Table V
Elemental Analyses of New Compounds

Compd	% calcd C	% calcd H	Mol formula	% found C	% found H
$(CH_3)_2CHCHCO_2CH_3$ (Cl)	47.85	7.36	$C_6H_{11}O_2Cl$	46.55	7.52
$CH_3(CH_2)_2CCO_2CH_3$ (Cl, CH_3)	51.07	7.96	$C_7H_{13}O_2Cl$	50.80	8.22
$CH_3CH_2CHCHCO_2CH_3$ (CH_3, Cl)	51.07	7.96	$C_7H_{13}O_2Cl$	50.97	8.06
$CH_3CHCH_2CHCO_2CH_3$ (CH_3, Cl)	51.07	7.96	$C_7H_{13}O_2Cl$	51.17	7.86

trophotometer and NMR spectra were measured on a 60-MHz Jeol C-60 HL NMR spectrometer at 25° using Me_4Si as an internal standard. Reaction products analyses were done on a Yanagimoto Model GCG 550 gas chromatograph employing a flame ionization detector and a 1.5 m × 3 mm copper column packed with Apiezon grease L 15% on Celite 545 of 80–100 mesh. The column was operated at 50–200°, with nitrogen as a carrier (30 ml/min) and hydrogen of flow rate 30 ml/min. The yields shown in Tables I–III were determined by the internal standard method.

Typical Procedure for the Chlorination in Table I. Butyric acid (17.62 g, 0.2 mol), concentrated H_2SO_4 (1.96 g, 0.02 mol), and *m*-dinitrobenzene (2.78 g, 0.017 mol) were placed in a 100-ml four-necked flask fitted with a Dimroth condenser, a thermometer, and a gas inlet tube with sponge glass end. After gaseous N_2 was passed through the reaction mixture for ca. 30 min to expel oxygen, the butyric acid was chlorinated at 120° for 3 hr by bubbling a mixture of gaseous chlorine (flow rate ca. 100 ml/min) and oxygen (200 ml/min) dried with concentrated H_2SO_4 with magnetic stirring in the dark. After completion of the reaction, chlorine remaining in the solution was expelled out by bubbling N_2 gas into it for ca. 30 min. In general, a fraction of the reaction mixture (0.5–1.5 g) was added with water (10 ml) and extracted three times with chloroform (each 10–20 ml). The dried chloroform extract, after being dried with anhydrous Na_2SO_4 and vacuum distilled, was esterified with diazomethane in ether and the ether solution was analyzed by GLC.

Typical Procedure for the Chlorination in Tables II and III. In a 300-ml four-necked flask fitted with a Dimroth condenser, a thermometer, and a gas inlet tube were placed isovaleric acid (61.2 g, 0.6 mol), chlorosulfonic acid (6.20 g, 0.06 mol) as an acid catalyst, and chloranil (0.743 g, 0.003 mol). After being passed with N_2 gas for ca. 30 min to expel oxygen, a mixture of Cl_2 and O_2 gas (in a mole ratio of 2:1) were introduced into the substrate in the dark at 140°. Aliquots (2 ml) of the reaction mixture were taken out at given intervals of time and esterified by refluxing with a mixture of concentrated H_2SO_4 (0.05 ml), methyl alcohol (3 ml), and ethylene dichloride (8 ml) for 10 hr. The cooled mixture was separated and the organic layer was washed successively with water, aqueous $NaHCO_3$, and again with water. The organic solution was dried over anhydrous Na_2SO_4 and then analyzed by GLC.

The analogous work-up was applied to other acids. The elemental analysis data for new compounds among obtained α-chloro acids are shown in Table V.

Registry No.—Chlorosulfonic acid, 7790-94-5; chloranil, 118-75-2; isovaleric acid, 503-74-2; α-chloroisovaleric acid, 921-08-4.

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An Acid Protecting Group

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In some related work we were interested in utilizing an acid protecting[2] group that could be readily cleaved under mild acidic conditions as well as under catalytic-reductive conditions. The model studies reported herein indicate that an acid protected as its benzyloxymethyl ester can fulfill these two requirements.

