[CONTRIBUTION FROM THE POLYCHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

Cycloalkanone Peroxides. I. Preparation of "Cyclohexanone Peroxide" by Oxidation of Cyclohexanol

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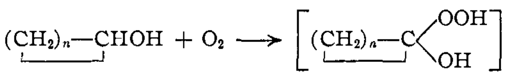
The autocatalyzed liquid phase oxidation of cyclohexanol with oxygen produces in high yields at moderate conversions a mixture of peroxides which are qualitatively equivalent to those produced by the reaction of cyclohexanone with hydrogen peroxide. Reaction of these peroxides with ferrous ion in hydrocarbon solution gives 68% yield of 1,12-dodecanedioic acid. Evidence is presented concerning the structure of these peroxides and the equilibria between the various forms.

The formation of coupled products from the reaction of tertiary alkyl hydroperoxides with ferrous ion has been reported recently.[1,2] Interest in applying this reaction to the so-called "1-hydroxycycloalkyl hydroperoxides" has led to a study of the synthesis of these compounds by oxidation of the corresponding cyclic alcohols.



$$(CH_2)_n\text{—}CHOH + O_2 \longrightarrow \left[(CH_2)_n\text{—}C\begin{matrix}OOH\\OH\end{matrix}\right]$$

Oxidation of Cyclohexanol.—Oxidation of cyclohexanol in glass vessels was found to take place readily above 100° in the presence of a peroxide initiator. The peroxides produced, however, decompose rapidly at these temperatures unless a high concentration of oxygen is maintained in the liquid. This stabilizing effect was shown by an experiment in which these peroxides in cyclohexanol solution at 90° decomposed only 2.5% in one hour when vigorously agitated with oxygen, compared to 70% decomposition under nitrogen under comparable conditions.[3]

Excellent yields of peroxides in the oxidation were obtained using a creased glass reaction flask and a high speed agitator, feeding in excess pure oxygen and allowing the reaction to absorb all oxygen possible. Reaction temperature was bracketed between the threshold temperature (95–105°) and the temperature at which vapor pressure of the liquid became sufficiently high to prevent solution of enough oxygen to maintain peroxide stability. Best results were obtained with a decreasing temperature gradient with time to compensate for the build-up of water and other low-boiling substances. Dimensions of the reaction flask and of the stirrer, and speed of agitation were critical due to the necessity of avoiding oxygen-deficient zones in the reacting liquid. Of various reactor designs evaluated, the creased flask was by far the most effective. Added calcium carbonate caused increased yields and decreased reaction rate, while certain metals, such as iron and copper, and apparently some fortuitous contaminants as well, had markedly adverse effects on the desired reaction. Representative data illustrating the effect of these variables are given in Table I. Commercial "cyclohexanone peroxide" (1%) was added as initiator. Under optimum conditions, a maximum of 15% of the original cyclohexanol could be converted to peroxide. The course of a typical oxidation is plotted in Fig. 1. Rate of oxygen uptake is roughly proportional to the peroxide concentration at constant temperature.

TABLE I

AUTOCATALYZED OXIDATION OF CYCLOHEXANOL

Excess O_2 feed, 1% "cyclohexanone peroxide" initiator, glass vessels. All reactions were run in creased flask reactor unless otherwise indicated. All conversions are net to analyzed peroxide, less peroxide initiator, based on cyclohexanol charged.

Variable	Temp., °C.		O_2 abs. rate[a]	Yield peroxide/O_2, %		Peak conv. to peroxide, %
	Init.	Final		at 2% conv.	at 10% conv.	
	125	120	5.5	80	65	12.5
	125	103	5.5	80	70	15.5
[b]	128	105	4.5	90	80	15.5
	140	[c]	13			8.5
[d]	125	125	6.0	40		
[e]	110	110	6.0	25		2.5
[f]	125	[c]	6.5	55		7
[g]	125	[c]	4.5	75	60	10
[h]	130	130				3.5
[i]	128	128	4.5	55		2.5

[a] Moles O_2 absorbed/hr./100 moles cyclohexanol charged, at a time corresponding to 2% conversion to peroxide. [b] 1% $CaCO_3$ in charge. [c] The desired constant temperature could not be maintained: accumulation of low-boiling substances caused reflux and temperature drop at end. [d] Cyclohexanol which had been in contact with brass strip 15 minutes at 70° (brass subsequently removed) used in charge. [e] Charge contained 1 p.p.m. Fe^{++}. [f] Low agitator speed (1800 r.p.m.). [g] Reaction run in creased bottle similar to Waring blendor container. [h] Reaction run in 40-mm. tube, O_2 fed *via* fritted disk at bottom, no mechanical agitation. [i] Air feed.

