Summary

When the dichloride, diamide, diethyl ester, dimethyl ester, mono-ethyl ester, monomethyl ester, mono-amide and imide of diphenic acid are heated with concd. sulfuric acid, each compound is transformed into a member of the diphenyleneketone-4-carboxylic acid series; these changes involve rotation of the rings in the biphenyl nucleus. The mechanism of the reactions has not been precisely determined since hydrolysis occurs in every case, even when special precautions are taken. No isomerization of phenanthridone was brought about by treatment with sulfuric acid. *p,p'*-Dinitrodiphenic acid is unique in that it does not form an anhydride or a ketone acid; a plausible explanation of the behavior of this compound may be found by postulating that the *meta* orienting nitro group in each ring loosens the hydroxyl group in the carboxyl and strengthens the bond which holds the hydrogen atom in the latter as well as the force holding the ring hydrogen which is *meta* to the nitro group.

The action of heat or of fuming stannic chloride does not isomerize phenoldiphenein. If the latter be maintained for some time at a temperature slightly above its melting point, carbon dioxide is evolved. In case this fact is used in an interpretation of the structure of phenoldiphenein, it might be employed as an argument against the diketone formula (II) which we have proposed for consideration.

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[CONTRIBUTION FROM THE EVANS MEMORIAL]

ETHER STUDIES

II. THE QUANTITATIVE DETERMINATION OF PEROXIDE AS A CONTAMINANT[1]

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Some three years ago, as the result of a too frequent incidence of respiratory difficulties subsequent to surgical operation (several bronchites and at least one broncho-pneumonia), a chemical examination was made of the ether used for anesthesia. This was found to be contaminated seriously, and as a result of this initial observation a simple analytical procedure was outlined and all ethers for anesthesia were subjected to examination.[2]

It was soon apparent that a very considerable percentage of ether samples (one-third of all the ethers examined) contained deleterious impurities and that aldehyde and more especially "peroxide" were the chief contaminants. As both of these substances are indicated as causes for exclusion by practically all of the Pharmacopeias of

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[1] Presented before the American Chemical Society, New Haven, April 5, 1923.

[2] The results of these analyses have been reported recently by the senior author [Rowe, in press, *Ind. Eng. Chem.*].

the world, the implication of these findings was felt to be highly significant. Critical analysis demonstrated the probability that these compounds were the outcome of oxidative changes in materials originally pure. To determine the amount of these changes, quantitative methods had to be devised and this report deals with the experimental work on the "peroxide" moiety.

Anesthetic ether as it is usually defined is a mixture of diethyl oxide with small amounts of water and of ethyl alcohol. This is in contact with a vapor phase containing various amounts of air and usually a catalytic agent in the form of the metal container. The possibilities of oxidation are reviewed in papers by Baskerville and Hamor[3] published in 1911. The spontaneous oxidation of ether has been observed severally to produce a wide variety of acids, aldehydes and "peroxides."

Clover[4] in a recent paper has made a study of chemical changes taking place when cork-stoppered bottles of ether are charged with air and allowed to stand. He found that ether peroxide developed first in a purified (not dried) ether, that light seems to have an important but not indispensable influence on peroxide formation, and that aldehyde is formed subsequently.

While many tests have been suggested for the qualitative determination of peroxides, the quantitative measurement has received much less attention. In fact, the treatment of the ether with acidified potassium iodide solution and subsequent titration of the liberated iodine with sodium thiosulfate solution, used in rough modification by Clover,[4] and the standard hydrogen peroxide titration with acid potassium permanganate seem to be the only suggestions.

Preliminary attempts to modify some of the seemingly more dependable of the numerous qualitative tests to quantitative uses gave only negative results. In a similar manner, while trial analyses with potassium permanganate gave concordant check determinations, the uncertainty on the one hand of the exact character and reaction capacity of the peroxide and on the other, the magnitude of the disturbing influence of alcohol, acetaldehyde and other possible impurities, led to a discontinuance.

