Benzoyl Peroxide- and Photo-induced Reactions of Diethyl Mesoxalate in Cyclohexane and Toluene

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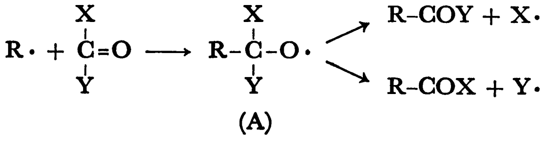
Benzoyl peroxide-catalyzed reactions of diethyl mesoxalate in cyclohexane gave ethyl cyclohexylglyoxylate (I) as the main product, accompanied by smaller amounts of diethyl cyclohexylhydroxymalonate (II), ethyl 2-oxobutyrate (III), and diethyl ethylhydroxymalonate (IV), while similar reactions in toluene gave no ethyl phenyl-2-oxopropionate. The α-ketoesters (I) and (III) and the hydroxymalonates (II) and (IV) were considered to arise from β-cleavage and hydrogen atom-abstraction, respectively, of alkoxy radicals A, which take place with addition of cyclohexyl and ethyl radicals to ketonic carbon of diethyl mesoxalate. Irradiation of cyclohexane and toluene solutions of diethyl mesoxalate gave II and diethyl benzylhydroxymalonate (V), respectively, as main products.

A number of reports have appeared on various free radical reactions which afford derivatives of carboxylic acids by direct introduction of such radicals as chloroformyl,[1,2] ethoxycarbonyl[3,4] and carbamoyl[5] radicals into hydrocarbons. However, α-ketocarboxylation and α-hydroxycarboxylation of hydrocarbons by free radical reactions have seldom been reported.[6] In a previous paper,[1] one of us (C.P.) reported on benzoyl peroxide-catalyzed reactions of ethyl chloroglyoxylate in cyclohexane which gave cyclohexanecarbonyl chloride as a main product, accompanied by a small amount of ethyl cyclohexylglyoxylate (I). The mechanism was interpreted in terms of a radical chain mechanism in which cyclohexyl radicals attack the carbon atom of the acid chloride function of ethyl chloroglyoxylate to cleave the carbonyl-carbonyl or carbon-chlorine bond. The mechanism would imply the addition of cyclohexyl radicals to carbonyl carbon of the acid chloride function and the subsequent β-cleavage of the radical A (Scheme 1).

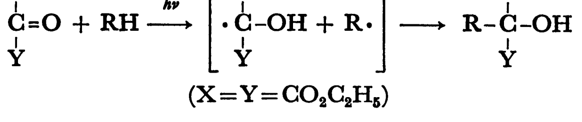


$$R\cdot + \overset{X}{\underset{Y}{C}}{=}O \longrightarrow \underset{(A)}{R{-}\overset{X}{\underset{Y}{C}}{-}O\cdot} \begin{array}{l} \nearrow R\text{-}COY + X\cdot \\ \searrow R\text{-}COX + Y\cdot \end{array}$$

$(X{=}Cl,\ Y{=}CO_2C_2H_5)$

Scheme 1.

If this is the case, a benzoyl peroxide-induced reaction of diethyl mesoxalate (DEM, $X{=}Y{=}CO_2C_2H_5$) in cyclohexane is expected to give ethyl cyclohexylglyoxylate (I) as a main product. Moreover, if DEM in an electronically excited state behaves in a similar way to that of excited aliphatic ketones such as acetone,[7] photoreactions of DEM in hydrocarbons will serve as a convenient method for the preparation of α-hydroxyesters as shown in Scheme 2. Thus, DEM is expected to be available for preparation of some α-keto- and α-hydroxy-esters.



$$\overset{X}{\underset{Y}{C}}{=}O + RH \xrightarrow{h\nu} \left[\cdot\overset{X}{\underset{Y}{C}}{-}OH + R\cdot\right] \longrightarrow R{-}\overset{X}{\underset{Y}{C}}{-}OH$$

