[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Optically Active Alkoxyl Radicals. II. Preparation and Properties of Optically Active α-Phenylethyl-*t*-butyl Peroxide[1]

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RECEIVED JANUARY 15, 1952

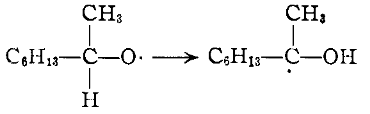
In order to learn whether alkoxyl radicals are able to undergo the rearrangement $R{-}\overset{R'}{\underset{H}{C}}{-}O\cdot \rightarrow R{-}\overset{R'}{C}{-}O{-}H$ the thermal decomposition of optically active α-phenylethyl-*t*-butyl peroxide in thiophenol solution at 125° was investigated. Optically active α-phenylethanol was obtained in 55% yield. It is concluded, therefore, that the alkoxyl radical $C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O\cdot$ is capable of abstracting a hydrogen atom from thiophenol without prior rearrangement to $C_6H_5{-}\overset{CH_3}{C}{-}OH$. Since the optical purity of the peroxide is not known, it can only be said at present that between 42 and 100% of the alkoxyl radicals $C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O\cdot$ are converted to α-phenylethanol without undergoing rearrangement.

The thermal decomposition of alkyl nitrites in the vapor phase has been studied by Steacie and by F. O. Rice who proposed the mechanism[3]

$$\begin{gathered}RCH_2ONO \longrightarrow RCH_2O\cdot + NO\\ RCH_2O\cdot + RCH_2ONO \longrightarrow RCH_2OH + R\dot{C}HONO\\ R\dot{C}HONO \longrightarrow RCHO + NO\\ \hline 2RCH_2ONO \longrightarrow RCHO + RCH_2OH + 2NO\end{gathered}$$

Recently it has been found that the liquid phase pyrolysis of optically active 2-octyl nitrite at 100° gives 2-octanone, 2-octanol and nitric oxide and the 2-octanol (80% yield) is optically pure[1]; this, of course, is completely consistent with the above sequence.

If the foregoing mechanism is accepted then it follows that a secondary alkoxyl radical is optically stable and that a rearrangement such as



$$C_6H_{13}{-}\overset{CH_3}{\underset{H}{C}}{-}O\cdot \longrightarrow C_6H_{13}{-}\overset{CH_3}{\underset{\cdot}{C}}{-}OH \qquad (1)$$

does not occur with facility, if at all, in the liquid phase at 100°.[4]

In principle, however, such a rearrangement is a real possibility since an O–H bond is stronger than a C–H bond.[5] Also the second free radical of eq. (1) will be stabilized by resonance with the dipolar structure[6] $C_6H_{13}{-}\overset{CH_3}{\underset{\ominus}{\ddot{C}}}{-}\underset{\oplus}{\ddot{O}}H$; such resonance is not present in the alkoxyl radical. Of further interest is the fact that an analogous rearrangement takes place readily even at room temperature.[7] Thus the

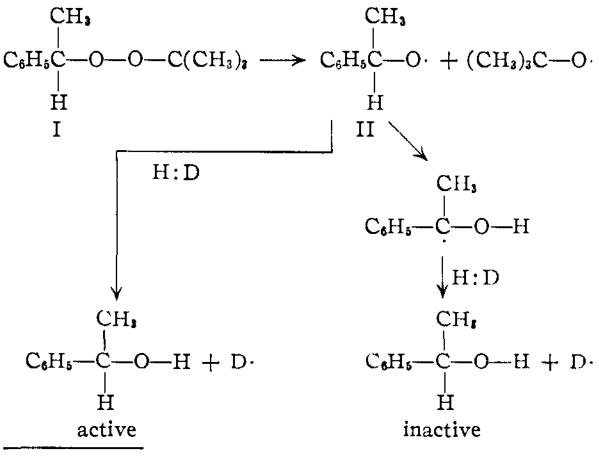
$$(C_6H_5)_3C{-}O\cdot \longrightarrow (C_6H_5)_2\dot{C}{-}O{-}C_6H_5$$

question of rearrangements in the sense of eq. 1 cannot be regarded as settled.

It is well established that the thermal decomposition of dialkyl peroxides occurs by rupture of the oxygen–oxygen bond[8]

$$R{-}O{-}O{-}R' \longrightarrow R{-}O\cdot + R'{-}O\cdot$$

This suggested a very direct means of producing optically active alkoxyl radicals, which, among other things, would provide a check on conclusions arrived at from experiments employing alkyl nitrites. Toward this end, the synthesis of optically active



$$C_6H_5\overset{CH_3}{\underset{H}{C}}{-}O{-}O{-}C(CH_3)_3 \longrightarrow C_6H_5\overset{CH_3}{\underset{H}{C}}{-}O\cdot + (CH_3)_3C{-}O\cdot$$

$$C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O\cdot \xrightarrow{H:D} C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O{-}H + D\cdot \quad \text{active}$$

$$C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O\cdot \longrightarrow C_6H_5{-}\overset{CH_3}{\underset{\cdot}{C}}{-}O{-}H \xrightarrow{H:D} C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O{-}H + D\cdot \quad \text{inactive}$$

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[1] Paper I in this series: N. Kornblum and E. P. Oliveto, THIS JOURNAL, **71**, 226 (1949).

