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Oxidizing Action of Hydroperoxides. Oxidation of Alkyl Aryl Ketones by Hydroperoxides

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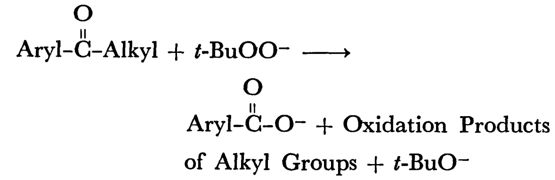
The oxidation of alkyl aryl ketones by *t*-butyl hydroperoxide under basic conditions gave products which resulted from the fission of the carbon-carbon bond between carbonyl carbon and alkyl carbon. The reaction was investigated using chiral alkyl aryl ketones. On the basis of the results, a probable reaction mechanism is proposed.

Oxidation of alkyl aryl ketones by peracids under acidic conditions, *i.e.*, Baeyer-Villiger oxidation, is well documented.[1] On the contrary, oxidation of alkyl aryl ketones by hydroperoxides under basic conditions has not been so familiar to chemists, although it has some mechanistically attractive features in its reaction. Some of the reactions have been investigated by one of the present authors(K.M.) and a tentative reaction mechanism has been proposed, but detailed investigations remained to be done.[2] Oxidation of alkyl aryl ketones by *t*-butyl hydroperoxide under basic conditions gave carbon-carbon fission products between $C_{carbonyl}$–C_{alkyl}, but none of those resulted from fission between $C_{carbonyl}$–C_{aryl} without dependency on the structure of alkyl groups (see Eq. 1). In this work we reinvestigated the reaction using chiral alkyl aryl ketones, and proposed the most probable reaction mechanism.



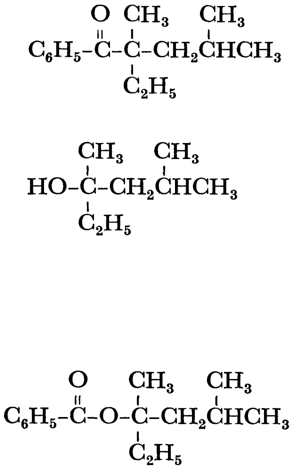
$$\text{Aryl-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-Alkyl} + t\text{-BuOO}^- \longrightarrow \text{Aryl-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-O}^- + \text{Oxidation Products of Alkyl Groups} + t\text{-BuO}^- \qquad (1)$$

Results and Discussion

Oxidation of Chiral Alkyl Aryl Ketones. Chiral alkyl aryl ketones **1**, **4**, and **7** were subjected to the reaction, and the optical rotations of the alcohols resulting from the alkyl groups were examined. Addition of 18-crown-6 in a reacting mixture was a new device of our present oxidation conditions; this was done to make the reacting mixture homogeneous.[2]

Oxidation of (*S*)-(−)-2-ethyl-2,4-dimethyl-1-phenyl-1-pentanone (**1**) by *t*-butyl hydroperoxide anion afforded benzoic acid and (*S*)-(−)-3,5-dimethyl-3-hexanol (**2**) of 100% optical purity, $[\alpha]^{25}_{5805}$ −3.5°, and ester (**3**). The optical purity and the absolute configuration of the isolated 3,5-dimethyl-3-hexanol was confirmed by the literature.[3,4] Thus, alkyl aryl ketone reacted with retention of the configuration of the alkyl group.

An analogous result was obtained in the reaction with (*R*)-(−)-2-methyl-1,2-diphenyl-1-butanone (**4**). The specific optical rotation of 2-phenyl-2-butanol (**5**) isolated from the reacting mixture showed the value $[\alpha]^{16}_{5805}$ +18.9°, optical purity 93%. Correlation of the absolute configurations between (−)-**4** and (+)-**5** has been independently reported by D. J. Cram *et al.*[5] and S. Mitsui.[6] Thus, 2-phenyl-2-butanol (**5**) obtained in this reaction has an *R*-configuration, indicating unambiguously retention of its configuration in the alkyl group in the course of the reaction. Minor but distinctive amounts of 1-methyl-1-phenylpropyl benzoate (**6**) was also obtained in this reaction.



