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# STUDIES ON PEROXY COMPOUNDS—XXIV* THE INTRODUCTION OF ACYLOXYGROUPS INTO SO-CALLED ACTIVE METHYLENE COMPOUNDS

## AN EXPERIMENT WITH BENZOYL PEROXIDE (CARBONYL $O^{18}$)

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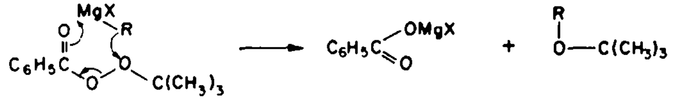
**Abstract**—By reacting benzoyl peroxide with sodium compounds of so-called active methylene compounds in non-hydroxylic solvents the benzoyloxy group is smoothly introduced into the methylene compounds. The work done in this field is reviewed. An experiment with labeled benzoyl peroxide shows that the oxygen-oxygen bond is directly attacked by the carbanion and that the formation of free benzoyloxy species is excluded.

## INTRODUCTION

IN RECENT years the interest in peroxide chemistry has increased and as a result a series of monographs[1] have been published. Thus it has been shown that peroxides may be produced from an ever-increasing number of chemical species and at the same time processes have been developed commercially. Reactions of such a simple and easily-available compound as benzoyl peroxide are still being studied in detail along different lines, and this paper will review work recently done by Lawesson *et al.* concerning reactions between benzoyl peroxide and sodium salts of active methylene compounds. Also an attempt to elucidate the mechanism is presented.

It has been found by Lawesson and Yang[2] that a Grignard reagent ruptures the oxygen-oxygen bond of t-butyl perbenzoate, thus giving a convenient method for the preparation of t-butyl ethers:



(1)

Lawesson and Frisell[3,4] have also extended this investigation and found further that t-butyl arylethers, on heating with catalytic amounts of *p*-toluenesulphonic acid, give the corresponding hydroxyaryls in almost quantitative yields.

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* Part XXIII: C. Berglund and S.-O. Lawesson, *Arkiv Kemi* **20**, 225 (1963).

[1a] C. Walling, *Free Radicals in Solution*. John Wiley, New York (1957).

[b] A. G. Davies, *Organic Peroxides*. Butterworth, London (1961).

[c] E. G. E. Hawkins: *Organic Peroxides-Their formations and reactions*. Spon, London (1961).

[2] S.-O. Lawesson, and N. C. Yang, *J. Amer. Chem. Soc.* **81**, 4230 (1959).

[3] S.-O. Lawesson, and C. Frisell, *Arkiv Kemi* **17**, 393 (1961).

[4] C. Frisell, and S.-O. Lawesson, *Org. Synthesis* **41**, 91 (1961).

A reinvestigation of earlier work[5,6] on reactions of Grignard reagents and magnesium bromide with benzoyl peroxide confirmed that the initial attack is on the oxygen-oxygen bond. If the Grignard reagent ($C_6H_5MgBr$) is considered as a mixture of magnesium bromide and diphenyl magnesium, the accommodation of the products phenyl benzoate, benzoic acid and bromobenzene is accounted for by the following mechanism:

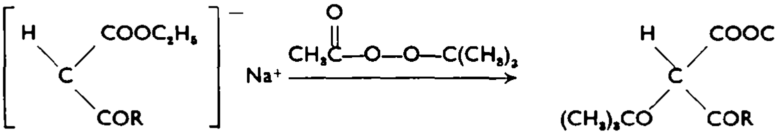
$$2\,C_6H_5MgBr \rightarrow (C_6H_5)_2Mg + MgBr_2 \tag{2}$$

$$MgBr_2 + (C_6H_5COO)_2 \rightarrow (C_6H_5COO)_2Mg + Br_2 \tag{3}$$

$$\tfrac{1}{2}(C_6H_5)_2Mg + (C_6H_5COO)_2 \rightarrow C_6H_5COOC_6H_5 + \tfrac{1}{2}(C_6H_5COO)_2Mg \tag{4}$$

$$\tfrac{1}{2}(C_6H_5)_2Mg + Br_2 \rightarrow C_6H_5Br + \tfrac{1}{2}MgBr_2 \tag{5}$$

