

prepared as described above and treated with an excess of 6 *M* ammonium hydroxide solution. The anhydride rapidly dissolved. The solution was evaporated to dryness under reduced pressure and the residue condensed with ammonium thiocyanate and acetic anhydride as described for the corresponding anilide. A little water (5 cc.) was added to destroy the excess acetic anhydride and the solution was again evaporated nearly to dryness under reduced pressure. On addition of water, the product separated. It was difficultly soluble in cold water, and could be conveniently crystallized from hot water, in which its solubility was about 1%; m. p. 208–209°.

*Anal.* (Micro-Kjeldahl). Calcd. for  $C_9H_{11}O_3N_3S$ : N, 18.35. Found: N, 18.51.

### Summary

1. Some new thiohydantoin derivatives of glutamic acid are described. Their formation is considered to show that the dehydration of acetylglutamic acid by acetic anhydride forms the true acetylglutamic anhydride, and not an azlactone.

2. When this anhydride reacts with amines, amide formation takes place at the carboxyl group most distant from the amino group. It is planned to extend the application of this reaction to the synthesis of  $\gamma$ -glutamyl dipeptides.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY AND THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN]

## A GENERAL METHOD FOR THE DETERMINATION OF HALOGENS IN ORGANIC COMPOUNDS<sup>1</sup>

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Halogen in an organic compound is determined, usually, by the Carius<sup>2</sup> or by the Lemp and Broderson<sup>3</sup> modification of the Parr<sup>4</sup> and Pringsheim<sup>5</sup> methods.

The Carius procedure suffers from a number of disadvantages, namely, the use of a sealed tube the preparation of which requires considerable skill, the use of a bomb furnace in which to heat the tube and the danger of glass splinters falling into the tube when the latter is opened. It requires a number of hours to perform an analysis and it is not always an easy matter to determine when the sample is completely oxidized.

The disadvantageous features of the Lemp and Broderson process are the possibility of incomplete fusion, the danger of rapid oxidation when

<sup>1</sup> This investigation was made possible by a grant from the Faculty Research Fund of the University of Michigan.

<sup>2</sup> Carius, *Ann.*, **136**, 129 (1865).

<sup>3</sup> Lemp and Broderson, *THIS JOURNAL*, **39**, 2069 (1917).

<sup>4</sup> Parr, *ibid.*, **30**, 764 (1908).

<sup>5</sup> Pringsheim, *Am. Chem. J.*, **41**, 386 (1904).

the sample is mixed with sodium peroxide and the difficulty of obtaining accurate results with very volatile compounds.

In the method to be described fuming sulfuric acid alone or in conjunction with chromic acid or a persulfate is used as the oxidizing agent instead of nitric acid or sodium peroxide. The process is carried out in an open apparatus of simple construction; hence all danger of explosion is eliminated. Since relatively large samples, 1 to 1.5 g. may be used, an unusual degree of accuracy can be attained. The oxidation of the sample is complete in a short time and the variety of compounds analyzed illustrates the general adaptability of the method. Very satisfactory results were obtained with such volatile compounds as ethyl bromide and with compounds difficult to oxidize such as chlorobenzene.<sup>6</sup> Moreover, in the event that the compound contains, in addition to halogen, metals such as mercury, arsenic, antimony or bismuth the latter can be determined readily as we have shown.

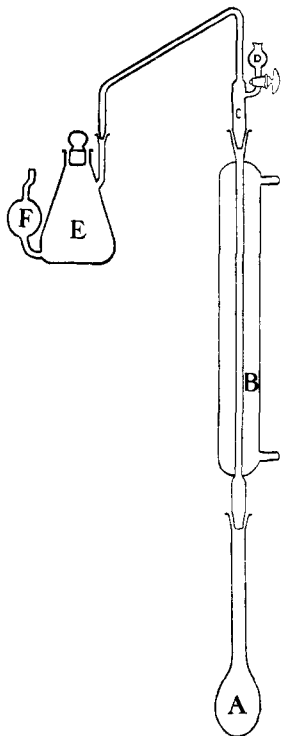


Fig. 1.

