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CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Studies in Organic Peroxides. XXIV. Preparation, Separation and Identification of Peroxides Derived from Diethyl Ketone and Hydrogen Peroxide

BY NICHOLAS A. MILAS AND ALEKSANDAR GOLUBOVIĆ[1]

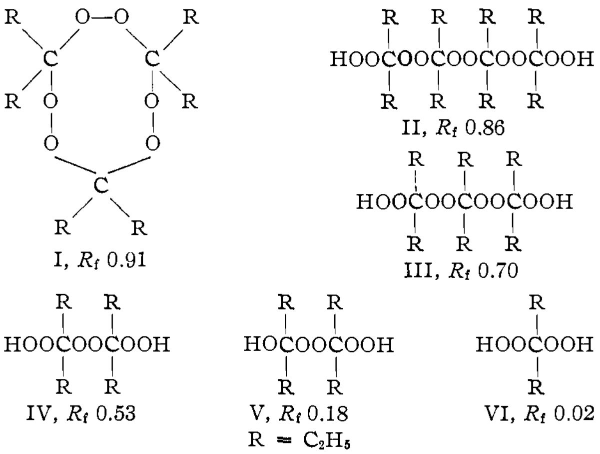
RECEIVED DECEMBER 17, 1958

Several new peroxides have been isolated and definitely characterized from the reaction of diethyl ketone and hydrogen peroxide. A chromatographic method using cellulose powder as an adsorbent has also been developed and used in conjunction with paper chromatography to separate some of these peroxides in the pure form.

In the preceding publication[2] it was shown that paper chromatography can be used for the detection and separation of organic peroxides. We have now adapted this method to guide us in the detection, separation and identification of organic peroxides derived from diethyl ketone and hydrogen peroxide. The chromatogram B of Fig. 1 in the preceding paper shows the presence of five peroxides which are formed from this reaction as revealed when potassium iodide–glacial acetic acid was used as the detecting agent. A sixth peroxide which is not shown failed to develop a spot with the detecting agent used. However, when hydrogen iodide–glacial acetic acid was used as the detecting agent a new spot appeared corresponding to an R_f of 0.91 which was attributed to a trimeric peroxide I.

When diethyl ketone was allowed to react at 0° with hydrogen peroxide in the presence of mineral acids a mixture of peroxides was obtained which was freed of excess hydrogen peroxide by extracting with a saturated ammonium sulfate solution dried and dissolved in petroleum ether. The mixture was chromatographed on a column of cellulose powder impregnated with dimethylformamide. The various peroxides were eluted with pentane saturated with dimethylformamide, and the fractions which gave single spots on paper chromatograms were combined and the pure peroxides isolated and identified by standard procedures. Of the six peroxides detected by paper chromatography, five have been separated and identified by this procedure and the sixth was detected but was too unstable to be isolated. They are labeled in the order in which they came out from the cellulose column. These are shown in Fig. 1.

The percentage of each peroxide present in the original mixture was estimated by paper chromatography and, in the above case, was found to be: I, 12.0; II, 0.4; III, 0.4; IV, 85.0; V, traces; and VI, 2.0%, respectively. Peroxides I, IV and VI could be separated from the mixture without resorting to cellulose powder chromatography. When the original mixture was dissolved in pentane and cooled to −70°, most of peroxide IV and traces of I separated as a crystalline mixture which could not be resolved into its pure components even after several crystallizations at low temperatures. However, when the crystalline mixture was subjected to sublimation at 3 mm. and at temperatures of 50–60°, the peroxide IV sublimed in the pure state and Compound I remained behind.



$HOOC(R)_2OOC(R)_2OOC(R)_2OOC(R)_2OOH$ (II); $HOOC(R)_2OOC(R)_2OOC(R)_2OOH$ (III); $HOOC(R)_2OOC(R)_2OOH$ (IV); $HOC(R)_2OOC(R)_2OOH$ (V); $HOOC(R)_2OOH$ (VI)

Fig. 1.—Peroxides derived from diethyl ketone and hydrogen peroxide.