[2] Allied Chemical and Dye Fellow, 1948–1949.

[3] M. Szwarc, *Chem. Revs.*, **47**, 143 (1950).

[4] The argument is based on the commonly held assumption that the radical RR′R″C· is incapable of maintaining optical activity (G. W. Wheland, "Advanced Organic Chemistry," Ed. 2, J. Wiley and Sons, Inc., New York, N. Y., 1949, p. 713).

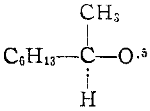
[5] K. S. Pitzer, THIS JOURNAL, **70**, 2140 (1948). Although this use of "bond strengths" is an oversimplification, it is noteworthy that for the saturated radical of eq. (1) the difference in "bond strengths" is *ca.* 11 kcal. per mole; if one employs "bond dissociation energies" the O-H bond is stronger than the C-H bond by *ca.* 23 kcal. per mole. For the arylated radical $C_6H_5{-}\overset{CH_3}{\underset{H}{C}}{-}O\cdot$ the C-H "bond dissociation energy" falls to *ca.* 77 kcal. per mole which is to be contrasted with 118 for the O-H bond (ref. 3, Table A1).

[6] Compare P. D. Bartlett and K. Nozaki, *ibid*, **69**, 2305 (1947).

[7] M. S. Kharasch, A. Fono and W. Nudenberg, *J. Org. Chem.*, **15**, 770 (1950); M. A. Spielman, THIS JOURNAL, **57**, 1117 (1935).

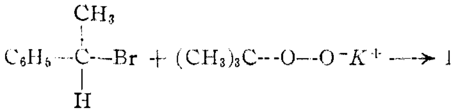
[8] Ref. 3, pp. 149–151; J. H. Raley, L. M. Porter, F. F. Rust and W. E. Vaughan, *ibid.*, **73**, 17 (1951).

α-phenylethyl-*t*-butyl peroxide (I) and its thermal decomposition in the presence of a donor of hydrogen atoms (H:D) was undertaken. The optically active α-phenylethoxyl radical (II) can go over to α-phenylethyl alcohol by two paths, only one of which will yield the active alcohol. It is especially noteworthy that in the arylated radical (II) the migration of hydrogen from carbon to oxygen is much more likely to occur than in the strictly aliphatic radical



$$C_6H_{13}-\underset{H}{\overset{CH_3}{C}}-O\cdot$$[5]

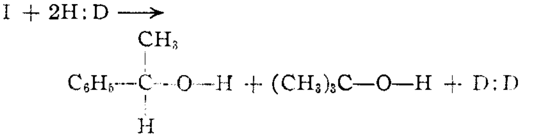
α-Phenylethyl-*t*-butyl peroxide (I) was obtained in 30–35% yield from α-phenylethyl bromide and the potassium salt of *t*-butyl hydroperoxide



$$C_6H_5-\underset{H}{\overset{CH_3}{C}}-Br + (CH_3)_3C-O-O^-K^+ \longrightarrow I$$

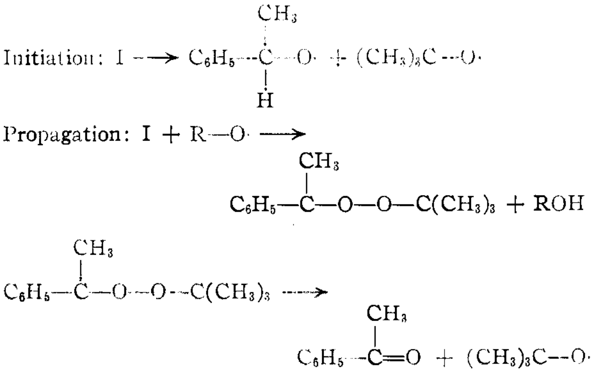
It was always contaminated with unreacted bromide and efforts to consume all the bromide by using an excess of the hydroperoxide salt resulted in a sharp decrease in the yield of I. Simple distillation of the peroxide failed to free it of the bromide and rectification was accompanied by slight decomposition of the peroxide. Consequently, a procedure was devised in which the bromide was removed by treating the crude product with thiourea; the resulting salt was then easily separated from the peroxide by washing with water.[9] This gave I of 99.92 ± 0.04 mole per cent. purity; it has the infrared absorption characteristic of a dialkyl peroxide.[10]

Attention was next directed to finding a good hydrogen donor (H:D) for reaction (2)



$$I + 2H:D \longrightarrow C_6H_5-\underset{H}{\overset{CH_3}{C}}-O-H + (CH_3)_3C-O-H + D:D \qquad (2)$$