**General Procedure.**—The apparatus, made entirely of pyrex glass (Fig. 1),<sup>7</sup> consists of a 300-cc. Kjeldahl flask (A) fitted with a condenser (B), 69 cm. long, by means of a ground-glass connection.<sup>7a</sup> The tube C is attached to the top of the condenser by means of a ground-glass joint. The total length of the vertical part of this tube is 15 cm., the length of the oblique part is 20 cm. D represents a bulb of 10-cc. capacity, E a 250-cc. Erlenmeyer flask to which a safety bulb F of 100-cc. capacity is connected. All ground glass connections should be coated with phosphorus pentoxide.<sup>7b</sup> The sample is placed in the Kjeldahl flask and sulfuric acid is added through the dropping funnel. The liberated halogen passes through the condenser and is absorbed and reduced to halide in the Erlenmeyer flask, which contains an alkaline solution of sodium arsenite.<sup>8</sup> The halide can be determined either gravimetrically or by the Volhard method. For very accurate results the gravimetric method should be used.

<sup>6</sup> The results obtained in the case of chloroform and carbon tetrachloride were somewhat too low. This is due, undoubtedly, to the fact that some volatile organic halide is formed and is not hydrolyzed completely by the alkali in the absorption flask. By means of a slightly modified procedure, to be mentioned in a subsequent paper, entirely satisfactory results can be obtained in the case of the above-mentioned compounds.

<sup>7</sup> This apparatus can be purchased from the Arthur H. Thomas Co., Philadelphia.

<sup>7a</sup> The ground-glass connections are held together by means of glass hooks, not shown in the figure, which are sealed to the apparatus.

<sup>7b</sup> Stephens, *THIS JOURNAL*, **52**, 635 (1930).

<sup>8</sup> Hönigschmid and Zintl, *Ann.*, **433**, 201 (1923), have shown that alkaline arsenite is the best reducing agent for free halogen.

In the event that liquid material is to be analyzed, thin-walled glass bulbs are prepared. A bulb is filled by placing it and the liquid sample in the apparatus shown in Fig. 2. The apparatus is evacuated through the side arm and then, upon allowing air to enter the apparatus, the bulb is filled automatically.

**Determination of Iodine.**<sup>9</sup>—After the sample, approximately one g., has been placed in the flask and 100 cc. of 10% sodium hydroxide solution, which contains about 1 g. of arsenious oxide, has been poured into the Erlenmeyer flask, 20 cc. of fuming sulfuric acid, containing 20–30% of sulfur trioxide, is added slowly through the dropping funnel. The mixture is boiled very gently for thirty minutes. During this time a rapid stream of water should flow through the condenser and no sulfur trioxide vapors should pass through the absorption flask. Thirty-five cc. of 95% sulfuric acid is added and the mixture boiled vigorously until it becomes colorless. Fifty cc. of water is added cautiously to the mixture, which should be kept at the boiling point to insure complete mixing. The water is then drained from the condenser, a small quantity of 30% hydrogen peroxide (Superoxol) is added carefully and the liberated iodine is driven through the condenser by boiling the solution. The addition of hydrogen peroxide and the heating are continued intermittently until all of the iodine has been liberated and absorbed. Ten cc. of peroxide is usually sufficient. It is advisable as a matter of routine practice to add, after the liberation of iodine is thought to be complete, about 5 cc. of a saturated solution of hydrazine sulfate. Any iodate which may have been formed is thus reduced. The mixture should be boiled for five minutes and hydrogen peroxide added to expel any iodine. The apparatus should be disconnected immediately to prevent "freezing" of the ground-glass connections. The contents of the absorption flask are now transferred to a 600-cc. beaker and carefully acidified with dilute nitric acid, methyl orange being used as the indicator. The iodide is precipitated by the addition of excess silver nitrate solution, then an excess of 5–10 cc. of concd. nitric acid is added to prevent the contamination of the silver halide with other silver salts. The solution is boiled until the silver iodide has coagulated. The precipitate is filtered into a weighed crucible, washed with 2% nitric acid solution, then with water and finally with acetone. The crucible is next dried at 130°. The time required for a complete analysis is 70–90 minutes.

