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Summary

A series of α-substituted N-methylpyrrolidines has been prepared and their dissociation constants measured. The variation of toxicity with the different α-substituents has been studied. The most negative substituent is shown to be the most toxic.

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The Micro Estimation of Halogens in Organic Compounds

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Numerous methods have been suggested for the estimation, on a micro scale, of halogens in organic compounds. Pregl[2] described two methods, the first involving combustion of the substance and the second an adaptation of the well-known Carius procedure. Although both methods give satisfactory results, they are open to criticism. Dieterle[3] and Nomura and Murai[4] have described methods based upon modifications of the macro procedure of Baubigny and Chavanne.[5] They used a mixture of concentrated sulfuric acid and potassium dichromate together with silver nitrate for the oxidation of the organic material before proceeding to the determination of the halide. Later, Willard and Thompson[6] described a method depending on the oxidation of the sample by means of fuming sulfuric acid to which, in certain instances, potassium persulfate was added. The halogen was distilled into alkaline arsenite and precipitated as silver halide. Zacherl and Krainick[7] modified the method of Nomura and Murai by employing a mixture of concentrated sulfuric acid, silver dichromate and potassium dichromate as the oxidizing agent and collected the halogen in a mixture of 0.01 *N* caustic soda with acid-free hydrogen peroxide, in which it was estimated by titration of the excess alkali. This method closely resembles the procedure of Viebock,[8] published a little earlier, in which the oxidizing agent consisted of a mixture of concentrated sulfuric acid and potassium dichromate with silver sulfate. Other methods

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(1) Commonwealth Fund Fellow.
(2) Pregl, "Quantitative Organic Micro Analysis," 3d ed., 1930.
(3) Dieterle, *Arch. Pharm.*, **259**, 73 (1921).
(4) Nomura and Murai, *Bull. soc. chim.*, [4] **35**, 217 (1924).
(5) Baubigny and Chavanne, *Compt. rend.*, **136**, 1197 (1903).
(6) Willard and Thompson, THIS JOURNAL, **52**, 1893 (1930).
(7) Zacherl and Krainick, *Mikrochem.*, **11**, 61 (1932).
(8) Viebock, *Ber.*, **65**, 493 (1932).

which have been described, as, for example, those of Moser,[9] and Leipert,[10] are concerned mostly with refinements in the determination of the inorganic halide after the oxidation is completed.

All these methods suffer in that they involve the use of intricate and delicate glass apparatus which must be specially constructed and is easily broken. They require, also, considerable manipulative skill. To overcome these difficulties we have now devised a rapid and accurate method depending on the oxidation of the substance with sodium peroxide in a modification of the Parr bomb. The use of sodium peroxide for this purpose is not new. Parr[11] and Pringsheim[12] have both investigated its use in this connection and the macro procedure for the estimation of halogens, from which our method is derived, was described by Lemp and Broderson.[13]

Many attempts were made to modify the method described by the latter authors before a reliable technique was obtained. The first bombs designed all failed because they were too large for the quantities of reagent we employ. With small quantities the heat of fusion is rapidly disseminated and this was so greatly facilitated by the size of the bomb and the large conducting surface which it offered that good fusions could not be made. An entirely new bomb was therefore designed. It consists of a fusion cup (A), a lid (B) and a clamp (C) to hold the lid in position. The cup has a depth of 25 mm. and an inside diameter of 13 mm. with walls 1.5 mm. thick and with a lip, on which the lid rests, 3 mm. wide. In order to facilitate fusion it was found necessary that the cup should differ from the Parr bomb in having a rounded base rather than a flat one. For ease of manipulation a small eyelet (e_1) is placed in the base of the cup. The lid of the bomb is held securely in position by means of an arch clamp as shown and a tight fit between the lid and the cup is ensured by a washer let into the under surface of the lid. The bomb is constructed of stainless steel but it was found necessary at a later stage to have the cup and the lid plated with platinum. The reason for this will appear in the experimental part. The proportions of the reactants had also to be changed to ensure unvaryingly successful analyses. The quantities used are given in the description of the method. The charge in the bomb described[14] is ignited by heating in a Bunsen flame but electrical ignition can be equally well used by fitting the lid with lead-in terminals to carry the current to a heating element imbedded in the fusion mixture.

We propose to extend the use of the apparatus to the estimation of other elements, such as sulfur, phosphorus and arsenic, in organic combination.