When peroxide I was decomposed in cumene at 130° a 31% yield of *crude* 2,3-dimethyl-2,3-diphenylbutane was obtained but none of the expected α-phenylethanol could be isolated. In contrast, a very appreciable amount (*ca.* 37%) of acetophenone was found. The rather remote possibility that the acetophenone could have arisen from the base-catalyzed decomposition of the peroxide,[9] the glass furnishing the alkalinity, was disposed of by the finding that peroxide I is readily decomposed when kept at 125° in a quartz system by itself. The major products are acetophenone (49% yield) and *t*-butyl alcohol (69% yield); lesser amounts of α-phenylethanol and acetone were also isolated.[11] It seems very likely that here the acetophenone is produced by a free radical chain sequence



$$\text{Initiation: } I \longrightarrow C_6H_5-\underset{H}{\overset{CH_3}{C}}-O\cdot + (CH_3)_3C-O\cdot$$

$$\text{Propagation: } I + R-O\cdot \longrightarrow C_6H_5-\overset{CH_3}{C}-O-O-C(CH_3)_3 + ROH$$

$$C_6H_5-\overset{CH_3}{C}-O-O-C(CH_3)_3 \longrightarrow C_6H_5-\overset{CH_3}{C}=O + (CH_3)_3C-O\cdot$$

Thiophenol proved to be an excellent medium for minimizing the chain reaction and achieving the reaction described by eq. (2). Upon heating peroxide I in thiophenol at 125° for ten hours, 55–57% yields of pure α-phenylethanol were obtained; small amounts of acetophenone (9–12%) were simultaneously produced.[12,12a] Significantly, the yields of pure diphenyl disulfide in these experiments ranged from 66–71%. Apparently thiophenol is a good enough donor of hydrogen atoms to be able to compete favorably with the peroxide itself, especially when used in large excess.

When levorotatory peroxide I, $\alpha^{24}D$ − 51.0° (l 1 dm.), was heated in thiophenol the α-phenylethanol produced had $\alpha^{25}D$ −10.6° (l 1 dm.); this was converted to the crystalline hydrogen phthalate ester, $[\alpha]^{23}D$ +9.8°. These rotations correspond to an optical purity of 24% for the alcohol and 27% for the hydrogen phthalate.[13] It is, therefore, clear that at 125° in the liquid phase a sizable fraction of the alkoxyl radicals II are able to abstract hydrogen from thiophenol without

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[9] In an early experiment an attempt was made to remove the unreacted α-phenylethyl bromide by treatment with piperidine; this not only removed the bromide but also converted a large portion of the peroxide into acetophenone. This led to the discovery that peroxide I is subject to a base-catalyzed elimination reaction which produces acetophenone and *t*-butyl alcohol [N. Kornblum and H. E. DeLaMare, THIS JOURNAL, **73**, 880 (1951)]. It is this sensitivity toward base which causes a drop in the yield of peroxide when an excess of the potassium salt of *t*-butyl hydroperoxide is employed.

[10] We are indebted to Dr. E. R. Blout of the Polaroid Corporation for the determination and interpretation of the infrared data (*cf.* Experimental).

[11] Unpublished work by Mr. S. L. Clark of this department. The analogous experiment conducted in glass also gave a 49% yield of acetophenone; *cf.* Experimental.

[12] The α-phenylethanol and acetophenone isolated from these experiments account for 64–69% of peroxide I. Had the α-phenylethoxyl radicals (II) undergone rearrangement of the carbon skeleton ethyl phenyl ether and (or) benzyl methyl ether would have resulted. Since no special effort was made to isolate these ethers the possibility remains that they are formed in minor proportions. An analogous rearrangement in which a phenyl group migrates is known for the neophyl radical (W. H. Urry and M. S. Kharasch, THIS JOURNAL, **66**, 1438 (1944); S. Winstein and F. H. Seubold, Jr., *ibid.*, **69**, 2917 (1947)).

[12a] ADDED IN PROOF.—The possibility that α-phenylethyl-*t*-butyl peroxide might undergo "straight reduction" by thiophenol in the cold without the formation of alkoxyl radicals was suggested by one of the referees. The following experiment (by Mr. S. L. Clark) shows that no such reaction occurs. A solution of the peroxide (0.0026 mole) in thiophenol (0.0156 mole) was allowed to stand for twenty-four hours at 25–28° under nitrogen. There was no change in refractive index and the infrared spectrum of the solution at the end of this time was completely identical with that of the freshly prepared solution.

[13] E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939). The α-phenylethanol obtained by decomposing the peroxide has the same sign of rotation as the original alcohol: $(-)\ ROH \xrightarrow{1} (+)\ RBr \xrightarrow{2} (-)\ R\text{-}O\text{-}O\text{-}C(CH_3)_3 \xrightarrow{3} (-)\ ROH$. Step one of this sequence is known to occur with inversion (E. D. Hughes, C. K. Ingold, *et al.*, *Nature*, **166**, 179 (1950)) and the third unquestionably goes with retention. Consequently, step two must go with inversion.

undergoing rearrangement. The precise fraction of alkoxyl radicals II which are converted into α-phenylethanol without rearrangement cannot be stated at present. It must be emphasized, however, that even though the alcohol is only 25% active, it is quite possible that none of the alkoxyl radicals rearranged.

