5. Tetraiodoeosin monomethyl ether has been prepared. It shows vivid red color indicating quinoid structure.
6. The absorption spectra of this series will be reported upon in a later paper.

PITTSBURGH, PA.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF PITTSBURGH.]

PHTHALIC ACID DERIVATIVES; CONSTITUTION AND COLOR, X.[1] TETRAIODOERYTHROSIN (OCTOIODOFLUORESCEIN) AND SOME OF ITS DERIVATIVES.

BY DAVID S. PRATT AND ARTHUR B. COLEMAN.

Received October 17, 1917.

Tetraiodoerythrosin or octoiodofluorescein is a new dye derived from fluorescein by substituting four iodine atoms for hydrogen in the phthalic acid residue and two in each of the resorcin residues of the molecule. Somewhat similar derivatives of ordinary fluorescein but without any iodine in the phthalic residue have been made commercially by methods of electrolysis, carrying on the reaction until the desired color has been obtained. Such compounds have varying percentages of iodine and are, *per se*, mixtures. A variety of ways were tried to obtain the definite fluorescein mentioned above with eight atoms of iodine in the molecule. An alkaline solution of tetraiodofluorescein was treated with iodine in potassium iodide solution. The mixture gradually lost its brilliant fluorescence and became light red in color, but the purified dye contained considerably less iodine than the desired tetraiodoerythrosin.

Subst. 0.3993; cc. 0.1 N $AgNO_3$, 20.91.
Calc. for $C_{20}H_4O_5I_8$: I, 75.80. Found: 66.46.

A second more successful method was to suspend tetraiodofluorescein in glacial acetic acid containing iodine and finely powdered potassium iodate, the latter being added to remove hydriodic acid as fast as formed. The mixture was heated in a water bath for 5 hours, during which time its color changed from dark red to orange-yellow. Longer heating or a higher temperature did not improve the yield. This method gave some of the desired product but the greater part of the material appeared to contain approximately six atoms of iodine.

The most satisfactory method found consisted in suspending 20 g. of pure tetraiodofluorescein in 200 cc. of absolute alcohol and adding to this 13 g. of iodine and 0.2 g. of iodic acid. The mixture was heated with reflux condenser for 12 hours, then diluted with water and acidified. A brown material settled out which was filtered off and heated 2 hours at 100° with glacial acetic acid containing 0.5 g. of potassium iodate, as this was found to improve the yield considerably. The material was finally filtered off and washed with dilute potassium iodide solution to remove

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[1] THIS JOURNAL, 40, 198 (1918).

free iodine, and the residue boiled with water repeatedly until the filtrate gave no test for halogen. This left a pink product which was still contaminated with lower iodinated products.

The best method available for further purification consists in dissolving the material in hot acetone. The resulting deep red solution was concentrated until it deposited bright yellow crystals of acetonate on cooling. These were filtered off and similarly recrystallized several times. Yield, about 21% theoretical.

A large amount of very soluble red material remained in the acetone, which was undoubtedly a mixture but consisted largely of hexaiodofluorescein. A portion of it was acetylated, purified as much as possible and analyzed.

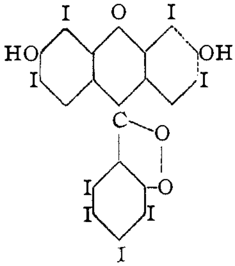
Subst. 0.2696; cc. 0.1 *N* $AgNO_3$, 13.99.
Calc. for $C_{24}H_{10}O_7I_6$: I, 64.99. Found: 65.86.

The material was not investigated further.

The yellow crystalline material from acetone was found to contain solvent of crystallization. Heated to constant weight at 120° it gave pure tetraiodoerythrosin.

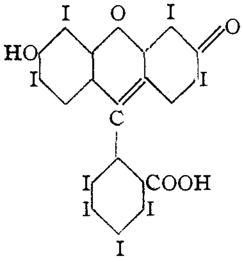
Subst. (I) 0.3344, (II) 0.1613; cc. 0.1 *N* $AgNO_3$, (I) 20.00, (II) 9.45.
Calc. for $C_{20}H_4O_5I_8$: I, 75.80. Found: (I) 75.90, (II) 74.36.

The compound freed from solvent of crystallization is a clear yellow and undoubtedly possesses the benzenoid structure



Tetraiodoerythrosin (yellow).

Prolonged heating at 140° causes it to go over to the dark red isomeric quinoid form represented by the structure



Tetraiodoerythrosin (red).

Tetraiodoerythrosin dissolves in alkaline solution with a very deep red color and faint bluish fluorescence. The sodium and potassium salts are only slightly soluble in cold water, readily on warming. A dilute alkaline solution dyes silk direct giving an attractive shade of red.

When a dilute solution is acidified it throws down a light pink hydrate so unstable that it loses water when its aqueous suspension is boiled, the pink color then being replaced by a light yellow. It rapidly gives the yellow tetraiodoerythrosin when dried at 100°.

