47% hydrobromic acid was boiled for 22 hours. The product (1.2 g.) separated from ether-ligroin as orange needles, or from acetic acid as red-brown plates; both had m.p. 263–264°.

Anal. Calc'd for $C_{13}H_8O_3$: C, 73.6; H, 3.8.
Found: C, 73.8; H, 4.1.

From the acetic acid-hydrobromic acid mother liquors, after 36 hours more heating, there was isolated 0.4 g. of a dark solid, impure crystals from alcohol, m.p. 190–200°. When this was allowed to stand for 15 minutes with acetic anhydride containing one drop of sulfuric acid, and then poured in water, it gave a colorless product, needles from benzene-ligroin, m.p. 140–142° which was probably *5'-acetoxy-2'-hydroxybiphenyl-2-carboxylic acid lactone*.

Anal. Calc'd for $C_{15}H_{10}O_4$: C, 70.9; H, 4.0.
Found: C, 71.2; H, 4.2.

1,4-Diacetoxyfluorenone, obtained by allowing 0.5 g. of V to stand for two hours with 5 ml. of acetic anhydride and one drop of sulfuric acid, formed yellow needles (0.6 g.) from alcohol, m.p. 175–176°.

Anal. Calc'd for $C_{17}H_{12}O_5$: C, 68.9; H, 4.1.
Found: C, 68.8; H, 4.3.

1,4,9-Fluorenetrione (III). A suspension of 1 g. of V and 2.1 g. of lead tetraacetate in 100 ml. of toluene was shaken for three hours and then filtered. The solution was washed with water, distilled to 15 ml., and treated with 15 ml. of ligroin. The precipitated solid was sublimed under reduced pressure, giving 0.54 g. of red needles, m.p. 188–189°.

Anal. Calc'd for $C_{13}H_6O_3$: C, 74.3; H, 3.0.
Found: C, 74.2; H, 3.1.

Measurements of E were carried out as previously described (1) using buffers 1,3,6, and 10 of Conant and Chow.

The red solution of 0.5 g. of III in 150 ml. of toluene containing 0.22 ml. of cyclopentadiene became light yellow when it was kept at room temperature for three days. Distillation to a small volume under reduced pressure and addition of ligroin gave a solid *1:1-adduct*, yellow plates from alcohol, m.p. 159–161°.

Anal. Calc'd for $C_{18}H_{12}O_3$: C, 78.2; H, 4.4.
Found: C, 78.1; H, 4.5.

The Thiele reaction. 1,2(?),4-Triacetoxyfluorenone (VI). A solution of 1 g. of III and 3 drops of sulfuric acid in 10 ml. of acetic anhydride was kept at room temperature for two days. Water then was added, and the product was crystallized from benzene, giving 1.26 g. of yellow needles, m.p. 211.5–213°.

Anal. Calc'd for $C_{19}H_{14}O_7$: C, 63.9; H, 4.0.
Found: C, 64.1; H, 4.1.

A mixture of 1.8 g. of the triacetate and 1.5 g. of aluminum chloride in 10 ml. of nitrobenzene was allowed to stand at room temperature for 36 hours. Removal of nitrobenzene with steam left a red solid. This was re-acetylated with hot acetic anhydride containing a little sulfuric acid, giving 1.4 g. of unchanged triacetate. A similar failure of the Fries reaction, and recovery of starting material occurred when the triacetate, aluminum chloride, nitrobenzene mixture was heated at 90–110° for three hours.

1,2(?),4-Trihydroxyfluorenone was obtained in 87% yield by boiling 1.2 g. of the triacetate with 10 ml. of methanol containing 0.3 ml. of sulfuric acid for 30 minutes. It formed maroon needles from acetic acid, m.p. 302–304°.

Anal. Calc'd for $C_{13}H_8O_4$: C, 68.4; H, 3.5.
Found: C, 68.7; H, 3.7.