The difficulty lies in the fact that the rotation of optically pure peroxide is not known. The α-phenylethyl bromide used in preparing the peroxide was, at best, 65% optically pure[14] which immediately sets the upper limit for the optical purity of the peroxide. There are, however, reasons for believing that this figure is too high.

For one thing, as the reaction progresses the bromide ions liberated serve to racemize unreacted α-phenylethyl bromide.[15] Also, even though the reaction is carried out so as to minimize peroxide formation by an S_N1 process there can be little doubt that some of the peroxide is produced this way and that, as a consequence, some racemization occurs.[16]

Despite these uncertainties it is safe to conclude that as a very maximum no more than 58% of the optically active α-phenylethoxyl radicals II racemize before abstracting a hydrogen atom from thiophenol. This is clear from the following considerations: (1) If the highest recorded value[14] for the rotation of α-phenylethyl bromide is that of the optically pure compound then the bromide herein employed had an optical purity of 65%. (2) The alcohol obtained on decomposing the peroxide is 27% optically pure. If no racemization occurs on converting the bromide to the peroxide, it follows that decomposition of the peroxide occurred with a 58% loss of activity.

There is no guarantee, however, that optically pure α-phenylethyl bromide has ever been prepared. If the rotation of this bromide continues to undergo upward revision, it will mean that less than 58% of the alkoxyl radicals are racemized before going over to the alcohol. Furthermore, for the reasons just discussed, there can be little question that peroxide formation is accompanied by racemization. This again means that the extent of racemization in the pyrolysis step is less than 58%.

The principal significance of the present findings lies in the demonstration that optically active alkoxyl radicals can be produced from an active peroxide, and that they have a significant measure of optical stability. Thus a substantial fraction (and perhaps all) of the α-phenylethoxyl radicals are able to remove a hydrogen atom from thiophenol before isomerization in the sense of eq. (1) occurs. In order to avoid the various uncertainties which made it impossible to obtain quantitative information concerning the α-phenylethoxyl radical, a study of the thermal decomposition of optically active α-phenylethyl nitrite is in progress.

Experimental[17]

Potassium Salt of *t*-Butyl Hydroperoxide.—The procedure reported in the patent literature[18] gives a product which is extremely hygroscopic and difficult to work with. The following method consistently gives a free-flowing crystalline salt not nearly as hygroscopic as the salt prepared according to Dickey and Bell.

A solution containing 28 g. (0.5 mole) of potassium hydroxide in 75 ml. of *ca.* 85% ethanol (any second phase separating is discarded) was added dropwise, with stirring, to 75 g. (0.5 mole) of 60% *t*-butyl hydroperoxide (Lucidol Corporation) while maintaining a temperature of 0 to 2°. The salt was then precipitated at 0° by adding *ca.* 500 ml. of ice-cold acetone to the clear solution. It was isolated by filtration, washed with cold acetone, and the residual acetone was removed *in vacuo* at 20–25°; yield 40–49 g. of white hygroscopic crystals. Calcd. for $C_4H_9O_2K$: active O, 12.48; K, 30.49. Calcd. for $C_4H_9O_2K \cdot C_2H_5OH$: active O, 9.18; K, 22.4. Found: active O, 9.83, 9.87; K, 23.9, 25.6, 24.7.[19]

The salt is known to crystallize with *t*-butanol of crystallization.[20]

α-Phenylethyl Bromide.—E. K. White Label phosphorus tribromide, 303.5 g. (1.12 moles), was added to a solution of 137 g. (1.12 moles) of α-phenylethanol (n^{20}_{D} 1.5280; purified *via* acid phthalate) in 100 ml. of anhydrous ether. The bromide addition was carried out dropwise while maintaining an internal temperature of 0 to −10°. The mixture was stirred at −10° for one hour after the addition of the bromide, then allowed to warm gradually to room temperature and after stirring for 12 hours at room temperature it was warmed on the steam-bath for one hour.

The product was poured, while stirring, into a suspension of crushed ice in water layered with ether. The ether layer was immediately separated, quickly washed with ice-water, twice with ice cold 10% sodium carbonate solution and again with ice-water. It was then dried over anhydrous magnesium sulfate followed by Drierite. The ether was removed by distillation and the residue was rectified[21]; yield 157.5 g. (76%) of colorless α-phenylethyl bromide; n^{20}_{D} 1.5620, b.p. 75–76° (6 mm.).

