

## Macrocyclic Synthesis. II. Cyclohexanone Peroxides

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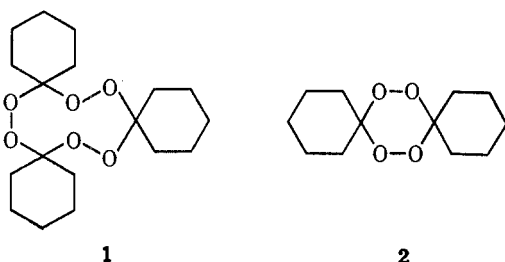
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The reaction of cyclohexanone with hydrogen peroxide to yield both the dimeric and trimeric cyclic peroxides has been investigated. It has been found that tricyclohexylidene peroxide is the kinetic product under most conditions and that dicyclohexylidene peroxide is easily formed from it. Improved syntheses of the peroxides, particularly for the trimer, have resulted.

The thermal and photochemical decomposition of peroxides of cyclic ketones has been found to provide a general and facile synthesis of macrocyclic compounds.<sup>1</sup> For this reason a better understanding of the synthesis of the requisite peroxides is required. The most important such peroxides are those of cyclohexanone. The term "cyclohexanone peroxide" has been applied to a number of different compounds, usually in the generic sense to mixtures of peroxides which find application as initiators in polymerization. Frequently, the actual structure of the peroxide in hand is not known. In general, yields are low and there is insufficient information about the intermediates and complex equilibria involved in the synthesis of cyclohexanone peroxides.

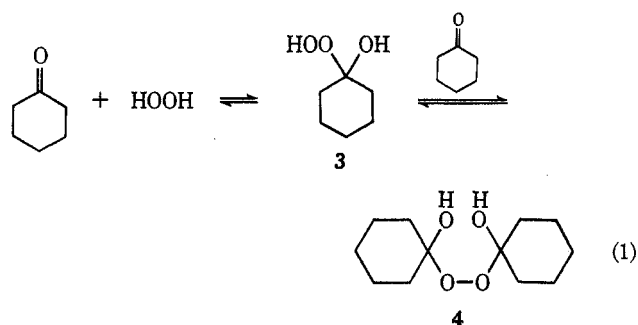
This report is concerned primarily with just two of the several cyclohexanone peroxides, dicyclohexylidene peroxide (2) and tricyclohexylidene peroxide (1). We have correlated much of the available data on the cyclohexanone-(hydrogen peroxide) reaction with our own findings to develop a mechanistic scheme which, in turn, has led to improved synthesis of these peroxides (1, 2).



Probably the focal point of present knowledge is the paper by Antonovskii, Nesterov, and Lyashenko<sup>2</sup> who have made a detailed study of the acid-catalyzed reaction of cyclohexanone and hydrogen peroxide. These investigators have, in part, rewritten the sequence of intermediates proposed by Criegee,<sup>3</sup> by Kharasch and Sosnovsky,<sup>4</sup> and by others.<sup>5</sup>

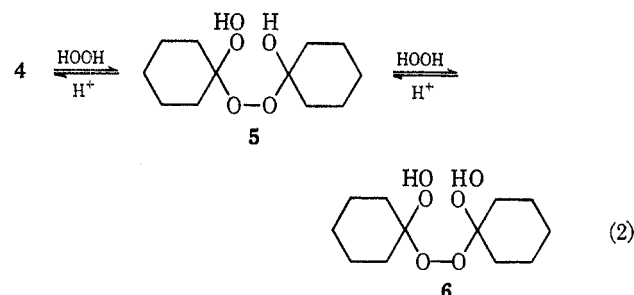
It was confirmed,<sup>2</sup> as asserted by Kharasch and Sosnovsky,<sup>4</sup> that treatment of cyclohexanone with hydrogen peroxide in neutral solution yields only the 1,1'-

dihydroxydicyclohexyl peroxide (4), even in the presence of a large excess of hydrogen peroxide (eq 1).