Principal by-products of the reaction were cyclohexanone, acids and esters, the latter presumably derived from overoxidation.

Commercial "Cyclohexanone Peroxide."—We shall show later that the peroxides produced by the oxidation are very similar to the "cyclohexanone peroxide" presumably produced commercially[4] by reaction of hydrogen peroxide with cyclohexanone followed by evaporation of solvent.[5] According to Criegee,[6] peroxides formed by this procedure contain chiefly dimeric peroxides such as II and III and possibly some IV, rather than the simple monomeric form I.

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(1) E. G. E. Hawkins, *Nature*, **166**, 69 (1950); E. G. E. Hawkins and D. P. Young, *J. Chem. Soc.*, 2804 (1950).

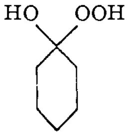
(2) M. S. Kharasch, A. Fono and W. Nudenberg, *J. Org. Chem.*, **15**, 754 (1950).

(3) A similar behavior has been reported for other types of peroxides; see P. D. Bartlett and K. Nozaki, THIS JOURNAL, **69**, 2299 (1947); H. C. Stevens, U. S. Patent 2,491,397 (1949).

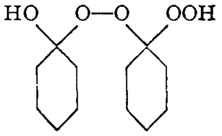
(4) Lucidol Division, Novadel-Agene Corp., Buffalo, N. Y.

(5) N. A. Milas, S. A. Harris and P. C. Panagiotakos, THIS JOURNAL, **61**, 2430 (1939); N. A. Milas, U. S. Patent 2,298,405 (1942).

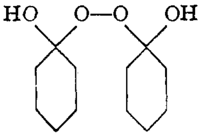
(6) R. Criegee, *Fortsch. der Chem. Forsch.*, **1**, 508 (1950).



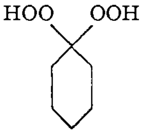
I



II



III



IV

A recent paper by Cooper and Davison[7] also substantiates the structures proposed by Criegee. This and other published data indicate that the structure II is the principal constituent of the commercial peroxide.

Our studies with commercial "cyclohexanone peroxide" and with peroxides produced by the oxidation of cyclohexanol have suggested that the situation is exceedingly complex and that there probably exists a large number of such peroxides which may be regarded as derivatives of I *via* its reaction with cyclohexanone, with hydrogen peroxide or with itself. In solution, a labile equilibrium exists between the various forms (including the parent equilibrium I $\rightleftarrows$ cyclohexanone + hydrogen peroxide). The position and rate of reaching equilibrium are dependent on the environment and other experimental variables.

The commercial peroxide is a solid with a wide melting range and is probably a mixture of several peroxides. The lability of the equilibrium between the various peroxide forms prevented their satisfactory separation by conventional techniques. However, qualitative inferences may be drawn from such experiments. Rapid precipitation of solid peroxide from a methanolic solution by rapid addition of water gave a 63% recovery of material indicated by analysis and melting point to be II. This product, if not filtered out immediately, would redissolve completely in about one hour and would not precipitate again on addition of more water.

In solution, commercial "cyclohexanone peroxide" undergoes slow dissociation to an equilibrium containing monomeric forms and possibly free hydrogen peroxide as well. A qualitative measurement of the degree of dissociation could be obtained by a single-stage solvent partition, the extent of dissociation being measured by the relative solubility in the aqueous and organic phases. Such data (Table II) show that the dissociation to water-soluble peroxides occurred most rapidly and completely in solvents of high dielectric constant. In the presence of acids or bases, the dissociation was extremely rapid. The addition of cyclohexanone to "cyclohexanone peroxide" solutions resulted in the formation of a higher percentage of peroxides soluble in the organic layer as would be expected.

Other partition studies indicated the virtual absence of dissociated forms in freshly prepared solutions in inert solvents.

Cooper and Davison[7] have followed the dissociation of II in solution spectroscopically and have concluded that it is in equilibrium with IV and cyclohexanone. We have independently carried out similar experiments with the same conclusion and furthermore have found a comparable behavior with the peroxide of the probable structure III (from reaction of two moles of cyclohexanone with one of hydrogen peroxide[5]). Very little free cyclohexanone was found to be present in either of these peroxides in the solid state, but in solution (in solvents such as carbon tetrachloride, chloroform and dioxane) the concentration of cyclohexanone rose with time to an equilibrium value. The extent and rate of dissociation were greater with III than with II.