Another sample, prepared in the presence of pyridine (see below), had, after rectification,[21] n^{20}_{D} 1.5619, b.p. 69.5° (3.5 mm.), d^{20}_4 1.3615. Calcd. for C_8H_9Br: C, 51.92; H, 4.90. Found: C, 52.05; H, 4.84; lit. values: n^{20}_{D} 1.5619[14]; d^{20}_4 1.311[22]; d^{23}_4 1.3107[23]; b.p. 88° (14 mm.).[14]

***l*-α-Phenylethanol.**—The alcohol was converted to the hydrogen phthalate ester according to Eliel[24]; yield 60–70%, m.p.[25] 107.5–108.5° (lit. value[24] 107–108°). Resolution[13] gave *l*-α-phenylethyl hydrogen phthalate, m.p. 84.5–85.5° (lit. value[13] 86°) which yielded *l*-α-phenylethanol, b.p. 81.2–81.8° (6 mm.); α^{28}_{D} −21.6° (*l* 0.50 dm.); n^{20}_{D} 1.5270; lit. values: b.p. 86.5–87.5 (8 mm.)[26]; α^{17}_{D} −11.04°, (*l* 0.25 dm.)[13]; n^{20}_{D} 1.5211[27]; n^{20}_{D} 1.5275.[28]

***d*-α-Phenylethyl Bromide.**—A solution containing 81.3 g. (0.3 mole) of phosphorus tribromide and 50 ml. of anhydrous ether was added to a solution of 33 g. (0.27 mole) of the *l*-α-phenylethanol of the preceding section, 21.3 g. (0.27 mole) of anhydrous pyridine and 50 ml. of anhydrous ether at −5 to −10°. After stirring for an additional hour at −10°,

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(14) This estimate is based on the highest rotation recorded for the bromide; α^{18}_{D} 131° (*l* 1 dm.) (W. Gerrard, *J. Chem. Soc.*, **848** (1945); 744 (1946); *Nature*, **160**, 467 (1947)). Also see Arcus and Boyd, *J. Chem. Soc.*, 1584 (1951).

(15) E. D. Hughes, F. Juliusberger, A. D. Scott, B. Topley and J. Weiss, *ibid.*, 1173 (1936).

(16) Gerrard's report that certain of his samples of α-phenylethyl bromide racemized upon distillation (b.p. 96° (20 mm.)) is also of interest (*ibid.*, 852 (1945)).

(17) Analyses by Dr. H. Galbraith.

(18) F. H. Dickey and E. R. Bell, U. S. Patent 2,403,709 (July 9, 1946).

(19) The active oxygen determinations were carried out using method (a) of D. M. Surgenor, Ph.D. Thesis, Massachusetts Institute of Technology, 1946.

(20) N. A. Milas and D. M. Surgenor, THIS JOURNAL, **68**, 205 (1946).

(21) Carried out in a 50-cm. glass spiral column fitted with total reflux, variable take-off head; *ca.* 5 plates.

(22) B. Holmberg, *Ber.*, **45**, 997 (1912).

(23) G. B. Tal'kovskii, *J. Gen. Chem.* (*U.S.S.R.*), **18**, 103 (1948); *C. A.*, **42**, 4962 (1948).

(24) E. L. Eliel, THIS JOURNAL, **71**, 3970 (1949).

(25) All m.ps. corrected except those above 200° which were determined on a Fischer-Johns Block.

(26) W. E. Doering and T. C. Aschner, THIS JOURNAL, **71**, 838 (1949).

(27) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

(28) R. Descamps, *Bull. soc. chim. Belg.*, **33**, 270 (1924); R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3739 (1948).

the reaction mixture was brought to 25–28° and held there for 12 hours while stirring. This was followed by one hour of gentle refluxing on the steam-bath.

The bromide was isolated as described by Gerrard.[14] Vacuum distillation (not rectification) gave 29.1 g. (58% yield), b.p. 67.2–68.8° (4 mm.); $n^{20}\mathrm{D}$ 1.5619, $\alpha^{26}\mathrm{D}$ +48.0° (*l* 0.5 dm.).

***l*-α-Phenylethyl-*t*-butyl Peroxide.**—In a three-neck flask fitted with a Hershberg tantalum stirrer, a thermometer, a wide bore dropping funnel and a reflux condenser, was placed a solution of 64.8 g. (0.35 mole) of *d*-α-phenylethyl bromide ($[\alpha]^{26}\mathrm{D}$ 86.1°, *l* 1 dm.; $n^{20}\mathrm{D}$ 1.5619) in 40 ml. of anhydrous *t*-butyl alcohol. Over a four-hour period 63.2 g. (0.39 mole) of the potassium salt of *t*-butyl hydroperoxide, partly dissolved and partly suspended in 300 ml. of anhydrous[29] *t*-butyl alcohol was added. During this time the mixture was stirred vigorously and the temperature remained between 25–30° without external cooling or heating. The reaction mixture was then stirred vigorously for 19 hours at 28–30° after which it was held at 40° for one hour. A dry nitrogen atmosphere was maintained in the system throughout.