The trihydroxy compound gave no crystalline product when a solution in alkali was treated with oxygen (compare trihydroxybenzophenone, ref. 3) under conditions which bring about oxidation of trihydroxynaphthalene (10). With acetic anhydride, the trihydroxy compound gave the triacetate from which it had been obtained. With diphenyldichloromethane (4) at 115° the trihydroxy compound was unchanged, but at 200° it gave an amorphous brown solid, insoluble in alkali.

When 0.4 g. of the trihydroxy compound suspended in 400 ml. of ether was treated with excess diazomethane (from 1 g. of nitrosomethylurea) and allowed to stand 24 hours, it gave a *hydroxydimethoxyfluorenone* (probably *1*-HO-, *2,4*-di-CH_3O-); red needles from benzene, m.p. 238–241°.

Anal. Calc'd for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7.
Found: C, 70.0; H, 5.0.

The hydroxydimethoxyfluorenone gave a deep blue color with aqueous potassium hydroxide. When an alkaline solution was treated with excess methyl sulfate, there was obtained *1,2(?),4-trimethoxyfluorenone*, orange needles from benzene, m.p. 144–146°.

Anal. Calc'd for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2.

Found: C, 71.4; H, 5.4.

Nitration of 1,4-dimethoxyfluorenone. To a solution of 5 g. of IV in 300 ml. of acetic acid was added 25 ml. of conc'd nitric acid. The mixture was stirred at 30° for one hour, then poured on ice. Crystallization from dilute acetic acid gave 5 g. of 1,4-dimethoxy-2(?)-nitrofluorenone, (VII) yellow needles, m.p. 202–203°.

Anal. Calc'd for $C_{15}H_{11}NO_5$: C, 63.2; H, 3.9.

Found: C, 63.1; H, 3.9.

2(?)-Amino-1,4-dimethoxyfluorenone. A suspension of 2 g. of VII and 3 g. of ammonium chloride in 200 ml. of alcohol was boiled while 22 g. of hydrated sodium sulfide in 25 ml. of water was added. This required 30 minutes. The mixture was boiled for 30 minutes more, then distilled to one-half its volume and diluted with water. Crystallization from alcohol and sublimation gave 1.7 g. of red-brown needles, m.p. 161°.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.6; H, 5.1.

Found: C, 70.5; H, 5.2.

When 1 g. of the amino-dimethoxyfluorenone was heated at 200° for five hours with 20 ml. of conc'd hydrochloric acid, and the resulting solution then was neutralized with soda, there was obtained 0.69 g. of 2,1,4(?)-aminohydroxymethoxyfluorenone. The same compound was obtained in less pure form using hydrobromic acid in acetic acid in an open vessel. The product sublimed under reduced pressure in the form of dark red-brown needles, m.p. 280–240°. It gave a dark blue solution in aqueous sodium hydroxide.

Anal. Calc'd for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6.

Found: C, 69.5; H, 4.6.

Diazotization. A solution of 2 g. of 2-(?)amino-1,4-dimethoxyfluorene in 100 ml. of hot water containing 12 ml. of sulfuric acid was cooled to 0° and treated with 0.7 g. of sodium nitrite. Amine sulfate was still undissolved after three hours; so more nitrite was added until nitrous vapors were faintly visible. After one hour the undissolved material was removed (1.5 g. of aminodimethoxyfluorene was recovered from this). The filtrate was added to 250 ml. of 5% copper sulfate and kept at 80° overnight. Sublimation of the precipitated brown solid and then crystallization from alcohol gave 0.2 g. of *1-hydroxy-4-methoxy-2-nitrofluorenone* orange crystals, m.p. 205–206°. The substance gave a nearly insoluble purple sodium salt.

Anal. Calc'd for $C_{14}H_9NO_5$: C, 62.0; H, 3.3; N, 5.2.

Found: C, 62.1; H, 3.4; N, 5.4.

An ether solution of the nitrophenol treated with excess diazomethane gave 1,4-dimethoxy-2(?)-nitrofluorenone, m.p. 199° alone or mixed with an authentic specimen.