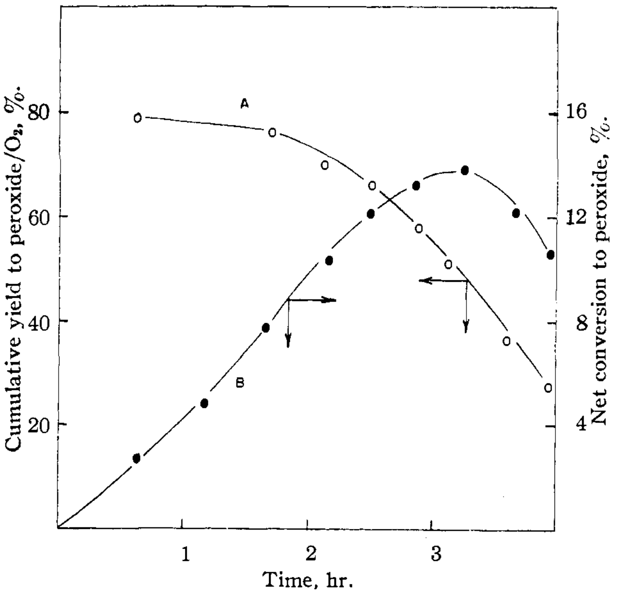


Fig. 1.—Yield (A) and conversion (B) in typical batch oxidation of cyclohexanol; 1.0% "cyclohexanone peroxide" initiator; t = 125° for first two hours, then decreasing gradually to 114° at end.

Table II

Dissociation of Commercial "Cyclohexanone Peroxide" in Solvents

Procedure: 10% solutions of peroxide in solvents indicated were allowed to stand at room temperature. At the end of the indicated time, 1-ml. samples were equilibrated between 20 ml. each of xylene and water–12% methanol, the layers were separated immediately and analyzed for peroxide.

Solvent	Total peroxide in water phase, % 5–10 min.	1.5 hr.	5 hr.	18 hr.
Methanol	48.3	67.2		74.3
Methanol–0.1% H_2SO_4	60.3			61.6
Methanol–0.1% NaOH	82.5			81.5[a]
Acetic acid	73.6		74.3	
Acetonitrile[b]		67.7[c]	73.8[d]	
Nitromethane[b]	61.3	62.0		
Acetone	45.8	59.8		75.2
Chloroform	45.5		71.2	71.0[e]
Benzene[f]	48.4	63.8		61.5
t-Butyl alcohol	46.1[g]		61.7	
Dioxane	43.2	44.6		
Ether	41.1	43.8		

[a] 20% of peroxide decomposed. [b] 5% solution. [c] 45 min. [d] 2.7 hours. [e] Addition of 16% cyclohexanol to this solution caused decrease to 55% water-soluble peroxides in 30 minutes. [f] 8% solution. [g] 15 minutes.

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[7] W. Cooper and W. H. T. Davison, *J. Chem. Soc.*, 1180 (1952).

Reaction of peroxides with ferrous ion to yield 1,12-dodecanedioic acid was used as a further indication of compositions and structures, as only I and II would be expected to yield the desired product.[7] Data, as given in Table III, substantiated the assigned structures.

TABLE III

YIELDS OF 1,12-DOCECANEDIOIC ACID

Reactions carried out in methanol solution using $FeSO_4 \cdot 7H_2O$

Probable structure and source of reactant	Yield, %
Commercial "cyclohexanone peroxide"	48–62[a]
Same, after 18 hours in methanol[b]	18
1-Hydroxy-1′-hydroperoxydicyclohexyl peroxide (II)	78
Mother liquor from the above preparation	26
1,1′-Dihydroxydicyclohexyl peroxide (III)	23[c]

[a] Range represents variation between different batches of peroxide. [b] Freshly prepared solutions (<15 min.) of peroxide in methanol were employed in other cases to minimize dissociation. [c] Probable dissociation in solution and/or presence of low concentrations of other peroxides in starting material.

Properties of Peroxides from the Oxidation of Cyclohexanol.—No feasible method was found for isolation or concentration of peroxides from crude cyclohexanol oxidation product due to the labile equilibria between various peroxide forms. Direct distillation resulted in loss of hydrogen peroxide, which loss could be decreased somewhat by rapid removal of distillate. In one case, a low yield of solid peroxide was recovered in the residue. Likewise, crystallization, precipitation, adsorption or extraction techniques were ineffective. Countercurrent distribution analysis indicated the presence of hydrogen peroxide as a major constituent with, however, considerable hydrolysis occurring during the experiment.