$C_6H_5\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}\overset{CH_3}{\underset{C_2H_5}{C}}\text{-}CH_2\overset{CH_3}{C}HCH_3$ **1** Bp 143—147 °C/15 mmHg** $[\alpha]^{25}_{5805}$ −11.8° (*c* 4.02, 99%-EtOH)

$HO\text{-}\overset{CH_3}{\underset{C_2H_5}{C}}\text{-}CH_2\overset{CH_3}{C}HCH_3$ **2** Bp 72—73 °C/50 mmHg $[\alpha]^{25}_{5805}$ −3.5° (*c* 5.36, 99%-EtOH)
Lit,[15] bp 152—153 °C *S*-(−) $[\alpha]^{25}_{D}$ −3.5° (*c* 8.5, 95%-EtOH)

$C_6H_5\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-O-}\overset{CH_3}{\underset{C_2H_5}{C}}\text{-}CH_2\overset{CH_3}{C}HCH_3$ **3** Bp 153 °C/28 mmHg (slightly decomp)
Specific rotation was not determined.

Fig. 1.

From the results of the above two reactions we can conclude that the reaction of alkyl aryl ketone proceeds with retention of the configuration around the alkyl carbon adjacent to the carbonyl carbon. However, chiral alkyl aryl ketone, in which the alkyl group has enolizable hydrogen, lost its chirality in the course of the reaction. This is exemplified in the reaction of chiral 2-methyl-1-phenyl-1-octanone (**7**). The reaction of chiral **7** under similar conditions gave a mixture of benzoic acid, 2-octanone, *t*-butyl alcohol, and some recovered **7**. 2-Octanol was not detected in the reacting mixture, but its oxidation product, 2-octanone, was found in a reasonable yield (25%). Though diagnosis from 2-octanol was not achieved, the recovered **7** showed no optical rotation, indicating complete loss of the chirality in the course of the reaction, presumably *via* enolization.[7]

In conclusion, oxidation of alkyl aryl ketones by *t*-butyl hydroperoxide anion may be formulated best as shown in Eq. 2. Thus, the previously proposed reaction mechanism including an attack of *t*-butyl hy-

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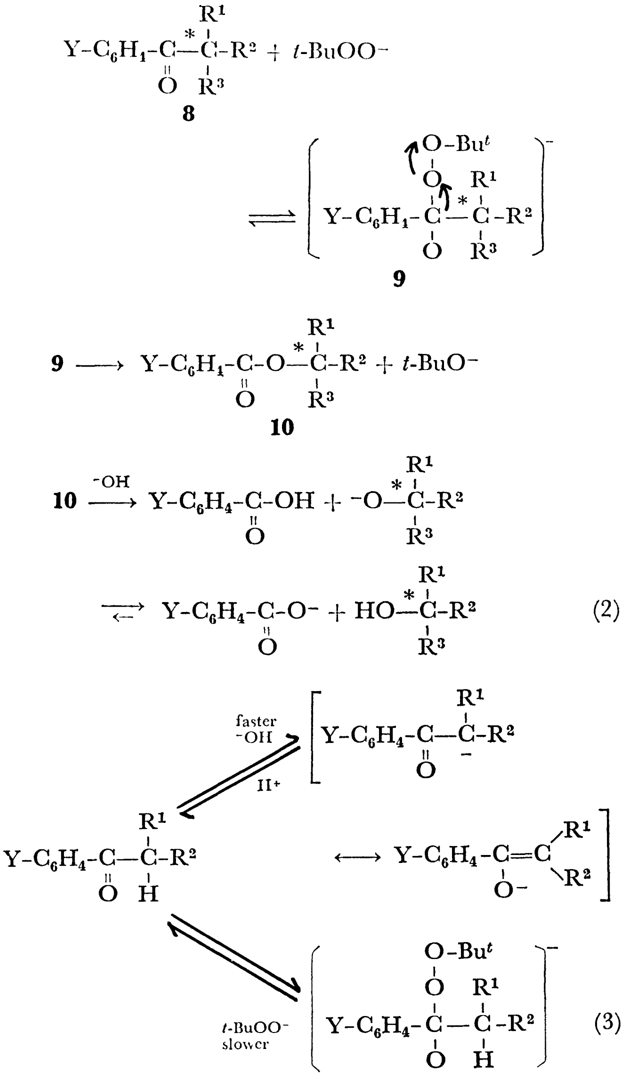
** 1 mmHg≈133.322 Pa.

