[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE DETECTION OF FREE RADICALS IN SOLUTION. I. THE REACTION OF PHENOXYETHYL BROMIDE WITH ISOPROPYLMAGNESIUM BROMIDE (OR WITH MAGNESIUM) IN THE PRESENCE OF ISOPRENE AND COBALTOUS HALIDES

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There are various diagnostic methods whereby reactions which proceed by free radical mechanisms may be demonstrated. Thus, to cite but a few examples, the presence of some free radicals in solution may be inferred from their attack on the solvent and the removal from it of a hydrogen or a halogen atom. The existence of other free radicals may be inferred from the formation of "dimeric" products (produced by abstracting an atom from a molecule), or from the addition of free radicals to olefins (polymerization, etc.). Nevertheless, there is still a very large number of free radicals the transient existence of which has not been demonstrated by unambiguous methods. Furthermore, there are many reactions (*e.g.* concerted reactions) where the evidence for the participation of free radicals has not been fully established. For instance, it has not been demonstrated whether free radicals participate in the formation of a Grignard reagent from an organic halide and magnesium.

In the present paper are presented data which suggest that a free phenoxyethyl radical is formed when phenoxyethyl bromide is treated with either isopropylmagnesium bromide (in the presence of a cobalt halide), or with metallic magnesium. Other papers in this series will deal with other types of radicals not recognizable by procedures previously employed.[1]

It has been shown (1) that phenoxyethyl bromide reacts with certain Grignard reagents (say phenylmagnesium bromide) in the presence of a small amount of cobaltous bromide to yield the following products:

1. $2C_6H_5MgBr + C_6H_5OCH_2CH_2Br \xrightarrow[\text{1-2 mole—\%}]{CoBr_2} C_6H_5C_6H_5 + C_6H_5OMgX$ (90%) + $CH_2{=}CH_2$ (81%) + $C_6H_5OC_2H_5$ (3-4%)

These findings, because of the small amounts of cobalt bromide used, suggest, but do not actually prove, that the cobalt sub-bromide (formed from the Grignard reagent and cobaltous bromide) first attacked the phenoxyethyl bromide to produce the free phenoxyethyl radical.

To demonstrate the free radical character of the reaction of phenoxyethyl bromide with sub-cobaltous bromide, we resorted to the method previously used

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[1] For examples of types of free radical reactions and references, the papers from this laboratory on "Reactions of Atoms and Free Radicals in Solution" should be consulted.

by us to demonstrate the formation of free RO• radicals (2), that is the generation of free radicals in the presence of butadiene, isoprene, or chloroprene.[2]

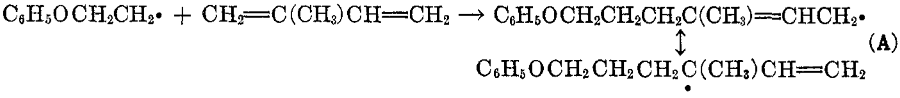
Two distinct methods[3] were used to generate the free phenoxyethyl radical. In one of them, isoprene was added to isopropylmagnesium bromide (0.35 mole); then cobaltous bromide (0.01 mole) and phenoxyethyl bromide (0.2 mole) were slowly added.

2. $(CH_3)_2CHMgBr + CoBr_2 \rightarrow (CH_3)_2CHCoBr + MgBr_2$

3. $(CH_3)_2CHCoBr \rightarrow (CH_3)_2CH\cdot + (CoBr)\cdot$

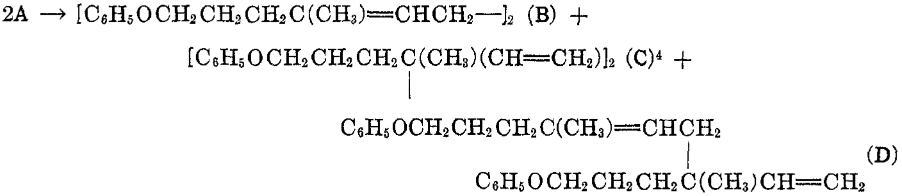
4. $(CoBr)\cdot + C_6H_5OCH_2CH_2Br \rightarrow C_6H_5OCH_2CH_2\cdot + CoBr_2$

5.



$$C_6H_5OCH_2CH_2\cdot + CH_2{=}C(CH_3)CH{=}CH_2 \rightarrow \begin{array}{c} C_6H_5OCH_2CH_2CH_2C(CH_3){=}CHCH_2\cdot \\ \updownarrow \\ C_6H_5OCH_2CH_2CH_2\underset{\bullet}{C}(CH_3)CH{=}CH_2 \end{array} \quad (A)$$