Despite the failure to characterize these peroxides directly, the following evidence indicates that the peroxides produced by oxidation of cyclohexanol are qualitatively equivalent to those produced by the reaction of cyclohexanone and hydrogen peroxide:

1. Reaction of the crude cyclohexanol oxidation product with ferrous ion under a variety of conditions gave 1,12-dodecanedioic acid in essentially identical yields as given by commercial "cyclohexanone peroxide" under comparable conditions (Table IV).

TABLE IV

REDUCTIVE COUPLING OF PEROXIDES

Reagent	Yield of dodecanedioic acid/peroxide, % Untreated product	Ketone treated[a]
Cyclohexanol oxidation		
Ferrous sulfate–methanol	40	44
Ferrous acetate–50% dioxane	41	45
Ferrous heptanoate–benzene	..	68
Ferrous caproate–toluene	44	64
Commercial peroxide		
Ferrous sulfate–methanol	46[b]	47
Ferrous caproate–toluene	49[c]	65

[a] Cyclohexanone added equivalent to 8 moles per mole peroxide present; mixture stood overnight at room temperature. [b] Peroxide in cyclohexanol solution. [c] Peroxide in toluene solution.

2. Chemical reduction of peroxides in a crude oxidation product resulted in recovery of cyclohexanone corresponding to an 82% yield, based on cyclohexanol consumed (yield of analyzed peroxide was 65% based on cyclohexanol consumed, with 10.4% of the original cyclohexanol converted to peroxides). Thus, not more than 18% of the cyclohexanol consumed could have been converted to extraneous peroxides. Moreover, the acidity of the product and the sensitivity of cyclohexanone to oxidation under these conditions indicate that the majority of the yield loss probably arose *via* overoxidation.

3. A material balance over the two-step synthesis of 1,12-dodecanedioic acid from cyclohexanol gave 43% yield of the acid and 16% of cyclohexanone, based on cyclohexanol consumed. The second step was carried out by the ferrous soap procedure described below. The above yields give excellent agreement with those determined for the two separate steps.

Synthesis of 1,12-Dodecanedioic Acid.—Reaction of commercial "cyclohexanone peroxide" with ferrous sulfate in methanolic solution was found a convenient laboratory synthesis of 1,12-dodecanedioic acid. Improved yields were obtained by use of a preliminary reaction with added cyclohexanone followed by treatment with a hydrocarbon solution of a ferrous soap as the coupling agent. Advantages of this procedure were most marked with cyclohexanol oxidation product as the starting material. Yields of 68% were obtained, compared to 40% for the ferrous sulfate–methanol procedure. This improved yield may be attributed to decreased dissociation of the peroxides under these conditions. As shown in Table IV, improved yields were only obtained when both these reaction modifications were employed.

The material balance data given above indicate that essentially none of the cyclohexanone added prior to the coupling step was consumed.

At no time during the investigation was any explosion or violent decomposition encountered. Peroxide concentrations could not be made to detonate either by heat or by impact.

Experimental Details

Source of Materials.—Cyclohexanol was redistilled at atmospheric pressure through a three-foot packed column. This material gave the same oxidation rates and yields as did material purified by sodium sulfite followed by potassium permanganate treatment.

Cyclohexanone was redistilled as above.

"Cyclohexanone peroxide" was obtained from the Lucidol Division, Novadel-Agene Corporation, Buffalo, N. Y. *Anal.* (variable from batch to batch): Peroxide equivalent weight (equivalent weight calculated from peroxide anal.) 63.0 to 66.0, m.p. 47–58° to 72–74°.

Oxidation of Cyclohexanol.—Optimum results were obtained using a 500-ml. creased Pyrex flask, fitted into a high speed propeller type agitator with a glass ball joint stirrer bearing, and reflux condenser. All reactor accessories were of glass with ground joints lubricated by silicone grease. The charge consisted of 280 g. of cyclohexanol plus 2.8 g. of commercial "cyclohexanone peroxide." In starting up, the agitator was adjusted to give about 3500 r.p.m., and an oxygen flow of 300 ml. per minute was started, which provided an excess over the amount absorbed by the reaction. The solution was then heated rapidly to 125°, at which temperature the reaction was maintained. If a product containing about 9 to 10 mole % peroxide was desired, the oxidation was terminated after about 10 l. of oxygen had been consumed. In oxidations run beyond this point, the reaction temperature was reduced progressively. At the end of a run, the mixture was cooled to essentially room temperature before discontinuing oxygen flow or agitation.