Peroxide VI failed to crystallize at low temperatures with IV and I, but when the mother liquor from the original crystallization was cooled to −70° and moist air was blown through the solution, a crystalline product separated out which, when dried in air at room temperature, analyzed as the monohydrate of peroxide VI. That this was the monohydrate was shown by removal of water at 40° under high vacuum and analyzing the residual gum. Moreover, when the gum was redissolved in pentane and moist air was blown through the solution, the monohydrate crystalline peroxide re-formed. The other peroxides in the mixture could be separated only by cellulose powder chromatography.

Although some of the peroxides shown in Fig. 1 are interconvertible, all are probably formed from the unstable 3-hydroxy-3-hydroperoxypentane (VII). In the cyclanone series it has already been shown[3,4] that the initial peroxide formed between a cyclanone and hydrogen peroxide is 1-hydroxy-

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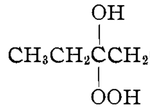
(1) Lucidol Research Assistant.

(2) N. A. Milas and I. Belič, THIS JOURNAL, **81**, 3358 (1959).

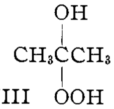
(3) N. A. Milas, S. A. Harris and P. C. Panagiotakos, *ibid.*, **61**, 2430 (1939).

(4) N. A. Milas, U. S. Patent 2,298,405 (1942).

cyclanyl hydroperoxide-1. This has been confirmed recently by Kharasch and Gosnovsky.[5] Moreover, Schenck and Becker[6] have recently isolated from the photosensitized oxidation of isopropyl alcohol 2-hydroxy-2-hydroperoxypropane (VIII) and found that it is decomposed completely by water into acetone and hydrogen peroxide. It is therefore conceivable that in our experiments in which aqueous hydrogen peroxide was used the initial intermediate VII did not survive isolation or detection on the paper chromatograms.



$CH_3CH_2C(OH)(OOH)CH_2CH_3$ VII



VIII $CH_3C(OH)(OOH)CH_3$

When hydrogen peroxide in anhydrous *t*-butyl alcohol or ethyl ether was allowed to react with diethyl ketone at room temperature and the unreacted hydrogen peroxide removed by saturated ammonium sulfate solution, the only peroxide detected by paper chromatography was 3,3-dihydroperoxypentane (VI). It was then suspected that this peroxide might be the precursor of most of the other peroxides isolated from our reaction. The possible interconversion of the various peroxides is shown schematically in Fig. 2 in which R stands for ethyl group.

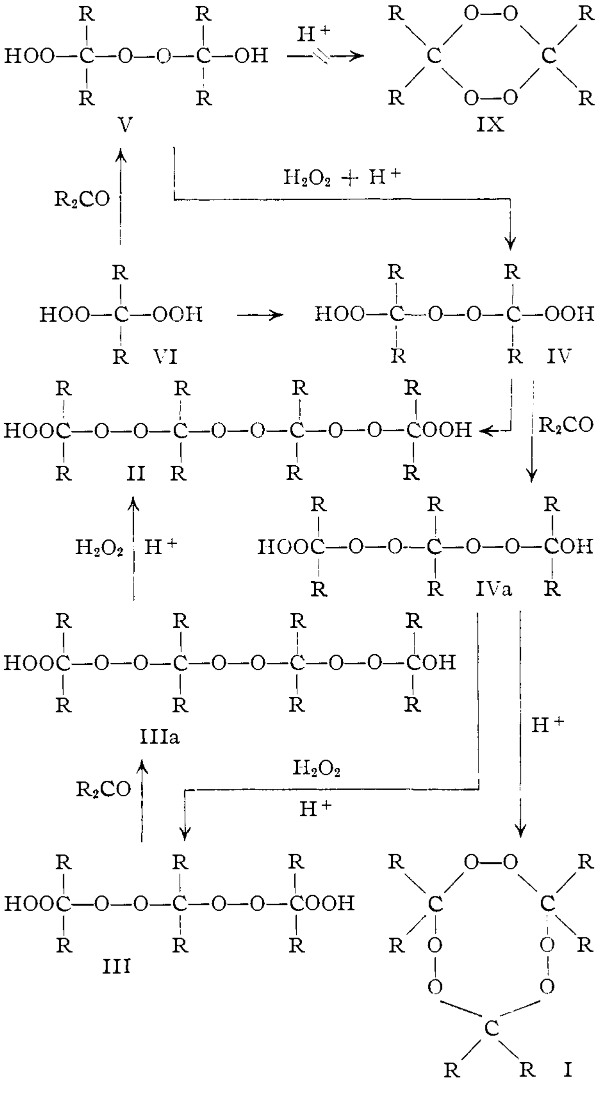
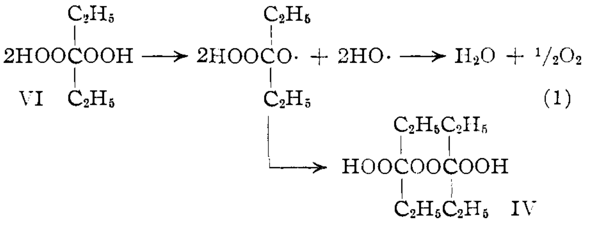