The benzyloxymethyl esters can be synthesized in good yields by reaction of the sodium salt of the acid with benzyl chloromethyl ether in hexamethylphosphoramide[3,4] at room temperature. Employing these reaction conditions,

$$\underset{\text{I or II}}{R{-}\overset{O}{\overset{\|}{C}}ONa} + PhCH_2OCH_2Cl \xrightarrow[\text{room temp}]{HMPA} \underset{\text{III or IV}}{R{-}\overset{O}{\overset{\|}{C}}OCH_2OCH_2Ph}$$

I, R = n-C_5H_{11}; II, R = Ph; III, R = n-C_5H_{11}; IV, R = Ph

benzyloxymethyl hexanoate (III) and benzyloxymethyl benzoate (IV) were prepared in 73 and 68% yields, respectively.

Hydrolysis of the benzyloxymethyl esters III and IV with an aqueous HCl–THF solution at room temperature for 2 hr afforded the corresponding acids hexanoic V and benzoic VI in good yields.

$$\underset{\text{III or IV}}{R{-}\overset{O}{\overset{\|}{C}}OCH_2OCH_2Ph} \xrightarrow[\text{room temp, 2 hr}]{\text{aq HCl-THF}} \underset{\text{V or VI}}{R{-}\overset{O}{\overset{\|}{C}}OH}$$

V, R = n-C_5H_{11}; VI, R = Ph

$$\text{III or IV} \xrightarrow[\substack{\text{ETOH, 1 atm,}\\ \text{room temp}}]{5\%\ Pd/C\text{-}H_2} \text{V or VI}$$

Reductive removal of the benzyloxymethyl group in esters III and IV was readily achieved by reduction of III and IV, respectively, with 5% Pd/C in ethanol in the presence of hydrogen at 1 atm at room temperature. These results are summarized in Table I.

Experimental Section

Benzyloxymethyl Hexanoate (III). Sodium hexanoate (13.8 g, 0.1 mol), benzyl chloromethyl ether (15.7 g, 0.1 mol), and hexamethylphosphoramide (80 ml) were placed in a 250-ml flask fitted with a stopper and the resulting mixture was allowed to stir at room temperature for 2 days. The reaction mixture was poured into 700 ml of water and extracted with 2 × 500 ml of hexanes. The hexane extracts were combined and washed consecutively with a

Table I
Hydrolysis and Catalytic Reduction of Benzyloxy Esters

Esters	Hydrolysis	Catalytic reduction	Product	% yield
$PhCO_2CH_2OCH_2Ph$	aq HCl–THF		$PhCO_2H$	98
$PhCO_2CH_2OCH_2Ph$		5% Pd/C–H_2	$PhCO_2H$	100
$C_5H_{11}CO_2CH_2OCH_2Ph$	aq HCl–THF		$C_5H_{11}CO_2H$	75
$C_5H_{11}CO_2CH_2OCH_2Ph$		5% Pd/C–H_2	$C_5H_{11}CO_2H$	69

5% sodium bicarbonate solution (500 ml) and water (500 ml) and dried over anhydrous magnesium sulfate. Filtration and concentration of the organic phase on a rotary evaporator yielded an oil. Distillation of the oil afforded 17.2 g (73%) of benzyloxymethyl hexanoate: bp 101–104° (0.08 mm); ir (neat) ester band at 1750 cm^{-1}; NMR (CCl_4) δ 7.44 (s, 5 H), 5.4 (s, 2 H), 4.71 (s, 2 H), 2.25 (t, 2 H), 1.1–2 (m, 6 H) and 0.9 (t, 3 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.31; H, 8.41.

Benzyloxymethyl Benzoate (IV). Sodium benzoate (18.7 g, 0.13 mol), benzyl chloromethyl ether (20.2 g, 0.13 mol), and hexamethylphosphoramide (75 ml) were stirred at room temperature for 48 hr and the reaction mixture was worked up by the above procedure. Distillation afforded 21.2 g (68%) of benzyloxymethyl benzoate: bp 122–124° (0.06 mm); ir (neat) ester band at 1725 cm^{-1}; NMR (CCl_4) δ 4.74 (s, 2 H), 5.67 (s, 2 H), 8.02–8.22 (m, 2 H), 7.20–7.50 (m) and 7.30 (s) [(m) + (s), 8 H].

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.52; H, 5.89.

Ester Hydrolysis. Benzoic Acid VI. Benzyloxymethyl benzoate (IV, 1.0 g, 0.0041 mol) was dissolved in an aqueous HCl–THF solution (8 ml of concentrated HCl, 6 ml of H_2O, and 36 ml of THF) and the resulting solution was stirred at room temperature for 2 hr. The reaction solution was poured into 100 ml of H_2O and extracted with 2 × 100 ml of ether. The ether extracts were combined and extracted with 3 × 25 ml of 10% $NaHCO_3$. The aqueous basic layers were combined and washed with 75 ml of ether and then acidified carefully with concentrated HCl. The acidic layer was then extracted with 3 × 75 ml of $CHCl_3$ and the chloroform extracts were combined and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent on a rotary evaporator afforded 490 mg (98%) of benzoic acid, mp 121–122° (lit.[5] mp 122.4°). The NMR and ir spectra of benzoic acid were identical with those of an authentic sample.

