

1930

A new series of halogenated sulphone-phthaleins.

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A NEW SERIES OF HALOGENATED SULPHONE-PHTHALEINS

By

William Clouser Boyd

(A.B. Harvard, 1925; A.M. Harvard, 1926)

A Dissertation

submitted in partial fulfilment of the
requirements for the
degree of Doctor of Philosophy

GRADUATE SCHOOL

BOSTON UNIVERSITY

1930

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To Dr. Allan Winter Rowe, under whose inspiration this work was planned, and with whose vigorous cooperation it was completed, and to Dr. Burnham Sarle Walker, whose kindness was as unflinching as the ingenuity of his suggestions.

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VITA

William Clouser Boyd was born March 4, 1903 on a farm near Dearborn, Missouri, the son of William Oliver Boyd and Wilmuth Clouser Boyd. He attended the local grade schools, and entered Dearborn high school in 1918. In 1919 he entered Central high school, St. Joseph, Missouri from which he was graduated in 1922. In the fall of this year he entered Harvard University, concentrated in chemistry and received the degree of A.B. in 1925, and the degree of A.M. in 1926. He then became Teaching Fellow in Physiological Chemistry at the Boston University School of Medicine and carried on the research the results of which comprise this thesis, at the Evans Memorial Hospital, under the direction of Dr. Allan Winter Rowe, in the meantime taking further courses at Harvard and at Boston University. He is the co-author with Dr. S.B. Hooker of a paper "The Chances of Establishing Non-Paternity by the Determination of Blood Groups", (Science, n.s. 68 (no.1773) p. 620; J. Immunol. 16, 451 ('29))

William Thomas Boyd was born March 4, 1905 on a farm near
 Westport, Vermont, the son of William Oliver Boyd and
 Elizabeth Boyd. He attended the local grade school, and entered
 Central High School in 1923. In 1929 he entered Central High
 School, St. Joseph, Vermont from which he was graduated in 1932.
 In the fall of this year he entered Harvard University, where
 he studied chemistry and received the degree of A.B. in 1935, and
 the degree of A.M. in 1936. He then became Teaching Fellow in
 Physiological Chemistry at the Boston University School of Medical
 and carried on the research the results of which appeared in
 thesis at the Yale Medical School, under the direction of Dr.
 Allen Porter Bray, in the medical college further course at
 Harvard and at Boston University. He is the co-author with Dr. J. J.
 Porter of a paper "The Influence of Acetabular Inactivity on
 the Retention of Blood Plasma," (Science, N. Y. 63 (1948))
 N. Y. J. Animal. 1, 421 (1948)

At the suggestion of one of the readers, the names of compounds made for the first time by the author of this thesis are distinguished by being underlined in red.

At the suggestion of one of the members, the names of companies
were put on the list by the editor of this journal and distributed
by letter mentioned in 1901.

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ABBREVIATIONS

With the single exception that JACS is used instead of Am.Soc., the abbreviations used in the references to the periodical literature in this thesis are those used in Richter's "Lexikon der Kohlenstoff-Verbindungen", and Stelzner's "Literatur-Register der Organischen Chemie". These abbreviations follow. The names of journals not in this list are either abbreviated in an analogous manner, or written out in full.

The references are made as follows: first, the name of the author, if necessary; second, the abbreviation for the journal; third, the volume; fourth, the page; fifth (in parenthesis) the year (as ('71) = 1871), or the year of the abstract in the Zentralblatt (as(C72) = Zentralblatt, 1872), or Chemical Abstracts, (CA).

A	(Liebig's) Annalen der Chemie
A. ch.	Annales de chimie et physique
Am.	American Chemical Journal
JACS	Journal of the American Chemical Society
A.Pth.	Archiv für experimentelle Pathologie und Pharmakologie
Ar.	Archiv der Pharmazie
B.	Berichte der Deutschen Chemischen Gesellschaft
Bio. Z.	Biochemische Zeitschrift
Bl.	Bulletin de la Societe Chimique de France

INDEX

With the above mentioned list it is not intended to show the chronological order of the publications in the series. The list is arranged in alphabetical order of the authors' names. The names of journals are in italics. The names of books are in plain type. The names of articles are in small caps. The names of chapters are in small caps. The names of sections are in small caps. The names of subsections are in small caps. The names of paragraphs are in small caps. The names of sentences are in small caps. The names of words are in small caps.

The following is a list of the authors of the articles in the series. The names are in alphabetical order. The names of journals are in italics. The names of books are in plain type. The names of articles are in small caps. The names of chapters are in small caps. The names of sections are in small caps. The names of subsections are in small caps. The names of paragraphs are in small caps. The names of sentences are in small caps. The names of words are in small caps.

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- C. r. Comptes rendus de l'Academie des sciences
- Ch. J Chemische Industrie
- Ch. Z. Chemiker-Zeitung (Cöthen)
- Chem. N. Chemical News
- D. (Dingler's) Polytechnisches Journal
- D.R.P. Patentschrift des Deutschen Reiches
- El. Ch.Z. Electrochemische Zeitschrift
- Fr. (Fresenius') Zeitschrift für analytische Chemie
- Frdl. (Friedländer's) Fortschritte der Theerfarbenfabrikation
- G. Gazzetta Chimica Italiana
- H (Hoppe-Seyler's) Zeitschrift für physiologische Chemie
- J. Jahresbericht der Chemie
- J. pr. Journal für practische Chemie
- J. r. Journal der russischen physikalisch-chemischen
Gesellschaft
- J. Th. Jahresbericht der Thierchemie
- L.V.St. Landwirtschaftliche Versuchsstationen
- M. Monatshefte für Chemie
- P. (Poggendorff's) Annalen der Physik und Chemie
- P. C. H. Pharmaceutische Centralhalle
- P.Ch.S. Proceedings of the Chemical Society
- Ph. Ch. Zeitschrift für physikalische Chemie

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5	Die Arbeit als gesellschaftliche Tätigkeit
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- R. Recueil des travaux chimiques des Pays-Bas
- R.A.L. Atti della reale Academia dei Lincei
- Soc. Journal of the Chemical Society
- W. (Wiedermann's) Annalen der Physik
- Z. Zeitschrift für Chemie
- Z.a.Ch. Zeitschrift für anorganischen Chemie
- Z. Ang. Zeitschrift für angewante Chemie
- Z.B. Zeitschrift für Biologie
- Z.El.Ch. Zeitschrift für Electrochemie
- Z. Kr. Zeitschrift für Krystallographie

1. The first part of the report is devoted to a general survey of the situation in the country. It is followed by a detailed analysis of the economic and social conditions. The third part of the report is devoted to a study of the political situation. The fourth part of the report is devoted to a study of the cultural situation. The fifth part of the report is devoted to a study of the educational situation. The sixth part of the report is devoted to a study of the health situation. The seventh part of the report is devoted to a study of the housing situation. The eighth part of the report is devoted to a study of the transportation situation. The ninth part of the report is devoted to a study of the communication situation. The tenth part of the report is devoted to a study of the environment situation. The eleventh part of the report is devoted to a study of the international relations situation. The twelfth part of the report is devoted to a study of the future prospects of the country.

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I

HISTORICAL

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"omnis enim color omnino mutatur in omnis;
 quod facere haud ullo debent primordia pacto;
 immutabile enim quiddam superare necessest,
 ne res ad nilum redigantur funditus omnes.
 nam quodcumque suis mutatum finibus exit,
 continuo hoc mors est illius quod fuit ante.
 proinde colore cave contingas semina rerum,
 ne tibi res redeant ad nilum funditus omnes.

Lucretius--De Rerum Natura,
 Liber II, 749-756

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Adolf von Baeyer has described the line of thought leading up to his discovery of the phthaleins in his own words ¹: "Bei Versuchen, eine Kondensation unter Wasserabspaltung zwischen mehreren Molekülen von im Pflanzenkörper vorkommenden Phenolen zu bewirken, wollte ich Phtalsäureanhydrid als Entwässerungsmittel anwenden und schmolz dieses mit Pyrogallussäure zussamen."

The discovery of gallein, the first of the series, is described as follows ²: "Erhitzt man Pyrogallussäure mit Phtalsäure, oder besser mit Phtalsäureanhydrid, so färbt sich die anfangs farblose Flüssigkeit rot und wird nach kurzer Zeit beinahe undurchsichtig. Die Schmelze löst sich in heissem Wasser zu einer dunkelroten Flüssigkeit, die beim Erkalten kleine, körnige Kristalle eines neuen Farbstoffes, den ich Gallein nennen will, absetzt."

Zur Darstellung im grösseren Maszstabe hat es zweckmässig gezeigt, 1 Tl. Phtalsäureanhydrid mit 2 Tln. Pyrogallussäure einige Stunden auf 190 bis 200° bis zum Dickwerden der Masse zu erhitzen. Man löst die Schmelze dann in heissem Alkohol, filtriert und verdünnt mit Wasser, wobei sich ein sehr reichlicher, aus beinahe reinem Gallein bestehender Niederschlag abscheidet, der nur nach einmal aus heissem, verdünntem Alkohol umkristallisiert zu werden braucht".

¹ Adolf von Baeyer, Gesammelte Werke, page xxxii.

² B. 4, 457 (1871)

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Later on in the same paper he says, a propos of the reaction involved: "Jedenfalls ist hierdurch die Möglichkeit ausgeschlossen, dass die Phtalsäure mit zur Bildung des Galleins verwendet wird, und es kann die Reaction nur auf Wasserentziehung und vielleicht auf Oxydation beruhen."

Thus we see that the discovery of this very important class of compounds was the chance result of an experiment directed at a very different goal. And though Baeyer, like the genius he was, recognized the newness and importance of what had happened, the true reaction involved was confidently declared, at the outset, to be impossible.

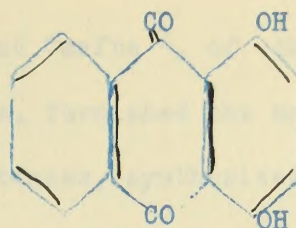
In the next paper ¹, the transformation of gallein into corulein, and the discovery of fluorescein are described.

In the third paper ², Baeyer announces that, contrary to his first paper, the phthalic anhydride really enters into the constitution of the product, and describes the use of concentrated sulphuric acid as a condensing agent. He describes experiments with α -naphthol, resorcin, hydroquinone, pyrocatechol, pyrogallol, phloroglucinol, and the preparation of phenolphthal^e_Ain, which he analyzes as $C_{20}H_{14}O_4$. He describes its reduction, by means of zinc dust and potassium hydroxide, to phenolphthalin. He shows that it contains two hydroxyl groups.

¹ B. 4, 555 ('71)

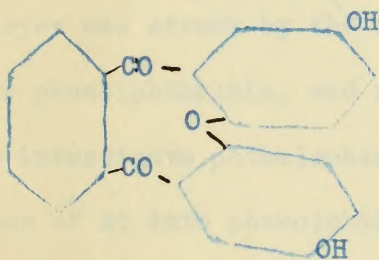
² B. 4, 658, ('87)

The fact that quinizarin, belongs to the anthraquinone series, the nucleus of which has a symmetrical structure, and arises in the same fusion mixture as

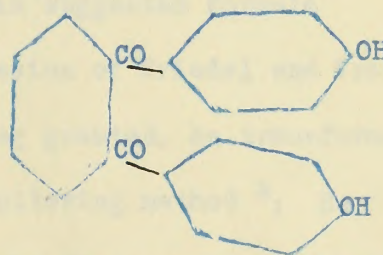


Quinizarin

hydroquinonephthalein, led Baeyer and Grimm to ascribe an analogous symmetrical structure to the latter, and naturally, to phenolphthalein.



Hydroquinonephthalein



Phenolphthalein

Baeyer and Caro ¹ discovered the tetra-brom derivative of fluorescein which they named eosin, were struck with its properties, and worked out a method for preparing it on a commercial scale which is still used. The Badische Anilin - u. Sodafabrik were putting it out as a dyestuff in 1875.

¹ B. 8, 146, ('75)



Cholesterol

The first two hydroxyl groups, which are located at the 3 and 14 positions, are secondary hydroxyl groups, while the hydroxyl group at the 3 position is a tertiary hydroxyl group.



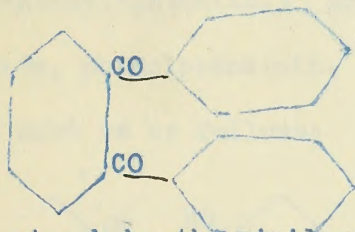
Progesterone

Progesterone is a steroid hormone that is produced by the adrenal cortex and the placenta. It is the precursor of all other steroid hormones. The structure of progesterone is shown above. It consists of a four-ring steroid nucleus with two hydroxyl groups at the 3 and 14 positions and a ketone group at the 20 position.



Androstenedione

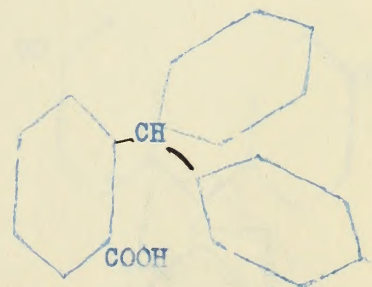
The publication, in 1877, by Friedel and Crafts ¹, of the method of synthesis now known by their names, furnished the next milestone of our story. To one of the substances, synthesized by them by the action of aluminum chloride upon phthalyl chloride and benzene, was ascribed the formula



and given the name phthalophenone.

Baeyer was struck by the similarity to his suggested formula for phenolphthalein, and requested permission of Friedel and Crafts to investigate phthalophenone. This being granted, he transformed some of it into phenolphthalein by the following method ²: He nitrated the phthalophenone, reduced to the diamine, treated with nitrous acid, and warmed in aqueous solution. The resulting product was identical with phenolphthalein.

Some chemists might have stopped here, but Baeyer continued his researches. He boiled the phthalophenone with concentrated alcoholic sodium hydroxide, reduced and found he had obtained a product which he identified with tri-phenyl-methane-carboxylic acid.



¹ C. 18 Juni ('77)
 Revue scientifique, 2 mars 1878 2
 B, 10, 1445
 A. ch. 6me. serie, v.1.

² B. 12, 642 ('79)
 A. 202, 36 ('80)

The following is a list of the
names of the persons who have
been appointed to the various
positions in the office of the
Commissioner of the General
Land Office, and the names of
the persons who have been
appointed to the various
positions in the office of the
Commissioner of the General
Land Office.

Commissioner of the General
Land Office
Assistant Commissioner
of the General Land Office

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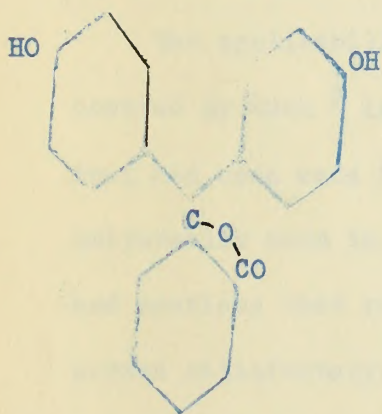
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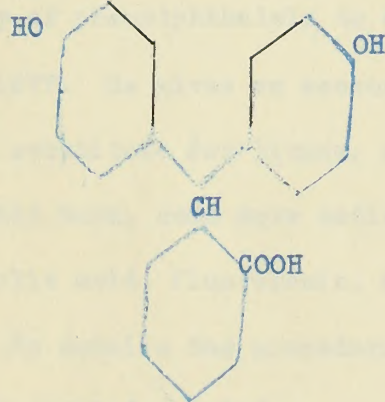
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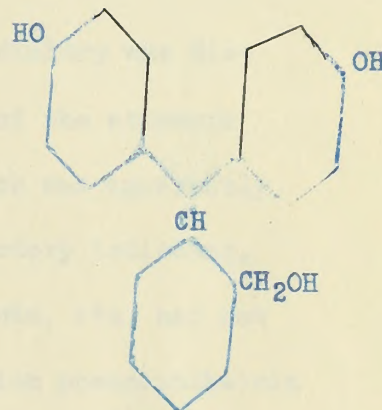
At one stroke, so to speak, he demolished his own theories and those of the obliging gentlemen Friedel and Crafts. The two phenyl residues introduced in the synthesis of phthalophenone are both attached to the same carbon atom, and it is not a phenone at all. (Baeyer renamed it di-phenyl-phthalid.) And the same is therefore true of its derivative, phenolphthalein. The formula of the latter and its derivatives must be as follows:



Phenolphthalein



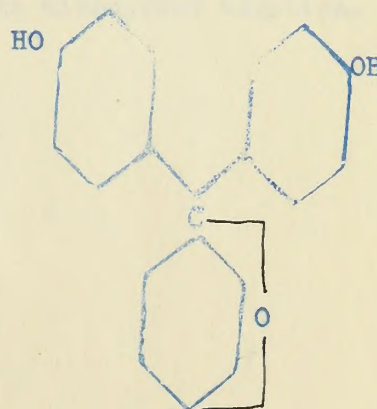
phenolphthalin



phenolphthalol

In this paper Baeyer points out the close similarity between the structure of phenolphthalein and rosolic acid.

The above formulas were also rendered more probable by the discovery made by Hessert ¹ in Baeyer's laboratory that phthalaldehyde is not really an aldehyde but the inner anhydride of o-benzyl alcohol-benzoic acid.



rosolic acid

¹ Hessert, B 10, 1445 ('77)
 B 11, 237 ('78)

At the same time, in the case of the synthesis of the compounds with the
of the existing compounds (alcohol and ether). The first group contains
the compounds in the synthesis of which the same was used as starting
the same starting material, and it is not a question of all. The same
material is used in the synthesis of the compounds, and the same is the case of
the synthesis of the compounds. The synthesis of the compounds and the
synthesis of the compounds can be as follows:



In this case, the reaction is the same as in the case of the synthesis of the
the synthesis of the compounds and the synthesis of the compounds and the
synthesis of the compounds.



The same reaction is also
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Then in a magnificent series of three papers ¹, Baeyer recounts the progress of his knowledge of these substances, sums up previous work, and gives the results of a stupendous amount of fresh work. Here for the first time we find described: crystallographic data for phenolphthalein, syntheses of phenolphthalein-sulphonic acid, tetra-brom-phenol-phthalein, di-imido-phenolphthalein, p-cresol-phthalein, numerous derivatives of these, and many other substances. The work of a giant, indeed.

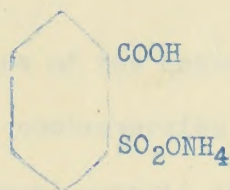
The applicability of phenolphthalein to acidimetry was discovered by Luck ² in 1877. He gives an account of the attempts that had been made to substitute for litmus, which was apparently universally used in this work, some more satisfactory indicator, and mentions that rosolic acid, fluorescein, cyanin, etc. had not proved satisfactory. He details the procedure with phenolphthalein substantially as it is carried out today.

Immediately following Luck's paper, the only papers published on the use of phenolphthalein as an indicator were distinctly unfavorable, most of the authors criticising one or another feature of the new indicator, but within a few years the increasing number of papers giving results obtained by means of it showed its widespread adoption.

¹ Baeyer, A 202, 36, 153, ('80); A 212, 340

² Luck, Fr. 16, 332 ('77)

The sulphone-phthaleins were discovered by Remsen¹. He reported the synthesis of resorcin-sulphone-phthalein by heating potassium o-sulphobenzoate with resorcin and sulphuric acid. He reported that he could also make the compound from saccharin in the same way. In his next paper ², however, Remsen reported that the substance he had supposed to be o-sulphobenzoic acid had really been the acid ammonium salt of the acid:



He succeeded in really making o-sulpho-benzoic acid, and from it

resorcin-sulphone-phthalein. Sohon ³, describes the preparation of o-sulpho-benzoic anhydride and a large number of derived sulphone-phthaleins.

A propos of the production of the sulphone-phthaleins from saccharin, it is of interest to note that it has been rediscovered independently several times since Remsen, and that the same workers have usually rediscovered also the fact that from saccharin can be

¹ Remsen, Am. Ch. J. 6, 180-1, (1884)

² Remsen, Am. Ch. J. 11, 73 (89)

³ Sohon, Am. Ch. J. 20, 257 (98)

The intermolecular forces are also affected by hydrogen bonding.

The synthesis of secondary amine-ethers is by heating primary

amines with alcohols and this is called the Gabriel phthalimide

method. It is also possible to synthesize secondary amines by the

reduction of nitriles. However, it is reported that the substance to be

reduced to a secondary amine will not really be the same as the

one which is intended in the synthesis.

Secondary amines are also formed by the reaction of

primary amines with alcohols.

Secondary amines are also formed by the reaction of

primary amines with alcohols.

Secondary amines are also formed by the reaction of

primary amines with alcohols.

Secondary amines are also formed by the reaction of

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Secondary amines are also formed by the reaction of

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Secondary amines are also formed by the reaction of

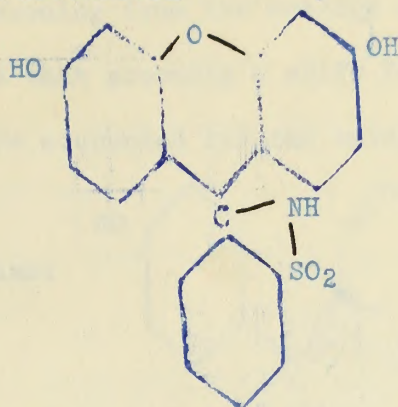
1. Journal of Organic Chemistry, 1951, 16, 100-1, (1951)

2. Journal of Organic Chemistry, 1951, 16, 101-1, (1951)

3. Journal of Organic Chemistry, 1951, 16, 102-1, (1951)

made analogous compounds, variously named sacchareins and sulfam-
phthaleins, as for example resorcin-saccharein ^{1,2,3,4.}

resorcin-saccharein



In the meantime one of the hottest controversies in the history
of a subject where the controversies have always been hotly contested --
in other words, structural organic chemistry -- was raging over the
structure of phenolphthalein, the structure of which had apparently
just been established by the great Baeyer.

This particular controversy began with a color -- with the color
which phenolphthalein develops in the presence of alkali. Baeyer had
assumed this color to be due to the formation of a series of salts,
some of them colored, with no breakage of the lactone ring until

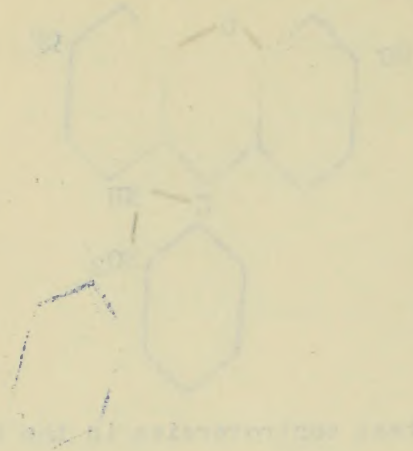
¹ Sisley, (C1897), II 847

² (C1899), I 718 (patent)

³ Monnet and Cartier, Bl. (3) 17, 690 (C97)

⁴ Dutt, Soc. 121, 2389 (22)

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alkali strong enough to produce decolorization was added. But Bernthsen ¹, and Friedländer ², reasoning from the analogy of fuchsin and rosolic acid, suggested that probably a shift from the lactoid to the quinoid structure accounted for the color.

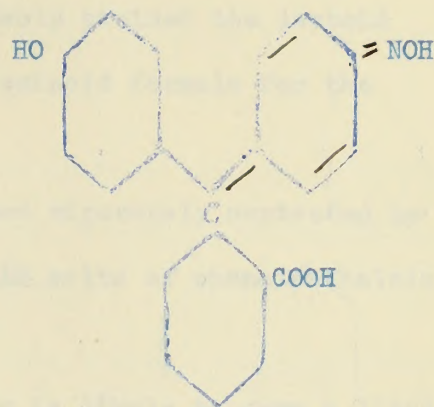
Friedländer supported this

idea by forming phenolphthalein-oxime:

by the action of hydroxyl-

amine on phenolphthalein

in alkaline solution.



For several years these two views, the so-called "ionic" and "quinoid" theories of the color of the phthaleins were both warmly and brilliantly defended by a considerable number of chemists of the first rank.

Friedländer's view was supported by Bistrzycki and Nencki ³, who made dibenzoyl-phenolphthalein from phenolphthalein in alkaline solution, but was objected to by Herzig and Meyer ⁴, who found that

¹ Bernthsen, Ch. Z. 104, 1956

² Friedländer, B. 26, 172 and 2258 (93)

³ Bistrzycki and Nencki, B. 29, 131 (96)

⁴ Herzig and Meyer, B. 28, 3258 (95)

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the white lactoid methyl ether could be made in good yield from the sodium salt of phenolphthalein; and by Meyer and Spengler ¹, who placed little confidence in the analogy between phenolphthalein and resorcin-phthalein (fluorescein), and insisted that the alkylation experiments, which incontestably yielded the lactoid ethers, were quite incompatible with a quinoid formula for the salts of phenolphthalein.

The views of Meyer and Spengler were vigorously contested by Green ², who prepared the colored quinoid salts of phenolphthalein and hydroquinone-phthalein.

This whole phase of the controversy is likely to seem a little unnecessary to a modern chemist, made familiar from the beginning with the concept of dynamic equilibrium. Of course the colorless lactoid ethers could be made from the solutions of the salts of phenolphthalein, because there is an equilibrium there between the lactoid and quinoid forms, and if you remove the lactoid form by esterifying it, the equilibrium will be displaced and more will form, resulting in a reaction that practically runs to an end.

A point more difficult to dispose of was brought up by K. Meyer and Hantzsch ³, who pointed out that phenolphthalein and its lactoid di-methyl ether both give red salts with hydrochloric acid at

¹ Meyer and Spengler, B. 38, 1318 (C 05)

² Green and King, B. 39, 2365, (C 06) B. 40, 3724, (C 07)

³ Meyer and Hantzsch, B. 40, 3479, (C 07)

The whole phase of the reaction is little known as regards mechanism. It is necessary to a certain extent, and perhaps from the beginning when the concept of formal equilibrium. Of course the relative amounts of the two forms could be calculated from the equilibrium constants, but this is not possible because there is no equilibrium between the two forms, and if you remove the iodide ions by reacting with a substance which will be oxidized and will form a reaction that practically runs to an end.

I would now like to discuss the reaction as it is known and to point out the points where the mechanism is still unknown. It is known that the reaction is a reaction between the iodide ion and the iodine molecule, and it is known that the reaction is reversible. The equilibrium constant is known, and it is known that the reaction is a reaction between the iodide ion and the iodine molecule, and it is known that the reaction is reversible.