Fig. 2.—Interconversion of peroxides derived from diethyl ketone and hydrogen peroxide.

The interconversion of the various peroxides was best studied by paper chromatography. For example, the conversion of peroxide VI to peroxide IV *via* peroxide V is easily understood, but its direct conversion to IV is not very common. Only one example is known in the literature; the conversion at high vacuum and at 85–90° of fluorenyl dihydroperoxide to dihydroperoxydifluorenyl peroxide.[7] In order to discover the mechanism of this conversion we allowed a sample of 3,3-dihydroperoxypentane (VI) to decompose in a closed system filled with pure nitrogen and connected to a graduated buret filled with a concentrated salt solution. After three weeks of standing at room temperature the gas evolved was analyzed and found to be pure oxygen. A paper chromatogram of the residue showed the presence of 3,3′-dihydroperoxy-3,3′-diphenyl peroxide (IV) as the main product with traces of peroxides II and III and a new as yet unidentified peroxide. Since the oxygen evolved was slightly more than the theoretical for the conversion of peroxide VI to peroxide IV (equation 1), and the paper chromatogram showed the presence of traces of peroxides II and III, it is quite possible that peroxide IV could also form a monoradical but to a much lesser extent than peroxide VI. This monoradical could



$$\underset{\text{VI}}{2\,\mathrm{HOOC(C_2H_5)_2OOH}} \longrightarrow 2\,\mathrm{HOOC(C_2H_5)_2O\cdot} + 2\,\mathrm{HO\cdot} \longrightarrow \mathrm{H_2O} + {}^1/{}_2\mathrm{O_2} \qquad (1)$$

$$\longrightarrow \mathrm{HOOC(C_2H_5)_2OOC(C_2H_5)_2OOH}\ \ \text{IV}$$

dimerize to form peroxide II or combine with the monoradical of peroxide VI to form peroxide III. Apparently both of these reactions seem to occur. The decomposition of peroxide VI was also studied at 50°. After 264 hours at 50° this peroxide decomposed almost completely into propionic and acetic acids. A paper chromatogram of the residue showed only the presence of small amounts of the original peroxide VI and no other peroxides.

An attempt was also made, following the method of Criegee and Metz,[8] to cause the conversion with lead tetraacetate of peroxide IV to the cyclic peroxide IX but without success. However, the conversion of peroxide IV to the cyclic peroxide I is readily effected by mineral acids in the presence of excess diethyl ketone. This conversion establishes the possible existence of the intermediate peroxide IVa. The existence of peroxide IIIa is likewise established by the isolation from the reaction mixture of peroxide II.

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(5) M. S. Kharasch and G. Gosnovsky, *J. Org. Chem.*, **23**, 1322 (1958).