The product was filtered, and the filtrate poured into 4 l. of water. The resulting suspension was extracted with ether and the ether layer was washed with acid potassium iodide solution (5 ml. of 6 *N* H_2SO_4/50 ml. of a saturated aqueous solution of potassium iodide) until no more iodine was liberated; prolonged contact is required for complete removal of hydroperoxide (usually several hours). The organic phase was next washed with dilute aqueous sodium thiosulfate until free from iodine, then given a thorough water-wash and dried over sodium sulfate. After removing the bulk of the ether under reduced pressure at room temperature the residual liquid was treated with 19 g. (0.25 mole) of thiourea and 100 ml. of dry acetone. The mixture was heated for one hour at 50–55°; during this time the reaction flask was periodically shaken. Undissolved thiourea (8.02 g.) was filtered off and the bulk of the acetone was removed *in vacuo*. The residue was dissolved in *ca.* 1 l. of water and this solution was thoroughly extracted with ether. The ether extract was dried, concentrated under reduced pressure at room temperature, and the residue was treated with 2,4-dinitrophenylhydrazine until no further precipitation occurred.[30] Acetophenone dinitrophenylhydrazone (*ca.* 20 g.) was removed by filtration, the filtrate was refluxed for ten minutes (steam-bath) and, after cooling, was poured into 3 l. of water. The product was thoroughly extracted with petroleum ether (b.p. 35–37°) and after filtration to remove any precipitated hydrazine or hydrazone, the petroleum ether solution was washed with dilute hydrochloric acid and then with water. The dry petroleum ether solution was concentrated at room temperature under reduced pressure and the residue was passed through a column of Norite and Celite (50–50). The column was developed and eluted with 35–37° petroleum ether; the colorless eluate was concentrated at room temperature after which the residue was distilled at 1 mm. (Table I).

TABLE I

Fract.	B.p., °C.	Wt., g.	$n^{20}\mathrm{D}$	$\alpha^{24}\mathrm{D}$ (*l* 1 dm.)
1	Up to 55.4	1.95	1.4862	−43.3
2	55.4–56.3	2.64	1.4825	−48.7
3	56.3–57	22.72	1.4809	−51.0
4	Last drop of distillate		1.4811	

Fraction 3 (33% yield) gave a positive test for acetophenone with the very sensitive dinitrophenylhydrazine reagent[30]; this sample of peroxide, which contained an estimated 0.5% of acetophenone was analyzed: *Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 74.35, 74.51; H, 9.18, 9.14.

Infrared examination[10] of Fraction 3 and of di-*t*-butyl peroxide revealed the presence of a strong absorption band at 11.4 μ in both cases; it is generally accepted that the band at 11.4 μ is the one associated with the peroxide linkage.[31]

A sample of racemic peroxide was prepared as described above except that in place of the final distillation the peroxide was molecularly distilled at room temperature in a Hickman-type still at 0.1–0.3 mm. After a small forerun all the remaining fractions had $n^{20}\mathrm{D}$ 1.4802 and did not give a precipitate with the sensitive dinitrophenylhydrazine reagent.[30] These fractions were combined (28.1 g.); d^{20}_4 0.9412; *MR*D (calcd.)[31a] 57.85, *MR*D (found) 58.65; the exaltation is precisely what one would anticipate for this peroxide.[31a] This sample of peroxide proved to be 99.92 ± 0.04 mole per cent. pure as shown by a time–temperature cooling curve.[31b] The freezing point corrected to zero impurity is −23.46 ± 0.05°.

Decomposition of α-Phenylethyl-*t*-butyl Peroxide in Cumene.—Cumene, 60 g. (0.5 mole, b.p. 151–152°, $n^{20}\mathrm{D}$ 1.4912), and 19.4 g. (0.1 mole) of α-phenylethyl-*t*-butyl peroxide ($n^{20}\mathrm{D}$ 1.4806) were placed in a 100-ml. flask equipped with a reflux condenser, a nitrogen inlet tube and an outlet from the top of the condenser to a Dry Ice trap. A stream of dry nitrogen was passed through the system until the bath temperature reached 90°. The cumene solution was held at 130–135° for 36 hours; at the end of this time there was nothing in the Dry Ice trap.

The product was rectified[21] at 26 mm. until the head temperature began to exceed 57°. Forty-two grams of cumene ($n^{20}\mathrm{D}$ 1.4920) was collected. A Dry Ice trap backing up the receiver contained 7.2 g. of material which consisted of 6.1 g. ($n^{20}\mathrm{D}$ 1.4035) frozen on the inlet tube of the Dry Ice trap, and 1.1 g. ($n^{20}\mathrm{D}$ 1.4138) which had not frozen at −78°. The larger fraction gave a positive ceric nitrate test for alcohols and was largely water-soluble. It presumably consisted chiefly of *t*-butanol and a little cumene. The 1.1-g. fraction probably contained some acetone (yellow-orange ppt. with 2,4-dinitrophenylhydrazine) as well as *t*-butanol and cumene. Neither of these fractions was investigated further.