droperoxide anion on carbonyl carbon and subsequent back-side attack of hydroxide anion on alkyl carbon[2] should be revised as described here. When one of R^1–R^3 was hydrogen, alkyl aryl ketone could be enolized to lose its chirality before attack by hydroperoxide anion. That the enolization of ketone occurred more quickly than the attack of hydroperoxide anion is suggested by the experimental results of the reaction of (—)-**7**.



Comparison of our Reaction with the Baeyer-Villiger Reaction. The characteristics of our reaction and the Baeyer-Villiger reaction are illustrated in Table 1. In the Baeyer-Villiger reaction, methyl and ethyl phenyl ketones (Rec. No. 1 and 2) gave preferentially carbon-carbon fission products between carbonyl carbon and phenyl carbon, whereas isopropyl and *t*-butyl phenyl ketones (Rec. No. 3 and 4) gave preferentially carbon-carbon fission products between carbonyl carbon and alkyl carbon. On the contrary, in our reaction all alkyl phenyl ketones gave carbon-carbon bond cleavage products between carbonyl carbon and alkyl carbon.

Thus, it is clear now that by choosing suitable reaction conditions of the peroxide oxidation one can attain a selective carbon-carbon bond cleavage of alkyl aryl ketones.

Experimental

All melting and boiling points are uncorrected. The infrared spectra were measured on a Hitachi 215 grating infrared spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-MH 100 spectrometer. Gas chromatography was carried out with a Hitachi gas chromatograph, Model 163. The optical rotations were measured on a Union high sensitivity polarimeter PM-70. Elemental analyses were carried out at the Analytical Center of Kyoto University.

t-*Butyl Hydroperoxide.* This peroxide was prepared by the literature method:[8] bp 38—39 °C/19 mmHg; lit:[8] bp 33—34 °C/17 mmHg.

*Preparation of 2-Ethyl-2,4-dimethyl-1-phenyl-1-pentanone (**1**).* This procedure is a modification of that employed by D. J. Cram.[5] A mixture of 2-ethyl-2,4-dimethylpentanoic acid (**11**, 57 mmol) prepared from 2,4-dimethylpentanoic acid by the procedure of P. E. Pfeffer *et al.*[9] and thionyl chloride (75 mmol) was allowed to stand overnight at room temperature, the excess thionyl chloride being evaporated under vacuum. Two successive portions of anhydrous benzene

Table 1. Comparison of Baeyer-Villiger reaction with the present reaction

Reaction No.	Ketone	Baeyer-Villiger reaction[a]			Present reaction[b]	
		$\text{Ph-O-}\overset{\overset{O}{\|}}{C}\text{-R}$ (%)	$\text{Ph-}\overset{\overset{O}{\|}}{C}\text{-O-R}$ (%)	Recovered ketone (%)	$\text{Ph-}\overset{\overset{O}{\|}}{C}\text{-OH}$ (%)	Recovered ketone (%)
1	$\text{Ph-}\overset{\overset{O}{\|}}{C}\text{-Me}$	85	0	15	45	55
2	$\text{Ph-}\overset{\overset{O}{\|}}{C}\text{-Et}$	80	7	13	60	40
3	$\text{Ph-}\overset{\overset{O}{\|}}{C}\text{-Pr}^i$	7	75	18	40	60
4	$\text{Ph-}\overset{\overset{O}{\|}}{C}\text{-Bu}^t$	0	76	24	40	60

Reaction conditions: a) ketone: 2 mmol; *m*-chloroperbenzoic acid: 2.4 mmol; solvent: $CHCl_3$(12 ml); temp: 28 °C; reaction time: 7 d. b) Ketone: 2 mmol; *t*-BuOOH: 6 mmol; KOH; 7 mmol; 18-crown-6; 0.8 mmol; solvent: C_6H_6(20 ml); temp: 70 °C; reaction time: 1 h.