¹ Paper and Journal, p. 101 (1930)
² Paper and Journal, p. 102 (1930)
³ Paper and Journal, p. 103 (1930)

16

temperatures below -30°C , and with aluminum chloride and with stannic chloride. They concluded that since forms undoubtedly lactoid could give a red coloration under certain conditions, there was no reason to posit the existence of anything else to account for the red colors observed with alkali.

At this stage, which may have seemed critical to some supporters of the quinoid theory, decisive evidence of a totally different sort was brought to bear on the question by R. Meyer and K. Marx¹, who compared the absorption spectra of the alkali salts of phenolphthalein, hydroquinone-phthalein, and fluorescein, and showed them to be quite similar. They assumed all three salts to have a quinoid formula. This has been supported by a considerable amount of later work which has shown that beyond question a deep-seated shift of configuration, without doubt a shift from lactoid to quinoid, takes place when the

¹ R. Meyer and Karl Marx, B. 40, 3603, (C 07)

temperature below -30°C, and with a certain chloride and with certain
chloride. They concluded that since these forms undoubtedly furnish
give a red coloration under certain conditions, there was no reason
to doubt the existence of anything else to account for the red color
observed with alkali.

At this stage, when they have treated alkali to some extent
of the alkali theory, deductive extension of a slightly different sort
was brought to bear on the question by J. Meyer and K. Marx,¹ who
considered the absorption spectra of the alkali salts of hydroquinone,
hydroquinone-chloride, and thiocyanate, and showed that to be quite
similar. They assumed all these salts to have a similar formula.
This has been supported by a considerable amount of later work which
has shown that beyond question a deep-seated shift of configuration,
without doubt a shift from double to single, takes place when the

¹ J. Meyer and K. Marx, *Ber. 35, 2005, (1902)*

red color with alkalies is developed ¹.

The fact that phenolphthalein is dibasic was definitely established by Kober and Marshall ², who, in a series of papers, described the preparation of the monobasic salts, and showed that

¹ Howe, Phys. Rev. 8, 687 (16)

Howe and Gibson, Phys. Rev. 10, 767, (17)

Orndorff, Gibbs, Scott, and Jackson, Phys. Rev. 17, 437 (21)

Formánek and Knop, Z. anal. Ch. 56, 273 (17)

Moir, Trans. Roy. Soc. S.Afr. 7, 8, 14, (18)

White and Achree, J.A.C.S. 40, 1092, (18)

Brode, J.A.C.S. 46, 585, (24)

Holmes, J.A.C.S. 46, 629, 633, (24)

Orndorff, Gibbs, and Shapiro, J.A.C.S. 47, 2767 (25)

48, 1327, 1994 (26)

49, 1541, 1545, 1588 (27)

50, 819, 1755, 2799 (28)

Thiel and Diehl, Sitzungs. Ges. Beförderung gesamt. Naturwissensch.

Marburg 62, 472 (CA, vol. 22, 4403)

² Kober and Marshall, J.A.C.S. 33, 62, 1780

34, 424

and other related subjects.

The fact that phenol is also a disinfectant is well known by labor and health officials, who, in a series of reports, described the preparation of the phenol solution, and showed that

1. The phenol solution is prepared by dissolving 100 grams of phenol in 1 liter of water.

2. The phenol solution is used for disinfecting surfaces.

3. The phenol solution is also used for disinfecting hands.

4. The phenol solution is used for disinfecting clothing.

5. The phenol solution is used for disinfecting linens.

6. The phenol solution is used for disinfecting floors.

7. The phenol solution is used for disinfecting walls.

8. The phenol solution is used for disinfecting ceilings.

9. The phenol solution is used for disinfecting furniture.

10. The phenol solution is used for disinfecting toys.

11. The phenol solution is used for disinfecting books.

12. The phenol solution is used for disinfecting papers.

13. The phenol solution is used for disinfecting records.

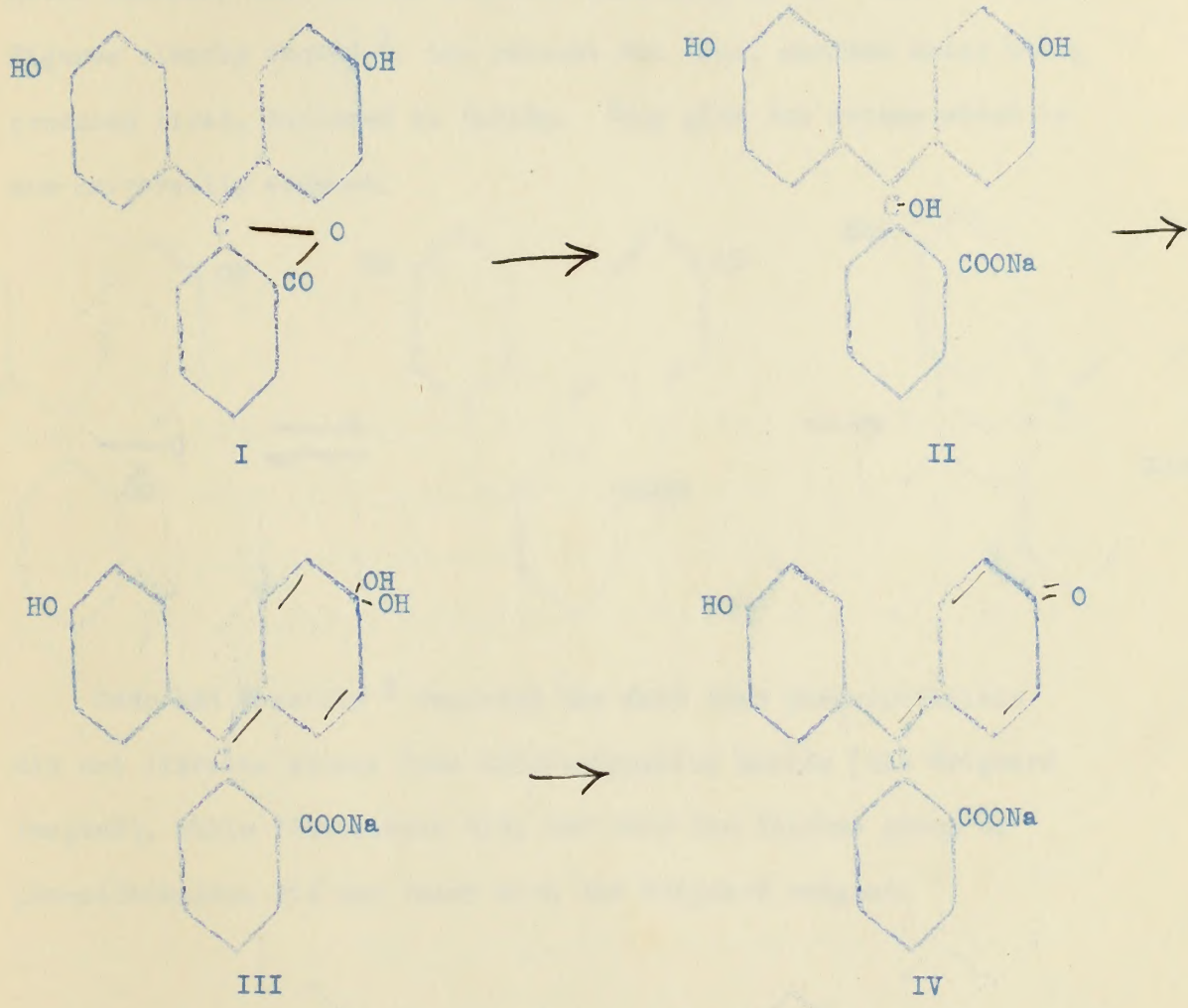
14. The phenol solution is used for disinfecting maps.

15. The phenol solution is used for disinfecting charts.

16. The phenol solution is used for disinfecting globes.

17. The phenol solution is used for disinfecting globes.

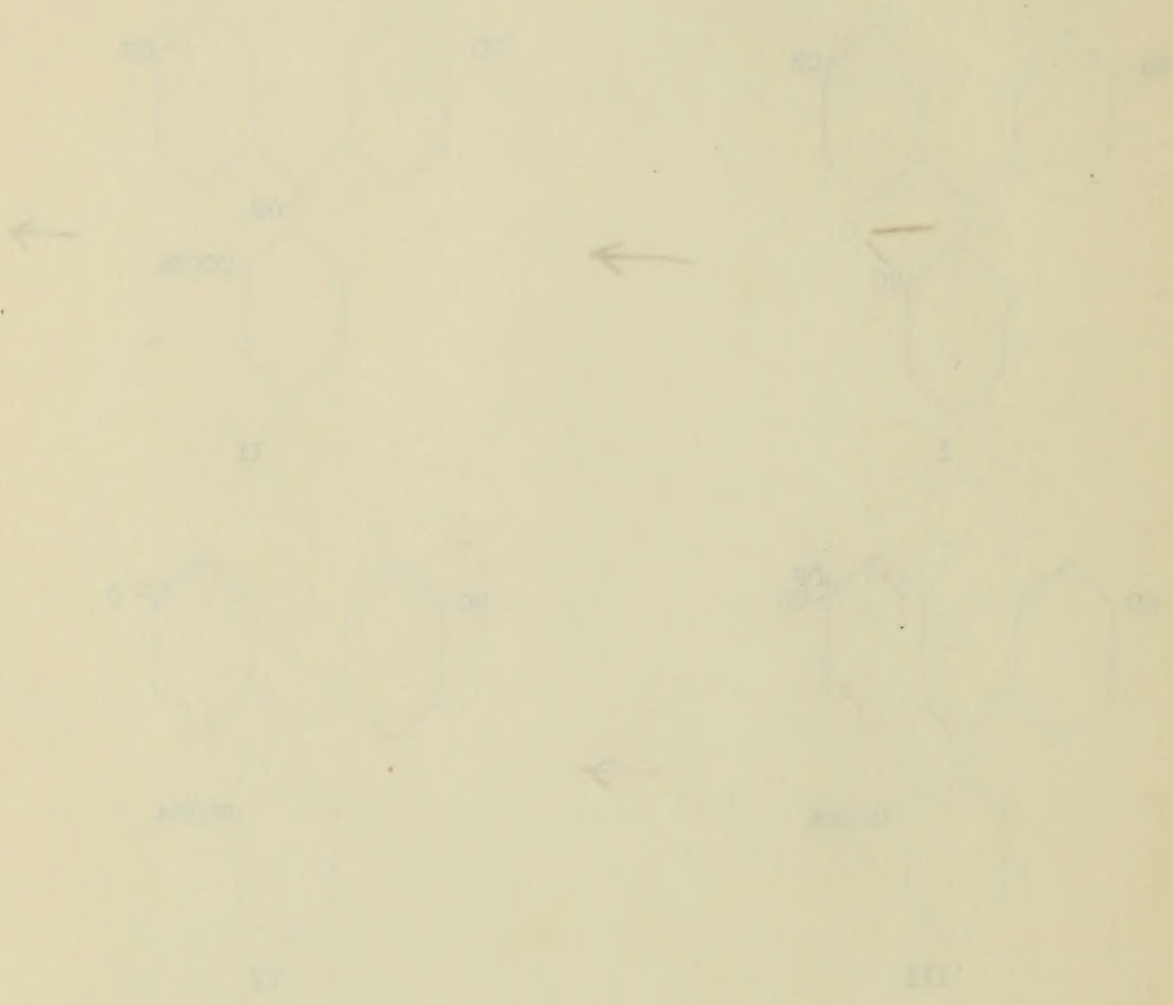
they were colorless. They pointed out that Gomberg's plausible scheme ¹:



¹ Gomberg, B. 40, 1880 (CA13)

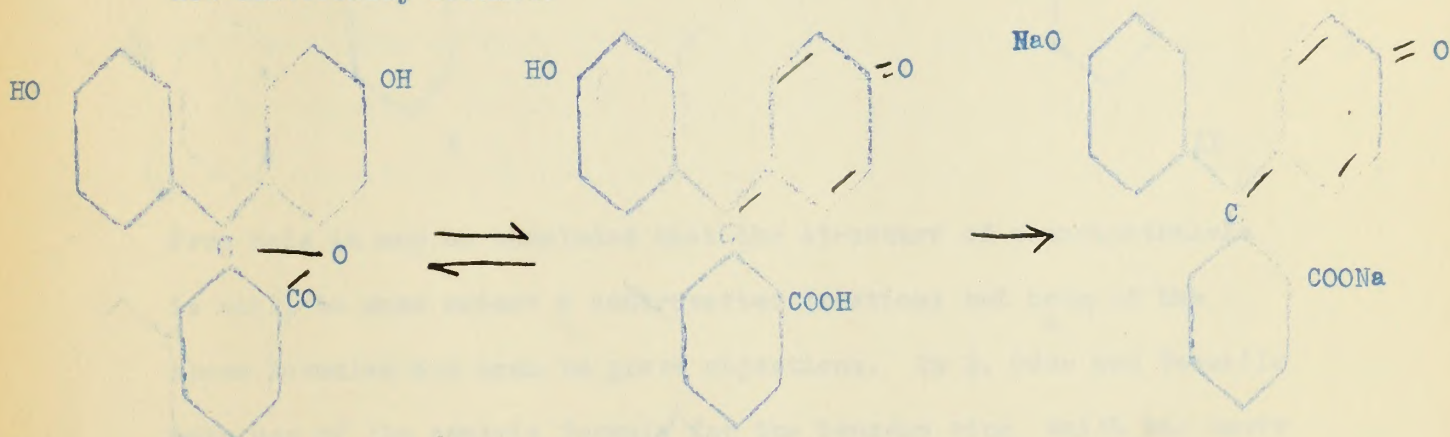
They were not related. They pointed out that the other's structure

is shown:



1. (1910) 1001, 1002, 1003

does not agree with the facts. Even disregarding the omission of one Na, the scheme means that in excess of alkali, full color is never reached, most of the compound remaining as II. But, as their figures clearly showed ¹, the reverse was true, maximum color being produced first, followed by fading. They give the scheme which is now universally assumed:



Oddo and Vassallo ² reported the fact that phenolphthalein did not liberate ethane from ethyl-magnesium halide (the Grignard reagent), while fluorescein did, and that the lactone group of phenolphthalein did not react with the Grignard reagent.

¹ J.A.C.S. 33, 68, (CA 13)

² Oddo and Vassallo, G. 42 (II) 204 (CA 13)

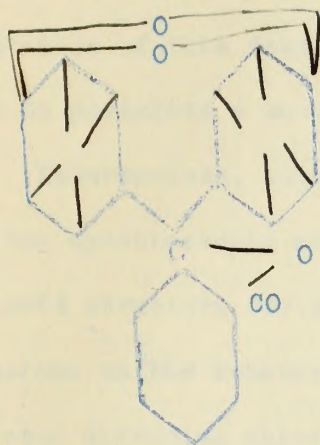
These are given in the Table, from which it is seen that
 the rate of reaction is independent of the concentration of
 the reactants, and is a function of the temperature only.
 The rate of reaction is independent of the concentration of
 the reactants, and is a function of the temperature only.
 The rate of reaction is independent of the concentration of
 the reactants, and is a function of the temperature only.



This reaction is reversible, and the equilibrium constant is
 given by the ratio of the concentrations of the products to
 the concentrations of the reactants. The equilibrium constant
 is a function of the temperature only, and is independent
 of the concentrations of the reactants and products.

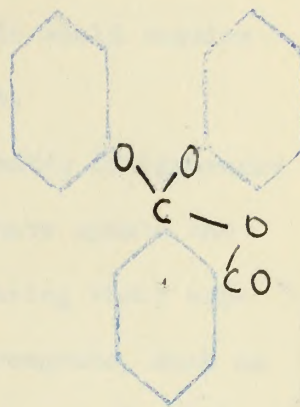
(1) $K = \frac{[C][D]}{[A][B]}$
 (2) $K = \frac{[C][D]}{[A][B]}$

They were thus lead to ascribe to phenolphthalein two alternative formulas:



I

or



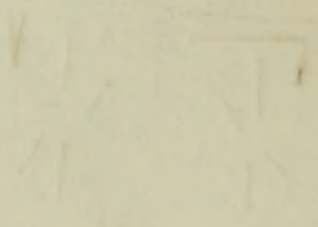
II

From this it may be concluded that the structure of phenolphthalein is still to some extent a controverted question; but both of the above formulas are open to grave objections. In I, Oddo and Vassallo make use of the centric formula for the benzene ring, which has never proven a conception capable of holding its own with others, such as that of Kekulé, and apparently are not aware of the much earlier work of Haller and Guyot¹, who, by obtaining the diphenyl carbamates of phenolphthalein, established the presence of two functional hydroxyl groups. There is no reason to expect a reaction with the lactone group, as is evident from work such as that of E. P. Kohler on such conjugated systems. In II, the fact that the diethyl ether of phenolphthalein made by the reaction of Friedel and Crafts from phenetole and phthalyl chloride is identical with that made by the

¹ Haller and Guyot, C. r. 116, 479 (C 93)

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direct ethylation of phenolphthalein ¹ is ignored. The interpretation of this fact on the basis of formula II would require one to postulate a hardly credible rearrangement.

Nevertheless, other Italian workers, apparently in ignorance of the spectroscopic evidence to the contrary, have upheld the quinoid structure for phenolphthalein itself, basing their conclusions on the behavior of certain copulating reagents, such as benzene diazonium chloride ². Their contentions have produced little impression upon the chemists of other lands, but whether this is due to the fact that the weaknesses in their arguments are universally recognized, or to the fact that few chemists read Italian, it would be difficult to say.

¹ Haller and Guyot, C. r. 120, 296 (C 95)

² Consonno and Apostolo, G. 51 (I), 60 (21)

It is not necessary to state that the
purpose of this book is to provide a
comprehensive and readable treatment
of the subject, and to do so in a
manner which is both concise and
clear. The book is intended for
students of the subject, and for
those who are interested in the
subject in general. It is not
intended as a text book, but
as a reference work. The book
is written in a simple and
straightforward manner, and
is intended to be read by
anyone who is interested in
the subject.

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The use of phenolphthalein in acidimetry has already been mentioned. This was an application to the measurement of the quantity factor of acidity, and of fundamental importance to analytical chemistry. But an application fully as important for biological chemistry was made possible by the theory of electrolytic dissociation introduced by Arrhenius ¹ in 1887. There arose directly from this idea the concept of hydrogen ion concentration, which made it possible to measure the intensity factor of acidity. A survey of the indicators suitable for hydrogen ion determination was opened in Nernst's laboratory in 1904 by Salessky ². This was extended in the same year by Friedenthal, by Fels and by Salm, and the results were summarized in Salm's famous table ³.

Then in 1909 came the classic work of Sørensen ⁴, who made an extensive investigation of the correspondence between colorimetric and electrometric determinations, and published a selected list of indicators which were relatively free from the so-called protein and salt errors. This has proven to be of the greatest value to the biochemist and physiologist. The Sørensen list was supplemented by

¹ Arrhenius, Ph. Ch. 1, 631 ('87)

² Salessky, Z. El. Ch. 10, 204 (C 04)

³ Ph. Ch. 57, 451 (06)

⁴ Sørensen, Compt. rend. Lab. Carlsberg 8, 1, 396
 Bio. Z. 21, 131, 201 (09)

The use of chromatography in solid-state physics has already been
 mentioned. This was an application to the measurement of the
quasi-Fermi level of electrons, and of hole concentration to
 analytical chemistry. For an application fully an important for
 physical chemistry was made possible by the theory of electrostatic
 interaction introduced by Bardeen ¹ in 1947. There arose directly
 from this idea the concept of hydrogen ion concentration, which made
 it possible to measure the intrinsic factor of solids. A survey of
 the literature available for hydrogen ion determination was given in
Bardeen's factor in 1948 by Bardeen ². This was extended in the
 next year by Bardeen, de Haas and de Haas, and the results were
 summarized in Bardeen's factor ³.

For in 1953 came the classic work of Shannon ⁴, who made an
 extensive investigation of the correspondence between electrostatic
 and electrostatic determinations, and published a selected list of
 indicators which were related only from the so-called protein and
cell errors. This has proven to be of the greatest value to the
 biochemist and physiologist. The Shannon list was suggested by

¹ Bardeen, Rev. Mod. Phys. 19, 62 (1947)

² Bardeen, Rev. Mod. Phys. 20, 37 (1948)

³ de Haas, Rev. Mod. Phys. 21, 401 (1949)

⁴ Shannon, Gen. Phys. Chem. 29, 100 (1953)

one from Clark and Lubs who studied an extensive series of indicators suggested by the syntheses of Acree and White¹ undertaken for the purpose of obtaining material for the study of the quinoid theory of indicators. The list of Clark and Lubs consisted principally of sulphone-phthaleins.

The lists both of Sørensen and of Clark and Lubs will be found in the well known book by Clark², from which has been taken most of the material for this brief survey of the history of the use of indicators for hydrogen ion determinations.

Sørensen, to avoid the somewhat awkward exponential expression initially used, also introduced the invaluable symbol p_H^+ , now usually written, for typographical convenience, pH. It may be of interest to quote the words of the original: "....., la grandeur de la concentration des ions hydrogène s'exprime par le facteur de normalité de la solution par rapport aux ions hydrogène, facteur indiqué sous la forme d'une puissance négative de 10.

..... le facteur de normalité de la solution sous le rapport des ions hydrogène ou, en d'autres termes, le nombre d'atomes-grammes d'ions hydrogène par litre est plus petit que 1 et peut être posé égal à 10^{-p} ,

¹ Acree and White Am. Ch. J. 39, 529 (08)

² Clark, W.M., "The Determination of Hydrogen Ions"

Williams and Wilkins, 1928. p. 92, p. 94.

one that has been studied in extensive detail in
the literature suggested by the synthesis of lower and higher
molecular weight for the purpose of obtaining detailed for the study
of the kinetic theory of hydrogen. The list of Clark and Latta
concerned principally of hydrogen-hydrogen.
The kinetic data of Anderson and of Clark and Latta will be
found in the well known book by Clark². The data which has been taken
out of the material for this brief survey of the history of the
use of indicators for hydrogen for hydrogen.
Anderson, in his first paper, suggested exponential expansion
initially used, also introduced the level of symbol α , and usually
written for exponential expansion. It may be of interest to
quote the words of the original: "..... is constant in
concentration and low hydrogen concentration but is constant in
is constant in report and low hydrogen. Anderson's data is
shown in the following figures in his
..... is constant in report and
low hydrogen in, as it is constant, in report and low hydrogen
hydrogen in report and low hydrogen in report and low hydrogen

¹ Clark and Latta, J. Chem. Phys., 1933, 1, 239 (20)

² Clark, J. Chem. Phys., 1933, 1, 239 (20)

ou pour le nombre p je propose le nom d'exposant des ions hydrogène et la désignation p_H . Par exposant des ions hydrogène (p_H) d'une solution, nous entendons donc le logarithme Brigg de la valeur réciproque du facteur de normalité de la solution relativement aux ions hydrogène.

Comme il n'est d'ordinaire pas question de solutions d'ions hydrogène plus fortes qu'une solution normale, j'ai choisi la définition ci-dessus de l'exposant des ions hydrogène, qui par suite sera généralement un nombre positif; il ne sera négatif que dans les cas bien rares où l'on a affaire à des solutions plus fortes que la normale."

At the same time the theories of buffer action were being developed. The power of certain solutions to resist changes in reaction was commented upon by Fernbach and Hubert¹, who, writing in French, likened the resistance of phosphate solutions to a "tampon". The word was adopted by Sørensen, and in the German rendition of his paper it became "Puffer", and thence the cognate English "buffer". Important among those who contributed to the understanding of the theory of this action may be mentioned L. J. Henderson².

¹ Fernbach and Hubert, C. r. 131, 293 (00)

² Henderson, L.J., Am. J. Physiol. 15, 257, (06)

J.A.C.S. 30, 954 (08)

Am. J. Physiol. 21, 173 (08)

Erg. Physiol. 8, 254 (09)

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Buffer solutions systematically covering the pH scale have been prepared by Sørensen ¹, and Clark and Lubs ². These also are described in detail in Clark's book.

This work on indicators made the phthaleins indispensable to the biologist as well as the chemist, and provided an impetus to further studies, and the preparation of new compounds.

According to a well-known story, of which it appears to be impossible to trace the sources, the purgative effects of phenolphthalein were discovered in the following manner. The tax collectors of the Hungarian government, in order to have a means of checking up on the "bootleggers" of the day, developed the practice of adding phenolphthalein to wine upon which the tax had been duly paid. Then, if any given sample of wine were suspected of being "moonshine", the government inspectors had only to take a small amount, dilute it, and add alkali. If the red color appeared, the tax had been paid, and if it did not, the wine was illicit. The wine makers, apparently being less skilled chemically than the bootleggers of to-day, did not know what the substance was that the government officials added, and consequently could not sophisticate their wines in this respect.

¹ Sørensen, *Prozesse. Ergeb. Physiol.* 12, 393 (12)

² Clark and Lubs, *J. Biol. Chem.* 25, 479 (16)

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The consumers of the wines, however, while they did not exactly discover the formula of the esoteric substance, did discover something about it, namely, that a large steady consumption of wine containing it produced continued diarrhoea.

This may be only a story, but it would seem that Liebermann did at any rate propose the use of phenolphthalein for such purposes, as other authors refer to his suggestion in their papers.

The first scientific study of the purgative effects of phenolphthalein is in a paper by Zaltón and Vámosy¹ from the Pharmacological Institute of the Royal Hungarian University at Buda-Pesth. The authors do not state how the phenomenon was brought to their attention, but detail experiments upon themselves and some of their friends which demonstrate quite clearly the efficacy of the substance.

Later articles by Vámosy², Tunnicliffe³, Fleig⁴, Dornblueth⁵, and Pattiez⁶ laid the foundations of our pharmacological knowledge of this substance. According to Pattiez, it is unaltered in the stomach,

¹ Zaltón and Vámosy, Ch. Z. 24, 679 (C 00)

² Vámosy, Ther. Gegenw. 43, 203 (02)

³ Tunnicliffe, Brit. Med. J. 2181, 1221 (02)

⁴ Fleig, Arch. inter. Pharm. 18, 327 (08)

⁵ Dornblueth, Münch. med. Woch. no. 52 (03)

⁶ Pattiez, J. pharm. Belg. 3, 685 (21)

The occurrence of the same, however, which they all not exactly
 However the results of the various experiments, all showed
 about 20. Finally, that a large amount of the substance
 is produced in the same manner.