The liberation of iodine from inorganic iodides seemed the most promising line of approach. Among the advantages of the method are (1) all peroxides react with potassium iodide in acid solution and liberate iodine;[5] (2) alcohol and acetaldehyde, in the quantities ordinarily occurring in anesthesia ether, would have little or no effect on the liberation of iodine, and hence the titration value in terms of the sodium thiosulfate could not be greatly influenced by these impurities.

Pure Ether.—For all control operations it was essential that an ether be available from which the offending substances were completely removed. Various methods have been suggested for the purification. A careful

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[3] Baskerville and Hamor, *J. Ind. Eng. Chem.*, **3**, 301, 378 (1911).

[4] Clover, This Journal, **44**, 1107 (1922).

[5] See Langheld on "Peroxides" in Houben-Weyl, "Die Methoden der organischen Chemie," Thieme, Leipzig, **1922.**

experimental testing of the more promising methods led to the adoption of that of Taylor and Smith[6] which is substantially as follows.

The ether is first shaken with concd. sulfuric acid until fresh portions produce no change of color, then allowed to stand in contact with fresh acid overnight. After it has been washed with water it is treated several times with a saturated solution of potassium permanganate (containing 20 g. of sodium hydroxide per liter). It is again washed with water, and then treated with concd. sulfuric acid for a short time. It is then washed, dried over calcium chloride, distilled, dried over sodium ribbon and distilled again. Finally, it is allowed to stand over sodium ribbon for several weeks and again distilled. Pure ether is the result.

The method described above in all essential points was used until the distillation was reached, when a different distillation apparatus was substituted. A large flask of a capacity of perhaps 4 liters, containing the ether over the metallic sodium, was fitted with a foil-covered stopper, through which passed a Hempel distilling head about 30 cm. in length, in turn connected with a Liebig condenser.[7]

Pure Alcohol.—At a later stage of the work it became necessary to prepare an alcohol which should be free from aldehyde. A brief review of the literature gave a number of methods. Preliminary study showed that the best results were obtainable by the method of Girard and Cuniasse.[8]

This involves the addition of 3 or 4 g. of *m*-phenylenediamine hydrochloride to every liter of 95% alcohol. The mixture is allowed to stand for several days, and then is fractionated slowly. The present authors found that it seems not only to eliminate aldehydes but also to remove all except small traces of peroxide. Whenever these substances occur in appreciable quantities in alcohol, this treatment is recommended as most efficient. The method was used throughout the investigation, collecting only the middle (50%) fraction, and using wholly fresh materials for each preparation. Alcohol thus prepared gives no color with Schiff's reagent in 48 hours.

The analytical system as originally defined consisted of the following components: (*a*) a solution of some neutral iodide; (*b*) a dilute acid solution; (*c*) the ether under investigation. Permutations were possible in the choice of iodide, acid, sequence in assembling and time of reaction.

Certain theoretical considerations arise at this point, and may be briefly discussed.

If the formula of the organic peroxide be represented by $(C_2H_5)_2O_2$, when dil. acid is added to ether containing this peroxide, the following equilibrium will result after a certain time interval: $(C_2H_5)_2O_2 + H_2O = (C_2H_5)_2O + H_2O_2$. After this equilibrium has been attained, no further change in the proportion of diethyl peroxide to hydrogen peroxide takes place. When the potassium iodide solution is added to this mixture, the hydrogen peroxide liberates iodine.

The reaction velocity of this is appreciable, but presumably that of the reaction between diethyl peroxide and hydrogen iodide is much slower. Therefore, if an appreciable

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[6] Taylor and Smith, This Journal, **44**, 2450 (1922).

[7] In the later studies, an apparatus made wholly of glass has been used. The flask was heated by means of an electric hot-plate. The temperature during distillation was kept at 35°. This purified ether, when treated with Schiff's reagent, produced no color reaction at the juncture of the two liquids within 30 minutes.