The residue from the rectification on cooling deposited white crystals. These were isolated by filtration and washed with a minimal amount of petroleum ether; yield 3.65 g. of crude dicumene (m.p. *ca.* 110–114°). The filtrate and petroleum ether wash were combined and treated in two portions with excess 2,4-dinitrophenylhydrazine[30]; yields (37% combined) of crude acetophenone 2,4-dinitrophenylhydrazone, 6.29 g. (m.p. 242.5°)[25] and 4.77 g. (m.p. 238-40°). The methanolic filtrate from the 2,4-dinitrophenylhydrazine treatment was purified as in the isolation of α-phenylethyl-*t*-butyl peroxide. At 0.5 mm. there was obtained 0.3 g. of distillate ($n^{20}\mathrm{D}$ 1.4830) and 3.76 g. of material which did not distil up to 122°. This was combined with the 3.65 g. of crude dicumene isolated previously (total yield 31%) and recrystallized from 95% ethanol. This gave 4.10 g. melting 108–114°. A second recrystallization gave material which began to shrink at 108° and melted 110–115°. The m.p. was not improved by extracting a petroleum ether solution of these crystals with 5% sodium hydroxide; lit. values: 115°,[32] 119–120°.[33] In view of the excellent analyses it seems likely that this "dicumene" is 2,3-diphenyl-2,3-dimethylbutane contaminated with small amounts of isomeric hydrocarbons. *Anal.* Calcd. for $C_{18}H_{22}$: C, 90.75; H, 9.25. Found: C, 90.7, 90.9; H, 9.37, 9.25.

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(29) A preliminary experiment indicated that the racemization of optically active α-phenylethyl bromide in *t*-butanol is promoted by small amounts of water.

(30) The reagent is prepared by adding *ca.* 10 ml. of 36% hydrochloric acid to each 100 ml. of methanol saturated with 2,4-dinitrophenylhydrazine. A slightly different reagent which consists of 10 g. of 2,4-dinitrophenylhydrazine, 17 ml. of 36% hydrochloric acid and enough methanol to give 1 *l.* of solution was used in all qualitative tests for carbonyl compounds. The sensitivity of this reagent may be gaged from the fact that a positive test is obtained with a chloroform solution containing 0.13% acetophenone. Acetophenone is produced by the action of the base $(CH_3)_3C\text{-}O\text{-}O^-$ on the peroxide.[9] In common with α-phenylethyl bromide it cannot be removed from the peroxide by ordinary distillation and upon rectification a small but unmistakable amount of decomposition occurs as evidenced by the further formation of acetophenone. It was necessary, therefore, to remove both unreacted α-phenylethyl bromide and acetophenone by chemical methods

(31) O. D. Shreve, M. R. Heether, H. B. Knight and D. Swern, *Anal. Chem.*, **23**, 282 (1951); E. R. Blout, private communication. Also see J. H. Raley, F. F. Rust and W. E. Vaughan, THIS JOURNAL, **70**, 1337 (1948).

(31a) N. A. Milas, D. M. Surgenor and L. H. Perry, *ibid.*, **68**, 1618 (1946).

(31b) B. J. Mair, A. R. Glasgow and F. D. Rossini, *J. Research Natl. Bur. Standards*, **26**, 591 (1941); *ibid.*, **35**, 355 (1945).

(32) M. S. Kharasch, H. C. McBay and W. H. Urry, *J. Org. Chem.*, **10**, 401 (1945).

(33) A. Klages, *Ber.*, **35**, 2638 (1902).

Decomposition of *l*-α-Phenylethyl-*t*-butyl Peroxide in Thiophenol.—A 500-ml. flask was fitted with a reflux condenser, a gas inlet tube and an outlet leading to two Dry Ice traps backed by a mercury safety valve. The flask, charged with 19.4 g. (0.1 mole) of *l*-α-phenylethyl-*t*-butyl peroxide (n^{20}D 1.4809; α^{24}D −51.0°, *l* 1 dm.) and 381 g. (3.46 moles) of thiophenol [b.p. 58.5–60° (14 mm.), n^{20}D 1.5898] was heated for ten hours at 125 ± 2° while maintaining a nitrogen atmosphere. At the end of this time the Dry Ice traps were empty.

The cold product was poured into 20% aqueous sodium hydroxide solution (*ca.* 4.5 moles) and the mixture was thoroughly extracted with ether. The ether solution was washed with dilute alkali (*ca.* 10%) and then thoroughly with water. After drying over anhydrous magnesium sulfate the ether was removed and the remainder distilled at 2.7 mm. Three fractions weighing 0.98 g., 5.70 g. and 2.39 g. were collected; n^{20}D 1.5280, 1.5294 and 1.5301, respectively. The middle fraction was largely *l*-α-phenylethanol; it had α^{25}_{D} −10.6° (*l* 1 dm.) and immediately gave a positive test for acetophenone.[30]

The residue from this distillation (17.4 g.) was recrystallized once from 95% ethanol to give 14.3 g. of diphenyl disulfide, m.p. 59–60° and mixed m.p. 59–60° (lit. value 60–61°[34]).

l-α-Phenylethanol was isolated as the acid phthalate ester from fractions 1, 2 and 3. These were combined and mixed with 11.9 g. (0.08 mole) of finely powdered phthalic anhydride and 7.1 g. (0.09 mole) of anhydrous pyridine. The mixture was heated at 75 ± 2° for three hours with occasional shaking. On cooling it was poured into dilute hydrochloric acid layered with ether. The aqueous phase was thoroughly extracted with ether and the combined extracts were washed with water. Following this, the ether solution was carefully extracted with aqueous sodium bicarbonate, dried over sodium sulfate and then used for the isolation of acetophenone (see below).