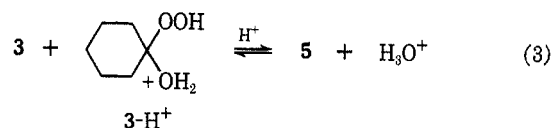


The presumed intermediate, 3, could not be isolated in this case; however, it should be noted that the corresponding derivative of  $\alpha$ -halocyclohexanones is known.<sup>4,6</sup>

In acidic solutions, depending on acid concentration, more highly peroxygenated compounds (5 and 6) are formed. As pointed out by Antonovskii, *et al.*,<sup>2</sup> earlier investigators had assumed, and quite reasonably, that the more highly peroxygenated derivatives, 5 and 6, were derived from 4 (eq 2).<sup>3-5,7,8</sup> Antonovskii, *et al.*,<sup>2</sup>



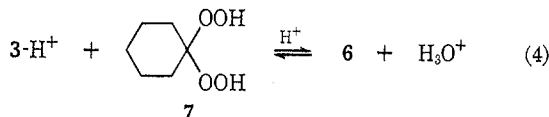
report evidence to the contrary. These investigators conclude that 1-hydroxy-1'-hydroperoxydicyclohexyl peroxide (5) appears to form directly from 3 in "weakly" acidic solutions, *i.e.*, eq 3. This conclusion is based on



their observation that conversion of 4 to 5 is appreciably slower than formation of 5 from cyclohexanone and hydrogen peroxide with acid (eq 3). Their argument is difficult to evaluate, however, because of the lack of data reported in the paper.<sup>2</sup>

(6) M. Schulz, K. Kirschke, and E. Höhne, *Chem. Ber.*, **100**, 2242 (1967).(7) A. Rieche, *Angew. Chem.*, **73**, 57 (1961).(8) M. Schulz and K. Kirschke, *Advan. Heterocycl. Chem.*, **8**, 165 (1967).(1) P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, Jr., and J.-C. Farine, *J. Amer. Chem. Soc.*, **90**, 817 (1968).(2) V. L. Antonovskii, A. F. Nesterov, and O. K. Lyashenko, *Zh. Prikl. Khim.*, **40**, 2555 (1967); *J. Appl. Chem. USSR*, **40**, 2443 (1967) (Consultant's Bureau English translation).(3) R. Criegee, W. Schnorrenberg, and J. Becke, *Justus Liebigs Ann. Chem.*, **565**, 7 (1949); R. Criegee and G. Lohaus, *ibid.*, **583**, 6 (1953).(4) M. S. Kharasch and G. Sosnovsky, *J. Org. Chem.*, **23**, 1322 (1958).(5) (a) N. Brown, M. J. Hartig, M. J. Roedel, A. W. Anderson, and C. E. Schweitzer, *J. Amer. Chem. Soc.*, **77**, 1756 (1955); (b) W. Cooper and W. H. T. Davison, *J. Chem. Soc.*, 1180 (1952); (c) N. A. Milas, S. A. Harris, and P. S. Panagiotakos, *J. Amer. Chem. Soc.*, **61**, 2430 (1939).

In more concentrated acid, **3** is converted to the *gem*-dihydroperoxide (**7**) and the 1,1'-dihydroperoxydicyclohexyl peroxide (**6**) is formed by reaction of **3**-H<sup>+</sup> and **7**, according to Antonovskii, *et al.*<sup>2</sup> (eq 4).



### Results and Discussion

Synthesis of dicyclohexylidene peroxide (**2**) has been reported in low yield<sup>4</sup> and it seems to be generally understood that **2** is formed by dehydration of the hydroxyhydroperoxy peroxide (**5**), *i.e.*<sup>8</sup>



We have repeated the Kharasch and Sosnovsky preparation of the dimer (**2**), and close examination reveals three distinct stages to the reaction. (1) Initially, on mixing, the cyclohexanone-(hydrogen peroxide) solution becomes warm and homogeneous. (2) On addition of glacial acetic acid and perchloric acid, followed by warming to 40°, a turbid solution develops. (3) Further heating of the solution to about 60° produces a clear solution which on subsequent work-up affords the dimer (**2**) in 14–23% yield.

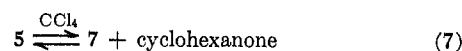
Our early attempts at the Kharasch–Sosnovsky synthesis yielded the trimeric peroxide **1** instead of the expected dimer **2**. Subsequently, we found that if the reaction is stopped during stage 2 (omitting heating to 40°), only the trimeric peroxide **1** is isolated, 72% yield; dimer **2** is produced by carrying the reaction through stage 3. This suggests that the trimer **1** is the kinetically controlled product and that dimer is the thermodynamically more stable product.

Accordingly, we treated pure trimer **1** under Kharasch–Sosnovsky conditions, *i.e.*, perchloric acid in acetic acid at 60° for 1 hr, and obtained the dimeric peroxide **2** in 53% yield. Repeating the same experiment at room temperature afforded only trimer, which was recovered in 82% yield.

