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.

PITTSBURGH, PA.

[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).

from a large test tube roughly fitting the neck of the flask and supported on a winding of asbestos cord to prevent the escape of sulfur trioxide and iodine. In preparing large amounts of tetraiodophthalic anhydride it is advisable to add the iodine in three portions of about 60%, 30% and 10%, waiting after each addition until the evolution of sulfur dioxide practically ceases. The preparation offered no special difficulties and good yields were always obtained.

The anhydride crystallized out of the strong sulfuric acid on cooling in the form of brilliant, yellow needles. The mixture was cooled to room temperature and slowly poured with stirring over cracked ice since considerable sulfur trioxide still remained in the acid and much heat was generated on dilution. The crystalline mass was repeatedly washed by decantation with warm water containing sulfur dioxide to remove sulfuric acid and iodine. The product so obtained is pure enough for use in making the phthalein. Yield, nearly theoretical. Further purification was achieved by dissolving in cold alkali and diluting. The dipotassium salt is fairly soluble in warm water, but care must be used to avoid excess alkalinity as iodine is removed with considerable ease. The practically neutral solution was heated to boiling by passing in steam and promptly acidified with hydrochloric acid. The steaming was continued one hour, during which the tetraiodophthalic acid gradually became finely crystalline. The solution was filtered hot and the pale yellow acid washed free from chlorides. It loses water very readily at 100° and goes over within a short time into the markedly deeper yellow-colored anhydride. Tetraiodophthalic anhydride may be recrystallized from nitrobenzene, better from phenol, in long, bright, yellow needles. It melts at 320–325° (corr.). Analysis by the lime combustion method:

Subst. (I) 0.1000, (II) 0.2244; cc. 0.1 *N* $AgNO_3$, (I) 6.10, (II) 13.79.
Calc. for $C_8O_3I_4$: I, 77.90. Found: (I) 77.42, (II) 78.00.

Phenoltetraiodophthalein.—A great deal of difficulty was encountered in causing tetraiodophthalic anhydride to condense with phenol. This appeared to be due largely at least to the insolubility of the former in hot phenol containing any dehydrating agent. The anhydride dissolved readily enough in melted phenol, but it was thrown out in long, yellow needles by the addition of even small amounts of sulfuric acid. These crystals did not redissolve and of course seriously reduced the yield of phthalein, at first practically to mere traces.

The difficulty was finally obviated by using a great excess of phenol and adding the sulfuric acid drop by drop as the reaction proceeded instead of all at the start as is customary. The question of temperature is also important if good yields are to be obtained. A typical preparation was as follows:

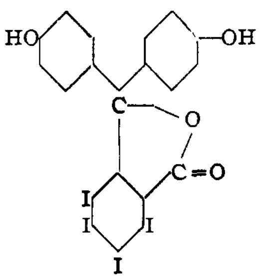
100 g. of powdered tetraiodophthalic anhydride were dissolved in 800 g. of colorless freshly distilled phenol by warming to 160°. It is important that the anhydride be in solution before any acid is added. 120 g. of fuming sulfuric acid containing 13% free sulfur trioxide were then added drop by drop to the above solution contained in a 2-liter round bottom flask provided with a mechanical stirrer. The addition of sulfuric acid required about 1 hour. At no time did any anhydride crystallize out. The temperature was then raised to 170° and 400 g. more of the fuming sulfuric acid were added very slowly and with constant stirring. This addition of acid should require about 2 hours, and at no time should anhydride crystallize out. Small tests portions were now removed from time to time, placed on a slide and examined under the microscope. Uncondensed anhydride forms yellow, prismatic crystals on standing, especially if a trace of alcohol be added to the preparation on the slide. Heating should be continued until few, if any, such crystals form, ordinarily about 5 to 6 hours being required in all, including the preliminary heating.

The clear, deep red reaction product while still hot was poured into hot water contained in large cylinders and repeatedly washed by decantation with hot water. This wash water, on cooling, deposited crystals in large amount of oxysulfobenzide, a constant by-product of the reaction. It was not found practical to attempt removing such a large excess of phenol by distillation as is ordinarily done in phthalein condensations.