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(9) Moser, *Mikrochem.*, Pregl-Festschrift, 293 (1929).

(10) Leipert, *ibid.*, 266 (1929).

(11) Parr, THIS JOURNAL, **30**, 764 (1908).

(12) Pringsheim, *Am. Chem. J.*, **31**, 386 (1904).

(13) Lemp and Broderson, THIS JOURNAL, **39**, 2069 (1917).

(14) Manufactured by the Parr Instrument Co., Moline, Illinois.

Experimental

Description of Method. (a) Mixing.—Thirty milligrams of a mixture of pure potassium nitrate and cane sugar, in the proportion of 3 : 1, is placed in the bottom of the bomb and about 5 mg. (accurately weighed by difference) of the sample is placed on the surface of the mixture. To this is added 1.5 g. of sodium peroxide and the lid fastened in position by means of the screw in the clamp. Finger tightness of the screw is sufficient. The contents are then intimately mixed by inverting and shaking the bomb thoroughly. Efficient mixing is important since otherwise a good fusion will not result. After shaking, the bomb is set upright and tapped so that the contents settle to the bottom. The apparatus is now ready for the fusion.

(b) Fusion.—The bomb is held by the milled head of the clamp screw (s), [either with tongs or by a piece of stout wire passed through the eyelet (e_2) in the head of the screw] in the hottest region of a good Bunsen flame. Care should be taken to avoid heating too near the lid or the rubber washer may soften and become sticky. The fusion is complete in about ten seconds, the exact time being easily determined since the disturbance within the cup can be felt. Theoretically the fusion is now completed but we have found it advisable to hold the bomb in the flame for a further five to ten seconds to complete the fusion throughout the whole mass. At the end of about fifteen to twenty seconds the apparatus is removed from the flame and cooled under the tap. This operation occupies about one minute. After cooling, the bomb is carefully wiped, opened and the inner side of the lid carefully washed with hot distilled water. The washings are collected in a Pyrex test-tube 25 mm. in diameter and 200 mm. in length. The cup is then inverted into the test-tube and about 10 cc. of hot distilled water added. It is usually necessary to tilt the tube to allow air to escape from beneath the cup and so ensure rapid solution of the charge. The test-tube is now covered with an inverted glass dish and the mixture left until completely dissolved. (This occupies three to five minutes and at this stage, with two cups, a second determination may be commenced.) The cup is then removed from the solution by lifting out by means of a hooked platinum wire inserted through the eyelet (e_1) in the base. It is carefully washed with distilled water and the washings added to the solution, which is then cooled in ice and treated with 5 cc. of concentrated, halogen-free nitric acid. The acid is added slowly, with rotation of the tube. Before acidifying, the solution may have been somewhat colored, but any such color disappears on addition of the acid. The acid solution is filtered with slight suction into another test-tube and the filtrate treated with 2 cc. of 5% silver nitrate solution. In the case of a chloride or bromide a precipitate immediately appears but in the case of an iodide, a precipitate may not be formed. This results from the fact that the iodide is further oxidized to iodate. Such an oxidation has not been observed to occur with the chlorides but it does occur to a limited extent with bromides and is practically quantitative with the iodides. Whether a precipitate appears or not, the solution is warmed by placing in a boiling water-bath and 100 mg. of finely powdered hydrazine sulfate added. This is not strictly necessary in the case of chlorides but we have considered it advisable, for the sake of routine, always to add the reducing agent. The halide is coagulated by continuing the heating and is

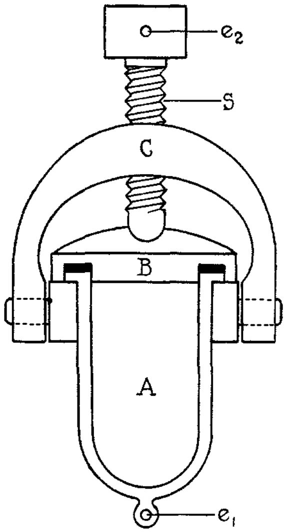

Fig. 1.

then cooled, filtered, dried and weighed according to Pregl, using the type of filter which he recommended.

The whole analysis occupies about forty-five minutes and two or three analyses per hour can be made with ease, using two cups.