6.



$$2A \rightarrow [C_6H_5OCH_2CH_2CH_2C(CH_3){=}CHCH_2{-}]_2\ (B) + [C_6H_5OCH_2CH_2CH_2C(CH_3)(CH{=}CH_2)]_2\ (C)^4 + \begin{array}{c} C_6H_5OCH_2CH_2CH_2C(CH_3){=}CHCH_2 \\ | \\ C_6H_5OCH_2CH_2CH_2C(CH_3)CH{=}CH_2 \end{array} \quad (D)$$

In the second method, phenoxyethyl bromide (0.05 mole), magnesium (0.08 mole), isoprene (0.2 mole), and ether (10 ml.) were gently heated while the mixture was stirred.

7. $C_6H_5OCH_2CH_2Br + Mg \rightarrow C_6H_5OCH_2CH_2\cdot + (MgBr)\cdot$

The addition of the free phenoxyethyl radical[5] to isoprene and the dimerization of the resulting free radical are indicated in equations 5 and 6.

Products corresponding to **B** and **D** were obtained by either of the methods just described. No attempt was made to separate these products since they do not have an important bearing on the problem here in question. Molecular

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[2] Towards free radicals, these diolefins are at least two hundred times as reactive as simple aliphatic terminal olefins (3). The diolefins have an additional virtue in that the free allylic radicals, formed by the addition of free radicals to the diolefins, dimerize (2).

a. $RO\cdot + CH_2{=}CHCH{=}CH_2 \rightarrow [ROC_4H_6]\cdot$
b. $2[ROC_4H_6]\cdot \rightarrow ROC_4H_6{\cdot}C_4H_6OR$

[3] The choice of isoprene was dictated by the considerations discussed in Reference (2), page 1557.

[4] These dimers, if formed in the dimerization of radicals of this type, must be present in very small amounts and have not been isolated in this or similar studies.

[5] This equation does not imply that free phenoxyethyl radicals are present in solution, and that they then add to isoprene. It is conceivable that the reaction is concerted, that is, that the isoprene molecule pulls off the free radical from the surface just when the magnesium pulls the bromine atom. Under these circumstances no free phenoxyethyl radicals are present in solution. However, the data here presented leave no doubt as to the existence of the free radical formed by the addition of the phenoxyethyl radical to isoprene. Additional evidence will be presented in a paper by Kharasch, Holton, and Nudenberg.

weight determinations and analyses were in agreement with the formula for any one of these isomers. The presence of compound **B** was demonstrated by ozonolysis of the mixture and isolation from the ozonolysis product of γ-phenoxypropyl methyl ketone (identified as the 2,4-dinitrophenylhydrazone) and succinic acid.

8. $[C_6H_5OCH_2CH_2CH_2C(CH_3){=}CHCH_2{-}]_2 + O_3 \xrightarrow{\text{Hydrol., etc.}}$

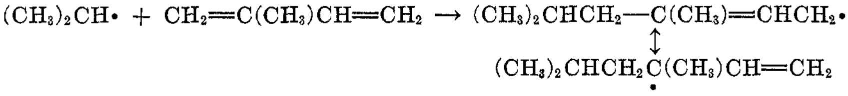
$C_6H_5OCH_2CH_2CH_2COCH_3 + COOHCH_2CH_2COOH$

Perbenzoic acid titrations indicated a minimum amount of 50% of **B**. The actual amount is undoubtedly larger (probably 80–85%) but since substances of similar structure were not available we were unable to plot curves for comparison of the rates of addition of perbenzoic acid.

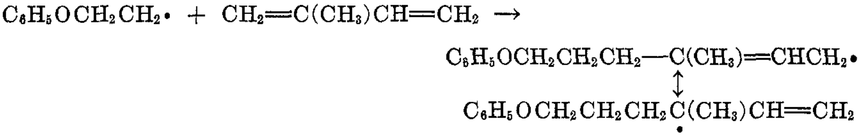
An interesting compound (besides **B** and **D**) was formed when a mixture of isopropylmagnesium bromide was treated with phenoxyethyl bromide in the presence of cobalt bromide. This product was not formed when magnesium was used instead of isopropylmagnesium bromide; it is best accounted for as follows:

9. $(CH_3)_2CHMgBr + CoBr_2 \rightarrow (CH_3)_2CHCoBr + MgBr_2$

10. $(CH_3)_2CHCoBr \rightarrow (CH_3)_2CH\cdot + (CoBr)\cdot$

11.