Tetraiodoerythrosin is insoluble in alcohol and glacial acetic acid and does not rearrange in the presence of either solvent to give the carbinol carboxylic acid. It dissolves easily in warm acetone from which it separates as a beautifully crystalline acetone addition product or acetonate.

Tetraiodoerythrosin Acetonate.—Pure tetraiodoerythrosin was dissolved in hot acetone. The pink solution on concentration gave bright yellow crystals which were carefully separated by filtration, using a hardened filter paper just previously washed with dilute nitric acid and distilled water. This was necessary, as the product is extraordinarily sensitive to alkalies, especially ammonia, so much so that an unwashed paper turned it red at once. Tetraiodoerythrosin should be much more delicate as an indicator for very dilute solutions than erythrosin itself.

The yellow crystals were dried to constant weight at room temperature in an atmosphere free from ammonia and then heated to 140°. The crystalline structure was thus lost.

Subst. 0.3769; weight lost 0.0200.

Calc. for $C_{20}H_4O_5I_8.C_3H_6O$: Acetone, 4.15. Found: 5.28.

The acetonate evidently contains one molecule of acetone. The fact that no such stable addition product forms with the lower iodinated fluorescein derivatives was utilized in the process of purification.

Tetraiodoerythrosin Diacetate.—Pure tetraiodoerythrosin was boiled gently for an hour with acetic anhydride containing some fused sodium acetate. The diacetate gradually separated out in the form of lemon-yellow crystals, that were purified by recrystallization from acetone. Yield, almost theoretical.

The pure product gave the following analysis:

Subst. (I) 0.1692, (II) 0.2643; cc. 0.1 *N* $AgNO_3$, (I) 9.53, (II) 14.77.

Calc. for $C_{24}H_6O_7I_8$: I, 71.32. Found: (I) 71 48, (II) 70.93.

The crystals are insoluble in ethyl acetate, readily soluble in acetone. They are unacted upon by 5% sodium hydroxide, but saponify very slowly on heating to boiling. The pure material gradually darkens above 200° with loss of iodine. The structure is benzenoid.

Tetraiodoerythrosin Dibenzoate.—Pure tetraiodoerythrosin was suspended in benzoyl chloride, 5 g. in 15 cc., and boiled gently for 30 minutes. The solution was then cooled and poured into an excess of alcohol. After washing the resulting precipitate of crude dibenzoate with alcohol to remove ethyl benzoate it was dissolved in hot chloroform. An equal volume of alcohol was added and the solution gradually concentrated to crystallization. Further recrystallizations from acetone after boiling with boneblack gave light yellow crystals of pure tetraiodoerythrosin dibenzoate.

Subst. (I) 0.2391, (II) 0.0851; cc. 0.1 *N* $AgNO_3$, (I) 12.43, (II) 4.42.

Calc. for $C_{34}H_{12}O_7I_4$: I, 65.60. Found: (I) 65.98, (II) 65.92.

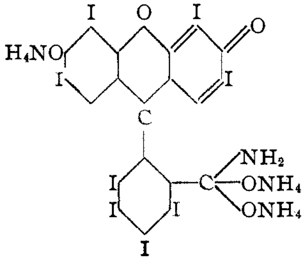
The dibenzoate decomposes without melting at about 300°. It is quite soluble in acetone and chloroform, insoluble in alcohol, and is not saponifiable by dilute sodium hydroxide. The extremely high formula weight of 1548 is notable, being surpassed by few if any compounds of known constitution. The yellow color demands a benzenoid structure.

Tetrammonium Salt.—A weighed sample of pure tetraiodoerythrosin in a porcelain boat was exposed to the action of dry ammonia until it reached constant weight. The yellow color changed to red at once, and ammonia was absorbed rapidly. Constant weight was reached after 12 hours, after which the sample was removed and heated at 120°. The following results were attained:

Subst. (I) 0.3748, (II) 0.6319. Gain in weight (I) 0.0179, (II) 0.0327. Loss in weight (I) 0.0170, (II) 0.0337.

Calc for $C_{28}H_4O_5I_8.4NH_3$: NH_3, 4.84. Found: by gain (I) 4.77, (II) 4.94; by loss (I) 4.54, (II) 5.09.

The reaction undoubtedly takes place in steps, first adding two molecules of ammonia with molecular rearrangement analogous to tetraiodofluorescein and tetraiodoeosin. The third molecule may then add in much the same way as ammonia adds to phthalic anhydride, giving amine and hydroxyl groups on the carboxyl carbon. A fourth molecule of ammonia would then convert hydroxyl to ONH_4. The salt is a brilliant dark red and must be represented by a quinoid structure, probably as:



since it leaves the brick-red form of tetraiodoerythrosin on heating. This gives a ready means of converting the ordinary yellow benzenoid modification into the red quinoid form.