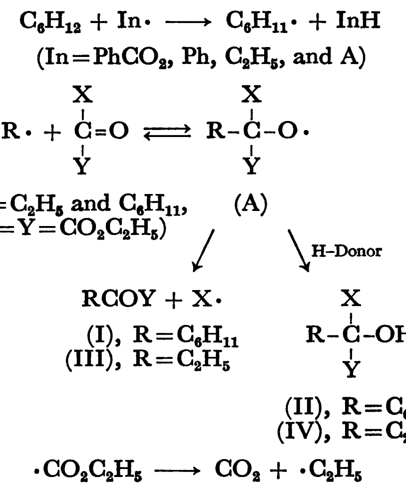
$(X{=}Y{=}CO_2C_2H_5)$

Scheme 2.

Results and Discussion

Benzoyl Peroxide-induced Reaction. When a cyclohexane solution of DEM (2.5 mol/l) containing a catalytic amount of benzoyl peroxide (BPO) (0.2 mol/l) was refluxed, ethyl cyclohexylglyoxylate (I), diethyl cyclohexylhydroxymalonate (II), ethyl 2-oxobutyrate (III) and diethyl ethylhydroxymalonate (IV) were obtained in 70—80% combined yields. The results are summarized in Table 1. Spectral data of the products (I)—(IV) are in line with the structures assigned (Table 2). The structures of (I) and (III) were unambiguously determined by direct compaison of their physical properties with those of the authentic samples and mixed melting point tests of their 2,4-dinitrophenylhydrazones with the authentic specimens.

The results support our prediction (Scheme 1), suggesting that ethyl and cyclohexyl radicals can add to ketonic carbon of DEM to generate alkoxy radicals A, which subsequently either abstract hydrogen atom from hydrogen donors to afford II and IV or undergo β-cleavage to give I and III. The mechanism is shown in Scheme 3.



$$C_6H_{12} + In\cdot \longrightarrow C_6H_{11}\cdot + InH$$

$(In{=}PhCO_2,\ Ph,\ C_2H_5,\ \text{and}\ A)$

$$R\cdot + \overset{X}{\underset{Y}{C}}{=}O \rightleftarrows \underset{(A)}{R{-}\overset{X}{\underset{Y}{C}}{-}O\cdot}$$

$(R{=}C_2H_5\ \text{and}\ C_6H_{11},\ X{=}Y{=}CO_2C_2H_5)$

$$\swarrow \qquad \searrow^{\text{H-Donor}}$$

$$RCOY + X\cdot \qquad R{-}\overset{X}{\underset{Y}{C}}{-}OH$$

$(I),\ R{=}C_6H_{11}$; $(III),\ R{=}C_2H_5$ $\qquad$ $(II),\ R{=}C_6H_{11}$; $(IV),\ R{=}C_2H_5$

$$\cdot CO_2C_2H_5 \longrightarrow CO_2 + \cdot C_2H_5$$

Scheme 3.

This type of addition of alkyl radicals to the carbon-oxygen double bond has not been fully investigated. Free radical addition to carbon-carbon multiple bonds

TABLE 1. BPO- AND PHOTO-INDUCED REACTION OF DIETHYL MESOXALATE IN CYCLOHEXANE AND TOLUENE

RH (g or ml)		DEM (g)	Initiator	Yield (%)[a]	Product ratio (%)[b]				
					(I)	(II)	(II)	(IV)	Others
C_6H_{12}	(20 ml)	8.7	BPO (1 g)	70—80	50	15	15	16	4
	(150 ml)	8.7	Photo	50	2	90	2	2	4
$PhCH_3$	(9.2 g)	8.7	BPO (1 g)		$PhCOCO_2C_2H_5$ (20), $PhCH_2CH_2Ph$ (30) Others (50)				
	(23 g)	8.7	Photo	20	(V) (60), Others (40)				

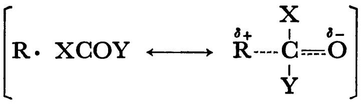
a) Isolated yield of α-keto- and α-hydroxy-esters based on unrecovered DEM. b) Determined by gas chromatographic analyses of reaction mixtures. The amount of others was estimated from the area-ratio in gas chromatogram.