This may be only a case, but it would seem that the same
 as any one proposes the use of chemical analysis for such purposes, as
 other authors refer to the experiments in their papers.

The first scientific study of the qualitative effects of the
 substance is in a paper by *W. H. and W. H.*, *Ann. Chem. Phys.*
 (1850), p. 100. The authors
 do not state how the substance was prepared, but their
 details are given in their paper, and also in their
 paper, which clearly shows the nature of the substance.

Later articles by *W. H.*, *Ann. Chem. Phys.* (1851),
 and *W. H.*, *Ann. Chem. Phys.* (1852),
 of this substance, according to *W. H.*, it is contained in the

1. *W. H. and W. H.*, *Ann. Chem. Phys.* (1850)
2. *W. H.*, *Ann. Chem. Phys.* (1851)
3. *W. H.*, *Ann. Chem. Phys.* (1852)
4. *W. H.*, *Ann. Chem. Phys.* (1853)
5. *W. H.*, *Ann. Chem. Phys.* (1854)
6. *W. H.*, *Ann. Chem. Phys.* (1855)

but is acted upon by the alkaline secretion of Brünner's glands in the small intestine, rendered soluble, and absorbed to the circulation. It is excreted by the feces and in the urine in traces.(Fleig). It is in part removed by the liver, where it is hydrolyzed, and the products oxidized to water and carbon dioxide, according to Pattiez.

The work of Vamossy led Abel and Rowntree¹ to investigate the pharmacology of a number of halogenated derivatives of phenolphthalein, in the hope of finding a suitable hypodermic purgative. They investigated a number of the products prepared by Orndorff², Remsen³, and Acree. Their chief interest was in the phenol-tetra--chlor-phthalein, which they found to be a mild purgative, even when administered hypodermically, and to be excreted entirely by way of the bile, with some reabsorption in the large intestine. At Rowntree's suggestion, Whipple, Mason, and Peightal studied the excretion of this substance in the bile when the liver was subjected to artificial lesions; Rowntree, Marshall, and Chesney applied the results clinically and developed the phenol-tetra-chlor-phthalein test of liver function. (For the details of this test see Kahn⁴.) It may be doubted if this test has any considerable diagnostic value.

¹ Abel and Rowntree, J. Pharm. and Exp. Ther. 1, 231 (09)

² Orndorff and Black, Am. Ch. J. 41, 349, (09)

³ Remsen, loc. cit.

⁴ Kahn, Functional Diagnosis, W.F.Prior Co. 1920. p. 114

A modification of this test destined to be of considerable importance was made by Graham¹, searching for some substance which would make possible X-ray photography of the gall-bladder, or, as it is usually called, cholecystography. Graham and Cole² hit upon this substance, which Abel and Rowntree (v.supra) had shown to be excreted through the bile. They tried tetra-iodo-phenolphthalein, but probably because of an impure sample, believed it to be too toxic, and recommended tetra-brom-phenol-phthalein as the best compromise.

In the meantime, Whitaker³, had been working in the same field, and had employed tetra-iodo-phenol-phthalein. His paper⁴ and that of Graham⁵, both describing the successful use of somewhat purer samples of tetra-iodo-phenol-phthalein, appeared practically simultaneously. The test as at present employed, consists of the intravenous, oral, or simultaneous intravenous and oral administration of the dye, followed by the taking of pictures after an interval of 6 to 12 hours. The X-ray findings have proved to be of the greatest value in diagnosis.

¹ Graham and Cole, JAMA 82, 613, (24)

² Graham and Cole, JAMA 82, 1777 (24)

³ Whitaker, and Milliken, Surg., Gyn., and Obst. 40, 17, (25)
646, (25)

⁴ Whitaker, and Milliken, Surg., Gyn., Obst. 40, 17, Jan. 1925

⁵ Graham, Cole, Copher, JAMA 84, 14, Jan. 1925

A modification of this test designed to be of qualitative
importance was given by ¹Wittaker, describing for some substances which
would cause positive X-ray photography of the cell-inclusion, or, as
it is usually called, the heterochromatin. Wittaker and Cole² first used
this substance, which they called the substance (A. Wittaker) but which is
referred to as the Wittaker. They first used the substance in the form
of a finely divided powder of an amount of 10 mgm. dissolved in 100
cc. of water, and mentioned that a few drops of the solution at the point of
injection.

In the present ³Wittaker, and some reports in the same field,
and the original paper by ⁴Wittaker, it is shown that the
dye is of the class of the heterochromatin and of the class of the
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of the heterochromatin and of the heterochromatin of the dye,
followed by the finding of the nature of the substance after an interval of 2 to 3 hours.
The X-ray findings have proved to be of the greatest value in diagnosis.

¹ Wittaker and Cole, Proc. Roy. Soc. (B), 1932, 21, 335 (1932)
² Wittaker and Cole, Proc. Roy. Soc. (B), 1932, 21, 335 (1932)

³ Wittaker, Proc. Roy. Soc. (B), 1932, 21, 335 (1932)
⁴ Wittaker and Cole, Proc. Roy. Soc. (B), 1932, 21, 335 (1932)

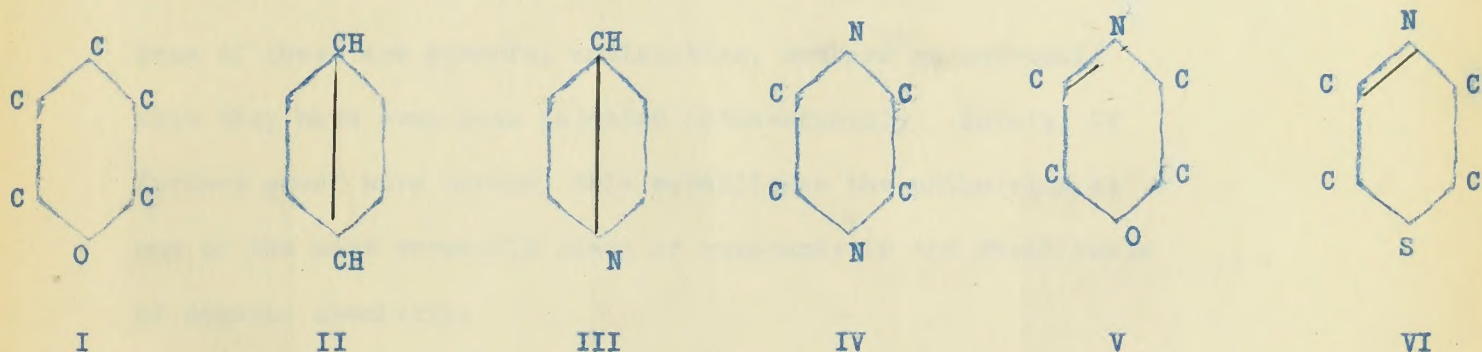
⁵ Wittaker, Proc. Roy. Soc. (B), 1932, 21, 335 (1932)

In the paper by Abel and Rowntree already referred to, they detail the results of an investigation of a sample of phenol-sulphone-phthalein supplied them by Remsen, and reported that it was excreted practically entirely in the urine, and did not seem to injure the kidneys of the experimental animals used. Then in a later paper by Rowntree and Geraghty¹, the now well known phenol-sulphone-phthalein (or, as it is often abbreviated, P. S. P.) test of renal function is proposed. (See Kahn, p. 246)

As carried out to-day, the test usually consists of the injection intramuscularly of a definite amount (1 c.c. of solution containing 6 mg.) of the phthalein, the collection of urine at the end of the first and second hours, and the reading of the amount of dye appearing in the urine, by means of making the urine alkaline, making up to a definite volume, and reading in the colorimeter against a standard. In normal renal function, by the usual procedure, at least 50% of the dye should be eliminated during the first two hours. It was these two function tests which suggested the present study. Knowing that sulphone-phthaleins were eliminated through the kidneys, and that halogens could be introduced into phthaleins so as to increase their density, and hence their opacity to X-rays, it was hoped that substances might be prepared which would permit X-ray pictures to be taken of the kidney while functioning. In any case, it was thought that a new series of a class of compounds which had already been proven so important and interesting could not fail to be of some value.

¹ Rowntree and Geraghty, J. Pharm. and Exp. Ther. 1, 579 (10)

To conclude this historical introduction, it only remains to speak of two further uses for substances of this class. Eosin, though the best known, is only one of a large series of the phthaleins which are employed as dyes¹. The fluorescence of eosin lends it the special applicability of being used to produce the so-called "changeable silk". The fluorescence of organic compounds, in other words the transformation of certain wave lengths of radiant energy into certain longer wave lengths (Stokes' rule of fluorescence) had been investigated by several workers, e.g. Meyer², who pointed out that it practically always accompanies the presence of certain "fluorophores" in the compound. He named the following groups as fluorophores.



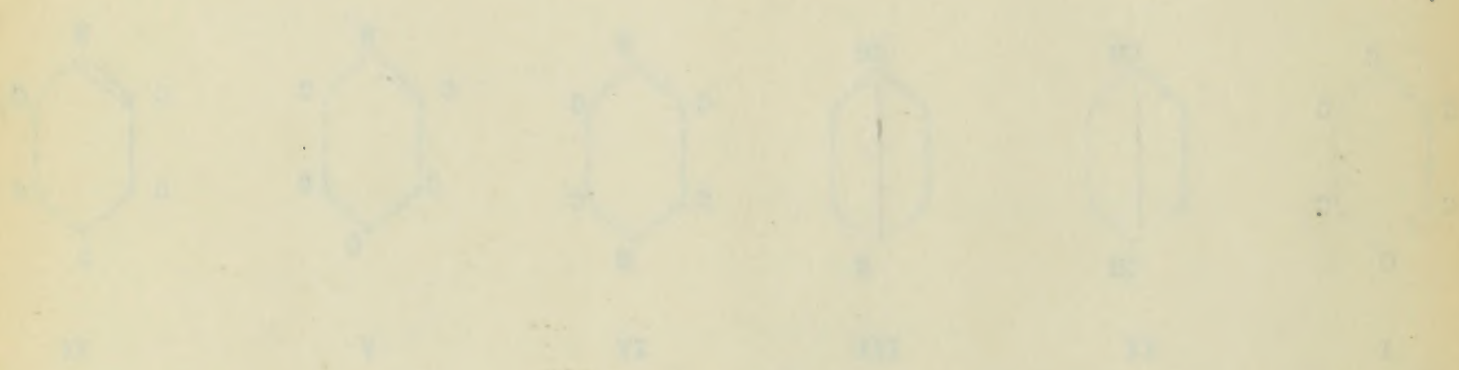
Of these, it is I, the pyrane ring, which accounts for the fluorescence of eosin and the compounds next to be mentioned.

¹ Cain and Thorpe "The Synthetic Dyestuffs"
Charles Griffin & Co., London, 1920, pp 100 - 113

² Meyer, Festschrift, d. Tech. Hochschule Braunschweig (1897)

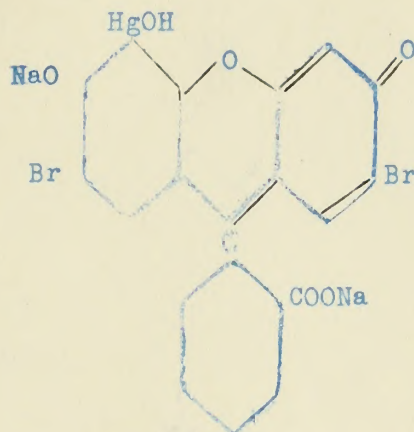
Meyer, Ph. Ch. 24, 468 (C 98)

To illustrate this important distinction, it will be useful to
 point out the difference in the behavior of the system. It is
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 the paper is devoted to the study of the stability of the system.

White¹ has produced the mercury derivatives of a number of phthaleins, among which the best known is mercurochrome 220 (di-brom-hydroxy-mercuri-fluorescein), probably:



Some of these are powerful antiseptics, but are so non-toxic that they have even been injected intravenously. Surely, if further proof were needed, this establishes the phthaleins as one of the most versatile class of compounds in the whole realm of organic chemistry.

¹ White, JAMA 73, 1483 (19)
JACS 42, 2355 (20)

It is noted that the structure of the compound is similar to that of the compound described in the literature.



The structure of the compound is similar to that of the compound described in the literature. The compound is a complex organic molecule with a central ring system and various substituents. The structure is drawn in a perspective view, showing the spatial arrangement of the atoms.

1954, 25, 1111 (19)
1954, 25, 1112 (20)

1. UNITED STATES OF AMERICA

PART II

EXPERIMENTAL

12-100

12-100

1. IODIZED PHENOL SULPHONE PHTHALEINS

A. IODIZED PHENOL SULPHONE PHTHALEINS

Substituted phenol-sulphone-phthaleins having the nucleus substituted in the usually positions have been found for some time. One of these, tetra-ortho-iodo-phenol-sulphone-phthalein,



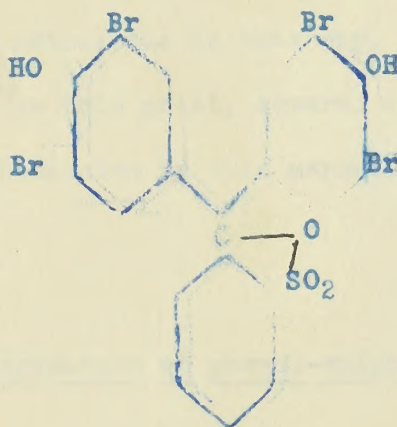
is widely used as an indicator under the name of 'ortho-iodo blue'. These compounds may be obtained with comparative ease from the corresponding phenol-sulphone-phthaleins. However, and after testing, can be substituted in the phthalate position by having the phthalate with a chlorine at ortho position. This compound is useful in various cases as a color indicator. It is a solid substance of iodine in aqueous potassium iodide solution, which is very sensitive, the phthalate itself serving as the indicator.

1. J. M. Pitt, J. Am. Chem. Soc., 41, 1000 (1919).

1. LISTED BELOW ARE THE NAMES OF THE

1. TETRA-IODO-ORTHO-SULPHO-BENZOIC ANHYDRIDE

Halogenated sulphone-phthaleins having the halogen substituted in the phenolic residues have been known for some time. One of them, tetra-brom-phenol-sulphone-phthalein



is widely used as an indicator under the name of brom phenol blue.¹ These compounds may be prepared with comparative ease from the corresponding sulphone-phthalein. Bromine, and often iodine, can be substituted in the phenolic residues by boiling the phthalein with a solution of the halogen in glacial acetic acid. Iodine is usually substituted from a cold solution of iodine in aqueous potassium iodide solution, which is kept alkaline, the phthalein itself serving as the indicator.

¹ JACS 38, 2776, 2779; 40, 1092; 41, 1205

1900-1901-1902-1903-1904-1905

Information relative to the various
substances in the various series has been
taken from the following sources:-



is usually used as an indicator when the test is made in the
presence of water. The test is made with the use of the
following apparatus:- The test is made in a test tube which is
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1900-1901-1902-1903-1904-1905

These methods are not vigorous enough to effect substitution in the phthalic anhydride residue, or the ortho-sulpho-benzoic anhydride residue, and the employment of more vigorous methods results in the destruction of the phthalein structure; so that four atoms of halogen per molecule of phthalein is apparently the maximum which can be attained starting from the phthalein. There is no record in the literature of any successful attempt to prepare more highly halogenated phthaleins in this way, but in order to obtain direct information on this point, several attempts were made to prepare halogenated phthaleins in this manner.

Halogenation of phenol-sulphone-phthalein

Bromination. 7g. (.02 mol) of pure phenol-sulphone-phthalein were dissolved in 100 c.c. glacial acetic acid, and brought to boiling. Then a solution of 13g. (.18 mol) of bromine gradually added. A reflux condenser was used to prevent escape of bromine and acetic acid. After refluxing the mixture for five hours, it was poured into water, washed, and recrystallized from alcohol. The product consisted of flesh colored crystals melting at 269-270°C. It gave a blue color with alkali, and had a pH range 3.0 - 4.6. It was obviously tetra-brom-phenol-sulphone-phthalein.

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Information of general interest

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Iodination. 7g. (.02 mol) of pure phenol-sulphone-phthalein were dissolved in 1L. of 1% sodium hydroxide solution, cooled, and a solution of 22 g. iodine in 30 g. of potassium iodide in 200 c.c. of water gradually added. The mixture was cooled by ice and stirred mechanically during the addition of the iodine, and kept alkaline by the addition of sodium hydroxide solution (10%). Five hours were allowed for completion of the reaction, the crude phthalein precipitated by the addition of acid, washed with potassium iodide solution, and recrystallized from alcohol. It consisted of reddish-blue crystals of high but indefinite melting point, and gave a dark blue color in alkali. Preliminary analyses showed that it certainly did not contain more than 59% iodine, and was therefore doubtless tetra-iodo-phenol-sulphone-phthalein.

Attempts were then made to employ a more vigorous method.

Method of Datta and Chatterjee¹ 7g. phenol-sulphone-phthalein were dissolved in nitric acid, and 22g. of iodine added. When the product of the first run, at the end of four hours, was poured into water, washed, and recrystallized, it gave a mixture of unchanged phenol-sulphone-phthalein and di- and tetra-nitro-phenol-sulphone-phthaleins. The second run was heated to 100° for four hours, and no substance giving the reactions of a phthalein could be detected in the mixture.

¹ JACS 39, 435, (17)

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was dissolved in 100 ml of...
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Method of Juvalta¹. 7g. phenol-sulphone-phthalein dissolved in 100 c.c. of fuming sulphuric acid containing 50% free SO₃, 22g. iodine added, and the mixture heated to 110° for four hours. No phthalein could be recovered from the mixture.

It was concluded that, in harmony with the findings of Pratt and Shupp² in preparing phthaleins halogenated in the phthalic anhydride residue, it would be necessary to introduce the halogen into the anhydride molecule before condensing it with the phenolic substance to form the phthalein.

Pratt and Shupp employed a modification of the method due to Juvalta. By a slight modification of their method it was found possible to prepare in good yield tetra-iodo-ortho-sulpho-benzoic anhydride, which is the parent substance of all the iodized sulphone-phthaleins prepared for the first time in the course of the present study. The details of a typical run are given below.

Preparation of Tetra-iodo-ortho-sulpho-benzoic anhydride

108 g. o-sulpho-benzoic anhydride (Eastman, practical grade) and 300 g. of powdered iodine were mixed in a long necked flask (an 800 c.c. Kjeldahl serves very well), and 500 c.c. of fuming sulphuric acid containing 50% free SO₃ added, with stirring. (Acid of this strength is ordinarily partly or completely solid, and may require melting). The flask, into the neck of which a test tube was loosely

¹ DEP 50, 177; Fortschr. Teerfarb.-fabrik 2, 93 (89)

² JACS 40, 257 (18)

Section 1
The first part of the paper is devoted to a description of the experimental apparatus and the method of measurement. The results of the measurements are given in the following table.

It was found that the rate of reaction is independent of the concentration of the reactants. This suggests that the reaction is of the zero order. The rate of reaction is found to be proportional to the surface area of the catalyst.

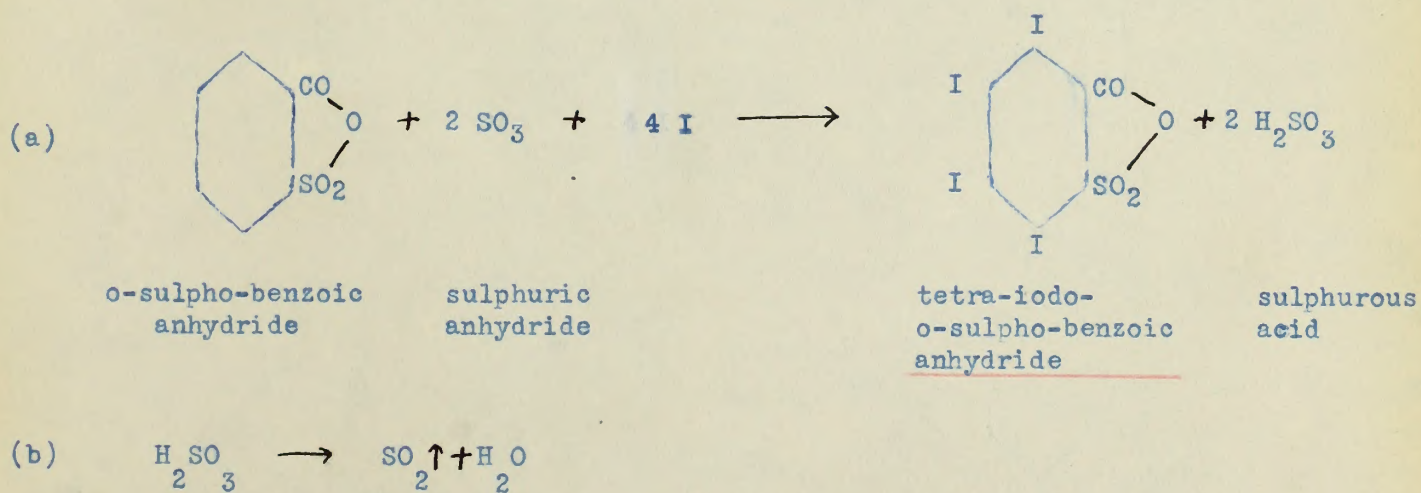
The results of the measurements are given in the following table. It is seen that the rate of reaction is independent of the concentration of the reactants. This suggests that the reaction is of the zero order. The rate of reaction is found to be proportional to the surface area of the catalyst.

Section 2

The second part of the paper is devoted to a discussion of the results of the measurements. It is seen that the rate of reaction is independent of the concentration of the reactants. This suggests that the reaction is of the zero order. The rate of reaction is found to be proportional to the surface area of the catalyst.

fitted by means of asbestos cord, to prevent the escape of too much iodine or sulphuric acid, was slowly heated in an oil bath, and the temperature kept between 110° and 120° until the evolution of SO_2 had practically ceased (5 to 10 hours). The temperature was then raised to 175° - 180° and held for about thirty minutes. The whole apparatus was then allowed to cool, and when cool, the practically solid contents poured into about 1.5 L. of water, and washed with successive portions of water containing sulphurous acid to remove the excess iodine. It was allowed to stand overnight with the final portion of wash water, the solid filtered off, washed with a little water, and dried in air. Yield 88%, calculated on the amount of o-sulpho-benzoic anhydride. The product so obtained is pure enough for making sulphone-phthaleins.

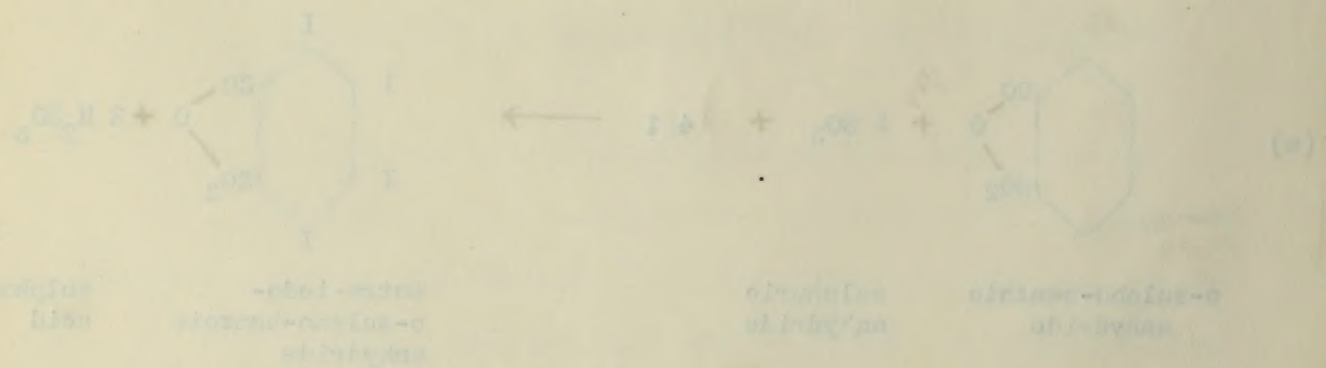
The reactions involved in this preparation may be summarized as follows:

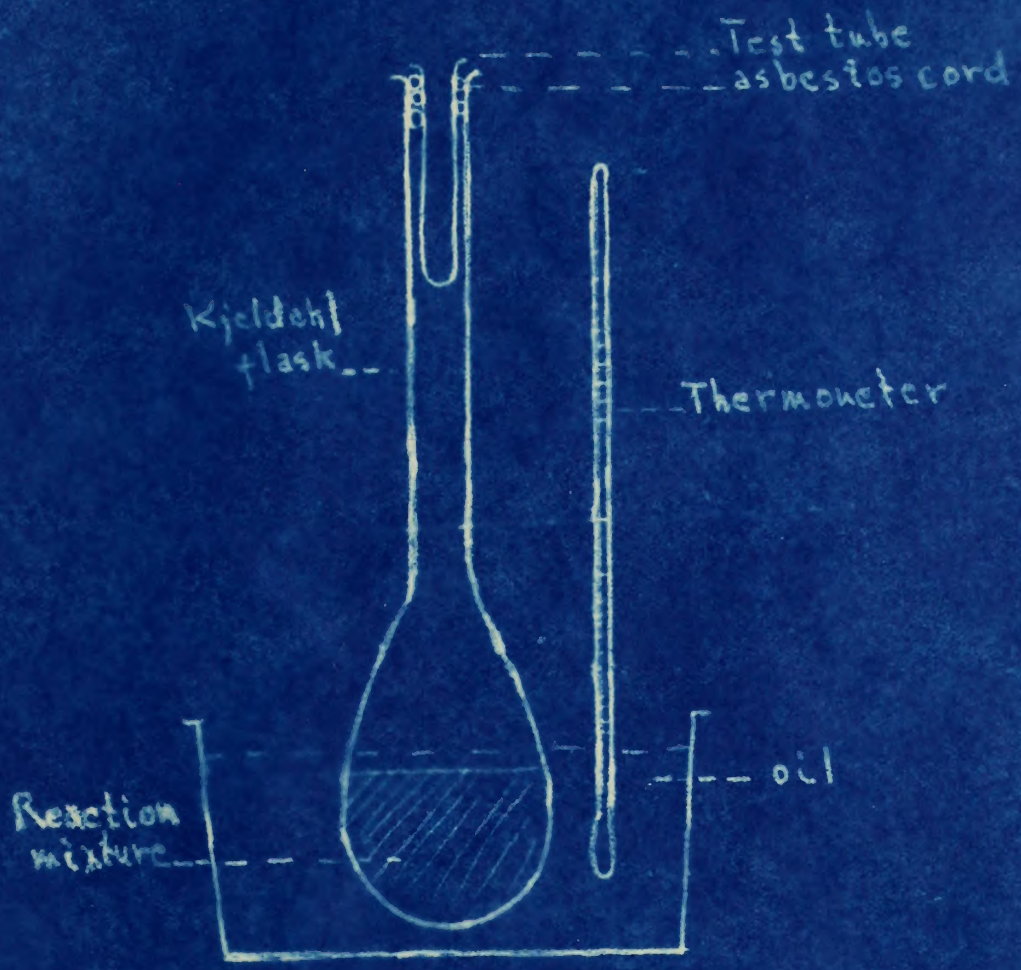


fitted by means of anhydrous acid, to prevent the escape of the acid
 fumes or volatile acid, was slowly passed in an all glass, and the
 temperature kept between 100° and 120° until the evolution of SO₂
 had practically ceased (5 to 10 hours). The temperature was then
 raised to 125° - 130° and held for about thirty minutes. The whole
 apparatus was then allowed to cool, and when cool, the gaseous
 solid contents passed into about 1.5 l. of water, and washed with
 successive portions of water containing potassium acid ferrioxalate
 excess iodine. It was allowed to stand overnight with the final
 portion of wash water, the solid filtered off, washed with a little
 water, and dried in air. Yield 80%, calculated on the amount of
 o-nitro-benzaldehyde. The product so obtained is pure enough
 for melting-point-determination.