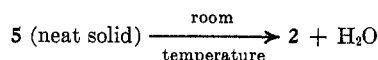


We have also investigated the new synthesis of Ledaal<sup>9</sup> and find, there too, that the initial product is trimeric peroxide **1** rather than dimer **2** as reported. The Ledaal procedure involves reacting cyclohexanone, hydrogen peroxide, and perchloric acid in acetonitrile and allowing the solution to evaporate, leaving the solid product. Duplicating the published procedure, we isolate trimer **1** in 82% yield. Further investigation, however, revealed the reaction to be sensitively dependent on temperature. We have not systematically investigated the effect of temperature, but we find that the Ledaal synthesis can yield dimer if the reaction is carried out at higher than average room temperatures, *i.e.*, between 25 and 30°. It is possible that the published Ledaal procedure was carried out at a sufficiently high temperature to yield dimeric peroxide. Alternatively, the trimer may have been converted to the dimer during work-up, possibly during recrystallization.

While it is apparent that trimer **1** is the more easily formed of the two peroxides and that it is a precursor of dimer **2**, it is not certain that the trimer always precedes the dimer. We have prepared pure **5** and subjected it to slightly modified “Kharasch–Sosnovsky” conditions at room temperature and obtain the dimer **2** in 67% yield (eq 5). Rieche and Bischoff<sup>10</sup> have also carried out this transformation. If the reaction is repeated at 5°, however, trimer **1** is isolated in high yield. The Ledaal synthesis can also be modified to yield 1-hydroxy-1'-hydroperoxydicyclohexyl peroxide (**5**) (dilute hydrogen peroxide). We have observed, as also noted by Cooper and Davison,<sup>5b</sup> that this peroxide **5** is partially dissociated in carbon tetrachloride solution as evidenced by the appearance of infrared absorption due to cyclohexanone; in potassium bromide no cyclohexanone absorption appears. We find that solid **5**, prepared by the Ledaal procedure,



on standing in the open at room temperature is slowly converted to dimer. The conversion can be followed by infrared (KBr). After 4 days a pure (by infrared) sample of **5** was found to contain a detectable amount of dimer **2**. After 1 month the sample had been completely converted to dimer. At no time was



any detectable concentration of trimer present. We conclude that while it appears that the dimer may be formed directly under some special conditions, it is clear that both the Ledaal and the Kharasch and Sosnovsky syntheses yield the trimer initially.

The acid concentrations used in the synthesis of the peroxides (**1**, **2**) are quite low and fall in the category of “weakly acidic” solutions according to the description of Antonovskii, *et al.*, who carried out their investigations in the absence of added solvent, making a direct comparison of the available data difficult. It was reported<sup>2</sup> that at higher acid concentrations, in the range of 1–3 *N*, even with a deficiency of hydrogen peroxide that a major product of the cyclohexanone-(hydrogen peroxide) reaction is the 1,1'-dihydroperoxydicyclohexyl peroxide (**6**).

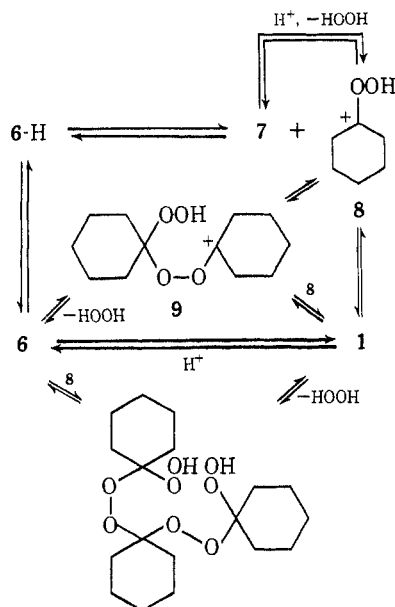
Interestingly, we find that the dihydroperoxy peroxide (**6**) is spontaneously converted to trimer **1** in high yield on its dissolution in methanol. Crude **6** (pure by infrared), prepared by a slight modification of Criegee's method<sup>3</sup> and still containing traces of mineral acid, was dissolved in methanol at room temperature. The solution began to warm immediately, and after a few minutes the methanol began to reflux as the result of a very exothermic reaction. After the reaction subsided, the solution was cooled to give the trimeric peroxide **1** in 81% yield.