$$(CH_3)_2CH\cdot + CH_2{=}C(CH_3)CH{=}CH_2 \rightarrow \begin{array}{c} (CH_3)_2CHCH_2{-}C(CH_3){=}CHCH_2\cdot \\ \updownarrow \\ (CH_3)_2CHCH_2\underset{\bullet}{C}(CH_3)CH{=}CH_2 \end{array}$$
(E)

12. $C_6H_5OCH_2CH_2Br + (CoBr)\cdot \rightarrow C_6H_5OCH_2CH_2\cdot + CoBr_2$

13.

$$C_6H_5OCH_2CH_2\cdot + CH_2{=}C(CH_3)CH{=}CH_2 \rightarrow \begin{array}{c} C_6H_5OCH_2CH_2CH_2{-}C(CH_3){=}CHCH_2\cdot \\ \updownarrow \\ C_6H_5OCH_2CH_2CH_2\underset{\bullet}{C}(CH_3)CH{=}CH_2 \end{array}$$
(A)

14. $\mathbf{E} + \mathbf{A} \rightarrow C_6H_5OCH_2CH_2\cdot C_5H_8\cdot C_5H_8CH(CH_3)_2$ (**F**)

The molecular weight and analyses of **F** are in very good agreement with the empirical formula here proposed. Furthermore, the compound, when ozonized (and worked-up in the usual way), gave γ-phenoxypropylmethyl ketone (identified as the 2,4-dinitrophenylhydrazone) and succinic acid. It is unfortunate that we have not as yet identified from the ozonolysis products a fragment containing the isopropyl group.

EXPERIMENTAL

Reaction of phenoxyethyl bromide with isoprene in the presence of isopropylmagnesium bromide and cobaltous bromide. A solution of freshly distilled isoprene (23.8 g.; 0.35 mole) in ether (100 ml.) was placed in a liter flask together with an ethereal solution of isopropylmagnesium bromide (138 ml. of 1.8 *N* solution; 0.25 mole) and the temperature of the whole was raised to 30–35°. Phenoxyethyl bromide (40.2 g.; 0.20 mole) in ether (50 ml.) was dropped in slowly over 30 minutes with simultaneous intermittent addition of cobaltous bromide (2.2 g.; 0.01 mole). The resultant dark-colored mixture was vigorously stirred for a further three hours, the temperature being maintained at 30–35°. The gas (a mixture of ethylene, propane, and propylene) which was evolved throughout the whole of this period was collected (1,200 ml.).

The reaction mixture was cooled, and the remaining Grignard reagent was decomposed by the slow addition of saturated aqueous ammonium chloride, with a further gas evolution ($\simeq$ 400 ml.). The ethereal layer was separated and washed with aqueous sodium hydroxide. The phenolic product (3.8 g.; 0.04 mole) was obtained by acidification of the alkaline solution. It solidified when seeded with a crystal of pure phenol.

The neutral product (44.2 g.) was obtained as a light brown oil after removal of the ether. Upon distillation, the following fractions were obtained: Fraction 1, a colorless oil (17.1 g.), b.p. 100–125°/13 mm. (0.085 mole); Fraction 2, a colorless oil (13.4 g.), b.p. 70–140°/0.15 mm.; Fraction 3, a residue of a viscous brown oil (13.5 g.).

Fraction 1. This gave a strong test for bromide and proved to be unchanged phenoxyethyl bromide.

Fraction 2. Upon distillation the following fractions were obtained: Fraction 2a, a colorless oil (1.9 g.), b.p. 80–110°/0.25 mm. which gave a slight positive test for halogen and had a molecular weight of 245. Fraction 2b, a colorless oil (2.1 g.), b.p. 110–147°/0.4 mm. This gave a negative test for halogen and had a molecular weight of 210. Fraction 2c, a residue (8.4 g.). This gave a negative test for halogen.

Anal. of Fraction 2c presumably $C_6H_5O(CH_2)_2 \cdot C_5H_8 \cdot C_5H_8CH(CH_3)_2$; $C_{21}H_{32}O$.
Calc'd: C, 84.00; H, 10.67; Mol. wt., 316.
Found: C, 83.74; H, 10.90; Mol. wt., 308.

A portion of fraction 2c (6 g.) was submitted to ozonolysis in ethyl acetate solution (300 ml.) at −80°. Ozone was passed into the mixture at the rate of ½ millimole/min. It had fully reacted with the unsaturated compound in 87 minutes. The water suspension of the ozonides was refluxed for four hours. Ether was added to the cooled suspension and separation of the acidic and neutral portions was carried out by the addition of sodium bicarbonate solution.