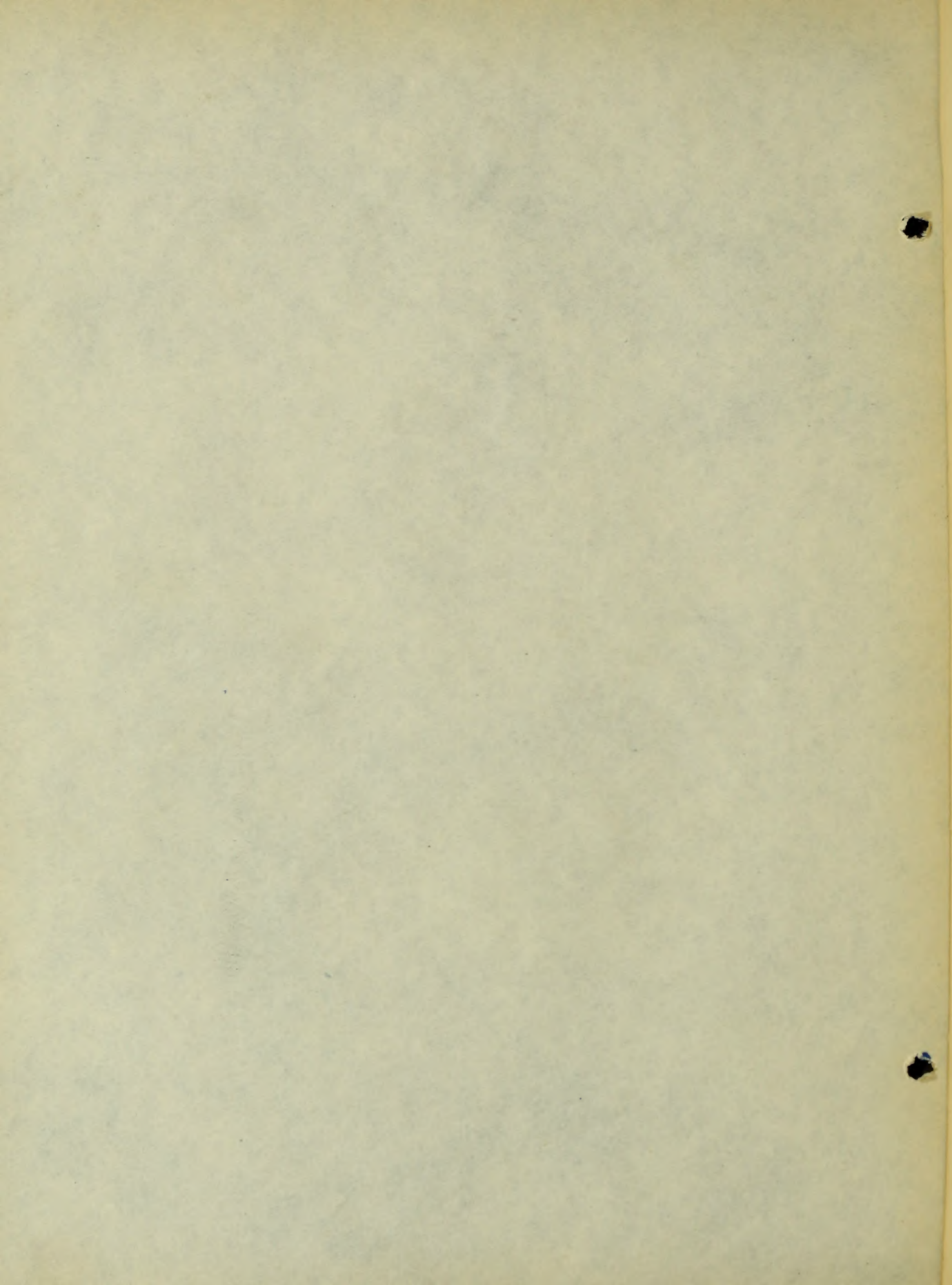
The reactions involved in this preparation may be summarized as

follows:

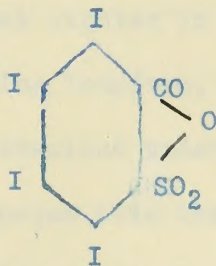




APPARATUS for IODINATION



Properties of tetra-iodo-ortho-sulpho-benzoic anhydride and purification of tetra-iodo-ortho-sulpho-benzoic anhydride.



Tetra-iodo-o-sulpho-benzoic anhydride is somewhat soluble in water, nitrobenzene, acetic acid, tetrachlorethane, chloroform, benzene. It is quite soluble in acetone and in alcohol, but cannot be recrystallized from either. When dissolved in acetone it forms a dark brown mass, owing, apparently, to the formation of an addition product, since tetra-iodo-o-sulpho-benzoic anhydride can be recovered from it by the action of warm nitric acid. In alcohol it supersaturates, forming, when concentrated, a yellow varnish-like mass, which is quite unmanageable. When recrystallized from chloroform it has a melting point of 132° (uncorr.), as against the melting point of the crude product of about 260° ; indicating the probable formation of some sort of addition product.

Preparation of 2,4,6-trinitrophenol (Picric acid)

Reaction of Phenol with Nitric acid



Phenol reacts with nitric acid to form 2,4,6-trinitrophenol. The reaction is carried out in several stages. In the first stage, phenol is nitrated with dilute nitric acid to form 2-nitrophenol. In the second stage, 2-nitrophenol is nitrated with concentrated nitric acid to form 2,4-dinitrophenol. In the final stage, 2,4-dinitrophenol is nitrated with concentrated nitric acid to form 2,4,6-trinitrophenol. The final product is a white crystalline solid that is soluble in water and has a melting point of 122°C.

It can, however, be recrystallized from a mixture of alcohol and acetic acid. (60 g. will require about 350 c.c. of a mixture consisting of 100 c.c. of 95% ethyl alcohol and 250 c.c. of glacial acetic acid.)

The product so obtained does not melt, but decomposes about 305° to 310°. It is somewhat lighter in color than tetra-iodo-phthalic anhydride, resembling iodoform, except for a faint greenish tinge. The crystals, when examined under the microscope, are small, imperfect platelets, more opaque than the coffin shaped crystals of tetra-iodo-phthalic anhydride.

The recrystallized product was prepared for analysis by drying in the oven at 140° for 6 hours. Iodine analyses were done by the method of Baubigny and Chavanne¹.

Analysis of tetra-iodo-ortho-sulpho-benzoic anhydride

The obvious analytical procedure for this compound is the determination of the percentage of iodine. The determination of carbon is attended with great difficulties because of the great stability of the substance, and serious difficulties are caused by the iodine and sulphur contained in it.

¹ "Organic Laboratory Methods" - Lassar-Cohn, Oesper-Adams-Clarke

	found	calc.
I ₂	73.8	74.0%
	74.1	
S	4.8	4.6

is not, however, so completely dried from a mixture of alcohol and acetic acid. (50 g. will require about 200 c.c. of a mixture consisting of 100 c.c. of 95% ethyl alcohol and 100 c.c. of glacial acetic acid.)

The product so obtained does not melt, but decomposes about 300° to 310°. It is somewhat lighter in color than beta-lactam. Italic anhydride, resembling iodolactam, except for a faint greenish tinge. The crystals, when examined under the microscope, are small, imperfect platelets, more opaque than the cotton thread crystals of beta-lactam anhydride.

The recrystallized product was prepared for analysis by drying in the oven at 100° for 2 hours. Iodine analysis was done by the method of Sandberg and Thomsen.

Analysis of beta-lactam anhydride

The above analytical procedure for this compound is the determination of the percentage of iodine. The determination of carbon is obtained with great accuracy because of the great stability of the substance, and even so slight variations are caused by the iodine and nitrogen contained in it.

Typical Laboratory Results - Iodine-Carbon, Oxygen-Nitrogen

Found	Calcd.
47.5	47.0
47.1	47.0
47.5	47.0

The customary procedure for the determination of halogens in the organic laboratory is that due to Carius. But this method is well known to be somewhat unsatisfactory for iodine¹, and in this case gave extremely erratic and unreliable results, perhaps because of the drastic treatment required to destroy this very stable compound. After numerous attempts to use this method, experiments were undertaken to determine whether another method, at the same time more accurate for iodine and less time consuming, could not be found.

The researches involved in this part of the work were partly bibliographical, and partly experimental. The number of proposed methods for the determination of iodine in organic compounds is very great, and practically every issue of Chemical Abstracts contains references to three or four new ones--a fact in itself suggestive of the widespread dissatisfaction with the existing methods. It was necessary to investigate this literature, test those methods which seemed to hold promise of applicability to the present problem, and test out modifications and combinations which might make them more applicable.

The results, both of the author's original experiments and of statements found in the literature, relating to methods which seem at all promising, are summarized below. So far as the author is aware, no such summary has before been published, and it is hoped that the present one might have some value for persons who may have occasion to analyze similar compounds.

¹ Clarke, "Handbook of Organic Analysis" Longmans, Green and Co., London, 1926. p.306

The primary procedure for the determination of organic nitrogen is that due to Debus. In this method it will know to be somewhat unsatisfactory for routine work, and in this case gave extremely erratic and unreliable results. Several attempts of the author's procedure required an average of 100 to 150 mg. of sample after numerous attempts to use this method. Experiments were undertaken to determine whether another method, or the same one, could be used for routine and less time consuming, results could be found.

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The results, both of the author's original experiments and of statements found in the literature, relating to methods which seem to all promising, are summarized below. So far as the author is aware, no such survey has before been published, and it is hoped that the present one might have some value for persons who may have occasion to analyze similar compounds.

Analysis of Iodine Compounds

I. Destruction of the substance to be analyzed.

1. In sealed tubes. The principal example of this is the Carius method. It does not give trustworthy values, for reasons difficult to determine. Possibly the prolonged heating to a high temperature with fuming nitric acid, which is necessary, results in the formation of some silver iodate, which is less soluble than silver iodide. Methods involving sealed tubes are, in general, inconvenient, time-consuming, and not without a certain element of danger.

2. In open tubes

(a) With nitric acid (b) With sulphuric acid. With either of these methods, of course, iodine escapes. Attempts to trap the escaping iodine are unsatisfactory, and if successful, would not insure volatilization of all the iodine, as a certain amount of iodic acid would be formed.

(c) With nitric acid and silver nitrate (d) With sulphuric acid and silver nitrate. If the mixture is heated sufficiently to insure complete decomposition, iodine escapes.

(e) With nitric acid and potassium permanganate. This method does not result in complete decomposition.

(f) With sulphuric acid, potassium dichromate, and silver nitrate. This is the method of Baubigny and Chavanne¹, which has proven the most satisfactory in the present work. It will be described more in detail later.

¹ "Organic Laboratory Methods", Lassar-Cohn, Oesper-Adams-Clarke.

1. Identification of the substance to be analyzed.

In order to identify the substance, the physical constants of the substance

should be determined. These constants are: melting point, boiling point,

density, refractive index, etc. These constants are usually determined

by comparing the constants of the substance with those of known substances.

Another method is the formation of characteristic derivatives, which is less

reliable than the first method. The constants of the derivatives are usually

higher than those of the substance, and are usually

characteristic of the substance.

2. In case of mixtures

(a) Distillation is a method of separating mixtures of liquids with different

boiling points. It is based on the fact that the more volatile component

of the mixture will vaporize more readily than the less volatile component.

The mixture is heated and the vapor is condensed and collected in a separate

receiving flask.

(b) Extraction is a method of separating mixtures of solids with different

solubilities. It is based on the fact that the more soluble component

of the mixture will dissolve more readily in a suitable solvent.

(c) Crystallization is a method of separating mixtures of solids with different

solubilities. It is based on the fact that the less soluble component

of the mixture will crystallize more readily from a solution than the more

soluble component. The mixture is dissolved in a suitable solvent and then

the solution is cooled, causing the less soluble component to crystallize

out of the solution.

(g) With aqueous sodium hydroxide. This is not vigorous enough to destroy the compound.

(h) With alcoholic sodium hydroxide. This will remove the iodine quantitatively from aliphatic compounds, but is too slow for ring compounds.

(i) With solid sodium hydroxide. Does not destroy the compound completely and is difficult to control, usually resulting in loss of material, or of iodine.

(j) With solid sodium hydroxide and sodium nitrate. This is also too violent, resulting in loss of material.

(k) With sodium carbonate. Incomplete.

(l) With sodium carbonate and sodium nitrate. This procedure is reasonably satisfactory, but must be carefully controlled, or iodine will be lost.

(m) With sodium peroxide.

(n) With barium peroxide. These methods are both too violent, and the decomposition is often not complete.

II. Treatment of the resulting solution.

1. Oxidation of the iodide to iodate.

2. Reduction of the iodate to iodide.

(a) With sulphurous acid. (b) With nitrous acid. These methods were shown to be satisfactory by experiments with known amounts of inorganic compounds.

(c) With solid rubber particles, there is no definite amount to destroy the compound.

(d) With insoluble rubber particles, this will remove the soluble quantities from the compound, but is not able to remove insoluble.

(e) With solid rubber particles, both the soluble and insoluble quantities are available to be removed, usually resulting in loss of material, or of latex.

(f) With solid rubber particles and soluble latex, this is also the solvent, resulting in loss of material.

(g) With solid particles, insoluble.

(h) With solid particles and soluble latex, this procedure is normally satisfactory, but must be carefully controlled, or latex will be lost.

(i) With solid particles.

(j) With solid particles, these particles are not lost, and the compound has its own set weight.

11. Treatment of the resulting solution.

1. Removal of the latex to latex.

2. Removal of the latex to latex.

(a) With solid particles, these particles were found to be satisfactory by experiment with known amounts of insoluble particles.

- 44
3. Releasing the iodine with sulphuric acid, and trapping the free iodine. This was unsatisfactory, because, to remove the iodine completely, the mixture had to be heated so hot that sulphuric acid distilled over, and interfered seriously.

III. Estimation of the resulting iodine compound.

1. Gravimetric.

(a) Precipitation in acid solution of silver iodide or iodate.

This is satisfactory in the method of Baubigny and Chavanne, but cannot be done if the compound were destroyed by fusion with an alkaline mixture in glass or quartz, for in that case, silicic acid precipitates.

(b) Precipitation in alkaline solution of silver iodide. If it is attempted to do this without the presence of sulphite, the mixture darkens, and the results are quite incorrect. If sulphite is present, the darkening does not occur, but the results are always too low. This was proven by experiments using a known amount of inorganic iodide.

2. Volumetric.

(a) Titration of the iodine liberated by the addition of iodate.

The acidity control must be quite exact, and this is usually difficult in the mixtures involved, so the results are quite variable.

(b) Titration of the excess silver nitrate after precipitation of the iodine as silver iodide.

... the iodine ...

III. Estimation of the available iodine content.

1. Method.

(a) Preparation of the solution of silver iodide.

This is satisfactory in the amount of ...

(b) Preparation of the solution of silver iodide.

It is necessary to ...

2. Results.

(a) Estimation of the iodine content in the solution of iodine.

The iodine content must be quite small, and this is usually ...

(b) Estimation of the iodine content in the solution of iodine.

The iodine content is ...

d. With thiocyanate. The end point is not satisfactory.

β. With potassium iodide solution (or direct titration of the iodide with silver nitrate). This is not impossible

but is far from satisfactory, owing to indefinite end points.

In general, volumetric methods do not seem to be satisfactory for the solutions obtained after any of the permissible methods of decomposition.

Analysis of tetra-iodo-ortho-sulpho-benzoic anhydride by the method of Baubigny and Chavanne.

In 40 c.c. of concentrated sulphuric acid (d. 1.84) there is dissolved by warming 1 g. of silver nitrate and 8 g. of powdered potassium dichromate, and the mixture cooled. The sample to be analyzed, (about .5 g), which has been weighed out in a tiny beaker of pyrex, is introduced, and dissolved gradually by heating and shaking. The decomposition may be performed in a long necked flask of hard glass, such as a 300 c.c. Kjeldahl digestion flask. To insure complete decomposition, the mixture is finally heated to boiling. After the mixture has cooled, it is transferred to a beaker, about 150 c.c. water added, and then reduced by the addition of an excess of concentrated sodium sulphite solution. (Sulphurous acid may be used, but so much is required that it increases the volume of the solution unduly.)

1. The following table shows the results of the analysis.

2. The following table shows the results of the analysis.

3. The following table shows the results of the analysis.

4. The following table shows the results of the analysis.

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18. The following table shows the results of the analysis.

19. The following table shows the results of the analysis.

20. The following table shows the results of the analysis.

The silver iodide is filtered off on a Gooch crucible, washed, the crucible dried at 120° in the oven, and weighed. The calculations are the same as in the Carius method. Any chlorine or bromine in the substance does not interfere, as they are evolved quantitatively as such during the decomposition.

The average accuracy obtained by this method may be judged from the following figures for tetra-iodo-phthalic anhydride, which was used to test the method. Its calculated percentage of iodine is 77.9%.

78.0%

77.6

77.6

77.7

The first bottle is filled with a good sample, water,
the original water at 100 is the original water. The calculation
for the water in the water, the relative of water in the
water is not important, as they are equal. The relative of water
during the calculation.

The relative amount obtained by this method was as follows from the
following figures for water-logged water, which was used in
the first bottle. The calculated percentage of water is 77.7.

- 77.7
- 77.0
- 77.2
- 77.7

(b) Biological properties of tetra-iodo-ortho-sulpho-benzoic anhydride.

The compound has a faint, slightly unpleasant taste . It is quite non-toxic. 200 mg. injected intravenously into a rabbit weighing 2 Kg. apparently produced no bad effects whatever. This corresponds to a dose of between 6 and 7 grams for a man. The author took 0.5 g. by mouth without any effect. Attempts to demonstrate the substance in the urine following this experiments were not successful.

Effect on bacteria. To cultures of B.Coli communis, there was added varying amounts of the substance in solution so that the resulting concentrations were, respectively, (a) 40 mg./cc., (b) 4 mg./cc., (c) 0.4 mg./cc. From these, subcultures were made at intervals of 1 min., 5 min., 30 min., 8 hours. Only in the case where the bacteria had been exposed to action of the 40 mg./cc. for 8 hours, did the subculture fail to grow. So it was concluded that tetra-iodo-ortho-sulpho-benzoic anhydride had no marked bacteriocidal action on B. Coli communis.

The author is indebted to Miss Elizabeth Tayian for assistance in this work.

The compound has a high, slightly negative charge. It is
quite non-toxic. 500 mg. injected intraperitoneally into a rabbit
weighing 2 kg. experimentally produced no bad effects whatever. This
corresponds to a dose of between 4 and 7 times for a man. The
author took 0.5 g. of the substance without any effect. Attempts to harm-
fulize the substance in the urine following this experiment were
not successful.

Effect on bacteria. In cultures of *S. typhi* organisms, there was

no effect on the growth of the organisms in relation to that of the
control concentrations were, respectively, (a) 40 mg./cc., (b) 4 mg./cc.,
(c) 1 mg./cc. When tested, substances were made at intervals of
1 min., 2 min., 30 min., 6 hours. Only in the case where the bacteria
had been exposed to action of the 40 mg./cc. for 2 hours, did the
experiment fail to grow. In it was concluded that some amino-acid-
oxidizing enzymes had no marked bactericidal action on *S. typhi*
organisms.
The author is indebted to Miss Elizabeth Taylor for assistance in
this work.

2. METHODS OF CONDENSING TETRA-iodo-ortho-sulpho-benzoic anhydride
WITH PHENOLIC SUBSTANCES

In the matter of condensing agents in the preparation of phthaleins, there is a wide choice. Baeyer, it will be remembered, discovered the first phthalein by simply fusing the mixture, without any condensing agent at all, and in fact Schon¹ recommends that in the preparation of phenol-sulphone-phthalein, no condensing agent be used. Baeyer himself² came to the conclusion that in general, ^{Zinc} chloride was the best, but in view of the high cost of this substance, the less satisfactory sulphuric acid could be recommended. Fuming stannic chloride³, stannous chloride⁴, and other compounds have been used. It was thought that before attempting the preparation of a series of these compounds, in large amounts, it would be advisable to conduct some experiments with the object of determining the best condensing agent for use with this particular series.

Preliminary experiments disclosed the fact that the tetra-iodo-ortho-sulpho-benzoic anhydride was much more difficult to condense with phenolic substances than the unhalogenated ortho-sulpho-benzoic anhydride, and that some condensing agent was necessary, but that the amount of the condensing agent was not especially important.

¹ Am. Ch. J. 20, 257
² Ann. 202, 36
³ Ann. 202, 153
⁴ J. Ch. Ind. Russia 1, 2628 (25)

Comparison of condensing agents. Tetra-iodo-ortho-sulpho-benzoic anhydride and freshly distilled phenol were mixed in the proportion of 1 g. of the former to 4 g. of the latter, and the mixture heated to bring about complete solution. 3 c.c. of this mixture was pipetted into a test tube, and 1 c.c. of a condensing agent added. The following were used: (a) no condensing agent, (b) fuming stannic chloride, (c) concentrated sulphuric acid, (d) fuming sulphuric acid containing 20% free SO₃, (e) zinc chloride, (f) aluminum chloride, (g) lead chloride, PbCl₂, (h) titanium tetrachloride, (i) phosphorous pentachloride, (j) phosphorous pentoxide.

The test tubes were all immersed in the same oil bath, and heated to 170° for five hours. Then they were removed, and the contents dissolved in 20 c.c. of 5% sodium hydroxide. Then they were each made up to 2 L. with water, and compared with each other in the colorimeter. The greater the depth of color, the greater the amount of phthalein produced, assuming no colored by-products. This assumption is substantially correct, for none of the by-products of such condensations give the intense colors with alkali which characterize the phthaleins. Therefore from the readings obtained, it was possible to calculate the relative efficiency of the various condensing agents. The average, in round numbers, of several such experiments is given in the following table, where stannic chloride is rated at 100.

Condensation of condensation products.

Several experiments and trials (which are not given in the report) of the effect of the factor of the factor, and the mixture used to give about equal amounts of each of the mixture was placed into a test tube, and 1 c.c. of a condensing agent was added. The following were used: (a) no condensing agent,

- (b) 10% aqueous sodium chloride,
- (c) concentrated sodium chloride,
- (d) 10% aqueous sodium chloride,
- (e) 20% aqueous sodium chloride,
- (f) 30% aqueous sodium chloride,
- (g) 40% aqueous sodium chloride,
- (h) 50% aqueous sodium chloride,
- (i) 60% aqueous sodium chloride,
- (j) 70% aqueous sodium chloride,
- (k) 80% aqueous sodium chloride,
- (l) 90% aqueous sodium chloride,
- (m) 100% aqueous sodium chloride.

The test tubes were all immersed in the same oil bath, and

heated to 100° for five hours. Then they were removed, and the contents of each in 20 c.c. of 95% sodium hydroxide. Then they were each made up to 100 c.c. with water, and compared with each other in the color-

order. The greater the factor of color, the greater the amount of

condensation product, and the greater the amount of condensation product. This experiment is substantially correct, for some of the products of such condensations

give the same color with alkali which characterizes the product.

Therefore from the results obtained, it was possible to calculate the

relative efficiency of the various condensing agents. The average, in

round numbers, of several such experiments is given in the following

table, where sodium chloride is rated at 100.

<u>Condensing Agent</u>	<u>Efficiency</u>
fuming stannic chloride	100
lead chloride	85
zinc chloride	50
sulphuric acid (concentrated)	35
sulphuric acid (fuming)	30
no condensing agent	25
aluminum chloride	0
titanium tetrachloride	0
phosphorous pentachloride	0
phosphorous pentoxide	0

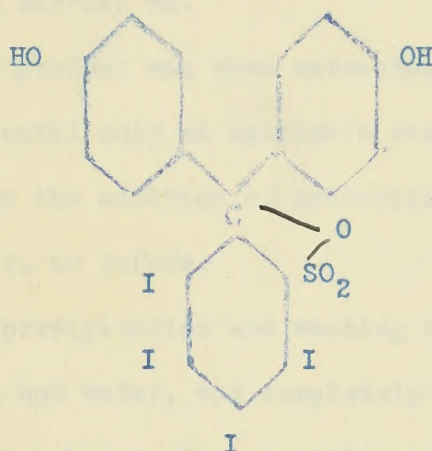
In addition to the evidence afforded by these figures, it was evident from the quality of the product that stannic chloride was immensely superior to all the others except lead chloride and zinc chloride. In the other cases, large amounts of gummy and tarry substances were produced which made the recrystallization of the phthalein practically impossible. Stannic chloride was used in all the condensations which follow.