The residue contained the desired phthalein, tetraiodofluoran, and some unchanged tetraiodophthalic anhydride. It was dried in a water oven to insure the absence of tetraiodophthalic acid by converting it into anhydride, as the former is somewhat soluble in alcohol while the latter is not. The residue was extracted several times with ethyl alcohol in which the amorphous phthalein in readily soluble, then filtered from fluoran and anhydride. The alcoholic solution of phthalein contained some tarry products to remove which it was boiled with repeated portions of boneblack until it became a clear red. Slow concentration of this solution deposited well-formed yellow crystals of phenoltetraiodophthalein; rapid concentration gave an amorphous product. Yield, about 70 g.

The material was purified by recrystallization from alcohol and glacial acetic acid, using boneblack and long boiling. It melts at 239–45° when amorphous.

The pure product is lemon-yellow in color, readily soluble in ordinary organic solvents, such as alcohol, ether, chloroform, glacial acetic acid, etc., when in the amorphous form, but much less so when crystalline. Its structure is to be represented as



Subst. (I) 0.1974, (II) 0.2178; cc. 0.1 *N* $AgNO_3$, (I) 9.59, (II) 10.45.
Calc. for $C_{20}H_{10}O_4I_4$: I, 61.78. Found: (I) 61.70, (II) 61.90.

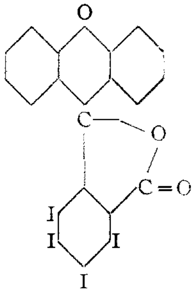
Phenoltetraiodophthalein undoubtedly owes its yellow color not to the presence of any quinoid arrangement of the molecule, but to the influence of four iodine atoms in shifting the absorption range into the visible spectrum. The proximity effect thus brought about by iodine in the anhydride is carried into the phthalein, provided the latter still conforms to the anhydride ring formation. The remaining carbonyl and anhydride oxygen are distinctly influenced chemically, as shown by the fact that phenoltetraiodophthalein does not react with hydroxylamine to give an oxime or with aniline to give an anilide, although both reactions are readily brought about with phenolphthalein itself. The color on spectroscopic investigation will, without question, correspond to that evidenced by the tetraiodophthalic anhydride. It was our intention to study the absorption spectra of all these compounds under a variety of conditions, in fact the principal theoretical points to be taken up were in this connection. The inability of London firms to make deliveries during the war of certain essential apparatus compels us to delay report on this portion of the work until a later paper.

Phenoltetraiodophthalein dissolves in alkali with a deep red color somewhat similar to that of ordinary phenolphthalein but lacking the purple tone. A weighed sample of the phthalein exposed to ammonia gas either dry or moist, failed to change color and did not gain in weight. Evidently no salt is formed under these conditions.

Tetraiodofluoran.—The residue that remained after extracting the phthalein with alcohol contained unchanged tetraiodophthalic anhydride and tetraiodofluoran. The former was removed with warm dilute alkali as the disodium salt and the final residue dissolved in hot glacial acetic acid. The solution was boiled with boneblack, and deposited, on concentration, yellow crystals of tetraiodofluoran. It is insoluble in alcohol, chloroform, acetone, ethyl acetate, phenol, nitrobenzene, and alcoholic alkali, very sparingly in acetic acid. The pure compound decomposes at about 319° (corr.).

Subst. (I) 0.1390, (II) 0.1414; cc. 0. 1*N* $AgNO_3$, (I) 6.89, (II) 7.02.
Calc. for $C_{20}H_8O_3I_4$: I, 63.16. Found: (I) 62.91, (II) 63.01.

The structure of the tetraiodofluoran is



Phenoltetraiodophthalein Diacetate.—The acetate was prepared by boiling for 1 hour a mixture of 5 g. of pure phenoltetraiodophthalein and 3 g. of fused sodium acetate in 15 cc. of acetic anhydride. The reaction product was poured on ice, filtered off and thoroughly washed. After drying it was dissolved in benzene containing a little acetic anhydride and boiled with boneblack for 4 days. The solvent was distilled off, and the acetate recrystallized from absolute methyl alcohol. Further crystallization from ethyl alcohol caused no change in the melting point of 230° (corr.). Yield, about 60%. Analysis:

Subst. (I) 0.2961, (II) 0.2116; cc. 0.1 *N* $AgNO_3$, (I) 13.06, (II) 9.32.
Calc. for $C_{24}H_{14}O_6I_4$: I, 56.04. Found: (I) 55.98, (II) 55.90.

The diacetate forms light yellow crystals similar in color to the phthalein. It is very readily saponified by aqueous alkali in the cold.