2,3-Dihydroxyfluorenone (VIII). Veratrole in benzene, treated with benzoyl chloride and aluminum chloride gave 89% of 3,4-dimethoxybenzophenone. Nitration according to the procedure of Reissert (6) gave 85% of 2-nitro-4,5-dimethoxybenzophenone. Reduction of this compound with hydrogen and platinum black gave 88%, or reduction with iron and dilute acetic acid gave 70%, of 2-amino-4,5-dimethoxybenzophenone. Diazotization and cyclization by Reissert's methods gave 53% of 2,3-dimethoxyfluorenone, m.p. 160–161°.

A mixture of 4.4 g. of dimethoxyfluorenone with 20 ml. of 47% hydrobromic acid and 5 ml. of acetic acid was boiled for 7 hours. The crude product, 3.55 g., had m.p. 230–235°; recrystallization from dil. alcohol and sublimation gave orange plates, m.p. 237–238°.

Anal. Calc'd for $C_{13}H_8O_3$: C, 73.6; H, 3.8.

Found: C, 73.5; H, 4.1.

A solution of 0.4 g. of the dihydroxy compound in 8 ml. of acetic anhydride containing one drop of sulfuric acid was kept at room temperature overnight. The product was crystallized from alcohol giving 0.43 g. of *2,3-diacetoxyfluorenone*, yellow needles, m.p. 169–170°.

Anal. Calc'd for $C_{17}H_{12}O_5$: C, 68.9; H, 4.1.
Found: C, 68.9; H, 4.3.

A solution of 3 g. of 2,3-dihydroxyfluorenone in 10 ml. of diphenyldichloromethane was kept at 80° for two hours and then at 160° for two hours. Dilution with ether caused precipitation of 3.5 g. of *2,3-benzohydrylidenedioxyfluorenone*, orange-yellow plates from alcohol, m.p. 172–173°.

Anal. Calc'd for $C_{26}H_{16}O_3$: C, 83.0; H, 4.3.
Found: C, 83.3; H, 4.6.

Nitration of 2,3-dimethoxyfluorenone. Considerable study was made of this reaction (fuming nitric acid, potassium nitrate and sulfuric acid, nitric acid in acetic acid, various temperatures and lengths of time were used), but the yield could not be raised above 35%. A solution of 10 g. of 2,3-dimethoxyfluorenone in 250 ml. of acetic acid was stirred at 25° while 40 ml. of conc'd nitric acid was added during five minutes. Stirring was continued for seven minutes more, and the mixture then was poured on ice. Crystallization from acetic acid gave 4.0 g. of *4(?)-nitro-2,3-dimethoxyfluorenone*, orange needles, m.p. 235–239°. A sublimed sample had m.p. 237–239°.

Anal. Calc'd for $C_{15}H_{11}NO_5$: C, 63.2; H, 3.9.
Found: C, 63.1; H, 4.1.

4(?)-Amino-2,3-dimethoxyfluorenone. A suspension of 1.2 g. of the nitro compound and 2 g. of ammonium chloride in 200 ml. of alcohol was treated with 15 g. of hydrated sodium sulfide in 25 ml. of water. The mixture was boiled for two hours, distilled to half its volume, and diluted with water. Crystallization from dilute alcohol gave red-brown needles (0.8 g.) m.p. 207–209°.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.6; H, 5.1.
Found: C, 70.6; H, 5.2.

When a solution of 1 g. (5-fold excess) of the acid chloride of ethyl hydrogen malonate in 15 ml. of chloroform was added to 0.3 g. of the preceding amine in 75 ml. of chloroform, there was formed *4(?)-carbethoxyacetamido-2,3-dimethoxyfluorenone*, long orange-red needles from alcohol, m.p. 299–300°.

Anal. Calc'd for $C_{20}H_{19}NO_6$: C, 65.0; H, 5.2.
Found: C, 64.8; H, 5.3.

The carbethoxyacetamido compound (0.14 g.) was not changed when it was boiled for one hour in 300 ml. of absolute alcohol containing 0.3 g. of sodium ethoxide, and 0.12 g. of it was recovered. This failure of the Camps reaction (11) indicates that the carbethoxyacetamido group is not in position-1, and is the basis for assigning orientations to the parent nitro compound and its derivatives.