Percentage

Compound

100	Lead chloride
85	Lead chloride
80	Lead chloride
75	Lead chloride (concentrated)
70	Lead chloride (concentrated)
65	Lead chloride
60	Lead chloride
55	Lead chloride
50	Lead chloride
45	Lead chloride
40	Lead chloride
35	Lead chloride
30	Lead chloride
25	Lead chloride
20	Lead chloride
15	Lead chloride
10	Lead chloride
5	Lead chloride

In addition to the various elements by these figures, it was
estimated from the quality of the product that various elements are
necessarily superior to all the others except lead chloride and the
chloride. In the other cases, large amounts of gas and heavy
substances were produced which were the result of the oxidation of the
various elements. These elements were used in all the experiments
which follow.

3. PHENOL-TETRA-iodo-SULPHONE-PHTHALEINPreparation of phenol-tetra-iodo-sulphone-phthalein

The first member of the new series to be prepared was the above compound. The details of a typical preparation are given below. The quality of the reagents necessary and the proper conditions are discussed later.

80 g. of tetra-iodo-ortho-sulphor-benzoic anhydride were dissolved in 320 g. of melted phenol, 80 g. of fuming stannic chloride added, and the mixture heated in an oil bath to 170° for eight hours. The flask was kept closed by a ground-in glass stopper containing a tube ending in a calcium chloride tube, located at a lower level than the glass stopper, to avoid contamination of the reaction mixture by reflux of the contents of the calcium chloride tube, which are eventually liquefied. The reaction mixture gradually became a deep red, lost its transparency, and became much more viscous.

Preparation of diethyl-2,4-dinitrophenylamine



The first portion of the raw material to be prepared was the above compound. The details of a typical preparation are given below. The quality of the reagents necessary and the proper quantities are given in Table I.

10 g. of diethyl-2,4-dinitrophenylamine was dissolved in 200 cc. of methyl alcohol, 10 g. of calcium chloride added, and the mixture placed in an 8-oz. bottle for 24 hours. The liquid was then allowed to crystallize in a glass vial at a temperature of 5°C. for 24 hours. The crystals were removed and the mother liquor evaporated. The crystals were washed with 5% methanol solution of the reagent and dried in the vacuum of the vacuum desiccator. The yield was approximately 8 g. The crystals were washed with 5% methanol solution of the reagent and dried in the vacuum of the vacuum desiccator. The yield was approximately 8 g.

At the end of eight hours it was poured into about six liters of hot water, stirred, and washed by decantation with successive portions of hot water until the phenol had practically all been removed. This required about two days, during which time other preparations were being carried on.

This washed raw product was then extracted with 2% sodium hydroxide solution, until only an insoluble residue remained; filtered, and reprecipitated by the addition of hydrochloric acid. It was then washed with hot water, as before.

This alternate precipitation and washing was carried on until the product was solid in hot water, and completely soluble in alkali. It was then dissolved in boiling glacial acetic acid, filtered, concentrated, and allowed to stand. From this acetic acid solution small, reddish-brown crystals were deposited. They were filtered off, and recrystallized from more acetic acid, as at first.

Experiments were made to determine the optimum temperature for the above condensation. A solution of tetra-iodo-ortho-sulpho-benzoic anhydride in melted phenol, in the proportion of one gram of the anhydride to four of phenol, was prepared, three cubic centimeters of this pipetted into a test tube, and the several samples heated at different temperatures. At the end of five hours the contents of each tube were dissolved in twenty cubic centimeters of 5% sodium hydroxide, made up to two liters and compared with each other in the colorimeter. From the

At the end of eight hours it was found that about six liters
of hot water, stirred, had passed by distillation into successive
portions of hot water until the amount had practically all been re-
turned. This required about two days, during which the other pro-
cessions were being carried on.

This method was found to be associated with 22 bottles
of various sizes, and only an insensible residue remained; likewise,
and recognized by the addition of hydrochloric acid. It was then
mixed with hot water, as before.

This mixture was filtered and washed and dried on a water bath
product was left in hot water, and completely soluble in alcohol. It
was then dissolved in boiling alcohol, water added, filtered, concentrated,
and allowed to stand. From this water and alcohol were removed,
brown crystals were obtained. They were filtered off, and recrystallized
from water, and dried.

Experiments were made to determine the optimum temperature for the
above combination. A solution of water-insoluble-substance
substance in alcohol (about 100 gms), in the presence of one gram of the sub-
stance to four of alcohol, was prepared, when white crystalline at this
highest rate a test tube, and the mixture rapidly heated at different
temperatures. At the end of five hours the contents of each tube were
dissolved in twenty cubic centimeters of 20 cubic centimeters, and
to see which was superior with each other in the crystallization, from the

readings obtained it was possible to calculate the relative yield at each temperature. The results are given in the following table, where the yield at the optimum temperature (170° C.) is arbitrarily set at 100.

Yields at various temperatures

<u>Temperature</u>	<u>Yield</u>
110 ^o	10
120	10
130	30
140	50
150	70
160	90
170	100
180	90
190	70

In the above experiments the temperatures were maintained within 2 to 3 degrees by regulating the amount of gas admitted to a burner under a small oil bath. For actual preparations, a variation of 5° was found to be admissable, and the temperature was found to be maintained constant with this degree of exactness by the following device:

The flask in which the condensation was being carried out was immersed in an oil bath, which was placed on an ordinary laboratory electric stove. Also immersed in the bath was a mercury-filled thermostat, which when the temperature rose, closed a circuit actuating a

Results obtained in our studies to determine the relative yields at each temperature. The results are given in the following table where the yield at the optimum temperature (170°C) is arbitrarily set at 100.

Yields at various temperatures

<u>Yield</u>	<u>Temperature</u>
10	110°
10	120
30	140
50	140
70	150
90	160
100	170
80	180
70	190

In the above experiments the temperatures were maintained within 2 to 3 degrees by regulating the amount of gas added to a burner under a small oil bath. For actual preparation, a reaction of 4- was found to be satisfactory, and the temperature was found to be maintained constant with this degree of accuracy by the following method. The flask in which the condensation was being carried out was immersed in an oil bath, which was placed on an ordinary laboratory electric stove. Also located in the bath was a mercury-filled thermometer, which when the temperature rose, closed a circuit controlling a

heavy relay which interrupted the current to the stove. This device performed satisfactorily without any attention throughout the present work.

The conditions determining the yield (and quality of product) are much more numerous than this brief discussion might indicate, and are not all independently variable, so that an exact determination of all the conditions optimal for this preparation would have involved an enormous amount of work, and was not attempted. For instance, up to a certain point, heating to a higher temperature for a shorter time was equivalent to heating to a lower temperature for a longer time. But partly as a result of consideration of the procedures of others in preparing analogous compounds, and as the result of experience gained in the numerous preparations involved in the present work, a set of conditions was arrived at which were, it was felt, a close approach to optimal conditions, and which were conformed to during all the later preparations. They may be summarized thus:

heavy relay which interrupted the current to the tubes. This device
retained satisfactorily without any attention throughout the present
work.

The conditions determining the yield (and quality of product) are
such that variations from this initial condition cause a decrease, and are
not all independently variable, so that an exact determination of all
the conditions which for this preparation would have resulted as
enough about all this, and was not necessary. For instance, as to
a certain point, heating to a higher temperature for a shorter time
was equivalent to heating to a lower temperature for a longer time,
and partly as a result of consideration of the procedure of other
in similar analogous compounds, and as the result of experience
gained in the present preparation, it was found in the present work,
that of conditions was varied as little as possible, it was held a close
control to certain conditions, and which were continued to during
all the later preparations. The way to reproduce them:

Preparation of phenol-tetra-iodo-sulphone-phthalein

Reagents

Freshly distilled colorless phenol.

Tetra-iodo-ortho-sulpho-benzoic anhydride, free from free iodine, and dry.

Pure fuming stannic chloride.

Proportions of Reagents

<u>Reagent</u>	<u>Parts by Weight</u>
Phenol	4
Anhydride	1
Stannic chloride	1

Temperature

165° - 175° C.

Time

5 - 8 hours.

Preparation of methyl-ethyl-amine-hydrochloride

Reagents

Twenty distilled water (grams).
Methyl-ethyl-amine-hydrochloride (grams).
From the above, and dry.
This being a strong solution.

Preparation of Reagents

<u>Weight</u>	<u>Volume in ml.</u>
100	1
100	1
100	1

Procedure

100 - 100 g.

Time

2 - 3 hours.

Purification of phenol-tetra-iodo-sulphone-phthalein

Tetra-iodo-phthalic anhydride can be easily recrystallized from benzene, tetrachlorethane, phenol, or a mixture of alcohol and acetic acid, yielding well-formed crystals. In the author's experience, only the last mentioned solvent can be used for the recrystallization of tetra-iodo-ortho-sulpho-benzoic anhydride, and the resulting crystals are small and imperfect. There may be added to this observation the fact that the phthaleins derived from tetra-iodo-phthalic anhydride are much more difficult to recrystallize than the parent substance.

In view of these facts, it is not surprising that the greatest difficulty was experienced in purifying phenol-tetra-iodo-sulphone-phthalein. It is readily soluble in ethyl alcohol, methyl alcohol, acetone, ethyl acetate. It is soluble in benzene, carbon tetrachloride, chloroform, tetrachlorethane, ether. But it cannot be recrystallized from any of these solvents. If the substance, even in a pure state, is dissolved in any of these, and the solution concentrated, the phthalein does not separate until practically all of the solvent has evaporated, when it coats the sides of the beaker with a hard uniform layer, like red paint. Repeated solution in alkali and precipitation by acid, while useful as a means of preliminary purification, cannot be relied upon to effect sufficient purification so the compound can be used biologically, or for analytical purposes.

Purification of phenol-soluble-substances

Phenol-soluble-substances can be easily crystallized from various solvents, such as benzene, or a mixture of alcohol and acetic acid, yielding well-formed crystals. In the author's experience, only the last mentioned solvent can be used for the crystallization of phenol-soluble-substances. There may be and the resulting crystals are small and imperfect. These may be added to this observation the fact that the substances derived from the phenol-soluble-substances are much more difficult to crystallize than the parent substance.

In view of these facts, it is surprising that the crystallization was attempted in benzene, which is not a good solvent. It is readily soluble in ethyl alcohol, which is a better solvent, ethyl acetate. It is soluble in benzene, carbon tetrachloride, chloroform, carbon disulfide, ether, but it cannot be crystallized from any of these solvents. If the substance, even in a very small amount, is dissolved in any of these, and the solution concentrated, the substance does not separate until practically all of the solvent has evaporated, when it coats the sides of the flask with a hard yellow layer, like the parent substance. Repeated solution in alcohol and precipitation by gold, which is used as a means of purification, cannot be relied upon to effect sufficient purification, as the compound can be used biologically, or for analytical purposes.

After many attempts, it was found that phenol-tetra-iodo-sulphone-phthalein could be recrystallized in the following manner. It was dissolved in boiling glacial acetic acid, filtered, and the solution concentrated. If it had not been concentrated too much, the solution, on standing, deposited small reddish-brown crystals of phenol-tetra-iodo-sulphone-phthalein.

Pratt and Shupp¹, in their paper already referred to, describe the use of bone-black in the purification of phenol-tetra-iodo-phthalein. This has often been used, and is certainly of value in the purification of phenolphthalein prepared by the use of sulphuric acid. After many trials of bone-black in connection with various solvents, it was eventually discarded as of no value in the present case.

The whole group of phthaleins with which the present study is concerned are exceedingly difficult to purify, and it is impossible to communicate through the medium of written language all of their peculiarities, a knowledge of which is necessary for working with them successfully. It can only be said briefly that during the preparation of phenol-tetra-iodo-sulphone-phthalein, there are formed a number of by-products, greater in amount than the phthalein. These are in large measure divisible into two classes; products insoluble in alkali, and products soluble in alkali but insoluble in acetic acid. Upon this the rationale of purification

¹ Pratt and Shupp, JACS, 40, 257 (18)

These many attempts to find the truth about the world...

...and the results of these attempts are...

...and the results of these attempts are...

...and the results of these attempts are...

...and the results of these attempts are...

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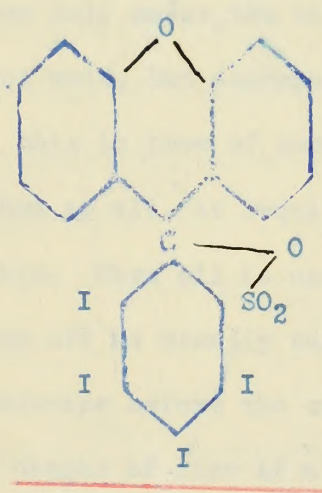
...and the results of these attempts are...

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...and the results of these attempts are...

...and the results of these attempts are...

largely depends. The nature of the by-products could not be more completely investigated in the time available for this study, but they include, as a relatively minor constituent, the analogue of fluorane:



...the nature of the ... products could not be ...
...investigated in the ... available for this study, but
...of a relatively strong ... , the ... of

Figure:



Properties of phenol-tetra-iodo-sulphone-phthalein

(a) Physical

Pure phenol-tetra-iodo-sulphone-phthalein, obtained as described above, consists of small imperfect crystals, of a reddish-black color. Crystal faces can be seen only under the high power of the microscope.

The compound does not melt, but decomposes about 210°. It may be said now that in general this is true of compounds of this group. If it is possible to melt them at all, it requires such a high temperature as to be hardly practicable. When oil is used in the melting point apparatus, the smoke given off is usually sufficient to obscure the major features of the landscape before the substance can be said to be liquid. (There is little danger of fire if a heavy transparent oil such as Nujol is used instead of the very inflammable cotton-seed oil usually recommended.) The smoke produced when sulphuric acid is used in the apparatus is equally dense, and even less soothing to the respiratory tract. Attempts were made to take a melting point using a bath of Rose's metal in the apparatus instead of oil or acid, but it was found that the melting point of many of the substances, assuming they could be melted at all, lay above the range of a mercury-filled thermometer. And in the case of the others, the so-called melting point really consisted in a gradual charring and decomposition. So it was concluded that, just as White found in the case of the mercuriochromes¹, the melting point could not be used as a critical constant for this group of compounds.

¹ White, JAMA, 73, 1483, (19)

The present work was carried out in the laboratory of the University of Chicago, and was directed by Professor E. Rutherford. It was a part of a larger project on the properties of gamma-rays from radium, which was carried out in the laboratory of the University of Chicago, and was directed by Professor E. Rutherford. The present work was carried out in the laboratory of the University of Chicago, and was directed by Professor E. Rutherford. It was a part of a larger project on the properties of gamma-rays from radium, which was carried out in the laboratory of the University of Chicago, and was directed by Professor E. Rutherford.

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The crystals obtained as outlined evidently contained moisture or acetic acid absorbed on the surface, or possibly in part as liquid of crystallization, for a sample of the air-dried substance lost weight on being heated to 180° for eight hours. A sample which weighed .5208 g. lost .0459 g., or 8.8%. The crystals were unaltered in appearance microscopically after this treatment.

Before analysis, the compound was heated to 180° for ten hours. The analyses were done by the method of Baubigny and Chavanne, as the same difficulties were experienced with other methods as in the case of the parent substance, tetra-iodo-ortho-sulpho-benzoic anhydride. Analysis gave the following figures:

	<u>Found</u>	<u>Calculated</u>
I ₂	59.0%	59.3%
	58.8	
	59.1	

The solubilities of the compound have already been mentioned in discussing its purification. It is readily soluble in methyl alcohol, ethyl alcohol, ethyl acetate, acetone, acetic acid. It is somewhat soluble in benzene, carbon tetrachloride, tetrachlorethane, chloroform, ether. It is only very slightly soluble in neutral water, but does dissolve to a sufficient extent to dye cloth immersed in the water. This will be referred to again more in detail.

The crystals obtained as outlined previously were washed with water or acetone and dried on the vacuum, or possibly in a light stream of nitrogen, for a sample of the air-dried substance lost weight on being heated to 150° for eight hours. A sample which weighed 0.1000 g. lost 0.0150 g., or 1.5%. The crystals were washed in benzene and dried in a vacuum.

Before analysis, the compound was heated to 150° for ten hours. The analysis was done by the method of Baughy and Johnson, as the same difficulties were experienced with other methods as in the case of the parent substance, ortho-toluene-sulfonic anhydride. Analysis gave the following figures:

Calculated	Found
58.12	58.12
	58.3
	58.1

The solubilities of the compound have already been mentioned in connection with the synthesis. It is readily soluble in water, alcohol, ethyl acetate, acetone, acetic acid. It is somewhat soluble in benzene, carbon tetrachloride, chloroform, ether. It is only very slightly soluble in methyl alcohol, and insoluble in a sufficient amount of the latter in which it is insoluble. This will be referred to again more in detail.

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The compound dissolves readily in dilute sodium hydroxide solution, forming the disodium salt. By dissolving the purified phthalein in the stoichiometric amount of standard sodium hydroxide solution, and evaporating to dryness, the disodium salt may be obtained as a dark reddish-black mass, with a bluish tinge. It is very difficult to free this from moisture. The solution of the disodium salt in water is an intense purple, quite similar to the color in alkali of phenol-tetra-iodo-phthalein.

The phthalein dissolves, apparently without change, in concentrated sulphuric acid, with the formation of the same purple color which characterizes its solution in alkali. This rather strange phenomenon has been noticed with most of the phthaleins which have been reported in the literature (see the introduction to this thesis), but has never received a completely satisfactory explanation.

The phthalein is very stable, and will resist heating to temperatures of 200° in air for an indefinite period, will withstand the action of concentrated cold sulphuric or hydrochloric acid.

In order to determine the pH range of the substance, it was necessary to prepare a series of buffer solutions of standard pH. In order that the same set might serve for work in the course in physiological chemistry in which the author was instructing, it was decided to make up the set described in Folin¹, and supplement them in the most alkaline range with the glycine mixtures of Sørensen. The solutions were prepared from standard stock solutions made up according to the directions of Clark and Lubs². These

¹ Folin, "Laboratory Manual of Biological Chemistry", Appleton & Co., N.Y. 1925, pp.49-53

² Clark, "The Determination of Hydrogen Ions", Williams and Wilkins, Baltimore, 1928, pp. 192-220

The compound dissolves readily in dilute sodium hydroxide solution, forming the sodium salt. On heating the purified substance in the hydrolytic amount of sodium hydroxide solution, and upon cooling to room temperature, the sodium salt may be obtained as a dark yellowish-black mass, with a black ring. It is very difficult to fuse with iron wire. The sodium of the sodium salt is water in an amount.

The sodium salt is soluble in alcohol, and is precipitated by the addition of dilute hydrochloric acid. The sodium salt is precipitated by the addition of dilute hydrochloric acid, and is precipitated by the addition of dilute hydrochloric acid. The sodium salt is precipitated by the addition of dilute hydrochloric acid, and is precipitated by the addition of dilute hydrochloric acid. The sodium salt is precipitated by the addition of dilute hydrochloric acid, and is precipitated by the addition of dilute hydrochloric acid.

The product is very stable, and will retain weight in vacuum at 200° in air for an indefinite period, with slight loss of weight on contact with moist air or hydrochloric acid.

In order to determine the degree of the substance, it was necessary to prepare a series of buffer solutions of constant pH. In order that the same set of curves for each of the curves in practical theory in which the buffer was functioning, it was tested by means of the substances in this, and suggested that in the case of the buffer with the various mixtures of phosphate. The solutions were prepared from standard stock solutions and according to the direction of Clark and Lusk. These

¹ Clark, "Laboratory Manual of Biological Chemistry," 2nd Edition, 1927, pp. 44-45.
² Clark, "The Determination of Phosphate Ions," Illinois and Michigan, 1927, pp. 141-150.

solutions were the following.

M/5 acid potassium phosphate (KH_2PO_4) solution

Merck blue label acid potassium phosphate was recrystallized three times from distilled water, and dried to constant weight at 110-115°C. 27.232 g. were dissolved in 1 L. of carbonate-free water, obtained by boiling distilled water, and allowing it to cool while protected by a soda-lime trap.

M/5 boric acid (H_3BO_3) M/5 potassium chloride (KCl) solution.

Boric acid was recrystallized three times from distilled water, and air dried in thin layers between filter paper for a week, then the constancy of weight checked by drying small samples in a desiccator over calcium chloride. The potassium chloride was Merck blue label potassium chloride, and was recrystallized three times from distilled water, and dried in the electric oven at 120°C. for two days. The solution contained 12.4048 g. of boric acid and 14.912 g. of potassium chloride in 1 L., made up with the carbonate-free water, which was used in all this work.

M/5 sodium hydroxide (NaOH) solution

This solution was prepared from an amalgam obtained electrolytically. A deep layer of redistilled mercury was placed in a conical separatory funnel. Over this was placed a saturated solution of recrystallized Merck blue label sodium chloride. It was found possible to

at the same time.

Section 10 (1) (a)

The first part of the section deals with the case where the person is a minor. It states that if the person is a minor, the court must have regard to the best interests of the child. This is a general principle that applies to all cases involving children. The court must consider the child's physical, emotional, and educational needs, as well as the child's relationship with their family and the wider community. The court must also consider the views of the child, where it is appropriate to do so.

Section 10 (1) (b)

The second part of the section deals with the case where the person is an adult. It states that if the person is an adult, the court must have regard to the best interests of the person. This is a similar principle to the one that applies to children, but it is applied to adults. The court must consider the person's physical, emotional, and educational needs, as well as the person's relationship with their family and the wider community. The court must also consider the views of the person, where it is appropriate to do so. The court must also consider the person's financial needs and the person's ability to care for themselves.

Section 10 (1) (c)

The third part of the section deals with the case where the person is a child or young person who is not a minor. It states that if the person is a child or young person who is not a minor, the court must have regard to the best interests of the person. This is a similar principle to the one that applies to children, but it is applied to child or young persons who are not minors. The court must consider the person's physical, emotional, and educational needs, as well as the person's relationship with their family and the wider community. The court must also consider the views of the person, where it is appropriate to do so.

use the regular 110 v. D.C. current for this electrolysis, by cutting down the voltage by the following simple device. The 110 v. line was connected to a bank consisting of a 100 w. and a 50 w. lamp in series. Then there was connected in parallel with the 50 c. lamp a circuit consisting of a 250 w. lamp, and the electrolytic cell, connected in series. The negative pole of this circuit entered the mercury in the electrolytic cell through a glass-protected platinum wire, and the positive pole entered the sodium chloride solution through a platinum electrode. The distance from this electrode to the surface of the mercury was about 6 cm., and the area of the mercury surface was about 150 sq. cm. Under these conditions the fall in potential across the cell was found to be 6 volts, and the current passing through it 0.65 amperes. The current was allowed to run continuously for about four days.

At the end of this time the amalgam was separated off, washed several times with distilled water, and reacted with carbonate-free water in a paraffined flask, protected from the CO₂ of the air. When the solution had reached the desired strength, it was siphoned off into a paraffined container containing CO₂-free air, which was connected to an automatically filling burette, likewise protected from the atmospheric CO₂. It was standardized, and diluted to exactly 0.2 N (M/5).

The hydrochloric acid against which this sodium chloride solution was standardized was prepared as follows: 6 L. of approximately 0.15 N. hydrochloric acid were made up from C.P. hydrochloric acid, and mixed

NOTE. The above preparation of c.p. sodium hydroxide solution follows in general the directions given in Clark (loc. cit.). The details are in part modelled after procedures observed at the Rockefeller, and are in part original with the author.

use the reported 110 v. D.C. current for this electrolysis, by cutting
down the voltage by the following simple ratio. The 110 v. line was
connected to a bank consisting of a 100 v. and a 50 v. lamp in series.
This current was connected in parallel with the 100 v. lamp & a nickel
resistor of a 250 v. lamp, and the electrolysis cell, connected in
series. The negative pole of this circuit entered the mercury in the
electrolytic cell through a glass-protected platinum wire, and the
positive pole entered the solution through a platinum-plated
electrode. The distance from this electrode to the surface of the
mercury was about 0.5 cm., and the area of the mercury surface was about
150 sq. cm. Under these conditions the cell is practically a Daniell
cell with a 5 v. e.m.f., and the current passing through it is
approximately 0.1 amp. The current was allowed to run continuously for about four days.
At the end of this time the mercury was removed, washed several
times with distilled water, and treated with carbon tetrachloride which is a
detergent for the removal of the oil on the wire. Then the solution
was removed from the beaker, it was allowed to stand in a beaker
containing concentrated H_2SO_4 which was removed by an electrolytic
filter. It was then introduced into the electrolytic cell. It was
decolorized, and dried to exactly 0.2 g. (Wt.).
The electrolytic cell against which this solution was introduced
was standardized and prepared as follows: 0.1 g. of standard UO_2
electrolytic cell were made up from 0.1 g. hydrochloric acid, and dried
to constant weight. The above preparation of c.p. sodium hydroxide solution follows in
general the directions given in their (loc. cit.). The details are
in part omitted after procedure described at the Institute, and the
in part omitted with the author.