(6) G. O. Schenck and H. D. Becker, *Angew. Chem.*, **70**, 504 (1958).

(7) R. Criegee, W. Schnorrenberg and J. Becke, *Ann.*, **565**, 7 (1949).

(8) R. Criegee and K. Metz, *Chem. Ber.*, **89**, 1714 (1956).

Not all mineral acids catalyze the formation of all six detectable peroxides. With sulfuric acid all six were formed while with hydrochloric acid peroxide V was not detected.

Experimental

3,3'-Dihydroperoxy-3,3'-dipentyl Peroxide (IV).—To 6.8 g. (0.1 mole) of 50% hydrogen peroxide cooled at 0° was added with stirring 24 g. (0.025 mole) of concd. sulfuric acid. Diethyl ketone (8.6 g., 0.1 mole) was then added dropwise with constant stirring in the course of 20 min. and the mixture stirred at 0° for 3.5 hr. longer. The mixture was then extracted with 200 cc. of petroleum ether and the extract shaken with 2 × 100 cc. of saturated ammonium sulfate solution followed by four times with water and dried over magnesium sulfate. The dried mixture was filtered and the petroleum ether removed at room temperature under reduced pressure (50 mm.). Using a dry stream of air, the residue was subjected to a high vacuum (0.2–0.3 mm.) and at 35–40°. A paper chromatogram of the final residue (55–60% based on the ketone used) showed the presence of six peroxides with peroxide IV as the main product (85%).

The crude mixture was redissolved in dry petroleum ether (1:1) and, with proper protection from moisture, cooled to −70° whereby voluminous crystals separated out. The supernatant liquid was carefully decanted and the crystallization repeated three times. A paper chromatogram of the final crystals showed the presence of peroxide IV contaminated with traces of peroxide I. For final purification the crystals were sublimed in vacuum (3 mm.) and at 55–60° and the sublimate, m.p. 30.6°, showed a single spot on the paper chromatogram with an R_f 0.53.

Anal. Calcd. for $C_{10}H_{22}O_6$: C, 50.38; H, 9.31; (O), 20.15; mol. wt., 238. Found: C, 50.49; H, 9.13; (O), 19.91; mol. wt., 227 (in exaltone).

The infrared spectrum of this peroxide 10% in chloroform showed the following bands in cm.$^{-1}$; the number in parenthesis gives the intensity of each band: 3480(8); 3000(7.5); 2920(6); 1465(7.5); 1445(6); 1410(4); 1380(7); 1350(4); 1335(3.5); 1280(4); 1210–1235(4); 1155(7); 1130(6.5); 1120(5.5); 1070(3.5); 1045(3): 1015(2); 970(8.5); 920-(7.5); 905(5); 860(4).

Using the procedure of Brewster and Cotte, Jr.,[9] the bis-*p*-nitrobenzoate of peroxide IV was prepared; m.p. 121° dec. from ethyl alcohol.

Anal. Calcd. for $C_{24}H_{28}N_2O_{12}$: C, 53.74; H, 5.26; N, 5.22. Found: C, 54.39; H, 5.43; N, 5.22.

Attempt to Convert Peroxide IV with Lead Tetraacetate to Peroxide IX.—Using the method of Criegee and Metz,[8] 1.19 g. of peroxide IV was dissolved in 10 cc. of glacial acetic acid and to the solution was added slowly 3.22 g. of 70% lead tetraacetate in glacial acetic acid. The mixture became hot and had to be cooled under running water. Considerable evolution of oxygen was observed during the addition and when this subsided the mixture was allowed to stand at room temperature for 0.5 hour then diluted with 50 cc. of water and extracted with ether. The ether extract was washed several times with water, followed by saturated solution of sodium bicarbonate, dried and the ether removed. A paper chromatogram of the residue failed to reveal the presence of the cyclic peroxide IX although it showed the presence of IV as the main peroxide with II, III, V and VI present in smaller amounts and I in traces. In addition one spot of an unidentified peroxide appeared with an R_f between those of peroxides IV and V. This spot also appeared in several of the chromatograms of the original peroxide mixtures, but the amount of the peroxide was so small that it resisted isolation.