Hexanoic Acid V. Benzyloxymethyl hexanoate (III, 3.0 g, 0.0126 mol) was dissolved in an aqueous HCl–THF solution (6 ml of H_2O, 8 ml of concentrated HCl, and 51 ml of THF), the resulting solution was stirred at room temperature for 2 hr, and the reaction mixture was worked up by the above procedure. The organic solvent was removed by distillation at 1 atm and the resulting oil was then distilled under vacuum to afford 1.1 g (75%) of hexanoic acid, bp 115–123° (40 mm) [lit[6] bp 107° (15 mm)]. The NMR and ir spectra of hexanoic acid were identical with those of an authentic sample.

Catalytic Reduction. Benzoic Acid VI. To a solution of benzyloxymethyl benzoate (1.0 g, 0.0041 mol) in absolute ethanol (15 ml) was added 5% Pd/C (400 mg) and the resulting mixture was reduced with H_2 at 1 atm at room temperature. After a hydrogen uptake of 97.6 ml, the reaction mixture was filtered through Celite 545 and the Celite was washed with additional ethanol. The organic filtrate was dried over anhydrous magnesium sulfate; filtration followed by removal of the solvent afforded 500 mg (100%) of benzoic acid, mp 121.6–122.3° (lit.[5] mp 122.4°). The NMR and ir spectra of benzoic acid were identical with those of an authentic sample.

Catalytic Reduction. Hexanoic Acid V. To a solution of benzyloxymethyl hexanoate (III, 3.0 g, 0.0126 mol) in absolute ethanol (20 ml) was added 400 mg of 5% Pd/C, the resulting mixture was reduced at 1 atm at room temperature, and the reaction mixture was worked up by the above procedure. The organic solvent was removed by distillation at 1 atm. The oil residue was dissolved in 10% $NaHCO_3$ (50 ml) and extracted with 100 ml of ether. The ether phase was extracted with 35 ml of 10% $NaHCO_3$ and the basic layers were combined and carefully acidified with concentrated HCl. The acidified mixture was extracted with 3 × 150 ml of chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent at 1 atm afforded an oil. Vacuum distillation of the oil afforded 1.0 g (69%) of hexanoic acid, bp 115–118° [lit.[6] bp 107° (15 mm)]. The NMR and ir spectra of hexanoic acid were identical with those of an authentic sample.

Registry No.—I, 10051-44-2; II, 532-32-1; III, 55887-43-9; IV, 55887-44-0; V, 142-62-1; VI, 65-85-0; benzyl chloromethyl ether, 3587-60-8.

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Reactions of Oxetane with Imine Salts Derived from Cyclohexanone

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In connection with our interest in the use of α-methyleneoxetane[1] in nucleophilic ring-opening reactions, e.g., in the Robinson annelation, we have investigated the possibility of alkylating enolates or imine salts with oxetane (trimethylene oxide). For comparison, we have also studied the analogous reactions with an epoxide, propylene oxide. Ring-opening reactions of oxetanes with Grignard,[2-4] organolithium,[3,5] and organoaluminum[6] reagents are known, but few reactions with C-functional nucleophiles are reported.[7] Many nucleophilic ring-opening reactions of epoxides are reported, including reactions with imine salts and with enolates of β-dicarbonyl compounds.[7c,d,8-10]

We have been able to alkylate enolates of cyclohexanone with propylene oxide, but not with oxetane. However, we have found that the imine salt[11] of cyclohexanone is alkylated by both oxetane and propylene oxide in good yields.

When propylene oxide was treated with the lithium or bromomagnesium enolates of cyclohexanone,[12a] the alkylated product **2**[9b,10,14] was formed in low to moderate yields. However, when oxetane was treated with these enolates[12] under a variety of conditions, none of the expected alkylation products, **4**[15] or **5**,[15,16] was detected.[17]

The reaction of oxetane with the bromomagnesium salt of the imine (**3**) of cyclohexanone, followed by acetic acid hydrolysis,[11e] gave the hemiketal **4** in 80% isolated yield. A