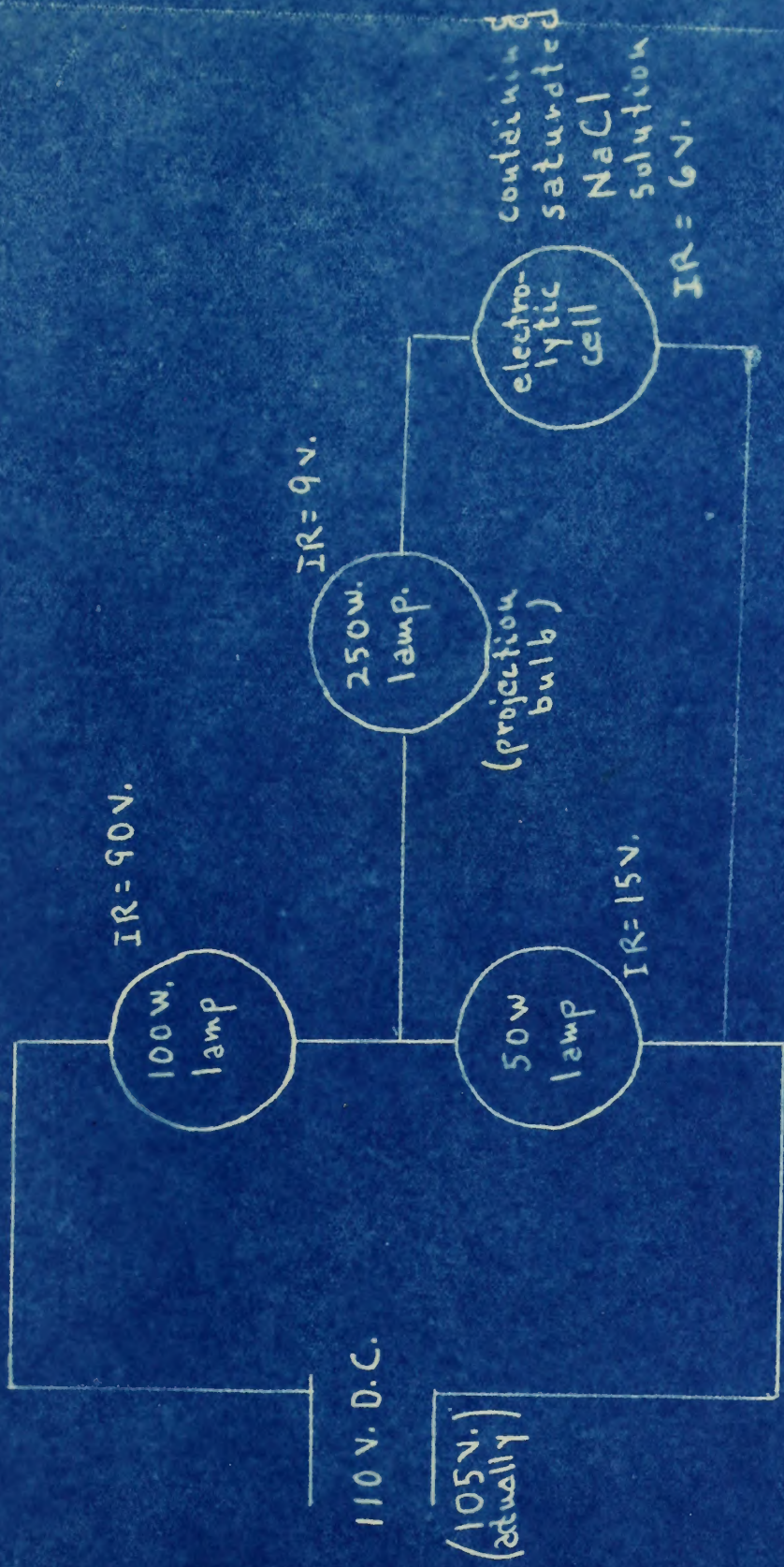


DIAGRAM OF CIRCUIT
 FOR ELECTROLYSIS

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thoroughly. After the mixture had stood for a day, samples of it were taken with a standardized pipette and precipitated by the addition of a slight excess of silver nitrate solution. The precipitates were allowed to stand in the dark until clear, then filtered off on weighed Gooch crucibles containing a fine mat. The precipitate was thoroughly washed on the Gooch and dried at 120°C . in the electric oven, cooled in a desiccator, and weighed. From the weights so obtained (which checked to one part in one thousand) the normality of the acid was calculated.

M/5 acetic acid (CH_3COOH) solution

C.P. acetic acid was distilled under reduced pressure, a solution somewhat stronger than .2 N made up, standardized against the standard sodium hydroxide solution, diluted to exactly 0.2 N, and checked.

Glycine ($\text{CH}_2\text{NH}_2\text{COOH}$) sodium chloride (NaCl) solution

7.505 g. Pfanstiehl glycine and 5.85 g. of sodium chloride, recrystallized three times, were dissolved in 1 L. of CO_2 -free water.

The standard buffer mixtures were then prepared from these stock solutions by diluting to 200 c.c. the proper amounts, as shown in the following table.

University. Along the minute bed about 100 ft. away from the
lake with a crystalline surface and crystallized by the addition of a
right amount of water, the crystallization was allowed
to take place in the same way as above, then filtered off on weighed paper
and dried in a vacuum at 100°C. The crystalline was thoroughly washed
with water and dried in a vacuum at 100°C. The crystalline was
then dried in a vacuum at 100°C. The crystalline was then dried in a
vacuum at 100°C. The crystalline was then dried in a vacuum at 100°C.

1.5.2. Preparation of the crystalline

The crystalline was prepared by the addition of a right amount of water
to the solution. The crystalline was then dried in a vacuum at 100°C.
The crystalline was then dried in a vacuum at 100°C.

1.5.3. Preparation of the crystalline

The crystalline was prepared by the addition of a right amount of water
to the solution. The crystalline was then dried in a vacuum at 100°C.
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The crystalline was prepared by the addition of a right amount of water
to the solution. The crystalline was then dried in a vacuum at 100°C.
The crystalline was then dried in a vacuum at 100°C.

Composition of Standard Buffer Mixtures

pH	c.c. 0.2 M CH ₃ COOH	c.c. 0.2 M NaOH
4.6	50	23.0
4.8	50	29.0
5.0	50	34.5
5.2	50	38.5
5.4	50	42.5
5.6	50	45.0

	c.c. 0.2 M KH ₂ PO ₄	c.c. 0.2 M NaOH
5.8	50	3.66
6.0	50	5.64
6.2	50	8.55
6.4	50	12.60
6.6	50	17.74
6.8	50	23.60
7.0	50	29.54
7.2	50	34.90
7.4	50	39.34
7.6	50	42.74
7.8	50	45.17
8.0	50	46.85

Composition of Standard Butyl Rubber

0.2 M Butyl	0.2 M CH ₂ Br	0.2 M CH ₂ Br
0.0	100	0.0
0.05	95	0.5
0.10	90	1.0
0.15	85	1.5
0.20	80	2.0
0.25	75	2.5
0.30	70	3.0
0.35	65	3.5
0.40	60	4.0
0.45	55	4.5
0.50	50	5.0
0.55	45	5.5
0.60	40	6.0
0.65	35	6.5
0.70	30	7.0
0.75	25	7.5
0.80	20	8.0
0.85	15	8.5
0.90	10	9.0
0.95	5	9.5
1.00	0	10.0

pH	c.c. 0.2 M H_3BO_3 KCl	c.c. 0.2 M NaOH
7.8	50	2.65
8.0	50	4.00
8.2	50	5.90
8.4	50	8.55
8.6	50	12.00
8.8	50	16.40
9.0	50	21.40
9.2	50	26.70
9.4	50	32.00
9.6	50	36.85
9.8	50	40.80
10.0	50	43.90

Sørensen's glycine mixtures

pH	Parts Glycine Solution	Parts 0.1N NaOH (carbonate-free)
10.42	5.5	4.5
11.01	5.1	4.9
11.25	5.0	5.0
11.51	4.9	5.1
12.04	4.5	5.5
12.33	4.0	6.0
12.60	3.0	7.0
12.79	2.0	8.0
12.97	1.0	9.0

Year	Value	Year	Value
1900	1.00	1900	1.00
1901	1.05	1901	1.05
1902	1.10	1902	1.10
1903	1.15	1903	1.15
1904	1.20	1904	1.20
1905	1.25	1905	1.25
1906	1.30	1906	1.30
1907	1.35	1907	1.35
1908	1.40	1908	1.40
1909	1.45	1909	1.45
1910	1.50	1910	1.50

Estimated figures

Year	Value	Year	Value
1911	1.55	1911	1.55
1912	1.60	1912	1.60
1913	1.65	1913	1.65
1914	1.70	1914	1.70
1915	1.75	1915	1.75
1916	1.80	1916	1.80
1917	1.85	1917	1.85
1918	1.90	1918	1.90
1919	1.95	1919	1.95
1920	2.00	1920	2.00

These mixtures were kept in bottles of paraffin. The pH range of the indicators was determined in the following manner.

In a clean test tube there were placed, from a dropping pipette, four drops of the buffer mixture, and five c.c. of carbonate-free water. Then there was added one to three drops, (depending on the phthalein being tested) of an alcoholic solution of the phthalein. Results were usually checked by using also a solution in a mixture of water and alcohol, containing enough alkali to form the sodium salt of the phthalein. In every case the two methods gave results which, for the purposes of the present work, were identical.

The phthalein was tested with solutions of varying pH, such as pH 5, 6, 7, 8, and 9, and the portion of the scale covered by its range approximately determined. Then the intervening steps in this range, and a few on either side, were tried, and the useful range of the phthalein as an indicator determined. On the whole this group of phthaleins was found to be rather poor as indicators.

pH range of phenol-tetra-iodo-sulphone-phthalein

Phenol-tetra-iodo-sulphone-phthalein has a useful pH range of 7.0 to 8.2. Its color changes in this interval from a brownish-yellow to a wine-purple.

These mixtures were kept in bottles of paraffin. The mixture

of the indicators was determined in the following manner.

In a clean test tube there were placed, from a dropping pipette,

four drops of the buffer mixture, and five c.c. of phosphate-free water.

Then there was added one to three drops, depending on the pH-value

desired, of an alcoholic solution of the indicator. Results were

usually checked by using also a solution in a mixture of water and

alcohol, containing about equal to four the volume of the indicator.

In every case the two methods gave results which, for the purposes of the

present work, were identical.

The indicator was tested with solutions of varying pH, such as

of 0.1, 0.2, 0.5, and 1, and the portion of the scale covered by the

range approximately determined. Then the indicator range in this

range, and a few on either side, were noted, and the useful range of the

indicator as an indicator determined. On the whole this group of indicators

was found to be rather poor as indicators.

PH RANGE OF PHENOL-PHTHALEIN-INDICATOR-MIXTURES

Phenol-phtalein-iodo-sulfate-mixtures were a useful pH range of

3.0 to 4.5. Its color changes in this interval from a pinkish-yellow

to a blue-purple.

Properties of phenol-tetra-iodo-sulphone-phthalein as a dyestuff

Like many of the phthaleins¹, this substance will dye silk and wool fast. This will be discussed more fully later. Phenol-tetra-iodo-sulphone-phthalein dyes silk a color which varies from brownish-yellow to reddish-walnut, depending on the method employed. It does not give an especially attractive shade, and would be too expensive to have commercial application, in any case.

X-ray permeability of phenol-tetra-iodo-sulphone-phthalein

As is well known², permeability to X-rays is practically free from such unpredictable variations as ^{is} permeability to electromagnetic radiation of visible wave lengths. The amount of mass interposed between the source and the observer determines the intensity of the transmitted X-rays, and the effect is practically independent of the form of chemical union in which the matter may be.

So it was expected that a 10% solution of phenol-tetra-iodo-sulphone-phthalein would offer the same resistance to the passage of X-rays as the same thickness of a 10% solution of potassium iodide, and this was verified experimentally. The same is of course true of the other phthaleins, and the matter will not be referred to again until the end of this discussion.

¹ Cain and Thorpe "The Synthetic Dyestuffs", Charles Griffin & Co. London, 1920, pp. 100 - 113

² M. de Broglie-"X-Rays", Methuen & Co., London, 1925, p.1, p.53

Kaye - "X-Rays", Longmans, Green & Co., London, 1923, p.105

Properties of chemical-physical-chemical-chemical

like that of the chemical, this substance will give the same result. This will be discussed more fully later. From this it follows that the chemical-physical-chemical-chemical reaction is reversible, depending on the method employed. It does not give an absolutely quantitative result, and would be too expensive to have quantitative application, in any case.

X-ray permeability of chemical-physical-chemical-chemical

As is well known, permeability to x-rays is practically five times as high as that to visible light. The amount of energy absorbed between the source and the observer depends on the intensity of the transmitted x-rays, and the effect is practically independent of the form of material upon which the x-rays are incident.

So it was expected that a 10% solution of chemical-physical-chemical-chemical would give the same results as the same solution of chemical-physical-chemical-chemical. The same is of course true of other substances, and the matter will not be referred to again until the end of this discussion.

¹ G. W. C. Milne, "The Spectroscopic Properties of Chemical-Physical-chemical-chemical", *Journal of Chemical Physics*, 1930, p. 100-110.

² E. de Broglie, "X-rays", *Nature*, 1928, p. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100.

(b) Biological properties of phenol-tetra-iodo-sulphone-phthalein

Toxicity. The toxicity of this substance has not been completely worked out. A dose of .12 g. per kilogram of body weight has been injected intravenously into several rabbits without producing any permanent damage that could be detected. The substance is made up for injection by dissolving a weighed amount in the calculated amount of sodium hydroxide solution, making up to some convenient volume, with isotonic saline if calculation shows the resulting solution would be hypotonic, and sterilizing. The last animal experiment involved the injection of 0.50 g. of the phthalein into a 2 Kg. rabbit. The animal died almost at once, probably of thrombosis, as a large clot was found in the heart on autopsy. The author has taken doses of 0.2 g. by mouth without any detectable effects.

Fate in the body. In the autopsy mentioned above, on an animal which had died within a few minutes of injection, the dye was easily demonstrated in the liver substance and the kidney, but could not be demonstrated in the blood.

In one experiment, 0.24 g. of the phthalein was injected intravenously into a rabbit weighing 2.1 Kg., the urine collected for 24 hours, made alkaline, made up to 200 c.c., and compared in the colorimeter with a standard containing a known amount of the dye per c.c. From the reading thus obtained, and the total volume of the urine, the amount of the dye excreted in the urine could be calculated. It was found that about 20% of the amount injected had been eliminated in the urine. Thus the substance is, at any rate in part, eliminated through the kidney, as was predicted before it was made.

(b) Statistical properties of the model

The model is a linear regression model with the following assumptions:
1. The error term is normally distributed with mean zero and constant variance.
2. The error term is independent of the explanatory variables.
3. The error term is independent of the dependent variable.
4. The error term is independent of the other error terms.
5. The error term is independent of the explanatory variables.
6. The error term is independent of the dependent variable.
7. The error term is independent of the other error terms.
8. The error term is independent of the explanatory variables.
9. The error term is independent of the dependent variable.
10. The error term is independent of the other error terms.

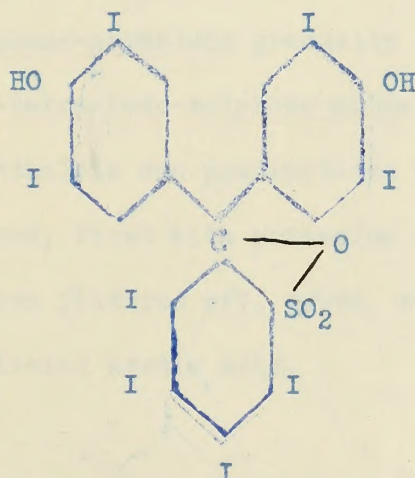
In the above model, the error term is assumed to be normally distributed with mean zero and constant variance. This assumption is reasonable if the error term is the result of many small, independent, random influences.

The model is a linear regression model with the following assumptions:
1. The error term is normally distributed with mean zero and constant variance.
2. The error term is independent of the explanatory variables.
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7. The error term is independent of the other error terms.
8. The error term is independent of the explanatory variables.
9. The error term is independent of the dependent variable.
10. The error term is independent of the other error terms.

Three of the experimental animals were X-rayed after injection, but in no case was the kidney more visible than might have been expected normally. More of this work will be necessary before a definite decision can be made, but progress is very slow, owing to the congestion in the X-ray department here.

Derivatives of phenol-tetra-iodo-sulphone-phthalein

(a) Tetra-iodo-phenol-tetra-iodo-sulphone-phthalein



To prepare this compound, 4 g. of phenol-tetra-iodo-sulphone-phthalein was dissolved in glacial acetic acid, and 3 g. of iodine added. The solution was refluxed for an hour, poured into water, washed, recrystallized from glacial acetic acid. The substance gave a green color in alkali, and in all respects agreed in properties with the tetra-iodo-phenol-tetra-iodo-sulphone-phthalein prepared by another method, but when it was attempted to repeat this preparation by this method no trace of the substance was ever again obtained, although in all half a dozen attempts were made. Fate had played one of the little tricks which

Some of the experimental results were reported in a preliminary communication at the meeting of the American Chemical Society in 1931. It is to be noted that the above results were obtained in a preliminary investigation of the reaction of the above compound with sodium hydroxide. The results are given in the following table.

Reaction of the above compound with sodium hydroxide

(a) Reaction of the above compound with sodium hydroxide



In preparing this compound, 4 g. of alcohol-soluble substance was dissolved in alcohol and 5 g. of sodium hydroxide was added. The solution was allowed to stand for 24 hours, and then the solvent was removed. The residue was washed with water, and the combined filtrate and washings were dried over calcium chloride. The substance was then distilled under reduced pressure, and the product was obtained as a colorless solid. The yield was 1.5 g. The boiling point was 100°C. at 10 mm. pressure. The refractive index was 1.45. The density was 1.15. The substance was identified by its melting point, which was 100°C.

she reserves for chemists, where some trace of impurity, or some un-noticed variation in the conditions, is the essential, and unreproducible factor. In this case, however, there is another method of making the substance.

30 g. of phenol-tetra-iodo-sulphone-phthalein were dissolved in 600 c.c. of 5% sodium hydroxide solution, cooled by ice, stirred mechanically, while a solution of 80 g. of iodine in 100 g. of potassium iodide in 200 c.c. of water was added during the course of half an hour. The mixture was kept alkaline by the addition of small quantities of 30% sodium hydroxide solution. The deep purple of the phenol-tetra-iodo-sulphone-phthalein gradually gave way to the green of the tetra-iodo-phenol-tetra-iodo-sulphone-phthalein. After one and one-half hours, the phthalein was precipitated by the addition of hydrochloric acid, and washed, first with potassium iodide solution, then with water. It was then filtered off, dried, washed with cold chloroform, recrystallized from glacial acetic acid.

Properties of tetra-iodo-phenol-tetra-iodo-sulphone-phthalein

The compound, purified as described above, consists of small, irregular crystals, of a reddish brown color. No melting point could be determined, and the phthalein is very stable.

the mixture for chemical analysis, which was done by iodometry, or some
un-assisted oxidation in the conditions, is the standard, and the
reproducible factor. In this case, however, there is a danger of error
of setting the standard.

50 g. of purest-iodine-iodine-sulfate was dissolved
in 500 c.c. of 5% sodium hydroxide solution, cooled to 10°, and
acidified, with a solution of 50 g. of iodine in 100 c.c. of
potassium iodide in 200 c.c. of water was added during the course of
half an hour. The mixture was kept alkaline by the addition of small
quantities of 5% sodium hydroxide solution. The dark purple of the
potassium-iodide-iodine-sulfate complex was very strong in the case of
the pure-iodine-iodine-sulfate-iodine-sulfate. After one and
one-half hours, the solution was precipitated by the addition of 100 g.
sulfuric acid, and washed. The white potassium iodide solution, when
with water, is not filtered off, dried, washed with cold water,
recrystallized from alcohol and dried.

Preparation of purest-iodine-iodine-sulfate-iodine-sulfate

The amount, portion or weighed above, consists of 50 g.
potassium iodide, of a reddish brown color. The solution color is
determined, and the solution is very stable.

Analysis after drying at 180° for 10 hours gave the following figures:

	<u>Found</u>	<u>Calculated</u>
I ₂	74.4	74.6%
	74.0	
	74.2	

The iodine method of Baubigny and Chavanne was used, as before.

The compound is soluble in alcohol, methyl alcohol, ethyl acetate, acetone, acetic, but in all to a less extent than phenol-tetra-iodo-sulphone-phthalein. It is practically insoluble in chloroform, ether, tetrachlorethane, and water. It can be dyed on silk or wool from a water bath containing a little acetic acid, giving a greenish-brown color.

The most disappointing property was its slight solubility in alkali. (In other words, the disodium salt is not very soluble in water.) This is so marked that a greater amount of organically bound iodine can be got into solution by using the disodium salt of phenol-tetra-iodo-sulphone-phthalein than by using this compound. This was so discouraging that such time as was available for biological experiments was devoted to other compounds, instead of this, which had seemed so promising before it was made.

The pH range of this phthalein is from 6.2 to 7. The color ranges from one shade of green to another, and it is hardly possible that the compound could be of any value as an indicator.

Analysis of the results of the following

Figure:

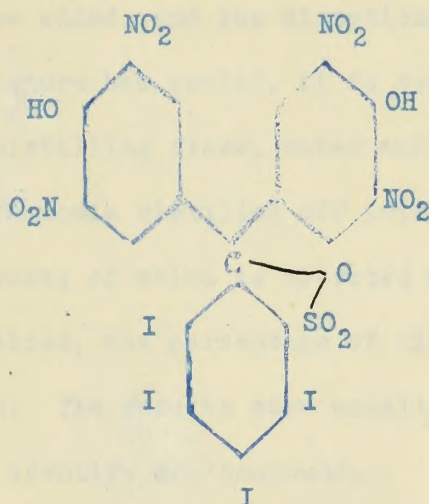
<u>Actual</u>	<u>Calculated</u>
74.4	74.4
74.0	
74.2	

The following method of handling the data was used, as before.

The amount of water in the soil is not constant, but varies with the amount of water in the soil. It is possible to determine the amount of water in the soil by measuring the amount of water in the soil. This can be done by using a soil moisture meter. The amount of water in the soil is not constant, but varies with the amount of water in the soil. It is possible to determine the amount of water in the soil by measuring the amount of water in the soil. This can be done by using a soil moisture meter.

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(b) Tetra-nitro-phenol-tetra-iodo-sulphone-phthalein

This compound was prepared by adding to 1 g. of phenol-tetra-iodo-sulphone-phthalein a mixture of 10 c.c. concentrated nitric acid and 5 c.c. fuming nitric acid, and warming almost to boiling on the electric stove. After about half an hour the mixture was poured into water, washed, and recrystallized from ethyl alcohol.

The compound crystallizes in small brown crystals, melting with decomposition at 190°C . It dyes silk (and the experimenter's hands) a peculiar greenish-black. This color can be used as a test for protein, but is no more sensitive than some of the tests already in use.

It may be analyzed for nitrogen by the Kjeldahl method by the following modified procedure:



This compound was prepared by adding to 1 g. of hexachloro-
cyclohexane-1,2-diol a mixture of 10 c.c. concentrated sulfuric acid
and 5 c.c. fuming nitric acid, and warming slightly in the
electric stove. After about half an hour the mixture was poured into
water, washed, and recrystallized from ethyl alcohol.

The compound crystallizes in small prisms, melting with
decoloration at 130°. It has mp 131 (and the experimental value)
a regular prismatic habit. This habit can be used as a test for purity,
but it is not certain that exactly the same habit is seen.

It may be analyzed for chlorine by the Volhard method by the following

method procedure:

To a weighed sample of the substance in a Kjeldahl digestion flask is added 20 c.c. of sulphuric acid. Then about 1 g. of zinc dust is gradually added, and the mixture gradually heated. When charring begins, a few crystals of copper sulphate and about 10 g. of potassium sulphate are added, and the digestion continued in the usual way. After the mixture has cooled, it is transferred quantitatively to a Kjeldahl distilling flask, water and 30% sodium hydroxide solution added, and the ammonia distilled off into a measured amount of standard acid, the excess of which is titrated with standard alkali. From the figures so obtained, the percentage of nitrogen in the substance can be calculated. The results were usually low, but good enough, it was felt, to identify the compound.

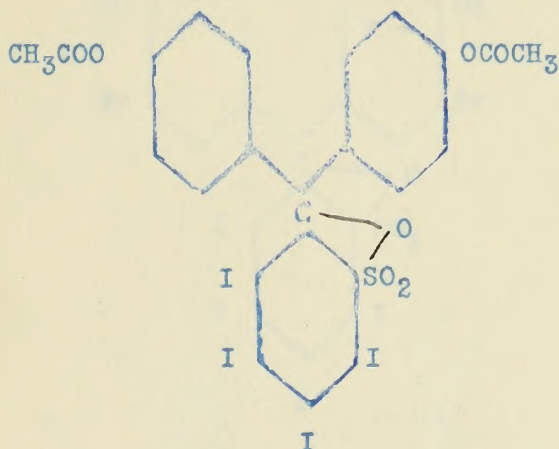
	<u>Found</u>	<u>Calculated</u>
N ₂	5.20	5.39
	5.23	

This compound is quite unsuitable as an indicator, and difficulty was experienced in determining its pH range. It probably lies between pH 6 and pH 7. The color in alkali is purple.

To a weighed sample of the substance in a standard solution
 which is added 20 c.c. of sodium hydroxide. The amount of acid
 that is produced is about, and the amount of sodium hydroxide
 required is 10 c.c. for a sample of 100 mg. of the substance
 of potassium chloride etc. added, and the amount of sodium
 hydroxide used. After the mixture has cooled, it is transferred
 to a standard solution flask, water and 20 c.c. of sodium hydroxide
 solution added, and the mixture diluted to 100 c.c. in a standard
 of standard acid, the excess of acid is titrated with standard alkali.
 From the figures so obtained, the percentage of chlorine in the sub-
 stance can be calculated. The results were usually low, but good
 enough, it was felt, to identify the compound.

Calculated	Found	
5.78	5.30	Cl
	5.12	

The compound is quite unstable as an indicator, and difficulty
 was experienced in determining its range. It properly lies between
 20 and 25. The color is blue in nature.

(c) Di-acetyl-phenol-tetra-iodo-sulphone-phthalein

Di-acetyl-phenol-tetra-iodo-sulphone-phthalein was prepared by boiling together 5 g. of phenol-tetra-iodo-sulphone-phthalein, 3 g. of freshly fused sodium acetate, and 15 c.c. of acetic anhydride for $1\frac{1}{4}$ hours. The mixture was poured onto ice. It was at first gummy, but solidified on standing over night. It was filtered off, washed with water, recrystallized from 95% ethyl alcohol.

The substance consists of light brown crystals, soluble in ethyl alcohol, methyl alcohol, acetic acid, acetone, practically insoluble in water. The melting point was 136°C .

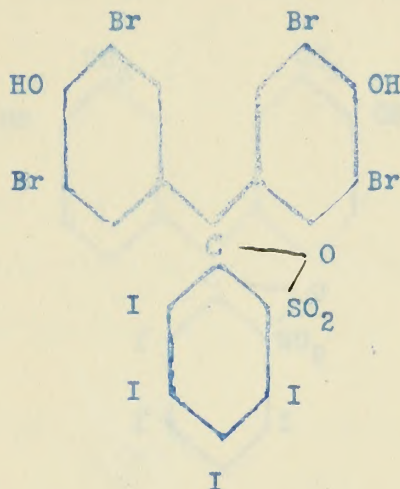
Analysis

	Found	Calculated
I_2	56.4	56.6%



11-oxo-1-phenyl-1,2,3,4-tetrahydronaphthalene was prepared by
boiling together 5 g. of phenyl-1,2,3,4-tetrahydronaphthalene, 5 g.
of triethylamine and 10 g. of acetic anhydride for
12 hours. The mixture was poured into 100 ml. of water and
the solidified product was washed with water, extracted with
ether, washed with 5% sodium bicarbonate solution in ether,
alcohol, washed with water, dried, and distilled. The boiling point was 140°
at 1 mm. The melting point was 110°.