An extension[7–9] of these findings with regard to active methylene compounds showed that sodiodiethylmalonate or sodioethylacetoacetate gave low yields of the corresponding t-butoxyderivatives when reacted with t-butyl peracetate:



(6)

$R = CH_3, —OC_2H_5$

The same t-butoxyderivatives were obtained by the catalyzed (catalyst: cuprous chloride) decomposition of t-butyl perbenzoate in diethyl malonate and ethyl acetoacetate, respectively.[10]

However, in contrast to reactions with sodium alkoxide in alcoholic solution, benzoyl peroxide reacts smoothly with sodiodiethylmalonate in benzene to give the diethyl O-benzoyl tartronate[11] and sodium benzoate, which means that the oxygen-oxygen bond is primarily attacked. As early as 1928 Bradley and Robinson[12] had made a similar observation while working on pyrylium salts of the anthocyanidin type, whereby the benzoyloxy group was introduced into ethyl benzoylacetate.

### O-*Acyltartronates*

Methods for the preparation of O-acyltartronates are known: they have been prepared by Conrad and Brückner[13] from diethyl bromomalonate and sodium acetate, by Dimroth and Schweizer[14] from diethyl malonate and lead tetraacetate, and by Jackson and Phinney[15] and Cope and Field[16] by acylating tartronic esters. The benzoyloxy group has now been introduced into a series of malonic esters by reacting

[5] H. Gilman and C. E. Adams, *J. Amer. Chem. Soc.* **47**, 2816 (1925).

[6] M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.* **50**, 2762 (1928).

[7] S.-O. Lawesson and C. Berglund, *Acta. Chem. Scand.* **13**, 1716 (1959).

[8] S.-O. Lawesson, T. Busch and C. Berglund, *Acta. Chem. Scand.* **15**, 260 (1961).

[9] S.-O. Lawesson, M. Andersson and C. Berglund, *Arkiv Kemi* **17**, 429 (1961).

[10] C. Berglund and S.-O. Lawesson, *Arkiv Kemi* **20**, 225 (1963).

[11] S.-O. Lawesson and T. Busch, *Acta. Chem. Scand.* **13**, 1716 (1959).

[12] W. Bradley and R. Robinson, *Chem. Soc.* 1541 (1928).

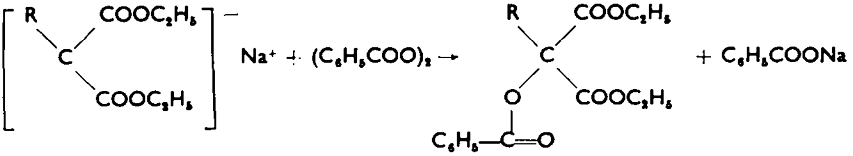
[13] M. Conrad and C. Brückner, *Ber. Dtsch. Chem. Ges.* **24**, 2993 (1891).

[14] O. Dimroth and R. Schweizer, *Ber. Dtsch. Chem. Ges.* **56**, 1375 (1923).

[15] C. L. Jackson and J. T. Phinney, *Amer. Chem. J.* **21**, 418 (1899).

[16] A. C. Cope and L. Field, *J. Org. Chem.* **14**, 856 (1949).

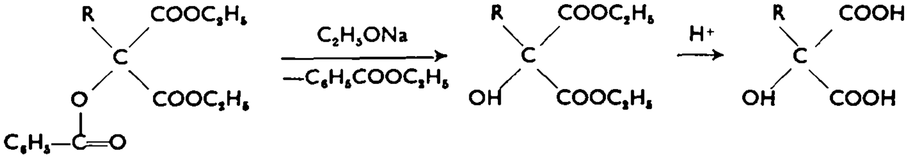
the corresponding sodium derivatives with benzoyl peroxide and at about 0°



(7)

(R = different alkyl, aryl and aralkyl groups, $-COOC_2H_5$, Cl, H, etc.)

