s, C-CH_3), 2.10 (3H, s, AcO), 2.15 (3H, s, AcO), 3.08 (1H, d, J=7.0 Hz, C_6-OH) (This signals disappeared on addition of D_2O.), 3.70 (3H, s, OCH_3), 4.11 (1H, t, $J_{4,5}$=7.0 Hz, H-5) [This signals shifted to 4.15 (1H, d, $J_{4,5}$=7.0 Hz) on addition of D_2O], 4.39 (1H, d, $J_{1,2}$=3.0 Hz, H-1), 5.18 (1H, dd, $J_{4,5}$=7.0 Hz, $J_{3,4}$=3.0 Hz, H-4), 5.42 (1H, dd, $J_{2,3}$=7.0 Hz, $J_{1,2}$=3.0 Hz, H-2), 5.89 (1H, dd, $J_{2,3}$=7.0 Hz, $J_{3,4}$=3.0 Hz, H-3), 7.25—7.65 (10H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1750 (C=O), 1445, 1380, 1258, 1230, 1080, 1040. *Anal.* Calcd. for $C_{25}H_{28}O_9S_2$: C, 55.96; H, 5.26; S, 11.94. Found: C, 56.06; H, 5.20; S, 11.88.

II (30 mg) was acetylated with acetic anhydride (1 ml) and pyridine (1 ml) overnight at room temperature. Usual working up gave the sirupy product (32 mg). This showed one spot (Rf=0.67) on TLC. NMR ($CDCl_3$) δ: 1.71 (3H, s, C-CH_3), 2.05 (3H, s, AcO), 2.15 (6H, s, 2×AcO), 3.72 (3H, s, OCH_3), 4.39 (1H, d, $J_{1,2}$=3.0 Hz, H-1), 5.05 (1H, d, $J_{4,5}$=8.0 Hz, H-5), 5.47 (1H, dd, $J_{4,5}$=8.0 Hz, $J_{3,4}$=3.0 Hz, H-4), 5.54 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{1,2}$=3.0 Hz, H-2), 5.95 (1H, dd, $J_{2,3}$=8.0 Hz, $J_{3,4}$=3.0 Hz, H-3), 7.25—7.65 (10H, m, aromatic H). Mass Spectrum[9] *m/e*: 578 (M^+), 469 (M^+-SC_6H_5), 409 (M^+-SC_6H_5-CH_3COOH), 367 (M^+-SC_6H_5-CH_3COOH-$COCH_3$).

9) The mass spectrum was determined on a Hitachi Model RMV-6E spectrometer at an ionizing voltage of 70 eV.

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A Novel Synthesis of α-Halo Carbonyl Compounds using Metal Halides

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The α-position of active methylene compounds which were activated by the carbonyl group was halogenated using metal halides in the presence of peroxides.

Various Halogenation methods, such as the reaction of carbonyl compounds with bromine[2] or chlorine,[3] with N-bromosuccinimide[4] or with sulfuryl chloride,[5,6] *etc.*,[7] have been reported for the preparation of α-halo carbonyl compounds. The reaction of carbonyl compounds with two mole equivalents of copper (II) halide[8,9] under reflux in various solvents has also been applied to prepare α-halo aldehydes and α-halo ketones. In this reaction, the use of two mole equivalents of copper(II) halide is necessary and the reaction solution becomes strongly acidic owing to evolution of hydrogen halide as follows:

$$(CH_3)_2CH\text{-}CHO + 2CuCl_2 \longrightarrow 2CuCl + HCl + (CH_3)_2\overset{Cl}{\overset{|}{C}}\text{-}CHO$$

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This report describes on the convenient and useful method for the preparation of α-halo carbonyl compounds using metal halides.

In a course of studying the alkylation of ketones with Grignard reagents, the authors recognized a little producing of α-halo ketones with normal products. This fact showed the possibility of α-halogenation of ketones being originated by magnesium halide which was one of the components of the Grignard reagents. Then, the halogenation reaction using magnesium halides was studied in details. It was found that the reaction of carbonyl compounds with one mole equivalent of magnesium halides in the presence of one mole equivalent of peroxides in various solvents, such as ether, tetrahydrofuran, *etc.*, at room temperature gave α-halo carbonyl compounds in satisfactory yields. Other metal halides in addition to magnesium halides, such as $CuBr_2$, CuBr, LiBr, LiI, *etc.*, were also useful under the same reaction condition. In this reaction, the presence of one mole equivalent of peroxides was necessary as seen in Table I. As peroxides, 30% H_2O_2(aq.), *m*-chloroperbenzoic acid (MCPB), dibenzoyl