TABLE 2. SPECTRAL PROPERTIES OF α-KETO- AND α-HYDROXY-ESTERS

Compound	IR (cm^{-1})[a]	*m/e* (M$^+$)	NMR (δ in CCl_4)
$C_6H_{11}COCO_2C_2H_5$ (I)	1750 (C=O) 1250 (C–O–C)	184	1.37 (3H, t), 1.18—2.05 (10H, m), 2.94 (1H, m), 4.26 (2H, q)
$C_6H_{11}\underset{OH}{C}(CO_2C_2H_5)_2$ (II)	3500 (–OH) 1740, 1230	b	1.30 (6H, t), 0.88—1.85 (10H, m), 2.10 (1H, m), 3.32[c] (1H, s), 4.21 (4H, q)
$C_2H_5COCO_2C_2H_5$ (III)	1720, 1230	130	1.1 (3H, t), 1.4 (3H, t), 2.8 (2H, q), 4.2 (2H, q)
$C_2H_5\underset{OH}{C}(CO_2C_2H_5)_2$ (IV)	3500, 1730 1240	b	0.87 (3H, t), 1.29 (6H, t), 1.96 (2H, q), 3.50[c] (1H, s), 4.21 (4H, q)
$PhCH_2\underset{OH}{C}(CO_2C_2H_5)_2$ (V)	3440, 1745 1230, 750 700	b	1.28 (6H, t), 3.24 (2H, s), 3.48[c] (1H, s), 4.19(4H, q), 7.18 (5H, m)

a) Liquid film. b) No parent peak. c) Disappeared in the presence of deuterium oxide.

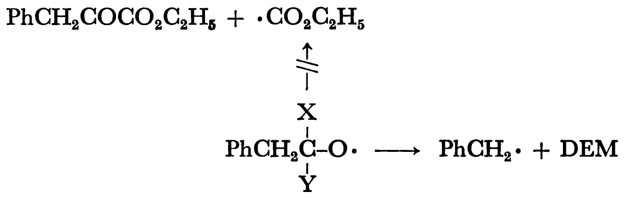
has been widely studied, several examples being reported on the addition of alkyl radicals to aldehydes,[8] biacetyl,[9] and hexafluoroacetone.[10] Reactions of cyclohexyl radicals with ethyl chloroglyoxylate[1] and oxalyl chloride[2] appear to fit the case. The reactions of alkyl radicals with some XCOY compounds are summarized in Table 3. There is a tendency of reactivities of XCOY toward alkyl radicals in relation to structures of XCOY; the formation of products by addition of alkyl radicals to carbonyl carbon of XCOY requires strong electron-withdrawing nature of X and/or Y and, moreover, the presence of a methoxyl group, a strong electron-donating group, in XCOY leads to lack of such addition reactions. Compare oxalyl chloride with phosgene and ethyl chloroglyoxylate with ethyl chloroformate and diethyl oxalate. This tendency of reactivities of XCOY toward alkyl radicals would be attributed to polar contributions to the transition state of additions of alkyl radicals to XCOY (Scheme 4). This transition state appears to be in line with that of β-cleavage of alkoxy radicals,[11] the reverse reaction of the addition of alkyl radicals to carbonyl compounds.



$$\left[R\cdot\ XCOY \longleftrightarrow \overset{\delta+}{R}\cdots\underset{Y}{\overset{X}{C}}\cdots\overset{\delta-}{O}\right]$$

Scheme 4.