Several reasonable pathways seem available for conversion of the dihydroperoxy peroxide (**6**) to trimer. One attractive explanation is that the reversal of the dihydroperoxy peroxide forming reaction occurs, followed either by trimerization of the ion **8** or by con-

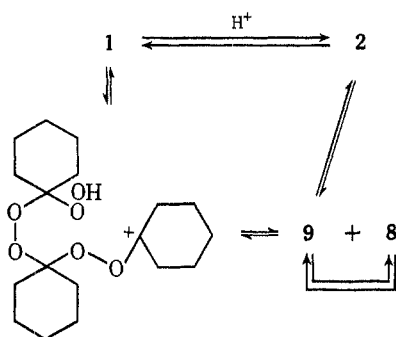
(9) T. Ledaal, *Acta Chem. Scand.*, **21**, 1656 (1967).

(10) A. Rieche and C. Bischoff, *Chem. Ber.*, **95**, 77 (1962).

denation of **8** and **6** and then cyclization. Direct formation of the ion **9** from **6** is equivalent, of course, to the first stage in **8** trimerization.



Although the trimeric peroxide **1** is easily isolated in high yield from the reaction of cyclohexanone and hydrogen peroxide and from the dihydroperoxy peroxide (**6**), its conversion to the dimer **2** is readily accomplished and can be rationalized most economically as follows.



In summary, it is evident that the reaction of cyclohexanone with hydrogen peroxide, under the acidic conditions usually employed, as well as the isolable intermediates along the way, yield tricyclohexylidene peroxide (**1**) as the kinetic product. The apparently thermodynamically more stable dimer **2** may be formed subsequently.

The synthesis of pure cyclohexanone peroxides, particularly the trimer **1**, has been considerably simplified. These findings have also permitted the ready preparation of several substituted cyclohexanone peroxides pursuant to the synthesis of substituted macrocyclic compounds.<sup>4,11</sup>

### Experimental Section

Infrared spectra were obtained with Perkin-Elmer spectrophotometers, Models 621 and 257. Nmr spectra were recorded using a Varian HA-100 spectrometer.

Hydrogen peroxide was obtained from the FMC Corp.

(11) P. R. Story, P. Busch, D. D. Denson, B. Lee, K. Paul, and J. A. Alford, unpublished work.

**Dicyclohexylidene Peroxide (2).**—The dimeric peroxide was prepared according to the Kharasch-Sosnovsky procedure<sup>4</sup> and by the Ledaal method.<sup>9</sup> The best yield obtainable by the Kharasch-Sosnovsky method was 23%: mp 128–129°; ir (KBr,  $\text{cm}^{-1}$ ) 3015 (w), 2940 (s), 2845 (m), 1445 (s), 1360 (m), 1340 (m), 1270 (s), 1258 (m), 1160 (s), 1030 (m), 948 (s, doublet), 928 (s), 850 (m), 831 (w), 821 (w).

**1-Hydroxy-1'-hydroperoxydicyclohexyl Peroxide (5).**—(A) The method of Kharasch and Sosnovsky<sup>4</sup> was used: mp 76–77° (65%); ir (KBr,  $\text{cm}^{-1}$ ) 3310 (m), 3210 (m), 2919 (s), 2825 (m), 1496 (m), 1399 (m), 1355 (m), 1278 (m), 1260 (m), 1167 (s), 1069 (s), 1057 (s), 981 (s), 951 (m), 925 (m), 915 (m), 870 (w), 840 (w), 821 (w). (B) Using the general procedure of Ledaal,<sup>9</sup> 981 mg (10 mmol) of cyclohexanone was dissolved in 10 ml of acetonitrile contained in a crystallization dish. To this solution was added 35 mg (10 mmol) of 98% hydrogen peroxide diluted with 2 ml of water and 2 drops of 70% perchloric acid. This mixture was stirred magnetically in an open fume hood until a white solid was obtained. The product amounted to 650 mg (53%) of **5**, pure by infrared analysis. After 1 month in the open at room temperature, this product was completely converted to the dimer **2**.

**Preparation of Dicyclohexylidene Peroxide (2) and Tricyclohexylidene Peroxide (1) from 1-Hydroxy-1'-hydroperoxydicyclohexyl Peroxide (5).**—(A) To a solution containing 4 g (16 mmol) of **5** in 100 ml of glacial acetic acid was added 5 ml of 10% perchloric acid in acetic acid. The reaction mixture was stirred at room temperature for 24 hr. After about 1 hr, a white solid began to form in the reaction mixture. On completion, the reaction mixture was filtered and the white solid was washed with water and air-dried. There was obtained 2.5 g (67%) of product, mp 123–126°, identical with the authentic dimer **2** by infrared comparison.