In order to speed up the procedure we have found it useful to weigh out the required quantities of sodium peroxide, potassium nitrate–sugar mixture and hydrazine sulfate into small tubes and then to scratch a mark on the tube at the level of the surface of the solid. Since these quantities do not have to be accurate within a few milligrams, later quantities are measured into the small tubes instead of being weighed out.

The results of a number of analyses by this method, on different types of compounds, are given in Table I.

The samples were all purified either by recrystallization to constant melting point, in the case of solids, or by distillation under reduced pressure, in the case of liquids. All the reagents used were also tested and found to be halogen-free.

TABLE I

Substance	Sample, mg.	Silver halide, mg.	Halide found, %	Halide calcd., %
Hexachlorethane	3.445	12.455	89.44	89.87
Chloro-*m*-cresol	5.464	5.465	24.74	24.88
	3.935	3.930	24.70	24.88
Chloracetamide	6.315	9.690	37.96	37.94
	4.325	6.632	37.93	37.94
p-Nitrobenzoyl chloride	5.283	4.110	19.24	19.06*
	6.061	4.675	19.06	19.06*
p-Toluene sulfonyl chloride	9.375	6.960	18.39	18.55*
	5.695	4.282	18.60	18.55*
Bromocamphor	3.510	2.848	34.53	34.60
	4.410	3.565	34.40	34.60
Bromoethylphthalimide	4.400	3.262	31.55	31.47
	4.194	3.100	31.45	31.47
Iodoform	5.216	9.322	96.59	96.70*
	5.295	9.465	96.61	96.70*
Monoacetone iodoxylose	4.305	3.362	42.21	42.30*
	4.731	3.695	42.21	42.30*
Ethyl chloroacetate	3.281	3.820	28.80	28.98*
	6.438	7.485	28.76	28.98*
Chlorovaleric acid	7.635	8.085	26.19	26.07*
	5.705	6.010	26.06	26.07*
Bromobenzene	6.089	7.242	50.62	50.88
	4.914	5.855	50.70	50.88
Ethyl bromoacetate	3.829	4.302	47.81	47.88*
	8.400	9.420	47.72	47.88*
Trimethylene bromide	3.392	6.317	79.26	79.19*
	4.646	8.640	79.14	79.19*

The weighing of liquids for the analysis is carried out in sealed thin-walled capillaries as described by Pregl. In the case of non-volatile liquids, the capillaries are opened before placing in the bomb and the procedure is then exactly as described above.

In one or two instances we have analyzed solids which could not easily be powdered. These we have weighed in a small, tin-foil container about 3 mm. deep and 3 mm. in diameter. The boat and contents are then placed in the bomb, shaken with the peroxide and the analysis continued in the usual way.

Use of Platinum Plated Bomb.—When new, the stainless steel bomb gave perfectly satisfactory results but after a few determinations the interior of the bomb became discolored. The silver halide precipitates were also discolored and the results obtained were too high. A careful elimination of the various possibilities, including retesting the reagents employed for the presence of halogens, indicated that the surface of the bomb was yielding some material to the fusion mixture. This also occurs with the macro bomb, if one may judge by the staining of the interior of the cup, but in that case the quantities involved do not significantly affect the result whereas they assume importance in the case of the small quantitites weighed in the micro estimation. The high figures obtained in three determinations and the corrected figures for *p*-nitrobenzoyl chloride after running a blank determination, are given in Table II. It is not at all certain that the figure obtained in the blank experiment will be constant and it was therefore necessary to plate the bomb with platinum to eliminate the errors arising from this source. The figures obtained with the plated bomb are included in Table I and are marked with an asterisk.

TABLE II

Substance	Sample, mg.	Silver halide, mg.	Halide found, %	Halide calcd., %	Corr. figure, for halide found, %	Blank, mg.
Iodoform	4.030	7.253	97.29	96.70		
	3.469	6.214	96.83	96.70		
p-Toluene sulfonyl chloride	5.290	4.405	20.60	18.55		
p-Nitrobenzoyl chloride	4.900	3.882	19.59	19.06	19.18	0.082
	5.245	4.120	19.43	19.06	19.06	0.082

Summary

A new method for the rapid and accurate micro estimation of halogens in organic compounds has been developed. It is based upon the oxidation of the compound with sodium peroxide in a modification of the Parr sulfur bomb. From the variety of substances analyzed, the method would appear to be applicable to all kinds of halogenated organic compounds.

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