On the other hand, BPO-induced reactions of DEM in toluene gave no ethyl phenyl-2-oxopropionate. Volatile products were obtained in low yields and found to consist of various compounds, in which ethyl phenylglyoxylate and bibenzyl were detected as the main products. Since yields of the other products were very low, no structural determination was carried out. The result appears to be in line with the mechanism discussed above, since β-cleavage of the radical A (R=



$$\begin{array}{c} PhCH_2COCO_2C_2H_5 + \cdot CO_2C_2H_5 \\ \not\uparrow \\ PhCH_2\underset{Y}{\overset{X}{C}}\text{–}O\cdot \longrightarrow PhCH_2\cdot + DEM \end{array}$$

(A)

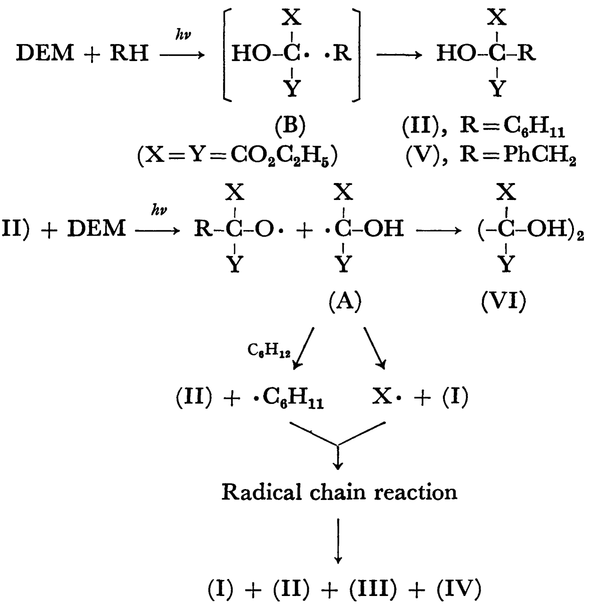
TABLE 3. ADDITION REACTION OF ALKYL RADICALS TO XCOY

Radical (R·)	X	Y	Product	Ref.
C_6H_{11} and C_2H_5	$CO_2C_2H_5$	$CO_2C_2H_5$	RC(OH)XY, RCOX	This work
C_6H_{11} and others	CH_3	$COCH_3$	RCOX	9a
C_3H_7 and C_6H_{13}	CF_3	CF_3	RC(OH)XY	10a
C_6H_{11}	Cl	$CO_2C_2H_5$	RCOX, RCOY	1
C_6H_{11}	Cl	COCl	RCOX	2
C_6H_{11}	Cl	Cl	No adduct[a]	2a
C_6H_{11}	Cl	OC_2H_5	No adduct[a]	3
C_6H_{11}	OC_2H_5	$CO_2C_2H_5$	No adduct[a]	1

a) No significant formation of adducts from peroxide-induced reactions in cyclohexane.

$PhCH_2$) is expected to occur exclusively in regenerating benzyl radicals and DEM, as is clarified in β-cleavage of alkoxy radicals containing a benzyl group.[12)]

Photo-induced Reaction. Irradiation of a cyclohexane solution of DEM (0.33 mol/l) with light longer than 320 nm at ambient temperature gave II as a main product, accompanied by small amounts of I, III, and IV (Table 1). The product distribution differes a great deal from that of the BPO-induced reaction, suggesting a different mechanism for the formation of II from the radical chain mechanism (Scheme 3). Dominant formation of II in the photoreaction might be interpreted by assuming that an excited DEM abstracts hydrogen atom from cyclohexane to afford a radical pair (B) in a solvent cage which predominantly undergoes the radical coupling to give II (Scheme 5).



Scheme 5.

However, the product distribution in the photoreaction was found to depend on the concentration of DEM in cyclohexane; as the concentration of DEM increases, yields of II begin to decrease at the concentration of *ca.* 0.5 mol/l, while the formation of I sharply increases (Fig. 1). Such a concentration effect could not be observed in BPO-induced reactions (Fig. 2). These results suggest an oxidation of II by excited DEM, giving radical (A). In a dilute solution, however, excited DEM has less chance to encounter II in its life. In the case of a concentrated solution, II is readily accumulated to a sufficient concentration for oxidation. If radical (A) is once generated by oxidation, then the radical chain reaction described in Scheme 3 can intervene. Thus, the higher the concentration of DEM, greater the tendency for radical chain reaction to occur. It is of interest to note that irradiation of a concentrated solution of DEM gave a mixture in low yields which revealed only the NMR signals of ethoxyl protons at δ 1.35 and 4.3 and an alcoholic proton at δ 3.9[13)] in an area-ratio of 7.5: 5: 1. The NMR spectra suggest that the mixture contains diethyl 1,2-diethoxycarbonyl-1,2-dihydroxysuccinate (VI). VI could not be obtained in pure form by preparative gas chromatography under any condition. Further investigation for VI was, therefore, not carried out. The reaction mechanism is shown in Scheme 5.