Phenoltetraiodophthalein Dibenzoate.—The benzoate may be prepared by boiling pure phenoltetraiodophthalein for an hour with benzoyl chloride. A rather more satisfactory method is to dissolve the phthalein in dilute alkali and shake the solution vigorously with successive small portions of benzoyl chloride. Alkali should be added at intervals to prevent the solution becoming acid. The completion of the reaction is shown by the disappearance of the red color.

The product, after thorough washing with dilute alkali, followed by water and finally alcohol, was crystallized from benzene. The melting point of 236° (corr.) was not altered by dissolving in chloroform and throwing out by the addition of alcohol.

Subst. (I) 0.1501, (II) 0.2202; cc. 0.1 *N* $AgNO_3$, (I) 5.82, (II) 8.70.
Calc. for $C_{34}H_{18}O_6I_4$: I, 49.29. Found: (I) 49.21, (II) 50.10.

The dibenzoate crystallizes in light yellow needles, difficultly soluble in alcohol and ether; easily in benzene, acetone or chloroform.

Phenoltetraiodophthalein Dimethyl Ether.—Pure phenoltetraiodophthalein was dissolved in alkaline solution and shaken vigorously with successive small portions of dimethyl sulfate taking care to avoid rise in temperature. The red color gradually disappeared as the ether precipitated out. The most satisfactory solvent for purification proved to be ethyl alcohol, from which, on very slow evaporation, the ether was obtained crystalline.

Subst. (I) 0.1593, (II) 0.2112; cc. 0.1 N $AgNO_3$, (I) 7.58, (II) 10.00.
Calc. for $C_{22}H_{14}O_4I_4$: I, 59.74. Found: (I) 60.39, (II) 60.09.

The dimethyl ether forms deep canary-yellow crystals which melt at 221° (corr.). It is quite soluble in chloroform, benzene, acetone, only slightly so in alcohol or ether. The structure is correctly represented by the benzenoid form, the yellow color being normal. The isomeric quinoid ether ester was not obtained.

Dinitrophenoltetraiodophthalein.—A suspension of 10 g. pure phenoltetraiodophthalein in 220 g. of sulfuric acid (sp. gr. 1.84) was heated to 90° for one hour with vigorous mechanical stirring, during which the deep red color of the suspended phthalein turned to a brick red. The material was cooled to room temperature and a mixture consisting of 33 g. of nitric acid (sp. gr. 1.43) and 40 g. of sulfuric acid (sp. gr. 1.84) was slowly added with stirring. After the nitrating acid had all been added the temperature was raised to 90° and maintained with constant stirring until a test sample dropped into dilute alkali showed only a few particles turning red. Prolonged heating would be necessary to cause complete nitration of these particles, and such is not desirable, as tars are readily produced and are exceedingly difficult to remove.

The reaction mixture was cooled and poured into water. The precipitated crude phthalein was dissolved in dilute alkali and reprecipitated by adding dilute hydrochloric acid. It was dried and extracted with ethyl alcohol to remove unchanged phenoltetraiodophthalein, then treated for a few minutes with warm acetone. The dinitro product is readily soluble in warm acetone while the tetranitro derivative is not.

Dinitrophenoltetraiodophthalein is soluble in hot ethyl alcohol, cold chloroform, ethyl acetate and acetone. It crystallizes only when pure, then giving yellow needles which decompose about 311–312° (corr.). Yield, 20%.

Subst. (I) 0.0447, (II) 0.1100; cc. 0.1 N $AgNO_3$, (I) 1.97, (II) 4.81.
Calc. for $C_{20}H_8O_8N_2I_4$: I, 55.67. Found: (I) 55.93, (II) 55.50.

The dinitrophenoltetraiodophthalein dissolves in dilute alkaline solution with a deep orange-yellow color. The distribution of the two nitro groups was not fixed, but it is more than probable that each phenol residue contains one nitro group in a position ortho to the hydroxyl.[1] This would give the structure

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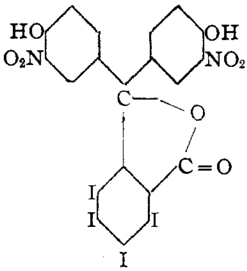
[1] THIS JOURNAL, **38**, 2486 (1916).



Discussion of probable structure in the yellow alkaline solution is reserved until spectroscopic data are available.