Diazotization of 4(?)-amino-2,3-dimethoxyfluorenone. A solution of 2 g. of the amine in 200 ml. of water and 15 ml. of conc'd hydrochloric acid was cooled to 5° and treated with aqueous sodium nitrite until a slight excess was present. The solution was mixed with 300 ml. of 10% cupric sulfate and kept at 85° for 24 hours. The brown precipitate was sublimed giving 0.4 g. of *4(?)-chloro-2,3-dimethoxyfluorenone*, orange, m.p. 180–190°. The product formed orange needles from alcohol, m.p. 191–192°.

Anal. Calc'd for $C_{15}H_{11}ClO_3$: C, 65.6; H, 4.1.
Found: C, 65.8; H, 4.3.

No phenolic substance could be isolated from the products of the preceding experiment. A similar experiment with sulfuric acid replacing the hydrochloric acid gave 0.2 g. of a sublimable substance, orange needles from alcohol, m.p. 202–204°, whose analysis (found C, 67.7; H, 4.2) did not suggest its identity, and which was not alkali-soluble.

3,4,5-Trimethoxybenzophenone (IX). Trimethylgalloyl chloride (12), benzene, and aluminum chloride gave a mixture of partly demethylated products which could not be resolved or remethylated satisfactorily. The desired compound was obtained by treating diphenylcadmium with 65 g. of trimethylgalloyl chloride. The organo cadmium reagent was prepared by treating 22 g. of magnesium in 700 ml. of ether with 145 g. of bromobenzene, and then adding 124 g. of dried cadmium chloride. The synthesis was carried out according to standard procedures (13); the ether-benzene solution of the crude product was washed with dilute sodium hydroxide. Evaporation gave 47 g. of yellowish crystals m.p. 70–75°. A portion chromatographed on alumina and then crystallized from ether at −75° formed colorless needles, m.p. 78–79°.

Anal. Calc'd for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9.
Found: C, 70.4; H, 5.7.

The *2,4-dinitrophenylhydrazone* formed orange needles from alcohol, m.p. 200–202°.

Anal. Calc'd for $C_{22}H_{20}N_4O_7$: C, 58.4; H, 4.5.
Found: C, 58.4; H, 4.1.

Acidification of the alkaline extract and the difficultly soluble solid sodium salt, which had been obtained by washing the foregoing crude ketone with alkali, gave 7.8 g. of a white solid, m.p. 120–124°. Recrystallization of this from ether-ligroin gave *4,3,5(?)-hydroxydimethoxybenzophenone,* colorless plates, m.p. 124–126°.

Anal. Calc'd for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5.
Found: C, 69.9; H, 5.7.

4,3,5(?)-Acetoxydimethoxybenzophenone, from the hydroxy compound with acetic anhydride and a little sulfuric acid, formed colorless needles from alcohol, m.p. 188–189°.

Anal. Calc'd for $C_{17}H_{16}O_5$: C, 68.0; H, 5.4.
Found: C, 67.7; H, 5.4.

Nitration of IX was attempted using nitric acid of varying strengths alone, in sulfuric acid, in acetic acid, in ether, and in chloroform, or using acetyl nitrate in acetic anhydride or benzoyl nitrate in carbon tetrachloride. All these reagents and others either caused no change or yielded 5-nitropyrogallol trimethyl ether, m.p. 99–100° alone or mixed with an authentic sample (7). The best yield was obtained with cupric nitrate in acetic anhydride (14).

SUMMARY

1,4,9-Fluorenetrione has been found to add one equivalent of butadiene, to undergo a typical Thiele acetylation, and to have an oxidation reduction potential of 0.819 v. Some chemical transformations of 1,4- and 2,3-dimethoxy-fluorenones are described; conversion to nitro, amino, and diazonium derivatives. Nitration of 3,4,5-trimethoxybenzophenone has given only 5-nitropyrogallol trimethyl ether.

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