were added and evaporated under vacuum. The residual oil consisted of 2-ethyl-2,4-dimethylpentanoyl chloride was used for the next step without further purification. To a hot benzene solution of diphenylcadmium prepared in the usual way[10] was added the above residual oil. The reaction mixture was held at reflux for 30 min and worked up in the usual manner to give **1** (72%): bp 143—147 °C/15 mmHg; NMR (CCl_4) δ=7.70—7.50 (2H, m), 7.40—7.10 (3H, m), 2.10—1.30 (5H, m), 1.20 (3H, s), 1.00—0.65 (9H, m); IR (CCl_4) 1670 cm^{-1} (C=O).

Found: C, 82.68; H, 10.21%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

Optical resolution of **11** with the aid of burcine to the procedure of W. v. E. Doering and K. B. Wiberg[11] was unsuccessful, but we have accomplished this using quinine by the following procedures. A mixture of **11** (29 g) and quinine (50 g) was dissolved in 66%-ethanol by heating. The solution was allowed to stand in a refrigerator, and then filtered to give colorless crystals. These were recrystallized fifteen times from 66%-ethanol to give a quinine salt (9 g): mp 97.5—98.5 °C. The salt was suspended in dilute sulfuric acid and extracted with ether. The etherial extract was washed with dilute sulfuric acid, dried over sodium sulfate, and then the solvent was removed. The residual oil was purified by distillation to give (—)-**11** (2.5 g): bp 138—140 °C/20 mmHg; $[\alpha]^{25}_{5805}$ $-22.7°$ (*c* 5.15, 99%-EtOH); lit[11] for (+)-**11**: bp 124—125 °C/12 mmHg; $[\alpha]^{25}_{D}$ $+21.42°$ (*c* 10.3, 95%-EtOH).

The active (—)-**1** was prepared in 85% over-all yield from (—)-**11** by use of the above procedure: $[\alpha]^{25}_{5805}$ $-11.8°$ (*c* 4.02, 99%-EtOH). The IR and NMR spectra of this ketone were identical with those of (±)-**1**.

*Preparation of 2-Methyl-1,2-diphenyl-1-butanone (**4**).* This ketone was prepared from 2-methyl-2-phenylbutanoic acid by the procedure given in the literature:[5,12] bp 139—140 °C/2 mmHg; lit:[5] bp 144—145 °C/2.5 mmHg.

Optically active (—)-**4** was prepared from (—)-2-methyl-2-phenylbutanoic acid: $[\alpha]^{20}_{5805}$ $-32.1°$ (*c* 4.04, C_6H_6); mp 87—88 °C; lit:[12] $[\alpha]^{23}_{D}$ $-30°$ (*c* 4.5, C_6H_6); mp 86—87 °C. After employing the above procedure to the synthesis of **4**, we obtained the active **4**: $[\alpha]^{20}_{5805}$ $-69.7°$ (*c* 3.8, C_6H_6); lit:[5] $[\alpha]^{25}_{D}$ $-63.7°$ (neat).

*Preparation of 2-Methyl-1-phenyl-1-octanone (**7**).* Ketone **7** was prepared in a yield of 84% by the Friedel-Crafts reaction of a mixture of 2-methyloctanoyl chloride (63 mmol), anhydrous aluminium chloride (75 mmol), and dry benzene: bp 130—131 °C/2 mmHg; lit:[13] bp 100 °C/0.01 mmHg.

Resolution of the 2-methyloctanoic acid was achieved in the following way. A mixture of 2-methyloctanoic acid (8.5 g) and cinchonidine (16 g) was dissolved in 95%-acetone by heating, and then allowed to stand in a refrigerator. The precipitated salts were collected by filtration and then repeatedly recrystallized using the same solvent until the optical rotation of the acid showed a very slight increase (twelve times). The salt was then decomposed in the usual manner to give (—)-2-methyloctanoic acid (745 mg): $[\alpha]^{20}_{5805}$ $-20.0°$ (*c* 1.8, C_6H_6); lit[14] for (+)-isomer: $[M]^{20}_{D}$ $+26°$ ($[\alpha]^{25}_{D}$ $+16.45°$).