By ethanolysis of the O-acyltartronate reesterification takes place and the ethyl benzoate is easily separated from the tartronate. Further hydrolysis also gave the tartronic acid very smoothly

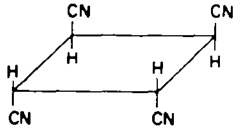


(8)

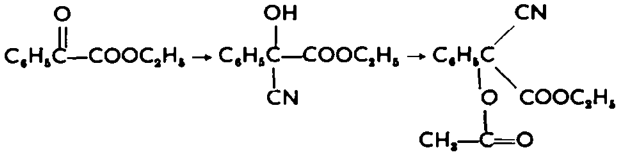
In one case (eqn 8; $R = C_6H_5$) decarboxylation took place after ethanolysis and hydrolysis, giving high yields of mandelic acid.

*The introduction of the acyloxy group into α-cyanocarboxylic esters*

Acyloxy derivatives of ethyl cyanoacetate, a type of compound which is of potential interest in connection with the preparation of amino acids or amino acid precursors, cannot be prepared by the method of Conrad *et al.*[13] or by the lead tetraacetate method.[14] Sadeh and Berger[17] treated for instance, ethyl bromocyanoacetate with potassium acetate in alcoholic solution but isolated as the sole product what was said to be 1, 2, 3, 4 tetracyanocyclo-butane



By an indirect route Testa *et al.*[18] have recently in a single case prepared ethyl α-phenyl-α-acetoxy cyanoacetate, starting from ethyl benzoylformate:



(9)

By adopting the benzoyloxy method different alkyl, aryl and aralkylsubstituted ethyl cyanoacetates have been allowed to react (as the sodium salt) with benzoyl peroxide and the benzoyloxy compounds were isolated in fair to high yields.[19] The benzoyloxygroup has also been introduced into t-butyl cyanoacetates.[20]

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[17] T. Sadeh and A. Berger, *Bull. Research Council, Israel* 7A, (March 1958) No. 2.

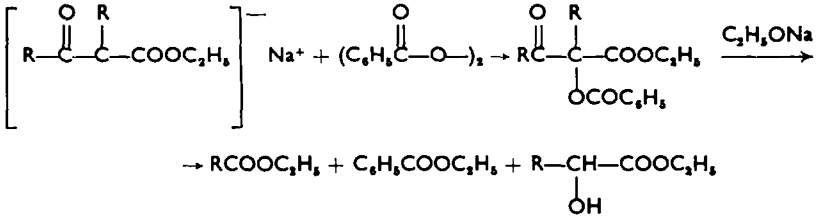
[18] E. Testa, L. Fontanella, G. F. Christiani and L. Mariano, *Liebigs Ann* **639**, 166 (1961).

[19] S.-O. Lawesson and C. Frisell, *Arkiv Kemi* **17**, 409 (1961).

[20] E. H. Larsen, H. J. Jakobsen and S.-O. Lawesson, unpublished results.