In a similar way, irradiation of a toluene solution of DEM gave diethyl benzylhydroxymalonate (V) in a moderate yield, accompanied by minor amounts of other volatile compounds and some polymeric materials.

Experimental

Melting and boiling points are uncorrected. IR spectra were measured with a Hitachi EPI-S2 spectrophotometer, NMR spectra with a JEOL JNM-MH-100 apparatus for solutions in carbon tetrachloride containing tetramethylsilane as an internal standard, and mass spectra with a Hitachi RMU-6E apparatus. Analytical gas chromatography was carried out with a Shimadzu GC-3BF apparatus using a column of Silicone DC 550 (20% on Shimalite W, 2 m) at 200 °C, and preparative gas chromatography with a Shimadzu GC-2C apparatus using a column of Silicone DC 550 (20% on Shimalite W, 2.3 m) at 200 °C.

Toluene and spectrograde cyclohexane (Nakarai Chemicals) were distilled over metallic sodium wire. Benzoyl peroxide was recrystallized from chloroform-methanol. DEM was prepared from diethyl malonate according to the method in literature[14)] and distilled from phosphorus pentoxide *in vacuo* prior to use.

BPO-Induced Reaction of DEM in Cyclohexane. A solution of DEM (8.7 g, 0.05 mol) and BPO (1 g, 0.004 mol) in cyclohexane (20 ml) was refluxed for 8 hr. After removal of cyclohexane, fractional distillation of the residue under reduced pressure gave two fractions, bp 60—100 °C/14 mmHg (2.5 g) and bp 110—135 °C/14 mmHg (4.5 g), and a residue (1 g). Gas chromatographic analyses showed that the former fraction contained predominantly DEM along with minor

Table 4. ANALHYTICAL DATA OF α-KETO- AND α-HYDROXY-ESTERS AND 2,4-DINITROPHENYLHYDRAZONES OF α-KETOESTERS

Compd.	Bp (°C/mmHg) or Mp (°C)	Found (%)			Formula	Calcd (%)		
		C	H	N		C	H	N
I	(125/22)	65.10	8.75		$C_{10}H_{16}O_3$	64.76	8.73	
I-DNP[a)]	[161—161.5]	52.59	5.63	15.61	$C_{16}H_{20}N_4O_6$	52.74	5.53	15.38
II	(111.5/2)	60.44	8.59		$C_{13}H_{22}O_5$	60.64	8.67	
III	(72/32)	54.88	7.70		$C_6H_{10}O_3$	55.37	7.75	
III-DNP[a)]	[140—141.5]	46.43	4.32	18.07	$C_{12}H_{14}N_4O_6$	46.45	4.55	18.06
IV	(120/21)	52.73	7.90		$C_9H_{16}O_5$	52.42	7.86	
V	(131/3.5)	63.14	6.81		$C_{14}H_{18}O_5$	63.15	6.95	

a) 2,4-Dinitrophenylhydrazone.

amounts of III, whereas the latter consisted of I, II, and IV over 90% in a *ca.* 8 : 1 : 4 ratio. From the former fraction, *ca.* 0.5 g of III was isolated by preparative gas chromatography. In a similar way, products I, II, and IV were also isolated by preparative gas chromatography. Analytical data of I—IV and 2,4-dinitrophenylhydrazones of (I) and (III) are listed in Table 4.

