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# Studies on Hypolipidemic Agents. I. 3-Benzoylglycidic Acid Derivatives

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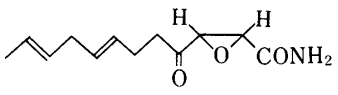
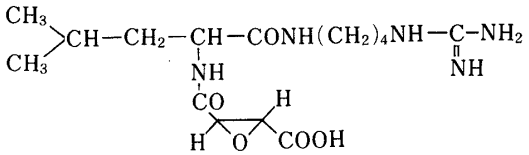
3-Benzoylglycidic acid derivatives were prepared and tested for hypolipidemic properties in normal rats. A structure–activity relationship study showed that *trans*-3-(phenoxybenzoyl)-glycidic acids have hypolipidemic activity. Among these compounds, *trans*-3-[4-(4-chlorophenoxy)benzoyl]glycidic acid (**38**) and *trans*-3-[4-(4-bromophenoxy)benzoyl]glycidic acid (**39**) possessed very potent activities.

**Keywords**——*trans*-3-benzoylglycidic acid; hypolipidemic activity; structure–activity relationship; Darzens condensation; clofibrate

Cerulenin[1] and E-64[2] are natural products which have a β-acylglycidic acid moiety in their structures (Chart 1). They have thiolprotease-inhibiting activity, and cerulenin is known to inhibit the biosynthesis of sterols or fatty acids. Since it was considered that the β-acylglycidic acid moiety is important for their unique biological activities, in an attempt to find a new bioactive agent, we investigated a series of 3-aroylglycidic acid derivatives, and found that some of them have potent hypolipidemic activities. This paper describes the synthesis and the structure–activity relationship of a variety of compounds having the 3-benzoylglycidic acid moiety.



cerulenin



E-64

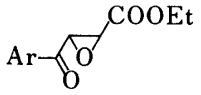
Chart 1

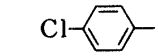
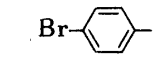
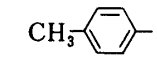
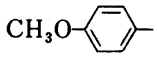
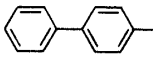
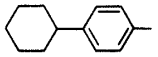
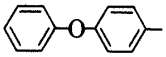
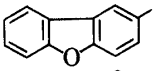
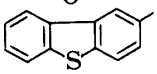
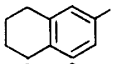
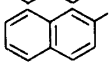
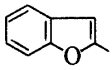
## Chemistry

The 3-benzoylglycidic acid derivatives listed in Tables I—VI were synthesized by the methods shown in Chart 2.

Ethyl *trans*-3-benzoylglycidates (II) were obtained by the Darzens condensation of α-haloacetophenones (I) with ethyl glyoxylate in the presence of sodium ethoxide (method A). The hydrolysis of II with sodium bicarbonate gave a mixture of the *trans*-3-benzoylglycidic acid (III) and the *cis* isomer (IV) in a ratio of 7 : 1[3] (method B). A mixture of **38** and **46** was also obtained in a ratio of 8 : 1 by hydrogen peroxide oxidation of 3-[4-(chlorophenoxy)benzoylacrylic acid (VII), which was prepared by the Friedel–Crafts acylation of the aromatic compound VI with maleic anhydride (method E). Compounds III and IV were separated by recrystallization from *n*-hexane–acetone.[4]

TABLE I. Physical and Biological Properties of Ethyl 3-Benzoylglycidates



| No. | Ar | Method[a] | mp (°C) (Recrystn. solvent[b]) | Hypolipidemic activity rank[c] | |
|---|---|---|---|---|---|
| | | | | Cholesterol | Triglyceride |
| 1 |  | A | 33—66 (H) | 0 | 0 |
| 2 |  | A | 58—59 (PE) | 0 | 1 |
| 3 |  | A | 63—63.5 (PE) | 0 | 1 |
| 4 |  | A | Oil[d] | 0 | 0 |
| 5 |  | A | Oil[d] | 0 | 1 |
| 6 |  | A | 82—85 | 0 | 1 |
| 7 |  | A | Oil[d] | 2 | 0 |
| 8 |  | A | Oil[d] | 2 | 2 |
| 9 |  | A | 80—83 (A–H) | 0 | 0 |
| 10 |  | A | 105—107 (A–H) | 0 | 1 |
| 11 |  | A | Oil[d] | 0 | 0 |
| 12 |  | A | Oil[d] | 0 | 0 |
| 13 |  | A | 74—76 (A–H) | 0 | 0 |

*a*) See Experimental.
*b*) A=acetone, E=ether, Et=ethanol, H=hexane, PE=petroleum ether.
*c*) Reduction levels were calculated as percentages with respect to the control value; less than 9% reduction=0, 10—19% reduction=1, 20—29% reduction=2, 30—39% reduction=3, 40—49% reduction=4, more than 50% reduction=5.
*d*) Purified by column chromatography.