[8] Quoted by Vasey: "Guide to the Analysis of Potable Spirits," **1904**.

quantity of diethyl peroxide exists at equilibrium, upon the addition of potassium iodide solution and titrating with sodium thiosulfate, some of the ethyl peroxide will not have completed its reaction with the hydriodic acid, and hence will not be estimated. The original mixture, therefore, should contain the iodide solution together with the dil. sulfuric acid solution and the peroxide in ether solution (or unknown ether sample). In this way, the hydrogen peroxide, as fast as formed, will react with hydriodic acid, the equilibrium will be displaced continuously to the right until the ethyl peroxide has been entirely converted into hydrogen peroxide, and this in turn has reacted to produce iodine. Under these conditions the entire peroxide content should be estimated by the thiosulfate titration.

Preliminary results showed that the double iodide of cadmium and potassium recommended by the Pharmacopeia[9] gave the greatest stability toward the influence of atmospheric oxygen. This solution was used in all the final measurements.

Attempts were made, however, to lessen the influence of atmospheric oxygen. The addition of the acid, only as an immediate preliminary to titration, was tried and found valueless, as indeed was anticipated.

Several mixtures were made consisting of 10 cc. of 10% aqueous cadmium iodide, 50 cc. of dil. sulfuric acid (prepared by mixing 100 cc. of concd. acid, d. 184, with 300 cc. of distilled water), and 10 cc. of ether containing hydrogen peroxide, and these were titrated at different time intervals with approximately 0.1 *N* sodium thiosulfate solution.[10]

The results obtained in terms of the thiosulfate are for 5 minutes, 4.83 cc.; for 90 minutes, 6.32 cc.; and for 24 hours, 11.60 cc. Two other solutions were titrated within the first hour giving, respectively, 4.20 cc. and 4.22 cc. They were allowed to stand for 24 hours and then required, respectively, 1.53 cc. and 2.52 cc. additional to remove the subsequently liberated iodine. A further 24-hour exposure produced iodine equivalent to 0.49 cc. and 0.93 cc., respectively. Obviously some agent lowered the reaction velocity of the iodine liberation by atmospheric oxygen. Later observations would seem to indicate that the liberated iodine catalyzes the initial reaction to some extent.

Series similar to these last were run with the aqueous liquid under a supernatant layer of benzene, the latter acting as a partial protection from atmospheric oxygen.

In a typical experiment, iodine requiring 8.43 cc. had been liberated at the end of 24 hours, while that formed in the succeeding two days required, respectively, 0.41 cc. and 0.16 cc. Other experiments showed no further liberation of iodine after the initial titration. While the results were fairly satisfactory, it was not felt that they warranted the inclusion of the additional step.

Two other modifications were studied, one an effort to catalyze the peroxide reaction with ferrous sulfate, the other, the addition of chloroform to dissolve the iodine. No material advantage accrued from the latter

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[9] United States Pharmacopeia, 9th ed., **1916.**

[10] The approximately 0.1 *N* sodium thiosulfate solutions used were protected from carbon dioxide by soda lime. After a few days, the concentration of the salt was determined by titrating the solution against known weights of resublimed Merck's Blue Label iodine. Check determinations at later periods showed that the solution was satisfactorily stable.

and the ferrous sulfate seemed to act as a negative catalyst. An ether liberating iodine equivalent to 4.75 cc. of thiosulfate solution required but 1.88 cc. in the presence of the iron salt.

With the first set-ups, the ether formed the upper layer of a two-phase system, and the iodine liberated was contained chiefly in the ether phase. At first a starch solution was employed, but later was given up, as the solution did not immediately produce the characteristic dark blue color with iodine. It did appear after considerable shaking, however. Moreover, the iodine was deposited on the sides of the flask and adhered quite tenaciously during the titration. The method was, accordingly, not satisfactory.

All of the earlier experiments involved a two-phase system, the disadvantages of which are manifest. A one-phase system was secured by dissolving the iodide in alcohol purified by the method already discussed.

A preliminary series of tests was made to study the influence of the acid used in the system; 25% trichloro-acetic acid, about 30% acetic acid, standard dil. sulfuric acid and 50% phosphoric acid were investigated. On the whole, sulfuric acid gave the most dependable results.