Ether was carefully removed from the neutral portion and the product was distilled to give:

(i) A fraction (0.3 g.), b.p. 90–120°/16 mm. This material gave a mixture of 2,4-dinitrophenylhydrazones, m.p. 90–150° which could not be purified further by crystallization or chromatography on a column of alumina.

(ii) A light yellow oil (1.4 g.), b.p. 147–151°/16 mm. A 2,4-dinitrophenylhydrazone was prepared and purified by chromatography on a column of alumina. Orange leaflets, m.p. 108–110°, were obtained [*cf. J. Am. Chem. Soc.*, **67**, 1423 (1945), 2,4-dinitrophenylhydrazone of γ-phenyloxypropyl methyl ketone, m.p. 109–110°].

Anal. Calc'd for 2,4-dinitrophenylhydrazone of $PhOCH_2CH_2CH_2COMe$: N, 15.63. Found: N, 15.70.

The aqueous phase was acidified with hydrochloric acid and continuously extracted with ether. On removal of the ether some solid (0.1 g.) crystallized from the residual oil and was collected on a filter. The residual oil was boiled under reflux for four hours with aqueous hydrogen peroxide (100 ml. of 10% solution). On cooling the water-insoluble material was removed by extraction with ether and the aqueous solution was evaporated to dryness. Succinic acid (0.7 g.) thus was obtained. The melting point of the acid (183–185°), after crystallization from acetone, was not depressed when mixed with an authentic specimen of succinic acid (183–185°).

Fraction 3. This material (13.5 g.) was dissolved in 2:1 petroleum ether-benzene and was chromatographed on a column (30 x 2 cm.) of alumina. Elution with the same mixed solvent gave a colorless oil, Fraction 3i (11.1 g.).

Anal. Calc'd for $[C_6H_5OCH_2CH_2C_5H_8—]_2$; $C_{26}H_{34}O_2$: C, 82.50; H, 9.05; Mol. wt., 378.
Found: C, 82.75; H, 10.08; Mol. wt., 360.

A portion of this (6 g. *ca.* 31 mmole double bond) material was ozonized in the manner previously described. Ozonolysis was complete in 79 minutes. The ozonides were decomposed in water and were separated into acidic and neutral fractions as previously described.

The neutral fraction on distillation at 135–140°/10 mm. gave a light yellow oil (2.2 g.). The 2,4-dinitrophenylhydrazone of this material melted at 108–109°. It did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of γ-phenoxypropyl methyl ketone.

The aqueous solution, heated as described previously, gave succinic acid (0.7 g.). Upon crystallization from acetone, the acid melted at 183–185°, and did not depress the melting point of an authentic sample of succinic acid.

Perbenzoic acid titration of Fraction 3i. [*Cf.* Kolthoff and Lee, *J. Polymer Sci.*, **2,** 209 (1947)] A portion of this fraction (0.3801 g.) was dissolved in chloroform (80 ml., alcohol-free) and cooled to 0°. Perbenzoic acid solution (10 ml. of 0.3 *molar*) cooled to 5° was then added and the solution was made up to 100 ml. with more alcohol-free chloroform. At the stated intervals 10 ml. of the solution, being kept at 0°, was added to potassium iodide (0.4 g.) in 0.4 *N* acetic acid (20 ml.) and the iodine liberated was titrated with standard thiosulphate solution. A blank of perbenzoic acid (0.03 mole) was titrated in the same way at each time.

Time	*% Double Bonds Consumed Assuming Mol. wt. = 378.5*
4 mins.	30.43
19 mins.	55.39
34 mins.	62.81
64 mins.	68.15
124 mins.	73.75
4 hrs. 4 mins.	76.41
8 hrs. 4 mins.	79.35
19 hrs. 4 mins.	81.60

The experiment described in this section was repeated three times with minor variations. Substantially the same results were obtained.

Reaction of phenoxyethyl bromide with isoprene in the presence of magnesium. Phenoxyethyl bromide (10.1 g.; 0.05 mole), magnesium (2 g.; 0.08 mole), isoprene (13.6 g.; 0.2 mole) together with ether (10 ml.) were stirred vigorously at room temperature without reaction ensuing even upon the addition of a crystal of iodine. On gently refluxing the mixture, reaction vigorously ensued, with separation of a white powder. As there was some mechanical loss more isoprene (10 g.; 0.15 mole) was added and boiling under reflux was continued for a further two hours. On cooling the product was poured into saturated aqueous ammonium chloride, and extracted with ether. The ethereal layer was separated and washed with sodium hydroxide solution (10%). Phenol was obtained by acidification of the alkaline solution. When distilled at 87–88°/26 mm. a colorless oil (1.2 g.; 0.012 mole) was obtained which solidified upon the addition of a crystal of phenol.