The other alkyl ester derivatives (V) were prepared by heating of the ethyl ester (II) in the corresponding alcohol (method C) or esterification of the free acid (III) (method D).

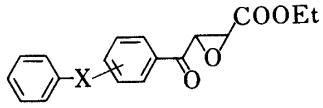
## Biological Method

Five-week-old male rats (six rats per group) were used. After prefeeding for a week, the test compounds, which were prepared as a suspension in 5% gum arabic aqueous solution, were orally administered to the rats at a daily dose of 100 mg/kg for 4 d. A 5% gum arabic aqueous solution was orally administered to rats of the control group. Eighteen hours after the final drug administration, the rats were anesthetized with diethyl ether and their blood was collected. The lipid concentration in the serum was determined with an auto-analyzer.

## Results and Discussion

The physical constants and biological data of the 3-benzoylglycidic acid derivatives are

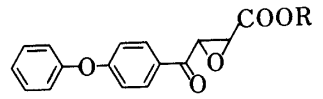
TABLE II. Physical and Biological Properties of Ethyl 3-Benzoylglycidates



| No. | –X– (Position) | | Method[a] | mp (°C) (Recrystn. solvent[b]) | Hypolipidemic activity rank[c] | |
|---|---|---|---|---|---|---|
| | | | | | Cholesterol | Triglyceride |
| 14 | –S– | (4) | A | Oil[d] | 0 | 2 |
| 15 | $-CH_2-$ | (4) | A | Oil[d] | 0 | 0 |
| 16 | $-CH_2O-$ | (4) | A | 65—66 (A–H) | 0 | 3 |
| 17 | $-CH_2CH_2O-$ | (4) | A | Oil[d] | 0 | 5 |
| 18 | –O– | (3) | A | Oil[d] | 0 | 0 |
| 19 | –O– | (2) | A | 96—98 (A–H) | 0 | 0 |
| 8 | –O– | (4) | | | 2 | 2 |

*a—d*) See footnotes in Table I.

TABLE III. Physical and Biological Properties of 3-(4-Phenoxybenzoyl)glycidic Acids



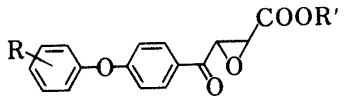
| No. | R | Method[a] | mp (°C) (Recrystn. solvent[b]) | Hypolipidemic activity rank[c] | |
|---|---|---|---|---|---|
| | | | | Cholesterol | Triglyceride |
| 20 | H | B | Oil[d] | 1 | 2 |
| 21 | Na | B | 130—133 (Et) | 4 | 4 |
| 22 | $CH_3$ | C | Oil[d] | 2 | 2 |
| 23 | $CH(CH_3)_2$ | C | Oil[d] | 3 | 3 |
| 24 | $n\text{-}C_5H_{11}$ | C | Oil[d] | 2 | 2 |
| 25 | $CH_2CH=CH_2$ | D | Oil[d] | 2 | 3 |
| 26 | $CH_2C\equiv CH$ | D | 100—101 (A–H) | 0 | 2 |
| 27 | $CH_2CH=C(CH_3)_2$ | D | Oil[d] | 1 | 1 |
| 28 | $c\text{-}C_5H_9$ | C | Oil[d] | 1 | 2 |
| 29 | $CH_2Ph$ | C | Oil[d] | 1 | 2 |
| 8 | $C_2H_5$ | | | 2 | 2 |

*a—d*) See footnotes in Table I.

shown in Tables I—VI.