(B) In this general procedure the peroxide **5** was added to an erlenmeyer flask containing acetic acid and 10% perchloric acid in acetic acid. The flask was then shaken until all the solid was dissolved. In experiment C, the mixture of solvent and catalyst was cooled in an ice bath before adding the peroxide.

In some experiments, crystals formed during the noted reaction time and were filtered, washed with water, and dried in air and then in a desiccator. This product was assigned designation "a." The filtrates and those reaction mixtures which yielded no "a" crystals were diluted with water to approximately three times their original volume. All crystals resulting therefrom were designated "b" and treated as before. In some experiments a heavy oil resulted from dilution. However, if allowed to stand at room temperature, the oil crystallized within a few hours with no detectable change in composition. Table I summarizes the experiments performed.

**Interruption of Kharasch-Sosnovsky Synthesis of 2 prior to Completion.**—To 24.5 g (0.25 mol) of cyclohexanone was added 28 ml of 30% hydrogen peroxide (0.25 mol) at room temperature. After 15 min, 50 ml of glacial acetic acid and 3 ml of 10% perchloric acid in acetic acid were added. The reaction mixture was then placed in a boiling water bath whereupon it became cloudy. The cloudy solution slowly became clear, at which point the reaction mixture was removed from the water bath. The hot solution was poured all at once onto 200 g of ice with stirring. After about 10 min, the mixture had deposited a heavy oil at the bottom of the flask. Left suspended in solution was a white precipitate. The precipitate and oil were collected separately, washed with water, dried, and recrystallized from methanol. The heavy oil yielded 2.7 g (9.6%) of cyclohexanone triperoxide (**1**), mp 85–88°, as identified by infrared comparison with authentic material.<sup>3</sup> The white precipitate, after recrystallization yielded 1.1 g (3.9%), mp 128–129°, of dicyclohexylidene peroxide (**2**).

**Tricyclohexylidene Peroxide (1) by a Kharasch-Sosnovsky-Type Reaction.**—To an erlenmeyer flask containing 19.6 g (0.20 mol) of cyclohexanone, 22.6 g (0.20 mol) of 30% hydrogen peroxide was slowly added with cooling, if necessary, to maintain room temperature. After stirring for 15 min, 100 ml of glacial acetic acid was added, followed by 2.4 ml of 10% perchloric acid in acetic acid. This mixture was stirred at room temperature for 24 hr. After this time the solution was diluted with 400 ml of water to yield a heavy oil and some solid material. (Note: Best results are obtained if the temperature is held near 20° throughout the reaction period.) The cloudy aqueous solution was decanted and diluted with an equal volume of water. The diluted decantate was cooled at 10° for 24 hr after which time the

TABLE I  
REACTIONS OF 1-HYDROXY-1'-HYDROPEROXYDICYCLOHEXYL PEROXIDE (5) IN  
ACETIC ACID WITH PERCHLORIC ACID AS CATALYST

Expt	Composition of reactants <sup>a</sup>			Temp	Time, hr	Crystals recovered	Mp, °C	Products <sup>b</sup>	Yield, g	Yield, %
	I (g)	II (ml)	III (ml)							
A	2	50	2.5	Room	24	a	128-130	2	0.22	42
B	2	50	0.25	Room	24	b	126-129	2	0.55	65
						a	128-129	2	0.45	
C	2	50 (propionic acid)	2.5	6°C	24	b	126-129	2	0.76	76
						a	72-84	1	1.40	
D	2	50	2.5	Room	1	b	121-129	2	1.26	68
E	2	50	2.5	Room	0.167	b	73-121	2:1 = 4:6	1.27	69
F <sup>c</sup>	2	5 2.5 ml of water	0.25	Room	24	a	71-81	2:1 (90%)	0.80	43
						b	74-91	1	1.27	68
G	2	5	0.025	Room	24	b	69-107	2:1 = 1:3	0.10	5
						a	73-114	2:1 = 4:6	1.27	68
H	2	5	0.25	Room	24	a	73-114	2:1 = 4:6	1.27	68
						b	70-107	0.13	8	

<sup>a</sup> Reactants are I = 1-hydroxy-1'-hydroperoxydicyclohexyl peroxide (5), II = acetic acid, III = 10% perchloric acid in acetic acid.