Calculated	Found
84.82	85.2

(d) Tetra-brom-phenol-tetra-iodo-sulphone-phthalein.

This compound was made by dissolving 1 g. of phenol-tetra-iodo-sulphone-phthalein in about 20 c.c. of glacial acetic acid, and adding, while boiling, 1 g. of bromine, and boiling for half an hour. The compound was poured into water, washed, and recrystallized from glacial acetic acid.

It consisted of brown crystals, giving a green color in alkali, but its sodium salt was practically as insoluble in water as that of tetra-iodo-phenol-tetra-iodo-sulphone-phthalein, so it was not investigated further.

It dyes silk a greenish-brown color, similar to that of tetra-iodo-phenol-tetra-iodo-sulphone-phthalein, but greener.

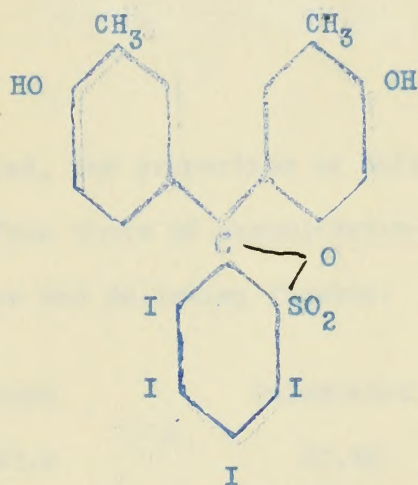


This compound was made by dissolving 1 g. of phenyl-ethyl-amine-oxide in 10 ml. of water, adding 10 ml. of 10% sodium hydroxide solution, and heating to boiling. The mixture was cooled, and the solid was washed with water. The solid was dried in a vacuum oven at 50°C. for 24 hours.

It consisted of small crystals, colorless to light yellow. The melting point was 100°C. (decoloration). It was not soluble in water, but soluble in alcohol, ether, and chloroform.

It gave a greenish-brown color, similar to that of formaldehyde, when treated with formalin.

4. ORTHO-CRESOL-TETRA-IODO-SULPHONE-PHTHALEIN



Preparation

The preparation of this compound does not differ in any essential particular from the preparation of phenol-tetra-iodo-sulphone-phthalein.

30 g. of ortho-cresol, which had been freshly distilled under reduced pressure, 9 g. of tetra-iodo-ortho-sulpho-benzoic anhydride, and 15 g. of fuming stannic chloride were heated to 160 - 165°C. for ten hours, the reaction mixture being protected from the moisture of the atmosphere as before. At the end of this time, the mixture was poured into about 1 L. of water, and washed repeatedly with hot water, being finally boiled with water, to remove the cresol. (The cresol is much more difficult to remove than the phenol from the preceding preparation, due to its relative insolubility in water, but the above procedure is preferable to any other which was tried, such as distillation under reduced pressure.)



Procedure

The oxidation of this compound does not differ in any essential particular from the preparation of phenol-formaldehyde-oxides.

0.5 g. of resorcinol, which had been freshly distilled under re-

duced pressure, 0.5 g. of ferric chloride was dissolved in 10 ml. of

10% of fuming sulfuric acid was heated to 100 - 120°. For two hours,

the reaction mixture was kept at this temperature for the oxidation of the resorcinol.

At the end of this time, the mixture was poured into about 1 l.

of water, and washed repeatedly with hot water, being finally washed with

water to remove the iron. (The product is very difficult to wash

from the glass flask, the procedure suggested, due to its solubility in

solubility in water, and the above procedure is not suitable to any other with

was tried, such as dilution with reduced pressure.]

When as much of the cresol had been removed as possible, the raw product was dissolved in about 2% sodium hydroxide solution, filtered, and reprecipitated with hydrochloric acid. This was repeated three or four times, the product washed with water, and recrystallized from glacial acetic acid.

Properties

As would be expected, the properties of this substance are not essentially different from those of phenol-tetra-iodo-sulphone-phthalein. Analysis for iodine gave the following figures:

	Found	Calculated
I	57.0	57.4%
2	57.2	

The sodium salt was found to be purple. It is not as soluble as the sodium salt of phenol-tetra-iodo-sulphone-phthalein, and the compound contains a smaller percentage of iodine, so no biological experiments were carried out with it.

Ortho-cresol-tetra-iodo-sulphone-phthalein has a pH range of pH 8.8 to 9.6, passing through various not very different shades of pink. It would probably not have any especial usefulness as an indicator.

The compound dyes silk shades similar to, and in fact practically indistinguishable from, those produced by phenol-tetra-iodo-sulphone-phthalein, ranging from a golden yellow to a walnut brown, depending on the method of application. But other conditions being the same, the shades produced by it are a trifle darker, as would be expected.

When an inch of the cream had been removed as possible, the new product was dissolved in about 20 sodium hydroxide solution, filtered, and reprecipitated with hydrochloric acid. This was repeated three or four times, the product washed with water, and reprecipitated from alcohol several times.

Properties

As would be expected, the properties of this substance are not essentially different from those of general-phenyl-ethane-quinoline. Analysis for sodium gave the following figures:

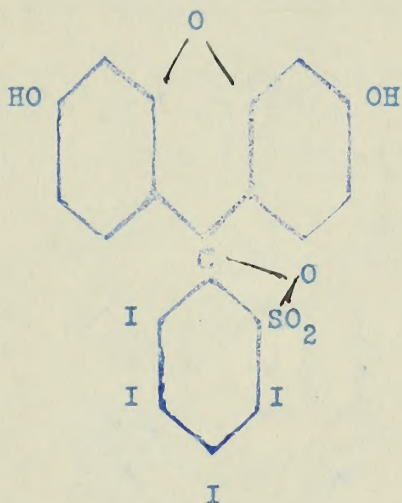
Calculated	Found
37.41	37.0
	37.2

The sodium salt was found to be purple. It is not as soluble as the sodium salt of general-phenyl-ethane-quinoline, and the compound contains a smaller percentage of sodium, as no biological experiments were carried out with it.

General-phenyl-ethane-quinoline has a range of 38.5 to 4.5, passing through various not very distinct shades of pink. It would probably not have any essential differences as an indicator. The compound gives a pink color similar to, and is not essentially indistinguishable from, those produced by general-phenyl-ethane-quinoline, varying from a golden yellow to a salmon color, depending on the method of application. But other conditions being the same, the shade produced by it is a little darker, as would be expected.

5. RESORCIN-TETRA-iodo-SULPHONE-PHTHALEIN

(Tetra-iodo-sulphone-fluorescein)



Preparation. This analogue of fluorescein and eosin was prepared in the following manner:

180 g. of resorcin, freshly distilled under reduced pressure, was melted, and 40 g. of tetra-iodo-ortho-sulpho-benzoic anhydride dissolved in it, 80 g. of fuming stannic chloride added, and the mixture, protected from the moisture of the air, heated to about 165° C. for ten hours. It was then poured into about 1.5 L. of water, and washed by decantation, finally being boiled with water. The boiling was stopped at intervals, the water poured off, the mass allowed to solidify, pulverized, washed by decantation, and boiled again with water. After as much purification as possible had been accomplished in this way (and it is important that

REPORT ON THE ANALYSIS OF THE SAMPLE

(The following information is for your information)



Preparation. This analysis of the sample was prepared in

the following manner:

100 g. of sample, freshly distilled water, 100 ml. of
water, and 50 g. of 10% sodium hydroxide solution dissolved
in 100 ml. of 50% sodium hydroxide solution, and the mixture, introduced
from the bottom of the flask, heated to about 100°C. for one hour. It
was then poured into about 100 ml. of water, and washed by decantation,
thoroughly with water. The solid was dried at 100°C., and
the water washed off, and was allowed to solidify, pulverized, and
by decantation, and dried again in water. After a few minutes
the particles had been recognized in this way (and it is important that

this treatment should be very thorough), the residue was dissolved in 2% sodium hydroxide, filtered, precipitated by the addition of hydrochloric acid, washed with water, boiled with water, and the solution in alkali repeated. After a sufficient amount of such preliminary treatment (which cannot be replaced by later treatment with bone-black), the substance can be recrystallized from glacial acetic.

The crystals come out practically black, and when they are filtered off and spread out to dry a curious phenomenon occurs. The crystals, which could be seen to have definite crystalline form, and felt to be firm, which may be sucked perfectly dry on the filter, and even washed with water or ether, when spread out to dry slowly melt down into a viscous liquid, which smells of acetic acid, and which eventually hardens into a black mass like deKhotinsky cement or Bakelite. This finally becomes hard enough to be ground to a powder, and it was such preparations that were used for the further study of this compound. Repeated recrystallization apparently did not improve the compound in this respect in the slightest.

Properties of resorcin-tetra-iodo-sulphone-phthalein.

This compound is soluble in the usual solvents; acetone, ethyl alcohol, methyl alcohol, ethyl acetate, chloroform, glacial acetic acid. It is slightly soluble in ether, and dissolves in water to a sufficient extent to form a dye bath. Its appearance, prepared as described above, was that of a black solid, with a greenish sheen. When dissolved in alkali it gives a red solution with a splendid greenish fluorescence.

This treatment should be very thorough, the solution was dissolved in

It is a very strong solution, prepared by the addition of 10-

grams of sodium hydroxide to 100 ml of water, boiled with water, and the solution

is added to the solution. After a sufficient amount of acid has been

added (which amount is indicated by later treatment with potassium

the substance can be reprecipitated from the solution.

The crystals form out immediately after, and they are filtered

off and dried on a dry surface, without changing color. The crystals

which could be seen in some details of crystallization form, and they are

which are filtered perfectly dry on the filter, and even washed with water

or ether, when turned out in dry state into a clean flask.

When crystals are washed with water, and which usually contain a small amount

the substance is washed with water. This usually contains some amount of

be found to be present, and it was not preparation that was used for the

further study of this compound. The crystals were reprecipitated by

not improve the substance in this respect in the experiment.

Preparation of sodium hydroxide in the laboratory

This experiment is similar to the one described above, when

aluminum, sodium chloride, sodium hydroxide, sodium carbonate, and

it is a mixture of sodium hydroxide in ether, and this mixture is used in a

amount to form a dry salt. The experiment is prepared as described above.

and that of a thick white, with a greenish color. The crystals in which

it is a very strong solution of a slightly greenish color.

1911
1912

Its pH range is about pH 8 - pH 10, but it would be quite useless as an indicator, as the change in color is not great, and takes place over a wide range.

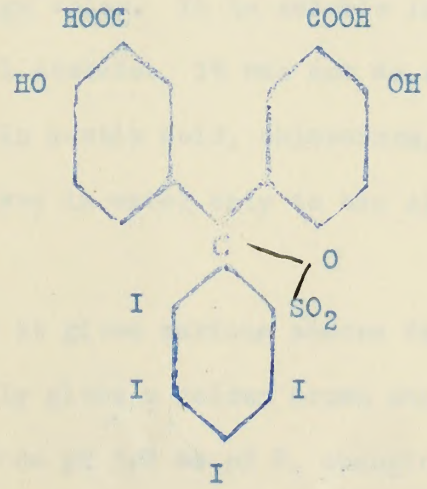
The compound dyes silk a rather handsome golden reddish-brown, with a faint fluorescence.

The solubility of its sodium salt is less than that of phenol-tetra-iodo-sulphone-phthalein, and it consequently has less promise as a possible means of visualizing the kidney.

Analysis. Analysis gave the following figures:

	Found	Calculated
I ₂	58.4%	58.4%

6. SALICYLIC-ACID-TETRA-IODO-SULPHONE-PHTHALEIN



Salicylic -acid-sulphone-phthalein was probably made for the first time in 1898 by Sohon¹, but has been recently rediscovered², like many

¹ Am. Ch. J. 20, 269, (1898)

² JACS 49, 3139 ('27)

The pH curve is shown in Fig. 10, but it would be quite useless as an indicator, as the change in color is not great, and takes place over a wide range.

The compound gives off a rather pungent rather reddish-brown, with a faint fluorescence.

The solubility of the sodium salt is less than that of methyl-ortho-into-naphthoquinone, and its conductivity has been found to be a possible means of measuring the amount.

Analysis. Analysis gave the following figures:

Calculated	Found	
58.42	58.42	1
		2

1. METHYL-ORHO-INTO-NAPHTHOQUINONE



Methyl-ortho-into-naphthoquinone was probably made for the first time in 1898 by Schott¹, but has been recently rediscovered² in the way

¹ Ann. Chem. Phys. (1898)

² Ann. Chem. Phys. (1927)

of the phthaleins. The two acid groups seemed to make it an interesting member of the series to include, so salicylic acid-tetra-iodo-sulphone-phthalein was made.

Preparation. 70 g. of pure, white salicylic acid was melted and 15 g. of tetra-iodo-ortho-sulpho-benzoic anhydride dissolved in it. Then 55 g. of fuming stannic chloride were added, and the mixture heated, protected from the moisture of the air, to 165° - 170°C. for twenty hours. It was treated like the crude resorcin-tetra-iodo-sulphone-phthalein with water, but although there was a larger proportion of impurity present, it was easier to purify. It proved easiest to recrystallize it from a mixture of alcohol and acetic acid, as it did not seem to be as soluble in pure acetic acid as resorcin-^{or}phenol-tetra-iodo-sulphone-phthalein.

Properties. The **product** so obtained consists of small, imperfect crystals of a rose-beige color. It is soluble in ethyl alcohol, methyl alcohol, acetone, ethyl acetate. It was not as soluble as the other members of this group in acetic acid, chloroform, and ether. As in the other cases, it dissolves in water only to the slight extent necessary to form a dye bath.

When dyed on silk it gives various shades depending on the mode of application, but usually gives a golden brown which is quite attractive.

Its pH range is from pH 7.2 to pH 8, changing from a yellowish-brown to a pinkish-purple. It would probably prove a moderately satisfactory indicator.

It was thought that the compound might have a special interest as a precipitant for calcium, but such work as was done did not give any promise of a lead toward a satisfactory micro-calcium method, as the magnesium salt was also quite insoluble.

Analysis

	Found	Calculated
I ₂	54.6	54.7%



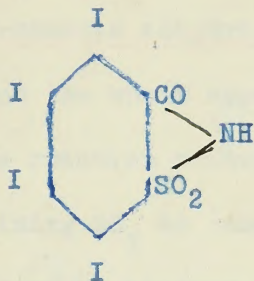
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It was thought that the amount of light from a special lamp
as a replacement for natural light would be the same as the
amount of light from a natural lamp. The results of the
experiments with the special lamp are as follows:

Results

Light intensity	100	100
Light intensity	100	100

7. TETRA-IODO-SACCHARIN

This compound is not really a member of the present series, but sacchareins¹ (compounds analogous to the phthaleins, but having a NH group instead of the lactone O of the phthalein) have been prepared from saccharin, as have also phthaleins themselves¹. Therefore, since saccharin was known to be eliminated through the kidneys², it seemed to be of considerable interest to synthesize tetra-iodo-saccharin.

¹ C 1899, I 718

Momnet and Cattier, Bl. (3) 17 690 (C 97)

Sisley, C 1897, II 847

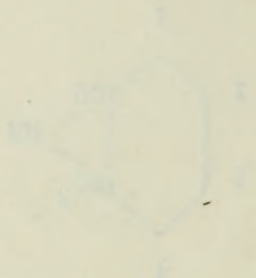
Remsen, Am. Ch. J. 6, 180 (84), 11, 73 (89)

Schon, Am. Ch. J. 20, 257 (98)

Dutt, Soc. 121, 2389 (22)

² Sollmann, "A Manual of Pharmacology", W. B. Saunders Co.,

Phila., 1926. p. 67.



This report is a preliminary report on the results of the work done during the past few months in the laboratory of the Department of Chemistry, University of California, Berkeley, California. The work was done under the direction of Professor R. S. Stein, and the assistance of Miss M. L. Huggins, Miss J. E. Huggins, and Miss M. J. Huggins. The work was supported by the National Science Foundation, Grant No. 100-100-100-100.

- 1. Stein, R. S., Huggins, M. L., Huggins, J. E., and Huggins, M. J., *J. Chem. Phys.*, **19**, 100 (1951).
- 2. Stein, R. S., Huggins, M. L., Huggins, J. E., and Huggins, M. J., *J. Chem. Phys.*, **20**, 100 (1952).
- 3. Stein, R. S., Huggins, M. L., Huggins, J. E., and Huggins, M. J., *J. Chem. Phys.*, **21**, 100 (1953).
- 4. Stein, R. S., Huggins, M. L., Huggins, J. E., and Huggins, M. J., *J. Chem. Phys.*, **22**, 100 (1954).
- 5. Stein, R. S., Huggins, M. L., Huggins, J. E., and Huggins, M. J., *J. Chem. Phys.*, **23**, 100 (1955).

Preparation. 25 g. of pure saccharin (Merck), 100 c.c. of fuming sulphuric acid containing 50% free SO₃, and 70 g. of pure, powdered iodine, were heated to 120° C. for about four hours, then heated to 175° C. for twenty minutes. The same apparatus described for tetra-iodo-ortho-sulpho-benzoic anhydride was used. The source of heat was then removed, and the whole apparatus allowed to cool to room temperature, and the reaction mixture was poured into water and washed with water containing SO₂ to remove the excess iodine. The crude product was dissolved in acetone, filtered, and concentrated. The compound crystallized easily from this concentrate, giving silky yellow crystals with a greenish tinge.

Properties. The silky greenish-yellow crystals of tetra-iodo-saccharin are somewhat soluble in acetone, and practically insoluble in everything else, including sodium hydroxide solution. The sodium salt is so insoluble that no attempts were made to use this compound biologically. It has a faint, bitter taste.

The crystals did not melt or otherwise alter even at 345° C. They contained carbon, iodine, sulphur, and nitrogen, as demonstrated by the usual tests. Analysis for nitrogen was carried out by the Kjeldahl method, a rather long time being required for digestion.

	Found	Calculated
N ₂	1.99	2.03%

Experiment 1. In a series of four experiments, the effect of temperature on the rate of reaction between hydrogen peroxide and potassium iodide was studied. The rate was measured by the volume of oxygen gas evolved in a fixed time. The results are shown in the following table.

Temperature (°C)	Volume of oxygen (cm ³)
10	10
20	20
30	40
40	80

Experiment 2. The effect of concentration on the rate of reaction between hydrogen peroxide and potassium iodide was studied. The rate was measured by the volume of oxygen gas evolved in a fixed time. The results are shown in the following table.

Concentration (M)	Volume of oxygen (cm ³)
0.1	10
0.2	20
0.4	40

The results show that the rate of reaction increases with both temperature and concentration. This is because the molecules have more energy and are more likely to collide and react.

Temperature (°C)	Volume of oxygen (cm ³)
10	10
20	20
30	40
40	80

Attempts to condense this substance with phenolic substances were made, using as condensing agents fuming stannic chloride, zinc chloride, and concentrated sulphuric acid. They were all failures, no substance having the properties of an indicator ever being produced. The steric hindrance caused by the four massive iodine atoms has completely wiped out the reactivity of the benzoic-imide group. One might be tempted to say that here we have a compound containing carbon, nitrogen, hydrogen, sulphur, oxygen, and iodine, arranged in the most stable configuration possible, but though it is improbable, new classes of simple organic compounds may remain to be discovered, and the statement might be a rash one to make.

Abstract to summarize this abstract of the general relations with
math, with an emphasis upon the general relations, the abstract
and somewhat separate side, they are all related, so abstract
under the properties of an abstract over their abstract. The abstract
abstract comes by the fact that the abstract is an abstract
and the reality of the abstract is the abstract. The abstract is
the abstract and the abstract is the abstract. The abstract is
abstract, abstract, and abstract, abstract in the abstract. The abstract
abstract, but though it is abstract, the abstract of abstract
abstracts are really to be abstract, and the abstract is a
and the abstract.

8. THYMOL-TETRA-iodo-SULPHONE-PHTHALEIN
9. ANTHRAQUINONE-TETRA-iodo-SULPHONE-PHTHALEIN
10. PYROGALLOL-TETRA-iodo-SULPHONE-PHTHALEIN

Attempts were made to prepare these compounds from tetra-iodo-ortho-sulpho-benzoic-anhydride, using various condensing agents, but the attempts were all failures, no substance having the properties of a phthalein ever being produced in any of them. It is easier to understand why these substances could not be made than it is to explain it in words. But in general, as the phenolic molecule becomes more complex, condensation with anhydrides, and especially the heavy tetra-iodo-ortho-sulpho-benzoic anhydride molecule, where steric hindrance must be considerable, becomes excessively difficult.

It is not intended to imply that the above compounds can not be prepared, and indeed, the author believes that, had occasion demanded, he could have made them a part of the present study, preparing them from more active parent substances, such as tetra-iodo-ortho-sulpho-benzoic anhydride di-chloride.

1. The first part of the report is devoted to a general survey of the situation in the country. It is followed by a detailed analysis of the economic and social conditions. The third part contains the author's conclusions and recommendations. The fourth part is a list of references.

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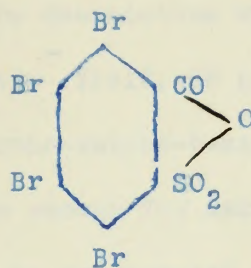
It is not intended to imply that the above mentioned are the only factors which influence the economic and social development of the country. There are many other factors which are not mentioned in this report. The author is aware of this and has tried to mention the most important ones.

B. BROMINATED SULPHONE-PHTHALEINS



[The following text is extremely faint and largely illegible due to fading. It appears to be a multi-paragraph description of the synthesis and properties of the brominated sulfone-phthaloin compound.]

1. SECTION NO. 1000-1000000

1. TETRA-BROM-ORTHO-SULPHO-BENZOIC ANHYDRIDE

Preparation. 25 g. of ortho-sulpho-benzoic anhydride (Eastman, practical grade), 1 g. of iodine, and 125 c.c. of fuming sulphuric acid containing 50% free SO_3 were mixed together in a long necked flask of about 300 c.c. capacity. The same set-up was used as in the preparation of tetra-iodo-ortho-sulpho-benzoic anhydride. About 39 c.c. of bromine was measured out into a flask, and added as described.

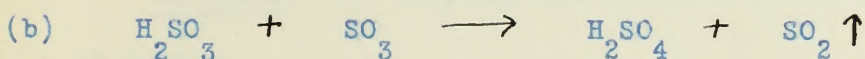
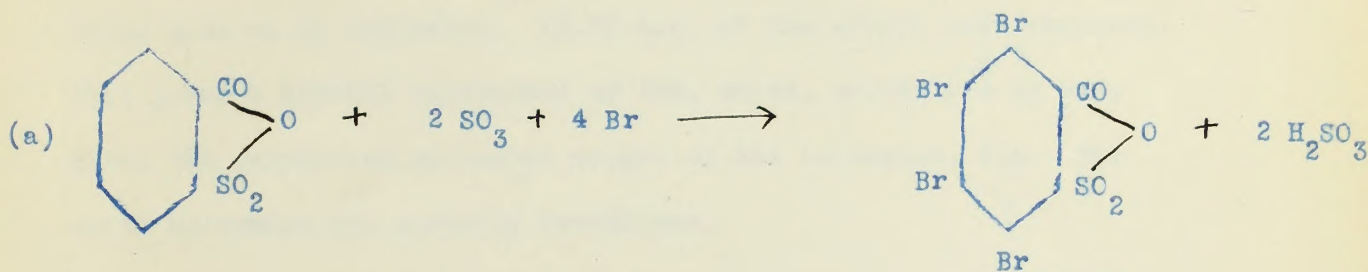
About two-thirds of the bromine was added, and the mixture heated to 80°C . in an oil bath until the bromine was all absorbed. The apparatus was then allowed to cool to room temperature, when about two-thirds of the remaining bromine was added, and the mixture heated to 100°C . until the bromine was absorbed, as before. The apparatus was again allowed to cool, two-thirds of the remaining bromine added, the mixture heated to 130° until the absorption of the bromine took place, and again allowed to cool. The next time all of the remaining bromine was added, and the mixture heated to 170°C . for thirty minutes, and finally allowed to cool.



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When cold the reaction mixture was poured into water, and the solid repeatedly washed by decantation with water containing a little sulphurous acid, and dried. Yield, 56 g. = 81%, calculated on the basis of the amount of ortho-sulpho-benzoic anhydride used. The compound so obtained is pure enough for making the phthaleins.

The preparation may be represented as follows. The iodine plays the part of a "carrier", but has not been included in the equation.



Purification. The substance is much more tractable than the corresponding iodine compound, and may be easily recrystallized from glacial acetic acid. The addition of alcohol is not necessary, as it is sufficiently soluble in the acid alone.

Properties

Color. The crystals obtained after washing and drying the crude preparation have a faint brownish color, which deepens on exposure to the light; but the pure compound, (recrystallized three times from glacial acetic acid) is pure white. The crystals are easily seen under the low power of the microscope as small, imperfect, hexagonal prisms.

The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the series $\sum_{n=0}^{\infty} a_n x^n$. It is shown that $f(x)$ is analytic in the region $|x| < 1$ and that it satisfies the functional equation $f(x) = 1 + x f(x^2)$. The function $f(x)$ is also shown to be the generating function of the sequence a_n .

$$f(x) = \sum_{n=0}^{\infty} a_n x^n = 1 + x f(x^2) = 1 + x \sum_{n=0}^{\infty} a_n x^{2n} = 1 + \sum_{n=0}^{\infty} a_{2n+1} x^{2n+1} + \sum_{n=0}^{\infty} a_{2n} x^{2n}$$

$$a_{2n+1} = a_{2n} \quad \text{for } n \geq 0$$

It is also shown that the function $f(x)$ is the unique solution of the functional equation $f(x) = 1 + x f(x^2)$ in the region $|x| < 1$. The function $f(x)$ is also shown to be the generating function of the sequence a_n .