Determination of Yield of "Cyclohexanone Peroxide" Plus Cyclohexanone in the Oxidation of Cyclohexanol.—A mixture consisting of 2.771 moles of cyclohexanol, 0.023 mole of peroxidic oxygen and 1.4 g. of calcium carbonate was processed as above at 125° for 2.5 hours, during which time 0.398 mole of oxygen was absorbed. The crude reaction product by analysis contained 0.311 mole (65%, based on O_2 consumed, corrected for peroxide added) of peroxidic oxygen and 0.031 equivalent of free acid. This was added with stirring at 25° over a one-hour period to a solution of 48.9 g. (0.388 mole) of sodium sulfite in 489 ml. of water. Subsequently, a solution containing 9.7 g. of sodium sulfite, 97 ml. of water and 37 ml. of acetic acid, was added, and the mixture was stirred for one and a half hours longer to complete the reaction. The resulting mixture was neutralized to phenolphthalein with 50% sodium hydroxide and steam distilled. On fractionation of the dehydrated steam distillate through a six-foot Podbielniak column, 2.327 moles of cyclohexanol and 0.387 mole of cyclohexanone (82%, based on cyclohexanol consumed) were recovered. These yields were verified by functional group and infrared analysis on the dehydrated steam distillate and on the separated products.

A control experiment using a solution of commercial "cyclohexanone peroxide" in cyclohexanol gave 102% recovery of cyclohexanone, based on analyzed peroxide charged.

Isolation of Peroxide of the Probable Structure 1-Hydroxy-1′-hydroperoxydicyclohexyl Peroxide (II).—To a solution of 10.0 g. of commercial "cyclohexanone peroxide" in 100 g. of methanol was added as rapidly as possible 60 ml. of water, followed by immediate filtration and drying for one hour at room temperature at 1 mm. pressure, yielding 6.3 g. of solid product, m.p. 73° (reported 76°).[6]

Anal. Calcd. for $C_{12}H_{22}O_5$: peroxide equiv. wt., 61.6. Found: peroxide equiv. wt., 61.8.

From the mother liquor was recovered an ill-defined crystalline peroxide, m.p. 38–58°, peroxide equivalent weight 66.8.

Preparation of the Peroxide of the Probable Structure 1,1′-Dihydroxydicyclohexyl Peroxide (III).—This material was prepared from anhydrous hydrogen peroxide (2 moles) and cyclohexanone (1 mole) by the method of Milas, Harris and Panagiotakos.[5] The product was a sirup which solidified after several hours at 0° and was recrystallized from ether at −40°, m.p. 68° (reported 68–70°).[5]

Anal. Calcd. for $C_{12}H_{22}O_4$: peroxide equiv. wt., 115.1. Found: peroxide equiv. wt., 114.8.

Preparation of 1,12-Dodecanedioic Acid from Commercial "Cyclohexanone Peroxide."—To 72.3 g. (0.26 mole) of solid ferrous sulfate heptahydrate was added under nitrogen 700 ml. of deaerated methanol. As soon as the salt was dissolved, a freshly prepared solution of 24.6 g. (0.190 mole of peroxidic oxygen) of commercial "cyclohexanone peroxide" dissolved in 300 ml. of deaerated methanol was added at room temperature with moderate agitation over a period of 2 to 5 minutes. The reaction was complete as soon as all the peroxide was added. A nitrogen atmosphere was maintained through the reaction.

The product was brought to *p*H 11 with 2 *N* sodium hydroxide, the methanol was removed on a steam-bath, and the mixture was boiled for 1 hour at *p*H 11 to complete the saponification. The cooled mixture was filtered, the filter cake was slurried twice with water containing a little sodium hydroxide, and the washes were added to the filtrate, which was acidified with concentrated sulfuric acid and boiled to remove traces of methanol and of volatile acids. An odor, characteristic of caproic acid, was present. The solution was cooled, and the crude 1,12-dodecanedioic acid was collected and dried in a vacuum oven at 80°. The yield of crude acid (m.p. 125–126.5°) was 12.3 g. (52%, calculated from the peroxide analysis of the starting material, the weight of product, and its neutralization equivalent). It was recrystallized twice from benzene; m.p. 127.5° (reported 129° cor.).[8] Its identity also was confirmed by X-ray analysis.