<sup>b</sup> The proportions of dimer 2 and trimer 1 in product mixtures were estimated by comparison of infrared spectra with spectra of several known mixtures in the ratios 1:3, 1:1, and 3:1. <sup>c</sup> The water added in this experiment is equivalent to the water content in the Kharasch-Sosnovsky procedure for preparing 2 from cyclohexanone and 30% hydrogen peroxide.

solution had cleared considerably and a white solid was formed. All the resulting oils and solids were combined and recrystallized from methanol to yield 14.8 g (72%) of trimer 1:<sup>3</sup> mp 91-92°; ir (CCl<sub>4</sub>, cm<sup>-1</sup>) 2940 (s), 2860 (m), 1453 (s), 1366 (m), 1279 (m), 1169 (m), 1078 (s), 951 (s), 932 (s), 858 (w).

**Tricyclohexylidene Peroxide (1).** By Ledaal-Type Reaction.<sup>9</sup>—A mixture of 9.80 g (0.10 mol) of cyclohexanone, 11.3 g (0.10 mol) of 30% hydrogen peroxide, 20 drops of 70% perchloric acid, and 100 ml of acetonitrile was placed in a shallow dish in a fume hood and allowed to stand at room temperature (preferably under 24°) for 5 days. After this time there remained only a white solid, 9.46 g (83%), which was shown to be "pure" trimer 1 by infrared comparison, mp 87-90°.

**1,1'-Dihydroperoxydicyclohexyl peroxide (6)** was prepared according to the method of Criegee:<sup>3</sup> mp 83.5-84°; ir (CCl<sub>4</sub>, cm<sup>-1</sup>) 3410 (s, singlet), 2940 (s), 2860 (m), 1449 (m), 1382 (m), 1270 (m), 1150 (s, doublet), 1088 (m), 1055 (s), 939 (s), 909 (m).

**Conversion of 6 to Triperoxide (1).**—To a stirred solution of methanol (10 ml) containing 2-3 drops of hydrochloric acid was added 10.2 g of 6 (44.3 mmol). The solution became warm immediately and a very exothermic reaction ensued causing the methanol to reflux. After 5-10 min the mixture was cooled in an ice bath and then allowed to stand at room temperature for 1 day. A solid sheet of crystals formed and after 4 days in the refrigerator (5°) an oily solid appeared. All the precipitated material was recrystallized from methanol to yield 7.41 g (81%) of cyclohexanone triperoxide (1), mp 91-92°.

**Recrystallization of Tricyclohexylidene Peroxide (1).**—Recrystallization of trimer 1 can be effected in methanol, 80% acetic acid, or acetone. If the trimer is dissolved in the minimum amount of hot methanol and then cooled, an oil will usually separate. On standing overnight or sometimes longer, the oil will solidify. The oil is pure trimer by infrared. If the trimer is

dissolved in a sufficient amount of methanol at room temperature and the solution is allowed to stand open to the air so as to allow evaporation of the methanol, the resulting very large crystals take two forms which can be separated by hand. One crystalline form is clear and melts at 87-87.5°. The other is white and melts at 92-92.5°. The two forms are identical by infrared comparison.

**Conversion of Tricyclohexylidene Peroxide (1) to Dicyclohexylidene Peroxide (2).**—A 50-ml erlenmeyer flask containing 1 g (2.9 mol) of tricyclohexylidene peroxide (1) in 5 ml of acetic acid and two drops of 10% perchloric acid in acetic acid was warmed at 60° for 1 hr. The solution remained clear throughout the warming period. On cooling, a white solid was deposited which on recrystallization from methanol yielded 0.53 g (53%) of dicyclohexylidene peroxide (2), mp 128-129°.

**Treatment of Trimer 1 under Kharasch-Sosnovsky Conditions at Room Temperature.**—A 50-ml erlenmeyer flask containing 1.0 g of trimer 1 and 5 ml of acetic acid was heated gently, just a sufficient amount to dissolve the solid. The homogeneous solution was cooled to room temperature and 2 drops of 10% perchloric acid in acetic acid was added. The flask was allowed to stand open overnight. The crystalline solid which formed during this time was collected, recrystallized from methanol, and dried to yield 0.82 g of tricyclohexylidene peroxide (1), mp 91-92°.

**Registry No.**—1, 182-01-4; 2, 183-84-6; 5, 71-18-2; 6, 2699-12-9.

**Acknowledgment.**—We thank the National Air Pollution Control Administration (AP 00580) for support of this work.