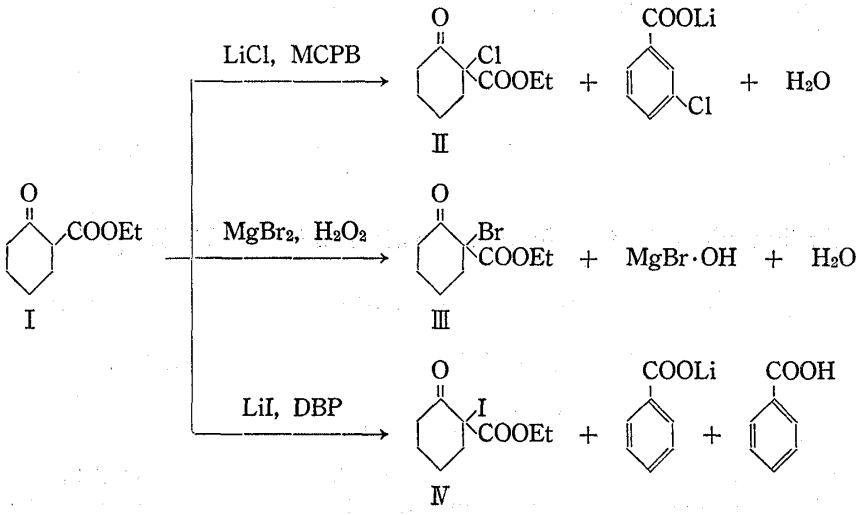
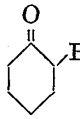


Chart 1

TABLE I. The α-Halogenation of Carbonyl Compounds

Carbonyl compounds	Reaction conditions (at room temp.) Solvents[b]	Metal halide (1 mole eq.)	Peroxide[c] (mole eq.)	Products	Yields[a] (%)
I	c	$MgBr_2$·etherate	H_2O_2 (0.1)	III	4.0
I	c	$MgBr_2$·etherate	H_2O_2 (0.5)	III	50.2
I	b, c	$MgBr_2$·etherate	H_2O_2 (1.0)	III	97.5
I	b, c	$MgBr_2$·etherate	MCPB (0.2)	III	16.5
I	b, c	$MgBr_2$·etherate	MCPB (1.0)	III	100
I	b, c	$MgBr_2$·etherate	DBP (1.2)	III	100
I	c	$CuBr_2$	H_2O_2 (1.0)	III	50.0
I	c	CuBr·H_2O	DBP (1.2)	III	97.7
I	a, c	LiCl	DBP (1.0)	II	61.6
I	a, c	LiI	DBP (1.0)	IV	72.0
$CH_2(COOEt)_2$	c	$MgBr_2$·etherate	H_2O_2 (1.0)	$BrCH(COOEt)_2$	80.0
	b, c	$MgBr_2$·etherate	H_2O_2 (1.0)		30.0

a) The yields were determined by the gas chromatographic analysis using a 6 ft. × 0.125 in. column containing 10% silicon (SE-30) at 90°.
b) a, tetrahydrofuran; b, ether; c, tetrahydrofuran: ether (1: 1)
c) MCPB: *m*-chloroperbenzoic acid, DBP: dibenzoyl peroxide, H_2O_2: 30 % H_2O_2 (aq.)

peroxide (DBP), *etc.*, were useful for this purpose and the reaction condition was able to be controlled to neutral, acidic or basic conditions by the kinds of employed peroxides. The reaction proceeded as Chart 1 and the results of the experiments were listed in Table I. The study on the mechanism of the reaction is in progress.

Experimental

The General Procedure for the Preparation of α-Halo Carbonyl Compounds——To a solution of a carbonyl compound (1 mole) in ether or tetrahydrofuran, a powdered metal halide (1 mole) or a solution or a suspension of a metal halide (1 mole) in ether or tetrahydrofuran was added at room temperature, and then a peroxide (1 mole) was added to the mixture with stirring at or below room temperature. The stirring was continued for two or three hours; the reaction was followed by the thin-layer chromatography. After the reaction was complete, a diluted $NaHCO_3$ (aq.) solution was added to the reaction mixture and the product was extracted with ether. The extracted solution was washed with water, and then dried over anhydrous magnesium sulfate. The solvent was concentrated under reduced pressure and the residual oil was purified by column chromatography on silica gel using chloroform as the eluting solvent. The reaction conditions and the yields of the products are listed in the Table I. These products obtained were identified with the standard samples.

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Antianoxic Effect of Meclofenoxate related to Its Disposition

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Effect of meclofenoxate against subacute anoxia in mice was tested in view of the fact that dimethylaminoethanol derived in the brain was sequentially metabolized from free alcohol to phospholipid. Some other agents were also tested to examine the test system used and to clarify the nature of meclofenoxate effect. Chlordiazepoxide, hexobarbital and meclofenoxate (either 20 min or 4 hr after intravenous administration) produced tolerance against anoxia, whereas methamphetamine exerted the opposite effect. An equimolar mixture of dimethylaminoethanol and *p*-chlorophenoxyacetic acid, the constituents of meclofenoxate, was ineffective in this system. Chlordiazepoxide enhanced the effect of methamphetamine, whereas hexobarbital and meclofenoxate (20 min after administration) diminished the methamphetamine effect. The results were discussed in relation to the disposition of meclofenoxate in central nervous systems.

Meclofenoxate (β-dimethylaminoethyl *p*-chlorophenoxyacetate hydrochloride) has a lot of central activities.[2] It was demonstrated[3] that the drug penetrated into brain immediately after intravenous administration, and was hydrolyzed into *p*-chlorophenoxyacetic acid and dimethylaminoethanol. The acid was eliminated from brain within several hours after administration. To the contrary, the alcohol moiety was metabolized as follows: free dimethylaminoethanol (whose brain level was maximum 5 min after administration) was phosphorylated to yield phosphoryldimethylaminoethanol (whose brain level was maximum at 20 min), which was in turn converted to phosphatidyldimethylaminoethanol (maximum at 4 hr).

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