The second part of the paper is devoted to the study of the properties of the function $g(x)$ defined by the series $\sum_{n=0}^{\infty} b_n x^n$. It is shown that $g(x)$ is analytic in the region $|x| < 1$ and that it satisfies the functional equation $g(x) = 1 + x g(x^2)$. The function $g(x)$ is also shown to be the generating function of the sequence b_n .

Melting Point After the recrystallized product had been dried in a desiccator to remove traces of acetic acid (which experience had already shown to be quite difficult to remove), the melting point of the compound was 219^o C. (uncorrected).

Molecular weight The molecular weight was determined by the neutral equivalent method. 0.7344 g. of the material was weighed out and titrated with 0.1450 N. hydrochloric acid, phenolphthalein being used as an indicator. 19.59 c.c. of the alkali were required. This gives a neutral equivalent of 258, which, multiplied by two, gives the calculated molecular weight of the substance, 516. The exact agreement was probably fortuitous.

Analysis. The compound was analyzed for bromine by the method of Carius.

	Found	Calculated
Br ₂	61.8	61.9%
	61.8	

Solubility. The substance is soluble in alcohol, acetone, glacial acetic acid, and to some extent in water.

Analysis The compound was analyzed for carbon by the method described in the literature. The results are given in Table I. The molecular weight was determined by the method of Rast. The results are given in Table II. The results are given in Table III.

Properties The compound is a white solid, melting at 100°C. It is soluble in benzene, chloroform, and carbon tetrachloride. The refractive index is 1.45. The density is 1.25. The results are given in Table IV. The results are given in Table V.

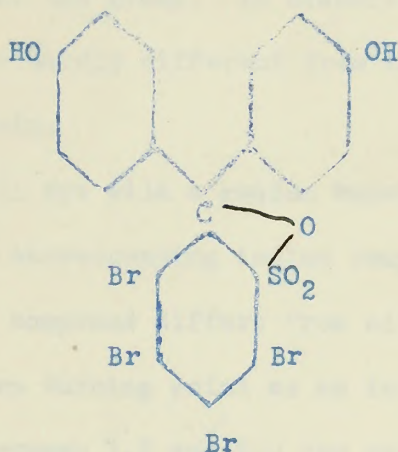
References The compound was analyzed for carbon by the method described in the literature.

Element	Found	Calculated
C	61.5	61.5
H	5.5	5.5

Conclusion The compound is a white solid, melting at 100°C. It is soluble in benzene, chloroform, and carbon tetrachloride. The refractive index is 1.45. The density is 1.25. The results are given in Table IV. The results are given in Table V.

Condensation of tetra-brom-ortho-sulpho-benzoic anhydride with phenolic substances.

For the purpose which primarily held the attention of the investigator, the brominated compounds did not offer the same chances of success as did the iodinated compounds, and though easier to study, were not worked out with the same thoroughness as the iodinated group. Therefore, for example, fuming stannic chloride was employed for all the condensations without making a series of tests with various condensing agents, as was done in the case of tetra-iodo-ortho-sulpho-benzoic anhydride.

2. PHENOL-TETRA-BROM-SULPHONE-PHTHALEIN

Preparation. 80 g. of phenol, which had been freshly distilled under reduced pressure, 20 g. of tetra-brom-ortho-sulpho-benzoic anhydride, and 20 g. of fuming stannic chloride were heated to 160°C. for five hours. The mixture was then poured into water, washed repeatedly by decantation and finally boiled with water, dissolved in about 2% sodium hydroxide, reprecipitated by the addition of hydrochloric acid, and this purification treatment repeated. Finally the crude product was dissolved in glacial acetic acid, filtered, concentrated, and allowed to stand. Reddish-black crystals were slowly deposited.



Preparation. 30 g. of alcohol, which had been freshly distilled
 under reduced pressure, 50 g. of formaldehyde, 10 g. of formalin, and 10 g. of
 sodium hydroxide, and 20 g. of formalin solution were heated at 100°C.
 for five hours. The mixture was then poured into water, washed with
 water, and extracted with ether. The ether extract was washed with
 water, dried over anhydrous calcium chloride, and distilled. The
 residue was then distilled under reduced pressure. The yield was
 10 g. of a colorless liquid, which was found to be formalin.

Properties. The recrystallized product consists of very small reddish-black crystals of high, but indefinite, melting point.

It is soluble in methyl alcohol, ethyl alcohol, acetone, ethyl acetate, chloroform, glacial acetic acid. It is practically insoluble in water, like all the group. It dissolves in alkaline solutions giving a purple color hardly different from that given by phenol-tetra-iodo-sulphone-phthalein.

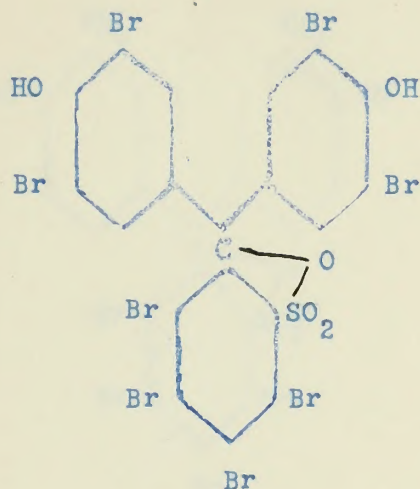
The compound will dye silk a golden brown shade very similar to that produced by the corresponding iodine compound.

This particular compound differs from all the others investigated in having a very sharp turning point as an indicator, or in other words, a short pH range. Between 7.2 and 8.0 the color changes from a light brown to a plum-purple, so abruptly that its turning point might almost be fixed at pH 7.4. It was felt that this substance might be of some value in titrations where an end point in this region is desired, but no work was done to ascertain how free it might be from the so-called protein and salt errors.

Analysis.

	Found	Calculated
Br ₂	47.5	47.7

Tetra-brom-phenol-tetra-brom-sulphone-phthalein



Preparation. This compound was prepared by dissolving 5 g. of phenol-tetra-brom-sulphone-phthalein in 100 c.c. of glacial acetic acid, adding 5 g. of bromine, and boiling the mixture for twenty minutes. It was then poured into water, washed, and recrystallized from glacial acetic acid.

Properties. The color of the compound so obtained is not very different from that of the parent compound. It is somewhat less soluble, especially in ether and chloroform.

It has a pH range of pH 5.6 - 7.0, but the color is some shade of bluish-green at all the hydrogen ion concentrations within this range, so its usefulness as an indicator would be practically zero.

It dyes silk a bluish green.

Analysis

	<u>Found</u>	<u>Calculated</u>
Br 2	65.3	65.2%

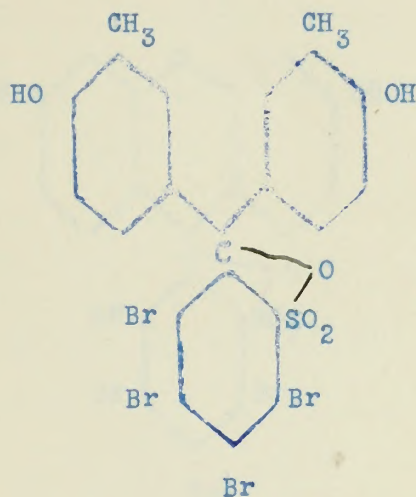


Preparation. This compound was prepared by heating 2 g of 2,2-dimethyl-1,3-dioxane-4-carboxylic acid in 100 ml of benzene solution, adding 5 g of water, and heating the mixture for twenty minutes. The white solid was washed, dried, and recrystallized from benzene solution.

Properties. The color of the compound is white to light yellow. It has a melting point of 100-105°C and a boiling point of 180°C. It is soluble in benzene, chloroform, and carbon tetrachloride. It is insoluble in water. The infrared spectrum shows a strong absorption at 1710 cm⁻¹ (C=O) and a weak absorption at 1640 cm⁻¹ (C=C). The NMR spectrum shows a multiplet at 7.2 ppm (aromatic H), a multiplet at 6.8 ppm (aromatic H), a multiplet at 6.4 ppm (aromatic H), a multiplet at 6.0 ppm (aromatic H), a multiplet at 5.6 ppm (aromatic H), a multiplet at 5.2 ppm (aromatic H), a multiplet at 4.8 ppm (aromatic H), a multiplet at 4.4 ppm (aromatic H), a multiplet at 4.0 ppm (aromatic H), a multiplet at 3.6 ppm (aromatic H), a multiplet at 3.2 ppm (aromatic H), a multiplet at 2.8 ppm (aromatic H), a multiplet at 2.4 ppm (aromatic H), a multiplet at 2.0 ppm (aromatic H), a multiplet at 1.6 ppm (aromatic H), a multiplet at 1.2 ppm (aromatic H), a multiplet at 0.8 ppm (aromatic H), a multiplet at 0.4 ppm (aromatic H).

Analysis

Found	Calculated
78.5%	78.5%
10.2%	10.2%
1.3%	1.3%

3. ORTHO-CRESOL-TETRA-BROM-SULPHONE-PHTHALEIN

Preparation. 100 g. of o-cresol, which had been freshly distilled under diminished pressure, 25 g. of tetra-brom-ortho-sulpho-benzoic anhydride, and 25 g. of fuming stannic chloride were heated to 165° C. for nine hours. The crude mass was purified with water, then by solution and reprecipitation with alkali and acid as usual, then re-crystallized from glacial acetic acid.

Properties. So far as they were investigated, they did not seem to be notably different from those of phenol-tetra-bromsulphone-phthalein.

Analysis

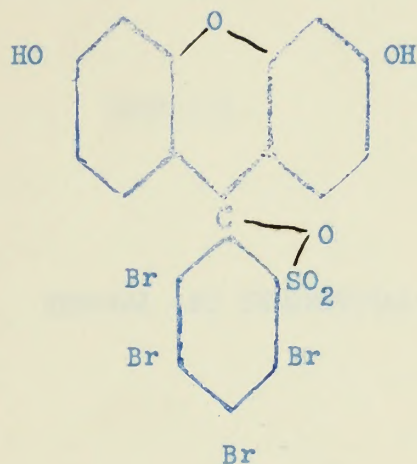
	Found	Calculated
Br ₂	45.6	45.7%



Procedure. 100 g. of a-100, which was previously
 washed with distilled water, 25 g. of extra-pure-sulfur-
 dioxide, and 25 g. of extra-pure-sulfur were placed in
 100 ml. of the water. The whole was then heated to 100°C.
 by boiling and the mixture was filtered and dried in a
 desiccator over anhydrous calcium chloride.

Procedure. 100 g. of a-100 were investigated, and the
 results are given in Table I.

<u>Table I</u>	
Sample	Yield
a-100	4.2

4. RESORCIN-TETRA-BROM-SULPHONE-PHTHALEIN

Preparation. 100 g. of freshly distilled resorcin, 30 g. of tetra-brom-ortho-sulpho-benzoic anhydride, and 30 g. of fuming stannic chloride were heated to 165°C . for ten hours. Treated with water, alkali and acid, and glacial acetic acid as usual.

Properties. The substance was a black solid, with a greenish sheen. It was soluble in the usual solvents, dissolving in alkali to give a red solution with a magnificent greenish fluorescence.

The substance dyed silk a light reddish brown which was rather attractive.

The substance was red in solution between the hydrogen ion concentrations of 10^{-8} and 10^{-10} , but did not possess any useful pH range, as the change was too gradual, and the color too complex.

Analysis.

	Found	Calculated
Br_2	46.5	46.7%

1. DISCUSSION OF THE EXPERIMENTAL PROCEDURE

It is shown in chapter 2 that the experimental results are in good agreement with the theoretical predictions of the theory of the photoelectric effect.

PART III

In the first part of the present chapter the general principles of the theory of the photoelectric effect are discussed.

GENERAL AND THEORETICAL

The general principles of the theory of the photoelectric effect are discussed in this chapter. It is shown that the experimental results are in good agreement with the theoretical predictions of the theory of the photoelectric effect.

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- (1) The general principles of the theory of the photoelectric effect are discussed in this chapter.
- (2) It is shown that the experimental results are in good agreement with the theoretical predictions of the theory of the photoelectric effect.
- (3) The general principles of the theory of the photoelectric effect are discussed in this chapter.
- (4) It is shown that the experimental results are in good agreement with the theoretical predictions of the theory of the photoelectric effect.

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A. COMPARISON WITH THE CORRESPONDING HALOGENATED PHTHALEINS

It is natural to compare these compounds with the corresponding compounds prepared by Pratt¹. They differ from them only in that a $\overset{|}{\underset{|}{\text{S}}}\text{O}_2$ group has been substituted (by roundabout methods, certainly) for a $\overset{|}{\underset{|}{\text{C}}}\text{O}$ group.

In the first place, the sulpho-compounds are throughout much harder to prepare. The author prepared for this work by repeating a large part of the work of Pratt, and makes this statement with confidence, even with feeling. And having been prepared, they are much harder to purify. This is due partly to a large number of by-products being formed, but principally to the fact that the compounds, perhaps because of greater asymmetry in the molecule, are naturally reluctant to form crystals.

The crystals of tetra-iodo-phthalic anhydride and of tetra-brom-phthalic anhydride are larger and better formed than those of the corresponding sulpho-compounds. These substances have a lighter, more fluffy feel than the rather sticky, amorphous sulpho-compounds.

It is proposed in the following pages to compare the two classes of compounds point by point.

¹ Pratt and Perkins, JACS 40, 198 (18)
Pratt and Shupp, JACS 40, 257 (18)
Pratt JACS 40, 1416 (18)
 41, 1290 (19)

Color. Tetra-iodo-ortho-sulpho-benzoic anhydride is about the same color (yellow) as tetra-iodo-phthalic anhydride, and the tetra-brom compounds are both colorless when pure. But the sulphone-phthaleins derived from tetra-iodo-ortho-sulpho-benzoic anhydride and from tetra-brom-ortho-sulpho-benzoic anhydride are dark red, almost black, in color, while the corresponding phthaleins are light yellow. It is possible that there is normally enough of the quinoid form present in the (otherwise pure) sulphone-phthalein to account for this difference. In that case, the sulpho-group would have produced a shift in the lactoid-quinoid equilibrium, in favor of the quinoid form. Support for this idea is found in the data presented under the next two points.

Color of the sodium salts. (color in alkali) The color of the phthaleins in alkali is practically indistinguishable from that of the corresponding sulphone-phthalein, so that the difference introduced in this respect is slight. But the alkali color is developed at a lower pH. Pratt does not report pH ranges in his papers, but the author of this thesis has determined the pH ranges of two of his compounds. They are herewith compared with the corresponding compounds of the present series.

<u>Compound</u>	<u>pH Range</u>	<u>Color</u>
(phenol-tetra-iodo-phthalein	9.0 - 9.6	Purple
(<u>phenol-tetra-iodo-sulphone-phthalein</u>	7.0 - 8.2	"
(tetra-iodo-phenol-tetra-iodo-phthalein	8.4 - 9.2	Blue
(<u>tetra-iodo-phenol-tetra-iodo-sulphone-phthalein</u>	6.2 - 7.0	"

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Color the substances dye silk. This is associated with the shift in turning point. The two phthaleins above mentioned, when applied to silk from a 5% acetic acid bath, leave it to casual inspection unchanged, though the application of alkali shows that the phthalein is attached to the silk, but in its colorless state. The corresponding sulphone-phthaleins, on the other hand, color silk, respectively golden yellow and brownish-green. It seems logical to suppose that the phthalein or sulphone-phthalein attached to the silk has the color which it would display in a solution of pH corresponding to the isoelectric point of the proteins of the silk. If this theory is true, the iso-electric point of silk proteins can be determined, from the above observations only, to lie between pH 7 and pH 8, probably at pH 7.2. This checks with the colors on silk given by the other sulphone-phthaleins. A summary of pH ranges, and of colors, is given at the end of this discussion.

Toxicity. It has been difficult to find data on the toxicity of these compounds. Phenol-tetra-iodo-phthalein is ordinarily administered intravenously in doses of about 40 mg. per Kg. of body weight in cholecystography, and while not dangerous, sometimes gives the patient a bad afternoon. Doses of as much as 120 mg. per Kg. of body weight of phenol-tetra-iodo-sulphone-phthalein have been injected intravenously into rabbits without any apparent damage either temporary or permanent, but of course the rabbit was not asked how he felt. It is probable, in view of such work as has been done, that the sulphone-phthaleins are certainly not more toxic than the corresponding phthaleins.

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Fate in the body. The p~~h~~thaleins are said to be excreted in the bile¹, and the sulphone-phthaleins, in part at any rate, in the urine². This is borne out by the author's work, described under phenol-tetra-iodo-sulphone-phthalein.

¹ Vamossy, Ther. Gegenw. 43, 203 (02)

Rosenthal and White, J. Pharm. 24, 265, (24)

² Abel and Rowntree, J. Pharm. and Exp. Ther. 1, 231 (09)

Page 10 of 10 - The following are the results of the
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B. SUMMARY OF PROPERTIES OF THE NEW SERIES

pH Ranges

<u>Compound</u>	<u>pH Range</u>
<u>phenol-tetra-iodo-sulphone-phthalein</u>	7.0 - 8.2
<u>o-cresol-tetra-iodo-sulphone-phthalein</u>	8. - 9.
<u>resorcin-tetra-iodo-sulphone-phthalein</u>	8. -10.
<u>tetra-nitro-phenol-tetra-iodo-sulphone-phthalein</u>	6. - 7.
<u>tetra-iodo-phenol-tetra-iodo-sulphone-phthalein</u>	6.2 - 7.0
<u>salicylic-acid-tetra-iodo-sulphone-phthalein</u>	7.2 - 8.6
<u>phenol-tetra-brom-sulphone-phthalein</u>	7.2 - 8.0
<u>tetra-brom-phenol-tetra-brom-sulphone-phthalein</u>	5.6 - 7.0
<u>resorcin-tetra-brom-sulphone-phthalein</u>	8. -10.

Color on silk The compounds were dyed on silk from a 5% acetic acid bath, usually, but sometimes from pure acetic acid. Where the turning point of the alkali was near the (assumed) iso-electric point of the silk proteins, it was sometimes possible to obtain a different shade by dyeing the compound on from a weak alkaline bath containing a large amount of sodium chloride. Samples of the cloth are given on the next page.

The author is of course not skilled in the application of dyestuffs, and much better results could have been obtained by a worker with practical experience, without any doubt.

Black marks on the bits of cloth are not due to the dye, but are marks made to identify the dye used, before the cloth was pasted into the typescript.

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phenol-tetra-iodo-sulphone-phthalein

(from 5% acetic acid)



o-cresol-tetra-iodo-sulphone-phthalein

(5% acetic acid)



resorcin-tetra-iodo-sulphone-phthalein

(5% acetic acid)



salicylic-acid-tetra-iodo-sulphone-
phthalein

(5% acetic acid)



tetra-nitro-phenol-tetra-iodo-
sulphone-phthalein

(5% acetic acid)



tetra-brom-phenol-tetra-iodo-
sulphone-phthalein

(5% acetic acid)



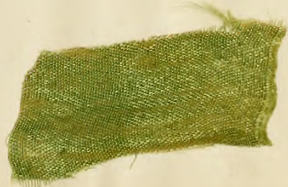
tetra-iodo-phenol-tetra-iodo-
sulphone-phthalein

(5% acetic acid)



tetra-iodo-phenol-tetra-iodo-
sulphone-phthalein

(sodium chloride and weak alkali)



phenol-tetra-brom-sulphone-phthalein

(5% acetic acid)



tetra-brom-phenol-tetra-brom-

sulphone-phthalein

(5% acetic acid)



resorcin-tetra-brom-sulphone-phthalein

(5% acetic acid)



Pratt's compounds on silk

For comparison, a few examples are given of other phthaleins, including two of the group prepared by Pratt, dyed on silk under similar conditions.

phenol-tetra-iodo-phthalein

(5% acetic acid)



tetra-iodo-phenol-tetra-
iodo-phthalein

(weak alkali and sodium chloride)



tetra-iodo-resorcin-phthalein

(5% acetic acid)



Table 1. Summary of data

For comparison, a few examples are given of other substances, including two of the group prepared by Prof. [Name], that are still under similar conditions.

Acetyl-phenyl-iodo-ethyl-amine
(1.5% acetic acid)

Acetyl-phenyl-iodo-ethyl-amine
(1.5% acetic acid)

Acetyl-phenyl-iodo-ethyl-amine
(1.5% acetic acid)

Color in alkaline solutions.

No attempt is made to make the names of the colors more than merely suggestive.

<u>Compound</u>	<u>Color</u>
<u>phenol-tetra-iodo-sulphone-phthalein</u>	purple
<u>o-cresol-tetra-iodo-sulphone-phthalein</u>	purple
<u>resorcin-tetra-iodo-sulphone-phthalein</u>	red with strong greenish fluorescence.
<u>salicylic-acid-tetra-iodo-sulphone-phthalein</u>	pink
<u>tetra-brom-phenol-tetra-iodo-sulphone-phthalein</u>	bluish-green
<u>tetra-iodo-phenol-tetra-iodo-sulphone-phthalein</u>	green
<u>phenol-tetra-brom-sulphone-phthalein</u>	purple
<u>o-cresol-tetra-brom-sulphone-phthalein</u>	purple
<u>resorcin-tetra-brom-sulphone-phthalein</u>	red with strong greenish fluorescence
<u>tetra-brom-phenol-tetra-brom-sulphone-phthalein</u>	blue

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Effect of substitution in the sulphone-phthaleins

Color. It is well known that the general effect of substitution of heavy atoms or groups in a compound is to shift the absorption bands in the direction of decreasing frequency. (See the references to Pratt's work, or the numerous references given to work on absorption spectra in the introduction to this thesis) Thus a colorless (apparently) substance may be colored after heavy groups have been substituted in it, because the absorption-bands have been shifted from the ultra violet into the visible spectrum. These ideas find qualitative support in the progression of the colors in alkali of phenol-tetra-iodo-sulphone-phthalein (purple or violet), tetra-brom-phenol-tetra-brom-sulphone-phthalein (blue), tetra-brom-phenol-tetra-iodo-sulphone-phthalein (bluish-green), and tetra-iodo-phenol-tetra-iodo-sulphone-phthalein (green).

More than this apparently cannot be said, and the writer has been assured by one of the workers in the field of the new quantum mechanics that the quantitative explanation of the color of organic compounds might be impossible, and at any rate could not be affected in the present state of our knowledge.

The light reflected by an organic compound is of course very complex, and only analysis of it by a photospectrometer would be even approximately objective.

Toxicity. Apparently the substitution in the phthalein molecules of any groups which are firmly bound does not greatly increase the toxicity of the compound. 0.5 g. of phenolphthalein is a large dose, but 6 to 7 g. of tetra-iodo-phenol-phthalein or phenol-tetra-iodo-phthalein can be administered. Even if the weight of the phthalein skeleton only be considered, there is still a much greater tolerance for the iodine-substituted-compound. Exact figures are lacking, but similar relations obtain in the sulphone-phthalein-series.

Fate in the body. There is some evidence that although phenol-sulphone-phthalein is practically completely excreted in the urine¹, the highly substituted phenol-sulphone-phthaleins, due probably to masking of the sulphone-group, which is kidney-specific, if the use of such a term may be permitted, are not so completely eliminated in the urine. This agrees with the observations of the present writer. See data under phenol-tetra-iodo-sulphone-phthalein.

Solubility The solubility of the sulphone-phthaleins themselves in organic solvents and of their alkali salts in water, is greatly diminished by halogen substitution.

Opacity to X-rays. As mentioned before, opacity to X-rays is merely a matter of mass, so the substitution of the halogen enormously increases the opacity to X-rays exhibited by the compounds.

¹ Abel and Rowntree, J. Phar. and Exp. Ther. 1, 231 (09)
 Rowntree and Geraghty, J. Pharm. and Exp. Ther. 1, 579 (10)

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The following are the main results of the present investigation:

1. The effect of the concentration of the solution on the rate of reaction was studied by varying the concentration of the reactants.

2. The effect of the temperature on the rate of reaction was studied by varying the temperature of the reaction mixture.

3. The effect of the presence of a catalyst on the rate of reaction was studied by comparing the rate of reaction with and without the catalyst.

4. The effect of the surface area of the solid reactant on the rate of reaction was studied by varying the surface area of the solid reactant.

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(The abbreviations used in this thesis are discussed in a note preceeding the introduction, q.v.)

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Section 1 - "The purpose of this Act is to provide for the better regulation of the business of insurance companies in this State."

Section 2 - "The Board of Insurance Commissioners shall be composed of five members, to be appointed by the Governor, one of whom shall be the Governor himself."

Section 3 - "The Board of Insurance Commissioners shall have the honor and title of 'The Board of Insurance Commissioners of the State of New York'."

Section 4 - "The Board of Insurance Commissioners shall hold office for a term of five years, and shall be eligible for re-appointment."

Section 5 - "The Board of Insurance Commissioners shall meet at the State Capitol at Albany, New York, on the first day of January next, and thereafter on the first day of January in each and every year thereafter."

Section 6 - "The Board of Insurance Commissioners shall have the right to call and receive from any insurance company in this State such information and documents as may be necessary for the proper discharge of its duties."

Section 7 - "The Board of Insurance Commissioners shall have the right to examine the books and accounts of any insurance company in this State, and to require the production of the same."

Section 8 - "The Board of Insurance Commissioners shall have the right to suspend or revoke the license of any insurance company in this State, and to require the company to pay the costs of such suspension or revocation."

Section 9 - "The Board of Insurance Commissioners shall have the right to make and enforce such rules and regulations as may be necessary for the proper discharge of its duties."

Section 10 - "The Board of Insurance Commissioners shall have the right to sue and be sued, and to defend itself in any court of law or equity."

Section 11 - "The Board of Insurance Commissioners shall have the right to employ such clerks and other personnel as may be necessary for the proper discharge of its duties."

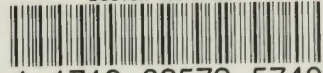
Section 12 - "The Board of Insurance Commissioners shall have the right to receive from the State such compensation as may be provided by law."

Section 13 - "The Board of Insurance Commissioners shall have the right to receive from any insurance company in this State such compensation as may be provided by law."

Section 14 - "The Board of Insurance Commissioners shall have the right to receive from any insurance company in this State such compensation as may be provided by law."

Section 15 - "The Board of Insurance Commissioners shall have the right to receive from any insurance company in this State such compensation as may be provided by law."

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