### *New methods for the preparation of α-hydroxyesters and acyloins*

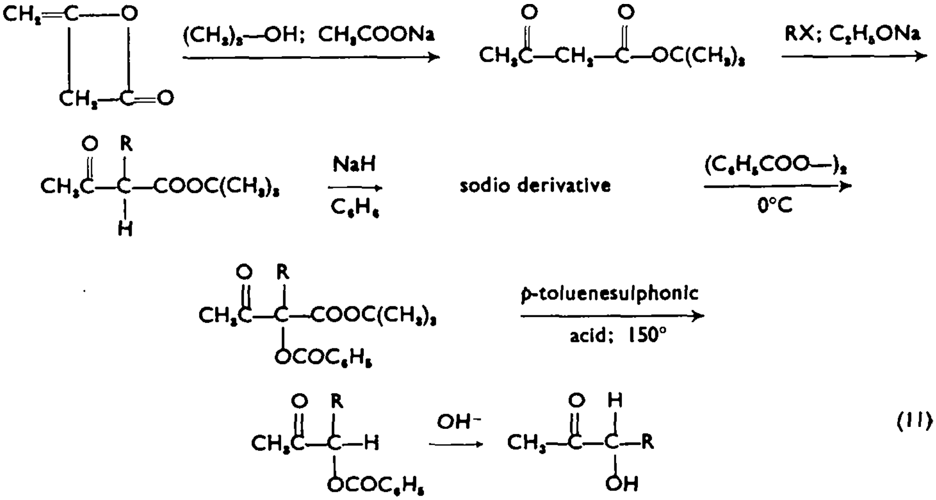
Acetoxy compounds have been prepared from ethyl acetoacetate by the lead tetraacetate method[14,21] or from ethyl α-chloroacetoacetate and sodium acetate.[22,23] By the benzoyl peroxide method the benzoyloxy group has been introduced into a series of different β-ketoesters[24] and high yields of products have generally been obtained. As had been observed earlier,[12] these esters are very stable with regard to acids and bases and thus very resistant to hydrolysis. However, by ethanolysis the corresponding α-hydroxyester can be prepared as in the following sequence:



$$\left[R-\overset{O}{\overset{\|}{C}}-\overset{R}{\overset{|}{C}}-COOC_2H_5\right]^- Na^+ + (C_6H_5\overset{O}{\overset{\|}{C}}-O-)_2 \rightarrow R\overset{O}{\overset{\|}{C}}-\underset{OCOC_6H_5}{\overset{R}{C}}-COOC_2H_5 \xrightarrow{C_2H_5ONa}$$
$$\rightarrow RCOOC_2H_5 + C_6H_5COOC_2H_5 + R-\underset{OH}{CH}-COOC_2H_5$$

(10)

A novel modification[25] of the acetoacetic acid synthesis provides a route to acyloins or α-hydroxyketones. t-Butyl acetoacetate, which is easily prepared in high yields from t-butyl alcohol and diketene, is alkylated and the benzoyloxy group is introduced into the α-position by reacting of the sodio derivative with benzoyl peroxide in benzene. Elimination of the t-butyl group and decarboxylation is accomplished by heating the ester at about 150° with a catalytic amount of p-toluenesulphonic acid; saponification under mild conditions then gives the acyloin:



$$\begin{matrix} CH_2=C-O \\ | \quad\quad | \\ CH_2-C=O \end{matrix} \xrightarrow{(CH_3)_3-OH;\ CH_3COONa} CH_3\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC(CH_3)_3 \xrightarrow{RX;\ C_2H_5ONa}$$
$$CH_3\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{R}{C}}-COOC(CH_3)_3 \xrightarrow[C_6H_6]{NaH} \text{sodio derivative} \xrightarrow[0°C]{(C_6H_5COO-)_2}$$
$$CH_3\overset{O}{\overset{\|}{C}}-\underset{OCOC_6H_5}{\overset{R}{C}}-COOC(CH_3)_3 \xrightarrow[\text{acid; }150°]{p\text{-toluenesulphonic}}$$
$$CH_3\overset{O}{\overset{\|}{C}}-\underset{OCOC_6H_5}{\overset{R}{C}}-H \xrightarrow{OH^-} CH_3-\overset{O}{\overset{\|}{C}}-\underset{OH}{\overset{H}{C}}-R$$

(11)

### *The introduction of the benzoyloxy group into β-diketones*

As far as is known to us no acyloxy derivatives of β-diketones have been prepared

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[21] L. O. Krampitz, *Arch. Biochem.* **17**, 81 (1948).

[22] H. Henecka, *Chem. Ber.* **81**, 179 (1948).

[23] H. Nahm, and W. Dirschel, *Chem. Ber.* **83**, 415 (1950).