Dinitrophenoltetraiodophthalein Diacetate.—The nitrophthalein is easily decomposed by heat so that special care must be used in acetylating it. A solution of pure dinitrophenoltetraiodophthalein in acetic anhydride containing a little fused sodium acetate was warmed for 15 minutes on a water bath. The reaction product was poured into cold water, filtered and washed. It was then purified by treating an acetone or chloroform solution with enough alcohol to cause crystallization on standing. Yield, about 60%.

Subst. (I) 0.2983, (II) 0.2882; cc. 0.1 *N* $AgNO_3$, (I) 12.26, (II) 11.94.
Calc. for $C_{24}H_{12}O_{10}N_2I_4$: I, 50.98. Found: (I) 52.16, (II) 52.58.

The pure product forms deeply yellow crystals sparingly soluble in alcohol even on heating, easily soluble in acetone and chloroform. Melting point 281° (corr.).

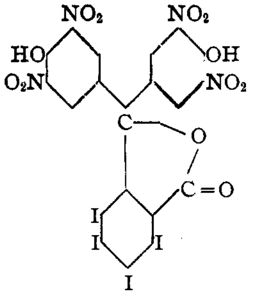
Tetranitrophenoltetraiodophthalein.—In the purification of dinitrophenoltetraiodophthalein there remained some yellow material insoluble in warm acetone. This was finally dissolved by long boiling with an excess of acetone. Concentration caused the substance to deposit slowly in clear, yellow crystals.

Subst. (I) 0.1048, (II) 0.1138; cc. 0.1 $AgNO_3$, (I) 4.25, (II) 4.66.
Calc. for $C_{20}H_6O_{12}N_4I_4$: I, 50.67. Found: (I) 51.47, (II) 51.97.

The presence of four nitro groups tended to cause the halogen determinations made in this way to run high, due to the formation of cyanides. For this reason the phthalein was dissolved in glacial acetic acid and reduced with zinc dust, and finally analyzed for nitrogen by the Kjeldahl method:

Subst. (I) 0.2215, (II) 0.0387; cc. 0.1 *N* HCl, (I) 8.55, (II) 1.68.
Calc. for $C_{20}H_6O_{12}N_4I_4$: N, 5.59. Found: (I) 5.33, (II) 6.08.

The material is evidently tetranitrophenoltetraiodophthalein. The yellow crystals decompose at about 311° (corr.). They are difficultly soluble in acetone and alcohol, readily in dilute alkaline solution with a yellow color, bordering on orange. The following structure should be assigned to the compound:



Tetrabromophenoltetraiodophthalein.—Tetrabromophenoltetraiodophthalein contains two bromine atoms in each phenol ring in addition to the iodone in the phthalic anhydride residue. It was made by dissolving 10 g. of pure phenoltetraiodophthalein in 150 cc. ethyl alcohol, and adding to this solution while boiling about 7 cc. of bromine in 50 cc. of glacial acetic acid. The reaction was complete in 15 minutes, and since the product was only slightly soluble in alcohol, it crystallized out as it formed. Yield, theoretical.

The crude material was recrystallized once from alcohol and obtained pure in yellow crystals melting at 311–312° (corr.). Analysis was made by the lime combustion method, weighing the combined halides in addition to titrating with standard ammonium thiocyanate.

Subst. (I) 0.1827, (II) 0.1822; cc. 0.1 *N* $AgNO_3$, (I) 12.31, (II) 12.49. Weight AgI + AgBr: (I) 0.2616, (II) 0.2653.

Calc. for $C_{20}H_6O_4Br_4I_4$: Br, 28.13; I, 44.63. Found: (I) Br, 27.26; I, 43.30; (II) Br, 27.68; I, 43.95.

Tetrabromophenoltetraiodophthalein is slightly soluble in hot alcohol, more so in ether, acetone and benzene, but difficult to obtain crystalline from any except the first. The compound indicates by its normal yellow color that it possesses the benzenoid formation, in which the bromine atoms are undoubtedly ortho to the hydroxyl groups. Dry ammonia has no effect on the phthalein, but aqueous alkali dissolves it with a clear deep blue color very similar to that given by thymolphthalein.

Tetrabromophenoltetraiodophthalein Diacetate.—The diacetate was made in an analogous manner to that used in making phenoltetraiodophthalein diacetate except that the time of boiling was reduced to 30 minutes. The crude product in benzene was boiled with boneblack, and finally obtained pure from chloroform by the gradual addition of alcohol. It forms bright yellow crystals which melt at 285° (corr.).