Separation of peroxides from crude cyclohexanol oxidation product by countercurrent distribution was carried out in a 24-tube Craig machine.[9] An oxidation product of 9.5% conversion to peroxides was used, with mutually saturated cyclohexanol and water as the solvent pair. After 16 transfers, two peroxide peaks were found corresponding to $Q = 75\%$ (70% of total) and to $Q = 0\%$ (30% of total, where $Q = 100C_w/(C_w + C_0)$ = percentage of peroxide in water phase. Commercial "cyclohexanone peroxide" and hydrogen peroxide in single stage extractions gave $Q = 1$ and 81%, respectively. The discrepancy between the latter value and the 75% found in the former experiment may be attributed to hydrolysis during the countercurrent distribution. Comparable data on cyclopentanol oxidation products will be presented in a subsequent paper.

Preparation of Ferrous Soap Reagent.—The procedure used for preparation of ferrous soap reagent may be illustrated by a typical preparation of ferrous caproate–benzene. A mixture of 69.6 g. (0.6 mole) of caproic acid and 100 ml. of distilled water was neutralized to phenolphthalein with 2 *N* sodium hydroxide. Additional caproic acid, 34.8 g. (0.3 mole), was added; and the solution was blanketed with nitrogen. To it was added 550 ml. of oxygen-free reagent benzene at room temperature with agitation, followed by a freshly prepared solution of 83.4 g. (0.3 mole) of ferrous sulfate heptahydrate in 600 ml. of water over a period of about 15 minutes. The lower layer was removed and the upper layer washed three times with 400 ml. each of oxygen-free water. Five grams of iron powder was then added, and the residual water was removed by distillation at atmospheric pressure. Such solutions were extremely sensitive to oxygen, much more so than solutions of ferrous sulfate, and were stored and handled under nitrogen atmosphere at all times. The reagent prepared in the above example analyzed 0.25 meq. per gram Fe^{++} or 1.40% Fe^{++}. More concentrated reagents could be prepared if desired.

Reductive Coupling of Peroxides in Cyclohexanol Oxidation Product.—An autocatalyzed oxidation of cyclohexanol was carried out by the standard procedure. A 237.36-g. portion of the crude product (calcd. to be derived from the oxidation of 224.65 g. of cyclohexanol (figure corrected for analyzed purity) plus 2.46 g. (0.020 mole) of commercial "cyclohexanone peroxide") containing by analysis 0.225 mole of peroxidic oxygen was added to 179.49 g. of cyclohexanone (figure corrected for analyzed purity). The mixture was allowed to stand overnight at room temperature. It was then blown with nitrogen and added with stirring at room temperature to 930 ml. of a solution of ferrous heptanoate in benzene containing by analysis 0.338 equivalent Fe^{++}. The product was diluted with water, neutralized with sodium hydroxide, and distilled, removing the oil layer and keeping the contents of the distillation flask neutral by addition of sodium hydroxide as required. The residue was digested with excess sodium hydroxide for two hours, filtered and washed with ether (this extract contained 0.5 g. of material, largely ester). It was then acidified with sulfuric acid and steam distilled to remove monobasic acids. From the residue was obtained by crystallization 19.30 g. of crude acid, neut. equiv. 127.2 (calculated 0.0758 mole, or 67.4%, based on peroxide). The raffinate was evaporated to dryness and extracted with ether and chloroform yielding 4.89 g. of dark semi-crystalline material, neut. equiv. 258. Analysis of a composite sample of the two crops of acids by countercurrent solvent distribution between 1:1 methanol–water and 1:4 petroleum ether–benzene indicated a total yield of 1,12-dodecanedioic acid of 0.0770 mole (68.4%).

The crude acid was decolorized with charcoal, recrystallized from benzene and aqueous methanol; m.p. 127°; neut. equiv.: calcd. for $C_{12}H_{22}O_4$ 115.1, found 115.4.

The steam distillate was fractionated in a six-foot Podbielniak column giving the following recoveries, which were verified by functional group and infrared analysis: cyclohexanol, 190.97 g.; cyclohexanone, 185.24 g.; calculated cyclohexanol consumed (crediting peroxide charge to oxidation) 0.3563 mole, cyclohexanone produced 0.0586 mole; yield of dodecanedioic acid based on cyclohexanol consumed, 43.2%, of cyclohexanone based on cyclohexanol consumed, 16.4%.

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(8) D. A. Fairweather, *Phil. Mag.*, [7] **1**, 944 (1926).

(9) L. C. Craig and O. Post, *Anal. Chem.*, **21**, 500 (1949).