The bicarbonate solution was acidified and extracted with chloroform. The chloroform solution was dried and then the chloroform was distilled off, the final traces being removed *in vacuo*. The hydrogen phthalate ester was dried to constant weight in a vacuum desiccator, 14.76 g. (55% yield); m.p., begins to shrink *ca.* 82° and melts 101–107.5°. Racemic α-phenylethyl hydrogen phthalate melts at 108° whereas the enantiomorphs melt at 86°.[13]

The acid phthalate thus isolated had $[\alpha]^{23}$D −18.5° in carbon disulfide (*c* 1.70, *l* 0.5 dm.) and $[\alpha]^{23}$D +9.8° in absolute ethanol (*c* 4.02, *l* 2 dm.). The *dl*-acid phthalate does not dissolve completely in carbon disulfide; it was necessary, therefore, to use a large half-angle shadow to get a reading on the somewhat turbid solution. Downer and Kenyon[13] report [α]D −65.8° in carbon disulfide; [α]D +36.5° in ethanol at "room temperature."

The dry ether solution (see above) gave the 2,4-dinitrophenylhydrazone of acetophenone, m.p.[25] and mixed m.p. 248–249°; yield 2.66 g. (0.009 mole). The rather unlikely possibility that this acetophenone is produced by the action of diphenyl disulfide on α-phenylethanol was not investigated. It is noteworthy that even in the absence of any additive acetophenone is produced (see below).

In a separate experiment it was shown that *t*-butyl alcohol is also formed, n^{20}D 1.3855, 3,5-dinitrobenzoate m.p., 141–142°; lit. values: n^{20}D 1.3878[35]; m.p. of dinitrobenzoate 142°.[36]

That α-phenylethanol is not derived from the reduction of acetophenone by thiophenol is shown by the following experiment. A solution of 6 g. (0.05 mole) of acetophenone and 11 g. (0.1 mole) of thiophenol was held at 125 ± 2° for 12 hours in a nitrogen atmosphere. A 98% recovery of acetophenone (as the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 246–247°)[25] was obtained.

Decomposition of α-Phenylethyl-*t*-butyl Peroxide in the Absence of Any Additive.—α-Phenylethyl-*t*-butyl peroxide (n^{20}D 1.4807), 1.34 g. (0.007 mole) was heated in a Pyrex flask for five hours at 125 ± 3°. The product was an opaque yellow-brown liquid having a pronounced odor of acetophenone. It was dissolved in petroleum ether (b.p. 35–37°) and washed with water. After removal of the petroleum ether the residual liquid was converted to the 2,4-dinitrophenylhydrazone; yield 1.02 g. (49%), m.p. 244–245°; m.p. of a mixture with an authentic sample of acetophenone 2,4-dinitrophenylhydrazone 245–246°.

The aqueous wash was saturated with potassium carbonate whereupon a few drops of a second phase appeared; this gave a positive ceric nitrate test.

Acknowledgment.—It is a pleasure to record our indebtedness to Messrs. S. L. Clark and K. L. Nelson of this Department for their assistance.

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(34) K. W. Rosenmund and H. Harms, *Ber.*, **53**, 2233, 2238 (1921).

(35) H. S. Davis and W. J. Murray, *Ind. Eng. Chem.*, **18**, 844 (1926).

(36) W. D. M. Bryant, THIS JOURNAL, **54**, 3760 (1932).

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Countercurrent Distribution Studies with Insulin

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RECEIVED JANUARY 25, 1952

A number of systems have been developed which permit the protein insulin to behave almost as an ideal solute as far as countercurrent distribution is concerned. The patterns obtained with different insulins have indicated a major component and varying amounts of minor components, some of which are biologically active. The major components of insulins from different species of animals appear to be identical as far as countercurrent distribution in its present stage of development is able to distinguish.

The recent technical improvements in countercurrent distribution both of a mechanical nature[1] and from the standpoint of the development of systems are now such as to warrant a serious attempt to apply the method to the most difficult problems of biochemistry. Certainly the purification and characterization of proteins fall within this category. An attempt is therefore being made to study proteins along the lines which have yielded valuable information with the higher polypeptides.

Insulin is a well known protein of considerable stability which is soluble in dilute alcohol solutions. It has been the subject of many investigations and often has served as a type substance for protein study. Certain preparations have passed reasonably well the criteria of purity given by electrophoresis, the ultracentrifuge and the solubility method.[2,3] Because of this background and the availability of samples on which such studies al-

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(1) L. C. Craig, W. Hausmann, E. H. Ahrens, Jr., and E. J. Harfenist, *Anal. Chem.*, **23**, 1236 (1951).

(2) E. Fredericq and H. Neurath, THIS JOURNAL, **72**, 2684 (1950).

(3) (a) B. Sjögren and T. Svedberg, *ibid.*, **53**, 2657 (1931); (b) J. L. Hall, *J. Biol. Chem.*, **139**, 175 (1941); (c) H. Gutfreund and A. G. Ogston, *Biochem. J.*, **40**, 432 (1946); (d) H. Gutfreund, *ibid.*, **42**, 544 (1948).