Subst. (I) 0.1990, (II) 0.1924; cc. 0.1 *N* $AgNO_3$, (I) 12.70, (II) 12.25. Weight of AgI + AgBr: (I) 0.2716, (II) 0.2587.

Calc. for $C_{24}H_{10}O_6Br_4I_4$: Br, 26.17; I, 41.56. Found: (I) Br, 26.13; I, 41.50; (II) Br, 25.41; I, 40.43.

Tetrabromophenoltetraiodophthalein Dibenzoate.—The benzoate was readily obtained by the Schotten-Baumann reaction as in the preceding case. The product so made was similarly purified and finally crystallized from hot chloroform by the addition of alcohol. Yield, about 80%.

Subst. (I) 0.2184, (II) 0.2110; cc. 0.1 *N* $AgNO_3$, (I) 12.91, (II) 12.33. Weight of AgBr + AgI: (I) 0.2752, (II) 0.2615.

Calc. for $C_{34}H_{14}O_6Br_4I_4$: Br, 24.76; I, 37.73. Found: (I) Br, 24.05; I, 38.20; (II) Br, 24.08; I, 38.24.

The dibenzoate forms yellow crystals melting at 213–215° (corr.), soluble in acetone, benzene, ethyl acetate and chloroform, slightly soluble in alcohol.

Tetrabromophenoltetraiodophthalein Dimethyl Ether.—The dimethyl ether was made by shaking an alkaline solution of the pure phthalein with dimethyl sulfate until the blue color disappeared. The dried precipitate so obtained was dissolved in chloroform, and the solution mixed with ethyl alcohol in about equal amount and concentrated by distillation until the ether crystallized out on cooling. The addition of alcohol to the hot chloroform solution does not throw down the ether in crystalline form, as was the case with the acetate and benzoate.

Subst. (I) 0.2789, (II) 0.2193; cc. 0.1 *N* $AgNO_3$, (I) 20.76, (II) 15.13. Weight of AgBr + AgI: (I) 0.4236, (II) 0.3157.

Calc. for $C_{22}H_{10}O_4Br_4I_4$: Br, 27.42; I, 43.56. Found: (I) Br, 27.52; I, 43.71; (II) Br, 26.87, (II) I, 42.67.

The dimethyl ether gave lemon-yellow crystals melting at 255° (corr.). It is readily soluble in acetone, benzene and ethyl acetate, much less so in alcohol.

Tetraiodophenoltetraiodophthalein.—This respresents the maximum iodine substitution possible in phenolphthalein. The product was made by dissolving 15 g. of pure phenoltetraiodophthalein in a slight excess of dilute alkali, cooling with ice, and gradually adding a solution of 30 g. of iodine in potassium iodide solution. The cold mixture was stirred mechanically during the addition of iodine, and kept alkaline by supplying sodium hydroxide to neutralize the hydriodic acid liberated by the reaction.

About 1 1/2 hours were allowed for completion of the reaction, during which the red color was replaced by a greenish blue. The crude phthalein was precipitated by acidification, well washed with dilute potassium iodide solution to remove excess iodine, followed by boiling water, and dried. It was then treated with cold chloroform to remove unchanged phenoltetraiodophthalein and dissolved in boiling alcohol. Slow concentration of the alcoholic solution and long standing gave the pure compound in deep yellow crystals. Yield, about 50%.

Subst. (I) 0.3792, (II) 0.2019; cc. 0.1 *N* $AgNO_3$, (I) 22.96, (II) 12.17.

Calc. for $C_{20}H_6O_4I_8$: I, 76.60. Found: (I) 76.85, (II) 76.50.

Tetraiodophenoltetraiodophthalein consists of over 75% iodine and still preserves its distinct character as a phthalein. The pure compound from alcohol forms clear, yellow crystals which decompose with loss of iodine at about 285° (corr.). It is difficultly soluble in ordinary solvents, especially when in the crystalline form. Dry ammonia does not give a salt, but the phthalein is readily soluble in aqueous alkali with a royal blue color.

Tetraiodophenoltetraiodophthalein Acetate.—10 g. of pure tetraiodophenoltetraiodophthalein and an equal weight of fused sodium acetate were boiled for 30 minutes with 40 cc. of acetic anhydride. The phthalein remained in suspension but was gradually acetylated. The products were poured into cold water and the acetate washed and dried. It was recrystallized until pure from chloroform by precipitating with alcohol. Yield, 60%.