As shown in Tables I and II, ethyl *trans*-3-(4-phenoxybenzoyl)glycidate (**8**) exhibited serum cholesterol- and triglyceride-lowering activity. Compounds **16** and **17** lowered only the triglyceride level. In comparison with **8**, sodium *trans*-3-(4-phenoxybenzoyl)glycidate (**21**) had a stronger activity, but the free acid (**20**) and the other ester derivatives did not show especially strong activities (Table III). Substitution at the phenoxy group of **8** had a considerable influence on the activity (Table IV). Compounds **30** and **34**, which have halogen at the *para* position, showed strong activities, and their free acids (**38**, **39**) had the strongest activities.

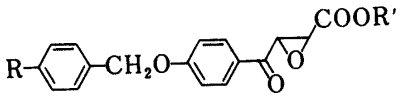
TABLE IV. Physical and Biological Properties of 3-(4-Phenoxybenzoyl)glycidic Acids



| No. | R | R′ | Method[a] | mp (°C) (Recrystn. solvent[b]) | Hypolipidemic activity rank[c] | |
|---|---|---|---|---|---|---|
| | | | | | Cholesterol | Triglyceride |
| 30 | 4-Cl | Et | A | 80—83 (E–H) | 3 | 2 |
| 31 | 3-Cl | Et | A | Oil[d] | 0 | 2 |
| 32 | 2-Cl | Et | A | Oil[d] | 1 | 3 |
| 33 | 3,4-diCl | Et | A | 78—79.5 (E–H) | 1 | 2 |
| 34 | 4-Br | Et | A | 85—85.5 (E–H) | 3 | 3 |
| 35 | 4-$CH_3$ | Et | A | Oil[d] | 1 | 0 |
| 36 | 4-$CH_3O$ | Et | A | Oil[d] | 0 | 0 |
| 37 | 4-$(CH_3)_2CH$ | Et | A | Oil[d] | 0 | 2 |
| 38 | 4-Cl | H | B, E | 155—157 (E–H) | 5 | 4 |
| 39 | 4-Br | H | B | 148—151 (E–H) | 5 | 4 |

*a*—*d*) See footnotes in Table I.

TABLE V. Physical and Biological Properties of 3-(4-Benzyloxybenzoyl)glycidic Acids



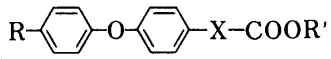
| No. | R | R′ | Method[a] | mp (°C) (Recrystn. solvent[b]) | Hypolipidemic activity rank[c] | |
|---|---|---|---|---|---|---|
| | | | | | Cholesterol | Triglyceride |
| 40 | H | H | B | 123—127 (A–H) | 1 | 5 |
| 41 | Cl | Et | A | 92—93.5 (E–H) | 1 | 4 |
| 42 | Cl | H | B | 138—142 (A–H) | 1 | 5 |
| 16 | H | Et | | | 0 | 3 |

*a*—*c*) See footnotes in Table I.

*trans*-3-(4-Benzyloxybenzoyl)glycidic acid derivatives, listed in Table V, showed hypotriglyceridemic activities, but had no effect on serum cholesterol.

Because compound **43**, which is the decarbonylated analogue of **8**, had no activity (Table VI), the ketone moiety must be essential for the activity. Compounds **44**[5] and **45**[5] showed the same properties as clofibrate[6] (ethyl 2-(4-chlorophenoxy)-2-methylpropionate), *i.e.*, they showed hypolipidemic activity but also increased the weight of the liver. Thus, it seems reasonable to consider that the epoxy moiety is desirable for inhibiting liver toxicity. The

TABLE VI. Comparison of Biological Properties



| No. | R | X | R′ | Hypolipidemic activity rank[c] | | Liver weight[a] change (%) |
|---|---|---|---|---|---|---|
| | | | | Cholesterol | Triglyceride | |
| 43 | H |  | Et | 0 | 0 | 13.8 |
| 44 | H |  | Et | 2 | 1 | 33.4 |
| 45 | H |  | Et | 2 | 2 | 16.6 |
| 46 | Cl |  | H | 2 | 5 | 4.7 |
| 38 | Cl |  | H | 5 | 4 | 5.5 |
| | Clofibrate | | | 4 | 1 | 35.5 |

*a*) Liver weight increase calculated as a percentage with respect to the control value.
*c*) See footnotes of Table I.