The light yellow oil (4 g.), obtained from the neutral fraction upon evaporation of the ether, was chromatographed on a column (30 x 2 cm.) of alumina. Elution with a mixture of 2:1 petroleum ether and benzene gave a colorless oil (3.8 g.) from which some white plates crystallized. Dilution of this mixture with additional petroleum ether gave a crystalline material (0.2 g.). The melting point of this material (97–98°) was not depressed on admixture with an authentic specimen of 1,4-diphenoxybutane.

The oil obtained by evaporation of the solvents was again chromatographed on a column of alumina. No solid material was eluted with solvents such as petroleum ether, or a mixture of 4:1 petroleum ether and benzene. Elution with benzene gave a colorless oil (3.5 g.; mol. wt. 346). The oil was again chromatographed on a column of alumina. It was eluted with a mixture of 19:1 petroleum ether and benzene. Upon evaporation of the solvent, an oil (Fraction 3i) was obtained (n_D^{20} 1.5422).

The analysis of sample 3i which is presumably $[C_6H_5OCH_2CH_2C_5H_8—]_2$ contaminated with a small amount of 1,4-diphenoxybutane gave the following results:

Anal. Calc'd for $[C_6H_5OCH_2CH_2C_5H_8—]_2$: C, 82.50; H, 9.05; Mol. wt., 378.

Found: C, 82.04; H, 9.47; Mol. wt., 359.

Ozonolysis of Fraction 3i. Ozonolysis [ozone passed at the rate of 0.5 mml/min. of a portion of this oil (2.8 g.)] was complete in 34 minutes. The ozonolysis and decomposition of the ozonides were carried out in the usual way. The neutral extract, after removal of the ether through a fractionating column gave the following fractions upon distillation: Fraction 1, a colorless liquid (0.3 g.) b.p. 65–75°/760 mm. which gave no positive test with 2,4-dinitrophenylhydrazine. Fraction 2, a colorless liquid (0.1 g.) b.p. 70–135°/25 mm. This gave a 2,4-dinitrophenylhydrazone as an oily solid which could not be purified by crystallization or chromatography. Fraction 3, a slightly yellow oil (1.1 g.) b.p. 162–165°/25 mm. gave a 2,4-dinitrophenylhydrazone identical with that from an authentic sample of γ-phenoxypropyl methyl ketone.

The aqueous fraction was worked up in the usual way to give succinic acid (0.4 g.).

Perbenzoic acid titration of Fraction 3i. A portion (0.3792 g.) in alcohol-free chloroform (80 ml.) was mixed at 0° with perbenzoic acid solution (0.3 mole; 10 ml.), the volume being made up to 100 ml. with more chloroform. The percentage of the double bonds consumed after a given time was determined in the manner previously described.

Time	*% Double Bonds Consumed Assuming Mol. wt. = 378.5*
4 mins.	71.99
19 mins.	70.15
34 mins.	75.77
64 mins.	80.13
2 hrs. 19 mins.	84.20
4 hrs. 4 mins.	84.49
8 hrs. 4 mins.	85.73
23 hrs. 4 mins.	88.70

The experiment described in this section was repeated, with minor variations, three times. Substantially the same results as described in this section were obtained.

SUMMARY

1. It has been established that, when isopropylmagnesium bromide is treated with phenoxyethyl bromide in the presence of small amounts of cobalt bromide and isoprene, two products are formed. One of them is undoubtedly formed by dimerization of the free radical

$$2[C_6H_5OCH_2CH_2C_5H_8]\cdot \rightarrow [C_6H_5OCH_2CH_2C_5H_8-]_2.$$

The other product is formed by dimerization of two unlike free radicals,

$$[(CH_3)_2CHC_5H_8]\cdot + [C_6H_5OCH_2CH_2C_5H_8]\cdot \rightarrow (CH_3)_2CHC_5H_8\cdot C_5H_8CH_2CH_2OC_6H_5.$$

2. It has been shown that phenoxyethyl bromide reacts with magnesium in the presence of isoprene to give a free radical, $[C_6H_5OCH_2CH_2\cdot C_5H_8]\cdot$, which then dimerizes.

3. The work is being continued.

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REFERENCES

(1) Kharasch, Stampa, and Nudenberg, *J. Org. Chem.*, **18**, 575 (1951).

(2) Kharasch, Arimoto, and Nudenberg, *J. Org. Chem.*, **16**, 1556 (1951).

(3) Kharasch, Simon, and Nudenberg, *J. Org. Chem.*, **18**, 328 (1952).