Subst. (I) 0.1501, (II) 0.1201; cc. 0.1 *N* $AgNO_3$, (I) 8.55, (II) 6.81.
Calc. for $C_{24}H_{10}O_6I_8$: I, 72.03. Found: (I) 72.29, (II) 71.97.

The diacetate is difficultly soluble in alcohol, readily in acetone, ethyl acetate and benzene. It forms pale yellow crystals melting at 288° (corr.).

Tetraiodophenoltetraiodophthalein Dibenzoate.—The dibenzoate was made by the Schotten-Baumann reaction and purified in the same way as the previous benzoates. Yield, 80%. A sample of the purified product gave the following analysis:

Subst. (I) 0.2223, (II) 0.3168; cc. 0.1 *N* $AgNO_3$, (I) 11.58, (II) 16.52.
Calc. for $C_{34}H_{14}O_6I_4$: I, 66.21. Found: (I) 66.11, (II) 66.18.

The dibenzoate forms light yellow crystals difficultly soluble in alcohol and ether, easily in benzene, chloroform, and acetone. The pure substance melts at 202–3° (corr.).

Tetraiodophenoltetraiodophthalein Dimethyl Ether.—The dimethyl ether was made in exactly the same way as the corresponding ethers previously mentioned. Acetone or chloroform are the best solvents, slow evaporation of either giving well-formed pale yellow crystals, decomposing at about 295–297° (corr.). Yield, 40%.

Subst. (I) 0.0968, (II) 0.1053; cc. 0.1 *N* $AgNO_3$, (I) 5.75, (II) 6.19.
Calc. for $C_{22}H_{10}O_4I_8$: I, 75.01. Found: (I) 75.39, (II) 74.61.

Summary.

1. Pure phenoltetraiodophthalein has been obtained in the form of yellow crystals, soluble in alkaline solution with a deep red color.
2. The benzenoid diacetate, dibenzoate and dimethyl ether have all been prepared in crystalline form.
3. Tetraiodofluoran was isolated as a by-product.
4. Dinitrophenoltetraiodophthalein and its diacetate were made.
5. Tetranitrophenoltetraiodophthalein was formed with the dinitro

product and purified. Both of these compounds are yellow and dissolve in alkali with an orange-yellow color.

6. Tetrabromophenoltetraiodophthalein results from the bromination of phenoltetraiodophthalein. It is a yellow crystalline product, soluble in alkali with a deep blue color.

7. The corresponding diacetate, dibenzoate, and dimethyl ether were made.

8. Tetraiodophenoltetraiodophthalein is a yellow crystalline substance soluble in alkaline solution with a deep blue.

9. Its diacetate, dibenzoate, and dimethyl ether are all yellow.

10. The absorption spectra and theoretical discussion of these substances will be reported upon in a later paper.

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THE MOLECULAR MECHANISM OF COLLOIDAL BEHAVIOR.

I. THE SWELLING OF FIBRIN IN ACIDS.

BY RICHARD C. TOLMAN AND ALLEN E. STEARN.

Received October 22, 1917.

In previous articles,[1] one of the authors has discussed the general behavior of colloidal systems from a *thermodynamic* point of view. In a series of articles, of which this is to be the first, it is proposed to subject a number of typical colloidal systems to an intensive study from a *molecular* or *microscopic* point of view. Such studies will provide a much more intimate and complete basis for the explanation and prediction of colloidal behavior than can be done on the basis of thermodynamic considerations alone. No special attempt will be made to preserve any logical order of publication for these articles.

The swelling of protein colloids in acid and in alkaline solution and the decrease in swelling produced by the addition of neutral salts is a matter, both of great physiological and pathological interest, and has been particularly studied by Fischer[2] in his important experimental and clinical researches. The purpose of the present work is to investigate the molecular mechanism by which such swellings and reductions in swelling are brought about. We may say in advance, that our experimental results are in accord with the theory that a colloidal gel, such as a piece of fibrin covered by water, is a fibrous sponge-like structure with many minute pores or pockets which are themselves full of water. The addition of acid or alkali is followed by the adsorption, respectively, of hydrogen or hydroxide ion on the surface of these pockets and a consequent increase in their size owing to electrostatic repulsion, the increase in size being accompanied, of course, by imbibition of solution. The further addition

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[1] Tolman, THIS JOURNAL, 35, 307, 317 (1913); *Science*, 44, 565 (1916).

[2] Fischer, "Edema and Nephritis," New York, 1915.