BPO-induced Reaction of DEM in Toluene. A mixture of DEM (8.7 g, 0.05 mol), BPO (1 g, 0.004 mol) and toluene (9.2 g, 0.1 mol) was heated at 114—115 °C for 8 hr. Fractional distillation under reduced pressure gave 6 g of DEM, 1.5 g of an oil (bp 70—146 °C/3 mmHg) and 1.5 g of a residue. Analytical gas chromatography showed that the oil consists of at least seven components. Two main components were isolated by preparative gas chromatography, identified as ethyl phenylglyoxylate and bibenzyl by driect comparison of their sepectral properties with those of authentic samples.

Photo-induced Reaction of DEM in Cyclohexane. A solution of DEM (8.7 g, 0.05 mol) in cyclohexane (150 ml) was irradiated by light filtered through a hexane solution of naphthalene (0.1 mol/l, 1 cm path length) from an Eikosha PIH 300 W high-pressure mercury arc at ambient temperature for 10 hr. After removal of cyclohexane, fractional distillation gave 2.2 g of DEM, 5 g of an oil (bp 130—137 °C/13 mmHg) and 1 g of a residue. Analytical gas chromatography of the oil showed that II was contaminated over 80%. Product (II) was purified by preparative gas chromatography and vacuum distillation.

Photo-induced Reaction of DEM in Toluene. A mixture of DEM (8.7 g, 0.05 mol) and toluene (23 g, 0.25 mol) placed in a test tube was irradiated by filtered light for 100 hr. Fractional distillation of the reaction mixture under reduced pressure gave 3.5 g of DEM, 3.5 g of an oil (bp 100—160 °C/6 mmHg) and 2 g of a residue. Analytical gas chromatography showed that the oil contains five products. From the oil, 1.8 g of the main product (V) was isolated by preparative gas chromatography and V was purified by vacuum distillation.

Concentration Effect to Product Distribution. In both BPO- and photo-induced reactions, 0.8 g (0.0046 mol) of DEM was used, the amounts of cyclohexane being varied. Conversion of DEM was set in 10—30%. In the case of BPO-induced runs, 0.1 g (0.4 mmol) of BPO was used. The reaction mixtures were directly subjected to gas chromatographic analyses, and the product distribution was determined. The results are shown in Figs. 1 and 2.

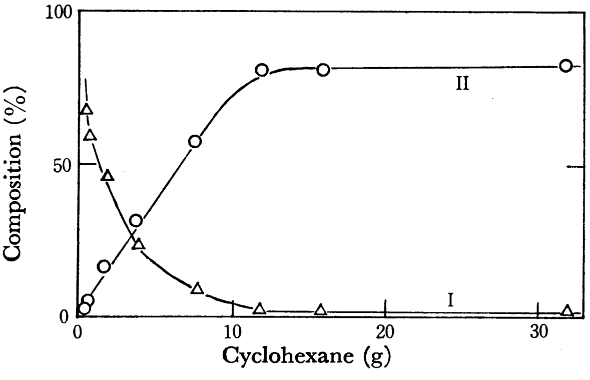


Fig. 1. Concentration effect on product distribution in photo-induced reaction of DEM in cyclohexane: DEM, 0.8 g; conversion, 10—30%.

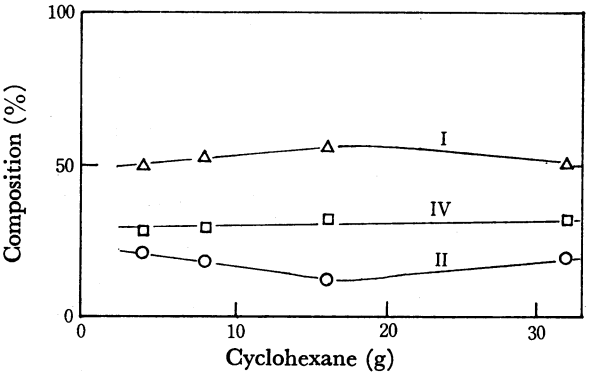


Fig. 2. Concentration effect on product distribution in BPO-induced reaction of DEM in cyclohexane: DEM, 0.8 g; BPO, 0.1 g; conversion, 10—30%.

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