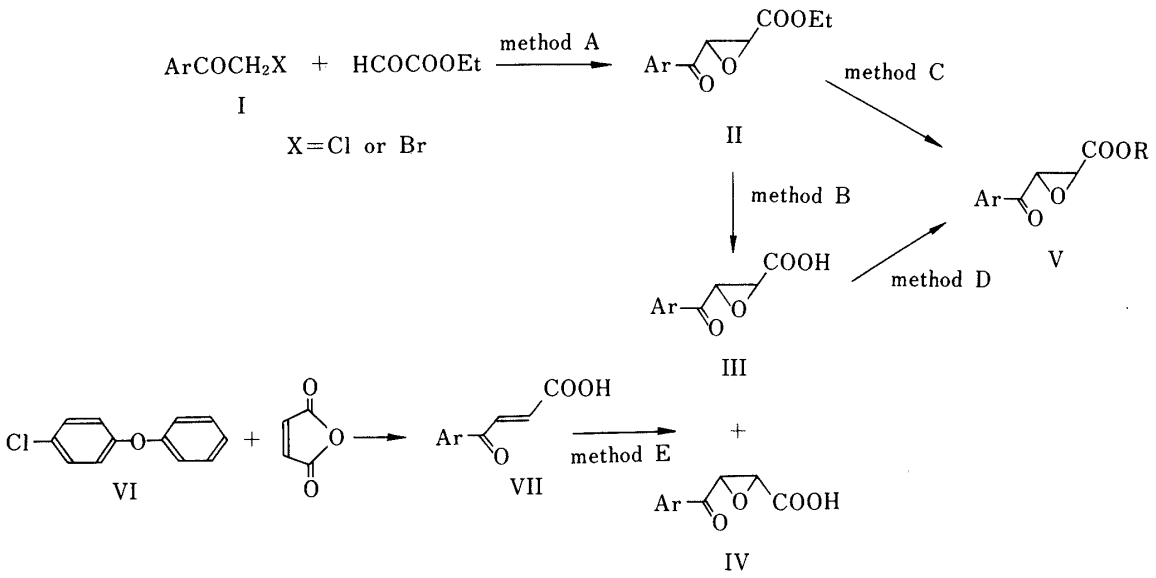



Chart 2

activity of the *trans* isomers was stronger than that of the *cis* isomers (compare **38** with **46**).

## Experimental

All the melting points are uncorrected. Infrared (IR) spectra were measured using a JASCO DS-301 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken at 60 MHz with tetramethylsilane (TMS) as an internal standard using a Hitachi Perkin-Elmer spectrometer (model R-20), in $CDCl_3$ unless otherwise noted. The chemical shifts were expressed as ppm downfield from TMS. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet and br = broad. The unit (Hz) of coupling constants (*J* Hz) is omitted. The lipid concentration in serum were estimated by the enzyme method (Daitest Series Kit, Dai-ichi Co., Ltd., Tokyo). A Hitachi model 712 auto-analyser was used.

**Method A**——A typical example is given to illustrate the general procedure.

Ethyl *trans*-3-Benzoylglycidate (**1**): A solution of NaOEt (5.15 g) in dry EtOH (100 ml) was added dropwise to a stirred and ice-cooled solution of ethyl glyoxylate (7.00 g) and phenacyl bromide (13.6 g) in dry EtOH (100 ml) for 1 h. The mixture was stirred for an additional 2 h at room temperature and EtOH was removed under reduced pressure. The residue was suspended in $H_2O$ (100 ml) and extracted with AcOEt. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel using hexane–acetone (10 : 1, v/v) as an eluent, and recrystallized from hexane–acetone to give **1** (6.00 g, 40.0%), mp 33—36 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1745, 1665. NMR $\delta$: 1.30 (3H, t, $J$=7), 3.63 (1H, d, $J$=2), 4.26 (2H, q, $J$=7), 4.39 (1H, d, $J$=2), 7.40—7.70 (3H, m), 7.85—9.12 (2H, m). *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.23; H, 5.37.

The following compounds were similarly prepared.