A series of parallel determinations comparing alcoholic and aqueous iodide solutions gave substantially equivalent results, as is shown in Table I.

TABLE I

COMPARISON OF AQUEOUS AND ALCOHOLIC SYSTEMS

1		2		3[a]	
25 cc. of aqueous 5% CdI_2+KI 25 cc. of dil. H_2SO_4 10 cc. of $H_2O + H_2O_2$		25 cc. of alcoholic CdI_2+KI 25 cc. of dil. H_2SO_4 10 cc. of $C_2H_5OH + H_2O_2$		25 cc. of alcoholic CdI_2+KI 25 cc. of dil. H_2SO_4 10 cc. of ether + H_2O_2	
	0.1 *N* $Na_2S_2O_3$		0.1 *N* $Na_2S_2O_2$		0.1 *N* $Na_2S_2O_3$
Min.	Cc.	Min.	Cc.	Min.	Cc.
8	3.47	11	3.75	5	3.94
9	3.51	17	3.98	6	3.95
27	3.60	24	4.05	8	3.97
42	3.68	..	..	22	4.23
..	..	..	..	25	4.29

[a] Included to show the characteristic course with a standard system.

Alcoholic iodide solution was found to be less stable than aqueous, showing a faint yellow color after two or three weeks. The aqueous solution was adopted and the relative merits of alcohol and glacial acetic acid for homogenizing the analytical system were thoroughly studied.

Since alcohol gave satisfactory results and could be prepared easily in a state of high purity, it was adopted as the homogenizing medium. Finally, after a large number of trials, only a few of which have been discussed, the process narrowed down to the procedure given in Table II.

TABLE II

COMPOSITION OF AN ANALYSIS

Control		Sample	
Cc.	Subs.	Cc.	Subs.
15	5% aqueous CdI_2 + KI soln.	15	5% aqueous CdI_2 + KI soln.
15	dil. H_2SO_4	15	dil. H_2SO_4
25	alcohol (purified as before)	25	alcohol (purified as before)
		10	the ether sample

Attempts were made to increase the sensitivity by using larger amounts of ether—which again separated the phases—and a more dil. thiosulfate, but were negatived in the light of experience. A colorimetric method based on the liberation of iodine was tried and discarded.

As has been previously indicated, the time factor in peroxide estimations is extremely important. It has been shown that, with increasing time intervals, the amounts of sodium thiosulfate used for titration, definitely and unmistakably increase. The final step was to determine the speed of the reaction for the production of iodine, both for ether samples and for controls at definite time intervals. By means of these measurements the approximate time necessary for the organic peroxide to react completely with the hydriodic acid, can be evaluated.

The results of a typical series of measurements are given in Table III.

TABLE III

TIME INFLUENCE ON IODINE LIBERATION-ANALYTICAL SYSTEM AS PREVIOUSLY STATED

Solution	Time Min.	Control Cc.	Titration (gross)			Titration (net)			Av. Cc.
			1	2	3	1	2	3	
A	15	0.14	0.22	0.21	0.20	0.08	0.07	0.06	0.07
	30	.15	.24	.27	.23	.09	.12	.08	.10
	45	.13	.29	.24	.28	.16	.11	.15	.14
	60	.15	.30	.23	.29	.15	.08	.14	.12
B_1	15	0.06	2.45	2.52	2.52	2.39	2.46	2.46	2.44
	30	.04	2.44	2.47	2.53	2.40	2.43	2.49	2.44
	45	.09	2.58	2.45	2.58	2.49	2.36	2.49	2.45
	60	.10	2.60	2.47	2.50	2.50	2.37	2.40	2.42
B_2	15	0.07	2.42	2.38	2.45	2.35	2.31	2.38	2.35
	30	.09	2.45	2.45	2.45	2.36	2.36	2.36	2.36
	45	.10	2.49	2.50	2.49	2.39	2.40	2.39	2.39
	60	.09	2.56	2.48	2.53	2.47	2.39	2.44	2.44
C	15	0.06	16.20	16.91	15.68	16.14	16.35	15.62	16.20
	30	.08	17.63	17.82	17.98	17.55	17.74	17.90	17.73
	45	.09	18.24	18.16	18.65	18.15	18.07	18.56	18.26
	60	.11	18.45	18.48	18.54	18.34	18.37	18.43	18.38

A = 0.0028% as H_2O_2; B = 0.056% as H_2O_2; C = 0.428% as H_2O_2.