Conversion of Peroxide IV to Peroxide I.—To a solution of peroxide IV (2.996 g.) in 5.25 cc. of diethyl ketone was added with gentle shaking 0.33 cc. of 98% sulfuric acid and the mixture allowed to stand at room temperature for 24 hr. A paper chromatogram of the resulting mixture revealed only a single spot corresponding to the R_f of the cyclic trimer I. Obviously the peroxide IV, under these conditions, was converted quantitatively to the peroxide I perhaps *via* the intermediate peroxide IVa.

3,3-Dihydroperoxypentane (VI).—The mother liquors from the removal of most of peroxide IV were combined and the solvent removed in vacuum. A paper chromatogram of the residue showed the presence of all original six peroxides. An attempt was then made to fractionate some of these by distillation at 95 and 105° and at a pressure of 0.3 mm., respectively. Even after prolonged distillation under these conditions the small amounts of distillates contained mixtures of peroxides IV, V and VI with traces of III while the residue still contained I, II, IV and VI as determined by paper chromatography.

Using a column (1.6 × 20 cm.) of silica gel (Davison 28–200), a mixture (0.36 g.) of all six peroxides in 36 cc. of petroleum ether was fixed on the column. The peroxides were eluted with petroleum ether–ethyl ether mixtures 9:1 and 1:1. Only small amounts of peroxides came through the column undecomposed as mixtures of I, II, III, IV with traces of V. Peroxides V and VI were almost completely destroyed.

Finally it was discovered that when the residue from the mother liquors was dissolved in dry petroleum ether and the solution cooled to −70° no solid separated out, but when moist air was allowed to pass through the solution for a short time a colorless crystalline product separated out which was removed and dried in air at room temperature; m.p. 44°. A paper chromatogram of this peroxide showed a single spot with an R_f of 0.02.

Anal. Calcd. for $C_5H_{12}O_4 \cdot H_2O$: C, 39.60; H, 9.15; (O), 20.75: mol. wt., 154. Found: C, 39.33; H, 9.44; (O), 21.02; mol. wt., 131 (in exaltone).

That this peroxide was the monohydrate was shown by drying the crystals in vacuum over phosphorus pentoxide for several hours whereby they lost the water and became a colorless oil.

Anal. Calcd. for $C_5H_{12}O_4$: C, 44.08; H, 8.89; (O), 23.51. Found: C, 43.93; H, 9.02: (O), 23.61.

When the above oil was dissolved in dry petroleum ether and moist air was passed through the solution a crystalline solid separated out which gave the same m.p. as the original peroxide, and mixed m.p. gave no depression.

The infrared spectrum of the crystalline peroxide 10% in chloroform showed the following bands in cm.$^{-1}$: 3620(4); 3400(8.5); 3000(4.5); 2920(4.5); 1610(3.5); 1460(7); 1445(6); 1378(5); 1345(5.6); 1335(5.5); 1290(3.5); 1275-(3.5); 1210–1235(4.5); 1155(5); 1120(6); 1070(2.5); 1040(3); 970(6); 915(7); 860(6).

The bis-*p*-nitrobenzoate of the above peroxide was prepared using the same method as that used with peroxide IV; m.p. 127–128° dec. from absolute ethyl alcohol.

Anal. Calcd. for $C_{19}H_{18}N_2O_{10}$: C, 52.53; H, 4.17; N 6.45; (O), 7.39. Found: C, 52.82; H, 4.16; N, 6.62 (O), 7.00.

3,3-Dihydroperoxypentane was also obtained as the main peroxide in about 2% yield with traces of peroxides III and IV from an equimolecular mixture of diethyl ketone and 50% hydrogen peroxide. The organic peroxides together with the unreacted ketone were extracted with pentane, the extract shaken with saturated solution of ammonium sulfate to remove the free hydrogen peroxide, dried and the solvent and unreacted ketone removed in vacuum. The residue was dissolved in pentane and crystallized at low temperatures using the technique previously described; m.p. 44°.