Optically active (—)-**7** was prepared from (—)-2-methyloctanoic acid. After the above procedure similar to the synthesis of **7** was employed, we obtained the active **7**: $[\alpha]^{20}_{5805}$ $-29.7°$ (*c* 2.9, C_6H_6); lit:[13] $[\alpha]_D$ $-21.5°$ (*c* 5, Et_2O), $[\alpha]_D$ 24.5°.

General Procedure for Oxidation of the Ketone with t-*Butyl Hydroperoxide.* Powdered analytical grade potassium hydroxide (5 mmol) was suspended in benzene (10 ml). After the air in the reaction vessel was expelled completely with dry nitrogen gas and the temperature of the oil bath reached 80 °C, a benzene solution (5 ml) of ketone (2 mmol) was added to the reaction mixture; then a benzene solution (5 ml) of *t*-butyl hydroperoxide (4 mmol) and 18-crown-6 (5 mmol) was added sequentially with an injector. The reacting mixture was stirred at 80 °C for 3 h and cooled in an ice-water bath. Ether (10 ml) was added to the reacting mixture and the resulting carboxylic acid was extracted with water (10 ml) and twice with aqueous sodium hydrogencarbonate solution (10 ml). The combined aqueous layer was acidified with dilute sulfuric acid and then extracted twice with ether (10 ml). The amount of acid extracted was determined by gas chromatography after methylating with diazomethane. The unreacted ketone and the neutral products in the residual organic layer were determined by gas chromatography and then isolated by column chromatography on silica gel for analyses.

*Oxidation of (±)-**1**.* The resulting mixture consisted of benzoic acid (44%), recovered ketone (47%), 3,5-dimethyl-3-hexanol (**2**, 32%): bp 72—73 °C/50 mmHg; lit:[15] bp 152—153 °C, and 1-ethyl-1,3-dimethylbutyl benzoate (**3**, 9%): bp 153 °C/28 mmHg (slightly dec); NMR (CCl_4) δ= 7.88 (2H, dd, *J*=8 and 2 Hz), 7.46—7.10 (3H, m), 2.10—1.64 (5H, m), 1.51 (3H, s), 1.04—0.80 (9H, m); IR (CCl_4) 1710 (ester C=O) and 1275 cm^{-1} (C–O–C).

Found: C, 76.84; H, 9.67%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

The specific rotation of **2** produced in the oxidation of (—)-**1** was as follows: $[\alpha]^{25}_{5805}$ $-3.5°$ (*c* 5.36, 99%-EtOH); lit:[15] $[\alpha]^{25}_{D}$ $-3.5°$ (*c* 8.5, 95%-EtOH).

*Oxidation of (±)-**4**.* Oxidation was done at 50 °C and the reaction products were analyzed as usual. The resulting mixture consisted of benzoic acid (65%), recovered ketone (20%), 2-phenyl-2-butanol (**5**, 13%): bp 111 °C/25 mmHg; lit:[16] bp 90—91 °C/14 mmHg, and 1-methyl-1-phenylpropyl benzoate (**6**, 9%): viscous oil; NMR (CCl_4) δ=7.98 (2H, dd, *J*=8 and 2 Hz), 7.50—7.10 (8H, m), 2.40—2.00 (2H, m), 1.92 (3H, s), 0.84 (3H, t, *J*=7 Hz); IR (CCl_4) 1720 (ester C=O) and 1270 cm^{-1} (C–O–C).

Found: C, 80.13; H, 7.21%. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13%.

The specific rotation of **5** produced from oxidation of (—)-**4** was as follows: $[\alpha]^{16}_{5805}$ $+18.9°$ (*c* 2.16, C_6H_6); lit:[16] $[\alpha]^{22}_{D}$ $+17.45°$ (neat).

*Oxidation of (±)-**7**.* The resulting mixture consisted of benzoic acid (41%), heptanoic acid (4%), hexanoic acid (4%), recovered ketone (57%), and 2-octanone (25%). 2-Octanol was not detected in the mixture.

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