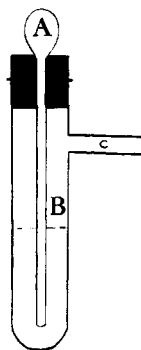


Fig. 2.

The results obtained with various purified iodine compounds and analyzed inorganic reagents are shown in Table I.

**Determination of Chlorine and Bromine.**—For compounds which contain chlorine or bromine the procedure is the same as described above except for the following variations. If the substance to be analyzed contains no metallic element, 0.5 g. of copper sulfate is placed in the Kjeldahl flask. Furthermore, after the sample has been heated for thirty minutes, a suspension of 10 g. of potassium persulfate<sup>9a</sup> in 20 cc. of 95% sulfuric acid is added through the dropping funnel. Any material which adheres to the condenser is washed into the flask with 15 cc. of 95% sulfuric acid. The mixture is boiled vigorously until the green color of the copper sulfate is pronounced. After draining the water from the condenser an excess of concd. potassium permanganate solution is

<sup>9</sup> The decomposition of an organic iodide with concentrated sulfuric acid and absorption of the liberated iodine was carried out without much success by Van Itallie, *Pharm. Weekblad*, **66**, 629 (1929).

<sup>9a</sup> Since much of the persulfate on the market is contaminated with perchlorate it is essential to make a blank determination, with starch as the organic material, according to the method outlined here for chlorine.

TABLE I<sup>a</sup>  
 DETERMINATION OF IODINE

Compound	Formula	I present, %	I found, <sup>b</sup> %	Error
Diphenylarsyl iodide	C <sub>12</sub> H <sub>10</sub> AsI	35.65	35.54	-0.11
Iodoform	CHI <sub>3</sub>	96.67	96.71	+ .04
<i>p</i> -Iodo-anisole	C <sub>7</sub> H <sub>7</sub> OI	54.24	54.19	- .05
$\beta$ -Iodonaphthalene	C <sub>10</sub> H <sub>7</sub> I	49.97	49.82	- .15
Diphenylstibyl iodide <sup>c</sup>	C <sub>12</sub> H <sub>10</sub> SbI	31.51	31.42	- .09

<sup>a</sup> In this table, as well as in those which follow, the analytical results were obtained gravimetrically. <sup>b</sup> Each of these results, as well as those recorded in the following tables, represents the average of two duplicates agreeing to within 0.00-0.08%. <sup>c</sup> In the case of diphenylarsyl iodide the iodine can be determined by hydrolysis of the iodide with alcoholic sodium hydroxide and determination of the iodine by the Volhard method. With diphenylstibyl and diphenylbismuthyl iodide, however, this procedure is not applicable since a volatile organic iodide, presumably iodobenzene, escapes from the alkaline mixture when it is heated.

added to the boiling solution and the mixture is boiled for about five minutes to expel any chlorine or bromine which may remain in the flask or condenser. In order to determine the amount of absorbed chlorine or bromine the procedure described above is used. A complete analysis can be made in 70-90 minutes.

In the case of chlorobenzene, a substance difficult to oxidize, decomposition by means of sulfuric acid and potassium persulfate requires considerable time. However, if 5 g. of chromic acid is placed in the flask with the sample and fuming sulfuric acid is then added, in the usual manner, the compound can be oxidized rapidly. The addition of persulfate or permanganate is unnecessary but an excess of chromic acid must be present when the oxidation is complete. In the event that a compound proves difficult to decompose by means of sulfuric acid and potassium persulfate, a suspension of chromic acid in concd. sulfuric acid may be added through the dropping funnel.

Organic iodine compounds are decomposed much more readily than chloro derivatives.

When an organic compound which contains chlorine and mercury is decomposed, the chlorine is not liberated quantitatively, since the mercuric chloride which is produced unites with the sulfuric acid to form HgCl<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>. In order to decompose the latter compound, 5 g. of granulated zinc, which reduces the mercury to an amalgam, is mixed with each gram sample before adding the fuming sulfuric acid.