This peroxide was also obtained as the sole peroxide when equimolecular quantities of diethyl ketone and hydrogen peroxide in anhydrous *t*-butyl alcohol or ethyl ether were allowed to stand for several days at room temperature. The reaction mixtures were worked up; the free hydrogen peroxide removed in the usual manner and the final product chromatographed. Only a single spot corresponding to that produced by peroxide VI was observed on the paper chromatogram.

Decomposition of Peroxide VI at Room Temperature.—In a special tube filled with pure nitrogen and attached to a calibrated buret with a bulb filled with saturated salt solution was placed 120.7 mg. of pure crystalline peroxide VI. After three weeks of standing at room temperature the solid gradually became liquid and the gas (5.04 cc. or 7.21 mg. at N.T.P.) evolved was found to be pure oxygen. The theoretical amount of oxygen corresponding to reaction (1) described is 6.27 mg. A paper chromatogram of the residue showed the presence of peroxide IV as the main product with peroxides II, III and V as by-products. The formation of the by-products seems to account for the extra oxygen evolved.

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[9] J. H. Brewster and C. J. Cotte, Jr., THIS JOURNAL, **77**, 6214 (1955).

When the decomposition was carried out at 50° none of the peroxides formed at room temperature were present in the residue. However, a paper chromatogram of the residue showed the presence of acetic and propionic acids as compared with control chromatograms of these acids.

1,1,4,4,7,7-Hexaethyl-1,4,7-cyclononatriperoxane (I).—The solvent from the mother liquors, after most of peroxides IV and VI had been separated, was removed in vacuum and the viscous residue dissolved in methyl alcohol and cooled to −70°. A white solid separated out which was recrystallized several times from methyl alcohol; m.p. 58–59°. This peroxide fails to react with potassium iodide in glacial acetic acid. However, it gives normal active oxygen values with hydrogen iodide in glacial acetic acid. A paper chromatogram using hydrogen iodide–glacial acetic acid as the spraying agent gave a single spot with an R_f of 0.91.

Anal. Calcd. for $C_{15}H_{30}O_6$: C, 58.78; H, 9.87; (O), 15.67; mol. wt., 306. Found: C, 58.52; H, 9.87; (O), 15.20; mol. wt., 302 (in exaltone).

The infrared spectrum 10% in chloroform showed the following bands in cm.$^{-1}$: 3000(7.5); 2920(4.5); 1460(7.5); 1445(6); 1375(3); 1345(4.5); 1335(4.5); 1280(5); 1210–1250(5); 1165(8); 1140(8); 1070(3.5); 1050(3.5); 1020 (3.5); 980(8.5); 960(6.5); 930(7.5).

1,1,4,4,7,7,10,10-Octaethyl-1,4,7-triperoxy-1,10-dihydroperoxide (II).—After most of peroxides I, IV and VI had been removed from the original mixture by standard procedures, it was not found possible to separate any other peroxides in the pure form, yet the final mother liquors, after most of peroxide I had been removed, still contained, according to our paper chromatographic analysis, all of the original six peroxides but I, IV and VI to a much lesser degree.

After much experimentation with cellulose powder chromatographic columns, we have found the following procedure satisfactory for the separation of all peroxides present in the final mother liquors. The solvent from these liquors was removed in vacuum and the residue dissolved in pentane (1:1). A column was prepared as follows: Cellulose powder (300 g., Whatman standard grade) was impregnated with 100 g. of dimethyl formamide in 600 cc. of ethyl ether. The ether was then evaporated at 50° and the impregnated cellulose washed once with pentane saturated with dimethylformamide. The cellulose was then pressed into a column (1.6 × 40 cm.) by pounding with a thick glass rod flattened and flanged at the bottom. The cellulose was held down by a heavy weight of mercury or lead sealed into a glass tube. Before fixing the peroxides on the column the cellulose was washed once again with pentane saturated with dimethylformamide. The peroxide mixture in pentane was then dropped on the top of the column and pentane saturated with dimethylformamide passed through the column at the rate of 3.2–3.3 cc. per min. Ten-cc. fractions were collected and examined by paper chromatography. The first few fractions contained peroxide I. After this, peroxide II began to come out. Thirty-two 10-cc. fractions which contained this peroxide were combined and concentrated in vacuum to about 30 cc. which was washed several times with water to remove the dimethylformamide, dried and the solvent removed in vacuum. A semi-solid separated out which was recrystallized at low temperatures and the crystals subjected to a vacuum over phosphorus pentoxide; m.p. 69–70°. This peroxide gave a single spot on the paper with an R_f of 0.86.