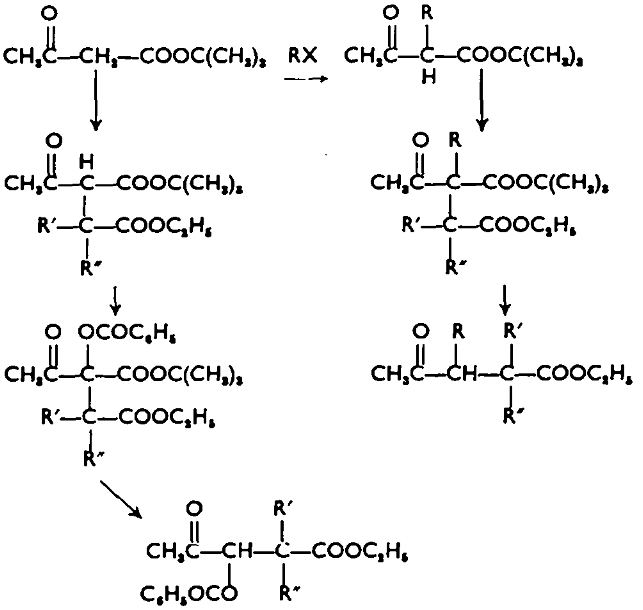
[24] S.-O. Lawesson, M. Andersson, and C. Berglund, *Arkiv Kemi* **17**, 457 (1961).

[25] S.-O. Lawesson, S. Grönwall, and M. Andersson, *Arkiv Kemi* **17**, 457 (1961).

earlier. By the peroxide method a series of derivatives were prepared.[26] Ethanolysis gave products of the acyloin-type.

### *A new route to levulinates and benzoyloxy-levulinates*[27]

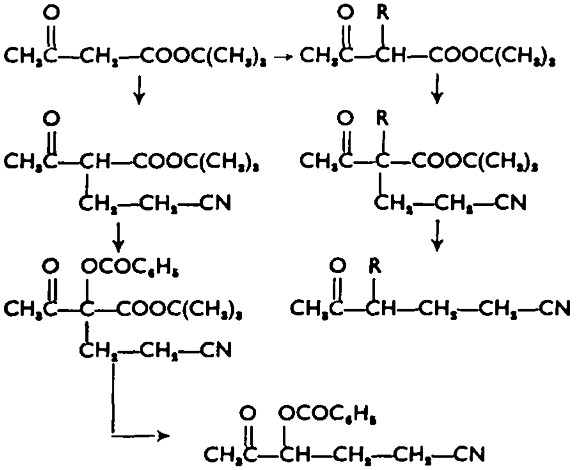
By reacting t-butyl acetoacetate with α-bromocarboxylic esters a derivative is prepared which then may react as its sodium salt with benzoyl peroxide; the benzoyloxy compound is thereby formed. Elimination of isobutylene and carbon dioxide then gives the benzoyloxy-levulinates



(12)

### *A new route to δ-ketonitriles and γ-benzoyloxy-δ-ketonitriles*[28]

The title compounds are obtained from t-butyl acetoacetate as follows:



(13)

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[26] S.-O. Lawesson, P-G. Jönsson, and J. Taipale, *Arkiv Kemi* **17**, 441 (1961).

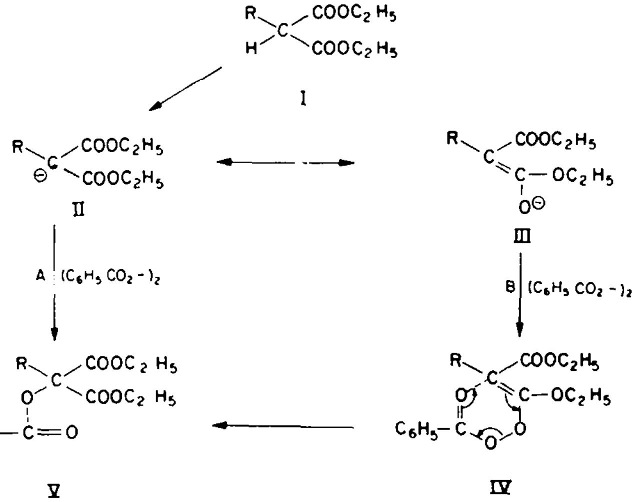
[27] S.-O. Lawesson, M. Dahlén, and C. Frisell, *Acta Chem. Scand.* **16**, 1191 (1962).