With Solution A, the concentration of peroxide is so small—less than 0.003%—that the analytical errors appear unduly large. With the B solutions the results are somewhat indeterminate. It would seem safe to assume that the major part of the reaction was complete in the first 15 minutes. With the more concentrated C solution the reaction is apparently drawing to completion at the end of one hour. Evidently with larger concentrations a more liberal allowance of time must be made if approximate accuracy is to be attained. The authors wish to emphasize that the method here described is not offered as an exact quantitative procedure. They do believe, however, that it offers a first approximation, permitting the determination of comparative results. The uncertainty of the exact nature of the peroxides in ether precludes the use of a proper standard for comparison. Until more light is thrown on the structural phase of the problem, the authors feel that the present method may at least facilitate further study.

In concluding this discussion of peroxide analysis, possible sources of error claim attention, namely, the influence, respectively, of aldehyde and of the ether itself upon the titration values observed.[11] Several possible relationships are suggested, and it was felt that they could be excluded only on demonstration. Direct sunlight must also be excluded rigorously. With the small quantities of material present, the error from this source may easily prove serious.

The influence of aldehyde was studied by adding known amounts of pure aldehyde (prepared by depolymerization of paraldehyde) to the samples as tested and noting the titrational values obtained. The results of a typical set of measurements are given in Table IV.

TABLE IV

INFLUENCE OF ALDEHYDE ON LIBERATION OF IODINE

	Solution	Control	Readings	Corrected	Av.
1.	Ether No. 1		0.19	0.12	0.11
		0.07	.17	.10	
2.	+0.1% of aldehyde	.07	.19	.12	.12
			.18	.11	
3.	Ether No. 2	.03	.13	.10	
			.12	.09	.10
4.	+0.2% of aldehyde	.03	.15	.12	
			.15	.12	.12
5.	Ether No. 3[a]				
	+0.4% of aldehyde	.13	.47	.34	
			.43	.30	.32
6.	+0.5% of aldehyde	.13	.41	.28	
			.45	.32	.30
7.	+2% of aldehyde	.13	.53	.40	
			.56	.43	.42

[a] The solvent ether contained traces of peroxide; hence the discrepancies between the corrected measurements and those made with pure ethers 1 and 2.

From these results it would appear that a concentration of aldehyde in ether up to about 1% has no (or a negligible) effect on the titrational value of sodium thiosulfate. Where the concentration of aldehyde is about 2%, the titrational value is only slightly increased.[12]

A few analyses of ethers responding positively to the qualitative test are given in Table V.

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[11] The influence of ether is under investigation at the present time and the results will be communicated in the near future.

[12] The difference noted corresponds to an absolute content of about 0.003% of peroxide.

TABLE V

SAMPLE ANALYSES

Ether	Controls	Titration	Titr. corr. Av.	Peroxide as H_2O_2%
		0.26		
1	0.10	.21	0.12	0.0028
	.09	.19		
2	.09	.28	.17	.0040
	.09	.25		
3	.09	.29	.18	.0042
	.09	.27		
4	.18	.52		
	.20	.55	.34	.0080
	.20	.52		
	.20	.55		
5	.37	.73	.38	.0090
	.34	.75		
6	.34	.84	.49	.0115
	.34	.86		
7	.34	1.00	.61	.0143
	.34	.93		

While all of these ethers contained but small amounts of peroxide, they were all subject to rejection by the official standard. A fair degree of correlation was observed in the relative indices of the two methods.

Conclusion and Summary

A method is described for the quantitative estimation of peroxides in ether based upon the interreaction of the former with acid cadmium and potassium iodides.

Various factors conditioning the reaction have been studied and the magnitudes of their several influences determined.

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