Anal. Calcd. for $C_{20}H_{42}O_{10}$: C, 54.29; H, 9.59; (O), 18.10; mol. wt., 442.5. Found: C, 54.45; H, 9.65; (O), 18.44; mol. wt., 461 (in exaltone).

The infrared spectrum 10% in chloroform showed the following bands in cm.$^{-1}$: 3480(6.5); 3000(7.5); 2920(4.5); 1465(7); 1450(6.5); 1380(5.5); 1350(5.5); 1275(4.5); 1210–1235(5); 1155(6.5); 1130(7); 1070(3.5); 1045(4); 1015(3); 960–975(6.5); 905–920(8); 865(4).

1,1,4,4,7,7-Hexaethyl-1,4-diperoxy-1,7-dihydroperoxide (III).—From several chromatographic separations, fractions which were collected immediately after those containing peroxide II and which showed a single spot on the paper chromatogram with an R_f 0.70 were combined, the dimethylformamide washed away as before and the pentane solution dried and the solvent removed in vacuum. A small amount of peroxide was obtained which could not be crystallized.

Anal. Calcd. for $C_{15}H_{32}O_8$: (O), 18.82. Found: (O), 19.00.

Following the removal of peroxide III from the column, fractions containing only peroxide IV were collected as shown by paper chromatograms containing single spots corresponding to R_f 0.53. Since this peroxide was obtained by other methods no attempt was made to isolate it from these fractions.

The quantities of peroxide V were so small that it was not possible to isolate it by this procedure. Peroxide VI was the last to come out from the chromatographic column and since this too was obtained by other means no attempt was made to isolate it from the column.

Acknowledgment.—The authors are indebted to Dr. Belič for the paper chromatographic analyses and for valuable discussion, to Dr. Nagy for all the combustion analyses, to Dr. Nelson and associates for the infrared spectra and to Lucidol Division of Wallace and Tiernan, Inc., for the financial support of this investigation.

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Reaction of Phenolic Mannich Base Methiodides and Oxides with Various Nucleophiles

BY PETE D. GARDNER, HOSSEIN SARRAFIZADEH RAFSANJANI AND LEON RAND

RECEIVED NOVEMBER 26, 1958

Several Mannich base methiodides and oxides derived from phenols have been shown to undergo reaction with OCH_3^-, CN^-, $(EtOOC)_2CH^-$ and H^- in basic media to give products derived from displacement of the nitrogen atom by the nucleophile. The ease with which reaction occurs is rationalized on the basis of electron release by the oxygen atom of the initially formed substituted phenoxide ion.

The displacement of tertiary and quaternary nitrogen atoms by nucleophilic reagents is a rather well known reaction.[1] Many substituted benzylamine derivatives, for example, have been induced to undergo reaction either as the amine or as the quaternary salt with such nucleophiles as cyanide ion, alkoxide and phenoxide ions, acetate ion and malonate ion. An inspection of reported yields and reaction conditions used reveals that, although the reaction is very general and useful synthetically, it proceeds with ease in relatively few systems. These examples are conspicuous in the ability of the alkylating moiety to sustain positive charge thus indicating that the reaction is facilitated by electron release to the carbon atom

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(1) For a good review of this type of reaction, see J. H. Brewster and E. L. Eliel in R. Adams, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 99–197.