[28] G. Näslund, A. Senning, and S.-O. Lawesson, *Acta Chem. Scand.* **16**, 1324 (1962).

By this simple elimination method of the ester group, the cyano group is not hydrolysed.

## THE MECHANISM

Nucleophilic attacks of oxygen on oxygen were not known until recently, but there is at least in one case strong evidence for such a reaction; the decomposition of benzoyl peroxide in phenol is, according to Walling and Hodgson's suggestion,[29] an ionic reaction with an arylperoxy ester as an intermediate; the decomposition by a Claisen-type rearrangement then leads to *o*-hydroxyphenyl benzoate. Denney *et al.*[30] have studied the same reaction by decomposing benzoyl peroxide (carbonyl $O^{18}$) in *o*-cresol and a somewhat modified mechanism was presented which excluded the formation of a free benzoyloxy radical. Further, there are in the literature other suggestions about reactions involving nucleophilic attack of oxygen on oxygen.[31-34] It is also known from work, especially by Denney *et al.*, that reactions of nucleophiles (for instance phosphines[35] and amines[36]) proceed by initial displacement on one of the peroxide oxygens and it is thus deduced that either form (II or III) of the malonate (I) (Scheme 1) will react according to route A or B.



Scheme 1

In route A the carbanion II will attack the oxygen-oxygen bond (the weakest in the molecule) directly giving the tartronate (V). The less probable nucleophilic attack of oxygen on oxygen (that means the attack of the enolate III on the peroxide linkage) would give a perester (IV) as an intermediate, which by an intramolecular rearrangement ought to give the tartronate (V).

The purpose of this research was to find out according to what route (Scheme 1) benzoyl peroxide reacted with sodium compound of so-called active methylene

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[29] C. Walling and R. B. Hodgson, *J. Amer. Chem. Soc.* **80**, 228 (1958).

[30] D. B. Denney and D. Z. Denney, *J. Amer. Chem. Soc.* **82**, 1389 (1960).

[31] P. Bladon, *J. Chem. Soc.* 2176 (1955).

[32] L. S. Levitt and E. R. Malinowski, *J. Amer. Chem. Soc.* **77**, 4517 (1955).

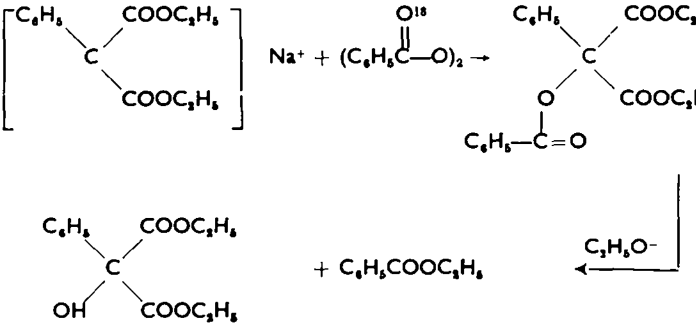
[33] E. R. Malinowski and L. S. Levitt, *J. Amer. Chem. Soc.* **80**, 5334 (1958).

[34] D. L. Ball and J. O. Edwards, *J. Amer. Chem. Soc.* **78**, 1125 (1956).

[35] M. A. Greenbaum, D. B. Denney, and A. K. Hoffman, *J. Amer. Chem. Soc.* **78**, 2563 (1956).

[36] D. B. Denney and D. Z. Denney, *J. Amer. Chem. Soc.* **82**, 1389 (1960).

compounds. For that reason we chose diethyl phenylmalonate as substrate and reacted its sodium compound according to the usual procedure with benzoyl peroxide labeled with oxygen-18 in both carbonyl positions. After removal of benzoic acid, the formed diethyl O-benzoyl phenyltartronate was treated with sodium alkoxide in ethanol to give ethyl benzoate:



(15)

An oxygen-18 analysis of the ethyl benzoate showed that it contained essentially all of the excess oxygen-18 originally present in one carbonyl group of benzoyl peroxide or in the diethyl O-benzoyl phenyltartronate. This finding shows that the reaction between benzoyl peroxide and the named sodiodiethylmalonate proceeds according to route A. Further, these results completely eliminate the formation of free benzoyloxy species during the reaction since this would have led to half of the oxygen-18 being in the ethyl benzoate and the other half in the tartronate. It is finally not inconceivable that reactions between benzoyl peroxide and sodium derivatives of active methylene compounds take place in the same manner as outlined above.