Silver Salt.—The silver salt was prepared by dissolving 5 g. of pure tetraiodoerythrosin in 600 cc. water containing 5 cc. concd. ammonium hydroxide. A slight excess of silver nitrate in solution was added which at once caused a separation of the monosilver salt as violet particles. The salt is very slightly soluble in an excess of ammonia, differing in this respect from the corresponding salts of tetraiodofluorescein and tetraiodoeosin. It was thoroughly washed with boiling water, filtered and dried to constant weight at 120°. Analysis for silver was made by treating for some hours with six-normal nitric acid in the cold, diluting, filtering and titrating silver with standard ammonium thiocyanate, using ferric alum as indicator.

Subst. (I) 0.3330, (II) 0.4622; cc. 0.1 *N* NH_4SCN, (I) 2.86, (II) 3.67.
Calc. for $C_{20}H_3O_5I_8Ag$: Ag, 7.45. Found: (I) 9.26, (II) 8.56.

High results are probably due to occluded or adsorbed silver nitrate. The silver salt of tertaiodoerythrosin possesses a very brilliant violet color. When treated with dilute nitric acid as above in the analysis it gives a reddish brown form of tetraiodoerythrosin.

Monomethyl Ether.—The methyl ether was readily obtained by vigorously shaking a solution of pure tetraiodoerythrosin in dilute sodium hydroxide solution with successive portions of dimethyl sulfate. A very dark red non-crystalline product separated out, easily soluble in acetone or chloroform, very slightly soluble in methyl or ethyl alcohol, and benzene. The substance is quite unstable, losing weight slowly even at 100° giving a dark brown residue. A sample dried to constant weight over calcium chloride gave the following data for methoxyl by the Zeissel method:

Subst. (I) 0.4728, (II) 0.0790. Weight AgI, (I) 0.0647, (II) 0.0106.
Calc. for $C_{20}H_2O_3I_8.OCH_3$: OCH_3, 1.11. Found: (I) 1.80, (II) 1.77.

This shows that it undoubtedly contains but one methoxyl radical.

Subst. (I) 0.2592; cc. 0.1 *N* $AgNO_3$, 13.85.
Calc. for $C_{21}H_6O_3I_8$: I, 75.01. Found: (I) 67.82.

The ether gives no color with cold dilute sodium hydroxide solution.

Summary.

1. Tetraiodoerythrosin, or octoiodofluorescein, has been made and isolated in pure condition.

2. It nornally is yellow and in the benzenoid condition, but the colored quinoid form was obtained by warming the dry ammonia salt.

3. The acetonate was obtained as a stable addition product, forming yellow crystals containing one molecule of acetone.

4. These derivatives are all extremely sensitive to alkalies, especially to ammonia.

5. The diacetate is also yellow. It saponifies very slowly.

6. Tetraiodoerythrosin dibenzoate was obtained as light yellow crystals. It has the remarkable formula weight of 1548.

7. Dry ammonia gives a brilliant red tetrammonium salt, probably a derivative of the quinoid diammonium salt.

8. The monosilver salt is a brilliant purple.

9. The monomethyl ether is deep fiery red.

10. A lower halogenated product consisting largely of hexaiodofluorescein was a constant by-product.

11. Spectroscopic studies of the above series will be reported upon in a later paper.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF PITTSBURGH.]

PHTHALIC ACID DERIVATIVES; CONSTITUTION AND COLOR, XI.[1] PHENOLTETRAIODOPHTHALEIN AND SOME OF ITS DERIVATIVES.

BY DAVID S. PRATT AND ASHER F. SHUPP.

Received October 17, 1917.

Phenolphthalein derivatives formed by condensing phthalic anhydride with phenol have offered especially interesting compounds for color studies ever since they were first prepared by Baeyer in 1871.[2] They also form one of our most valuable classes of indicators for acidimetry and alkalimetry. The preparation of phenoltetraiodophthalein with four atoms of iodine in the phthalic anhydride ring, and its derivatives containing in addition four atoms of bromine or iodine in the phenol residue, has been carried out to compare these phthaleins with known samples. It was anticipated that interesting and valuable properties might result from the increased unsaturation produced by such substitution, either from the standpoint of their hydrogen-ion concentration or their color.

Tetraiodophenolphthalein was probably obtained, although in an impure condition, by Rupp,[3] but he records very poor yields and colors which we did not obtain with the pure substance. He does not mention any of its derivatives.

Tetraiodophthalic anhydride can be prepared on a laboratory scale by slightly modifying the original method of Juvalta.[4]

Tetraiodophthalic Anhydride.—25 g. of phthalic anhydride and 90 g. of iodine were added to 100 cc. of commercial fuming sulfuric acid containing 50% free SO_3, and the mixture heated in an oil bath to 65° until the reaction neared completion. This stage can be judged by the cessation of bubbles of sulfur dioxide which continue to escape as long as iodination is proceeding. The temperature of the bath was then gradually raised to 175° and maintained for 15 minutes, then allowed to fall slowly. A long-neck round bottom liter flask was used with a condenser made

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[1] THIS JOURNAL, 40, 198 (1918).

[2] *Ber.*, 4, 659 (1871).

[3] *Arch. Pharm.*, 249, 56 (1911).

[4] Ger., 50,177; see also Rupp, *Ber.*, 29, 1634 (1896).