 TABLE II  
 DETERMINATION OF CHLORINE AND BROMINE

Compound	Formula	Cl present, %	Cl found, %	Error
<i>o</i> -Hydroxyphenylmercuric chloride	C <sub>6</sub> H <sub>5</sub> OHgCl	10.79	10.81	0.02
<i>p</i> -Chloro-acetanilide	C <sub>8</sub> H <sub>8</sub> ONCl	20.94	20.90	.04
<i>p</i> -Chlorobenzoic acid	C <sub>7</sub> H <sub>5</sub> O <sub>2</sub> Cl	22.65	22.70	.05
Chlorobenzene	C <sub>6</sub> H <sub>5</sub> Cl	31.51	31.47	.04
2,4-Dinitrochlorobenzene	C <sub>6</sub> H <sub>3</sub> O <sub>4</sub> N <sub>2</sub> Cl	17.50	17.51	.01
		Br present, %	Br found, %	
<i>p</i> -Bromo-acetanilide	C <sub>8</sub> H <sub>8</sub> ONBr	37.34	37.41	0.07
<i>p</i> -Nitrobenzyl bromide	C <sub>7</sub> H <sub>6</sub> O <sub>2</sub> NBr	37.00	36.99	.01
$\beta$ -Bromopropionic acid	C <sub>3</sub> H <sub>5</sub> O <sub>2</sub> Br	52.25	52.24	.01
9,10-Dibromo-anthracene	C <sub>14</sub> H <sub>8</sub> Br	47.58	47.51	.07
Bromobenzene	C <sub>6</sub> H <sub>5</sub> Br	50.91	50.90	.01
Ethyl bromide	C <sub>2</sub> H <sub>5</sub> Br	73.33	73.33	.00

In order to determine arsenic in diphenylarsyl iodide, the residual solution, obtained after decomposition of the sample, liberation and absorption of the iodine, is concentrated and the pentavalent arsenic reduced to the trivalent state by boiling the solution with hydrazine sulfate.<sup>10</sup> The concd. sulfuric acid solution is heated above 254° in order to destroy excess hydrazine, then diluted and the sulfur dioxide, formed by decomposition of the hydrazine sulfate, boiled off. Ten cc. of hydrochloric acid is added and the arsenic trioxide titrated, at 80°, with *N*/10 potassium bromate, using methyl orange as the indicator.<sup>11</sup> The arsenic may also be determined by the same procedure, without concentration of the solution, after reduction of the arsenic pentoxide with sulfur dioxide.

Antimony is determined in diphenylstibyl iodide in the following manner. The residual liquid in the Kjeldahl flask is transferred to a 250-cc. Erlenmeyer flask. The antimony salt is reduced to the trivalent state with sulfur dioxide, the solution diluted and boiled to remove excess sulfur dioxide. Ten cc. of concd. hydrochloric acid is added and the solution titrated, at 60°, with *N*/10 potassium bromate, using methyl orange as the indicator.

Diphenylbismuthyl iodide can be analyzed for bismuth<sup>12</sup> as follows. The residual sulfuric acid solution in the Kjeldahl flask is poured into a 400-cc. beaker, diluted and then treated with an excess of concd. ammonia water. The mixture is boiled in order to coagulate the bismuth hydroxide. The latter is filtered and washed several times with dilute ammonium hydroxide and dissolved in 20 cc. of concd. nitric acid. After dilution to 200 cc., the solution is heated to the boiling point and 3 cc. of a 10% solution of phosphoric acid added.<sup>13</sup> After the addition of rosolic acid, a 10% solution of trisodium phosphate is added, very slowly, to the boiling solution. The precipitate of bismuth phosphate is then filtered through a filtering crucible and washed with 1% ammonium nitrate solution which contains a drop of nitric acid per 100 cc. The precipitate is dried at 300°, ignited at the full heat of a Bunsen burner for five minutes and weighed as BiPO<sub>4</sub>. The bismuth may also, but less accurately, be determined as bismuth trioxide.<sup>14</sup> The nitric acid solution is diluted to 300 cc. and dilute ammonium hydroxide is added until a faint turbidity is obtained. After the addition of excess ammonium carbonate, the solution is heated to the boiling point, the precipitate filtered, washed with hot water and ignited.