## EXPERIMENTAL

The oxygen-18 analyses were carried out using the method of Doering and Dorfman[37] as modified by Denney and Greenbaum.[38]

*Benzoic acid*-$CO^{18}O^{18}H$. The procedure of Denney and Denney[39] was used.

*Benzoyl chloride*-$CO^{18}Cl$. The common procedure[39] was followed, which gave a yield of 89%, b.p. 83–85°/20 mm Hg $n_D^{20}$ 1·5530.

*Benzoyl peroxide-carbonyl*-$O^{18}$. The procedure of Denney and Denney was followed giving a yield of 55% pure product, m.p. 108–109°. Analysis showed it contained 1·60 atom % excess oxygen-18 in each carbonyl position.

### *Reaction of benzoyl peroxide-carbonyl* $O^{18}$ *with sodiodiethylphenylmalonate*

Sodium hydride 7·2 g (0·15 mole; 50% oil suspension) were covered with 200 ml dry benzene. 31·8 g (0·15 mole) diethyl phenylmalonate were added dropwise while stirring during 45 min and after another 2 hr, when all the hydride was consumed, the reaction mixture was cooled in an ice-water bath. 24·2 g (0·1 mole) benzoyl peroxide (16·1 g labeled benzoyl peroxide and 8·1 g unlabeled benzoyl peroxide) dissolved in 250 ml dry benzene were added intermittently to the malonate during 40 min. After being stirred overnight, the mixture was poured into water and the water phase extracted 3 times with ether. The combined extracts were washed with water until neutral, dried ($Na_2SO_4$), the ether was stripped off and the excess diethyl phenylmalonate distilled off. 35 g crude diethyl O-benzoyl phenyltartronate were isolated and after recrystallization from pet. ether had m.p. 79–81°. Analysis showed that this material contained 1·05, 1·11, 1·06, 1·11 (average 1·08) atom % excess oxygen-18. The I.R. spectrum of this material was also identical with that of a sample of diethyl O-benzoyl phenyltartronate, prepared from unlabeled material.

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[37] W. E. Doering and E. Dorfman, *J. Amer. Chem. Soc.* **75**, 5595 (1953).
[38] D. B. Denney and M. A. Greenbaum, *J. Amer. Chem. Soc.* **79**, 979 (1957).
[39] D. B. Denney and D. Z. Denney, *J. Amer. Chem. Soc*, **79**, 4806 (1957).

*Reaction of sodioalcoholate with* V(R = $C_6H_5$)

32·5 g diethyl O-benzoyl phenyltartronate were dissolved in 180 ml ethanol, and sodioalcoholate (from 4·2 g sodium in 180 ml absolute ethanol) was then added during 30 min at room temp. After being stirred for 24 hr at room temp, the reaction mixture was poured into water and the water phase extracted 4 times with ether. The ether phase was washed until neutral, dried ($Na_2SO_4$); and after the ether had been stripped off fractionation gave 10·8 g (79%) ethyl benzoate with b.p. 86–88° 12 mm Hg, $n_D^{20}$ 1·5044. The oxygen-18 analysis showed that this compound had 1·02, 1·02 (average 1·02) atom % excess oxygen-18. The I.R. spectrum was also commensurate with the assigned structure.

The aqueous phase was acidified and extracted continuously during 36 hr with ether. 10·1 g (75%) mandelic acid were isolated. The m.p. and mixed m.p. were 118–120° (from formic acid).

*Acknowledgement*—It is a pleasure to acknowledge the financial assistance of Lucidol Division, Wallace and Tiernan, Inc., Buffalo, N.Y., U.S.A.