Ethyl *trans*-3-(4-Chlorobenzoyl)glycidate (**2**): mp 58—59 °C (from petroleum ether). Yield 21.3%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1760, 1690. NMR $\delta$: 1.32 (3H, t, $J$=7), 3.67 (1H, d, $J$=2), 4.34 (2H, q, $J$=7), 4.41 (1H, d, $J$=2), 7.53 (2H, d, $J$=9), 8.05 (2H, d, $J$=9). *Anal.* Calcd for $C_{12}H_{11}ClO_4$: C, 56.59; H, 4.35. Found: C, 56.53; H, 4.47.

Ethyl *trans*-3-(4-Bromobenzoyl)glycidate (**3**): mp 63—63.5 °C (from petroleum ether). Yield 40.4%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1760, 1680. NMR $\delta$: 1.32 (3H, t, $J$=7), 3.67 (1H, d, $J$=2), 4.29 (2H, q, $J$=7), 4.37 (1H, d, $J$=2), 7.62 (2H, d, $J$=9), 7.90 (2H, d, $J$=9). *Anal.* Calcd for $C_{12}H_{11}BrO_4$: C, 48.18; H, 3.71. Found: C, 48.19; H, 3.85.

Ethyl *trans*-3-(4-Methylbenzoyl)glycidate (**4**): Oil. Yield 58.3%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1755, 1690. NMR $\delta$: 1.35 (3H, t, $J$=7), 2.48 (3H, s), 3.70 (1H, d, $J$=2), 4.34 (2H, q, $J$=7), 4.46 (1H, d, $J$=2), 7.37 (2H, d, $J$=9), 7.98 (2H, d, $J$=9). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.87; H, 5.95.

Ethyl *trans*-3-(4-Methoxybenzoyl)glycidate (**5**): Oil. Yield 25.0%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1750, 1695. NMR $\delta$: 1.32 (3H, t, $J$=7), 3.15 (1H, d, $J$=2), 3.85 (3H, s), 4.26 (2H, q, $J$=7), 4.27 (1H, d, $J$=2), 6.92 (2H, d, $J$=9), 7.95 (2H, d, $J$=9). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.10; H, 5.52.

Ethyl *trans*-3-(4-Phenylbenzoyl)glycidate (**6**): mp 82—85 °C (from hexane). Yield 31.8%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1740, 1690. NMR $\delta$: 1.32 (3H, t, $J$=7), 3.65 (1H, d, $J$=2), 4.25 (2H, q, $J$=7), 4.40 (1H, d, $J$=2), 7.35—7.65 (7H, m), 7.90—8.12 (2H, m). *Anal.* Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C. 72.93; H, 5.51.

Ethyl *trans*-3-(4-Cyclohexylbenzoyl)glycidate (**7**): Oil. Yield 62.0%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1755, 1695. NMR $\delta$: 1.31 (3H, t, $J$=7), 1.00—2.10 (10H, br m), 2.60 (1H, br s), 3.66 (1H, d, $J$=2), 4.28 (2H, q, $J$=7), 4.41 (1H, d, $J$=2), 7.32 (2H, d, $J$=9), 7.95 (2H, d, $J$=9). *Anal.* Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.22; H, 7.17.

Ethyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**8**): Oil. Yield 55.7%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1755, 1690. NMR $\delta$: 1.32 (3H, t, $J$=7), 3.67 (1H, d, $J$=2), 4.28 (2H, q, $J$=7), 4.37 (1H, d, $J$=2), 6.90—7.50 (7H, m), 8.05 (2H, d, $J$=9). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.33; H, 5.24.

Ethyl *trans*-3-(2-Dibenzofuranylcarbonyl)glycidate (**9**): mp 80—83 °C (from hexane–acetone). Yield 29.2%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1760, 1685. NMR $\delta$: 1.38 (3H, t, $J$=7), 3.79 (1H, d, $J$=2), 4.36 (2H, q, $J$=7), 4.57 (1H, d, $J$=2), 7.30—8.70 (7H, m). *Anal.* Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.73; H, 4.80.

Ethyl *trans*-3-(2-Dibenzothienylcarbonyl)glycidate (**10**): mp 105—107 °C (from hexane–acetone). Yield 29.3%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1755, 1685. NMR $\delta$: 1.35 (3H, t, $J$=7), 3.78 (1H, d, $J$=2), 4.34 (2H, q, $J$=7), 4.53 (1H, d, $J$=2), 7.27—8.80 (7H, m). *Anal.* Calcd for $C_{18}H_{14}O_4S$: C, 66.24; H, 4.32. Found: C, 66.37; H, 4.57.