TABLE III

## THE DETERMINATION OF METALS IN ORGANIC HALOGEN COMPOUNDS

Compound	Formula	Metal present, %	Found, %	Error
Diphenylarsyl iodide	C <sub>12</sub> H <sub>10</sub> AsI	As, 21.05	21.00	-0.05
Diphenylstibyl iodide	C <sub>12</sub> H <sub>10</sub> SbI	Sb, 30.23	30.20	- .03
Diphenylbismuthyl iodide	C <sub>12</sub> H <sub>10</sub> BiI	Bi, 42.65	42.57 (as Bi <sub>2</sub> O <sub>3</sub> ) 42.67 (as BiPO <sub>4</sub> )	- .08 + .02

The authors express their sincerest appreciation for the invaluable suggestions offered by Professors H. H. Willard and F. F. Blicke.

<sup>10</sup> Schulek and Villecz, *Z. anal. Chem.*, **76**, 81 (1929).

<sup>11</sup> Györy, *ibid.*, **32**, 415 (1893); Treadwell and Hall, "Analytical Chemistry," John Wiley and Sons, Inc., New York, **1928**, Vol. II, p. 580; Kolthoff and Furman, "Volumetric Analysis," John Wiley and Sons, Inc., New York, **1929**, Vol. II, p. 464.

<sup>12</sup> Moser, *Z. anal. Chem.*, **45**, 19 (1906).

<sup>13</sup> Stähler, *Chem.-Ztg.*, **31**, 615 (1907).

<sup>14</sup> Scott, "Standard Methods of Chemical Analysis," D. Van Nostrand Company, Inc., New York, **1927**, Vol. I, p. 74.

### Summary

A general method has been developed for the determination of halogens in organic compounds, based upon oxidation of the substance by fuming sulfuric acid and distillation of the halogen formed. If the compound to be analyzed contains arsenic, antimony or bismuth, these metals, in addition to the halogen, may be determined in the same sample very easily.

The method of analyses requires only a short time and possesses decided advantages over the Carius and the Lemp and Broderson modification of the Pringsheim-Parr procedure.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF ILLINOIS]

## THE STEREOISOMERISM OF DIPHENYL COMPOUNDS. IV<sup>1</sup>

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Although the evidence for the obstacle theory to explain the optical isomerism possible in certain types of substituted diphenyl compounds is increasing, much more experimental work is necessary before an entirely satisfactory analysis of this phenomenon may be expected. Previous work<sup>1b</sup> from this Laboratory has demonstrated that compounds having all four groups in the 2,2',6,6'-positions the same, may be resolved into optical antipodes provided each of the two rings is unsymmetrical in itself. This is substantial evidence against the theory that interference is due merely to the relative electrostatic charges on the substituted groups. The question as to how important may be the relative size of the groups in the 2,2',6,6'-positions requires further study. This investigation has involved a careful consideration of the probable interfering forces of such groups from x-ray data.

From x-ray data it is possible to calculate the distance between the two connecting carbon atoms in diphenyl as 1.45 Å. In the same manner and by assuming the usual angles in the benzene ring, the vertical distance between the 2,2'-carbon atoms in the benzene rings may be estimated as 2.90 Å. Also by x-ray data the relative distances between the centers of the carbon atoms in the benzene ring and of the atoms or groups attached to the benzene ring may be obtained. A question for which, at the present time, there is no experimental attack and which, therefore, cannot be settled, is the angle at which the substituting group in a benzene ring is attached. This angle must depend upon electrostatic forces

<sup>1</sup> Previous papers in this series are (a) Hyde and Adams, *THIS JOURNAL*, **50**, 2499 (1928); (b) Moyer and Adams, *ibid.*, **51**, 630 (1929); Stanley and Adams, *Rec. trav. chim.*, [4] **48**, 1035 (1929).