Ethyl *trans*-3-(5,6,7,8-Tetrahydro-2-naphthoyl)glycidate (**11**): Oil. Yield 70.1%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1760, 1695. NMR $\delta$: 1.35 (3H, t, $J$=7), 1.60—2.11 (4H, m), 2.63—3.05 (4H, m), 3.70 (1H, d, $J$=2), 4.35 (2H, q, $J$=7), 4.45 (1H, d, $J$=2), 7.09—7.35 (1H, m), 7.58—7.75 (2H, m). *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.92; H, 6.75.

Ethyl *trans*-3-(2-Naphthoyl)glycidate (**12**): Oil. Yield 51.9%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1750, 1690. NMR $\delta$: 1.35 (3H, t, $J$=7), 3.39 (1H, d, $J$=2), 4.35 (2H, q, $J$=7), 4.60 (1H, d, $J$=2), 7.55—8.15 (6H, m), 8.55 (1H, s). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.17; H, 5.42.

Ethyl *trans*-3-(2-Benzofuroyl)glycidate (**13**): mp 74—76 °C (from hexane–acetone). Yield 46.2%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1740, 1679. NMR $\delta$: 1.35 (3H, t, $J$=7, 3.81 (1H, d, $J$=2), 4.33 (2H, q, $J$=7), 4.42 (1H, d, $J$=2), 7.20—7.90 (5H, m). *Anal.* Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.46; H, 4.77.

Ethyl *trans*-3-(4-Phenylthiobenzoyl)glycidate (**14**): Oil. Yield 34.4%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1760, 1690. NMR $\delta$: 1.36 (3H, t, $J$=7), 3.68 (1H, d, $J$=2), 4.33 (2H, q, $J$=7), 4.40 (1H, d, $J$=2), 7.24 (2H, d, $J$=9), 7.54 (5H, s), 7.86 (2H, d, $J$=9). *Anal.* Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91. Found: C, 65.62; H, 4.80.

Ethyl *trans*-3-(4-Benzylbenzoyl)glycidate (**15**): Oil. Yield 53.1%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1760, 1690. NMR $\delta$: 1.31 (3H, t, $J$=7), 3.66 (1H, d, $J$=2), 4.05 (2H, s), 4.29 (2H, q, $J$=7), 4.40 (1H, d, $J$=2), 7.25 (5H, s), 7.34 (2H, d, $J$=9), 7.96 (2H, d, $J$=9). *Anal.* Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.28; H, 5.88.

Ethyl *trans*-3-(4-Benzyloxybenzoyl)glycidate (**16**): mp 65—66 °C (from hexane–acetone). Yield 38.7%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1750, 1670. NMR $\delta$: 1.31 (3H, t, $J$=7), 3.67 (1H, d, $J$=2), 4.28 (2H, q, $J$=7), 4.38 (1H, d, $J$=2), 5.15 (2H, s), 7.04 (2H, d, $J$=9), 7.39 (4H, s), 8.02 (2H, d, $J$=9). *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 70.05; H, 5.69.

Ethyl *trans*-3-(4-Phenethyloxybenzoyl)glycidate (**17**): Oil. Yield 32.2% IR $\nu_{max}^{neat}$ $cm^{-1}$: 1750, 1680. NMR $\delta$: 1.32 (3H, t, $J$=7), 3.12 (2H, t, $J$=7), 3.68 (1H, d, $J$=2), 4.26 (2H, t, $J$=7), 4.31 (2H, q, $J$=7), 4.38 (1H, d, $J$=2), 6.90—8.08 (9H, m). *Anal.* Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.38; H, 5.97.

Ethyl *trans*-3-(3-Phenoxybenzoyl)glycidate (**18**): Oil. Yield 26.5%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1750, 1690. NMR $\delta$: 1.30 (3H,

t, $J=7$), 3.61 (1H, d, $J=2$), 4.24 (2H, q, $J=7$), 4.31 (1H, d, $J=2$), 6.75—7.78 (9H, m). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 68.94; H, 4.99.

Ethyl *trans*-3-(2-Phenoxybenzoyl)glycidate (**19**): mp 95—98 °C (from hexane–acetone). Yield 28.0%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1755, 1690. NMR $\delta$: 1.04 (3H, t, $J=7$), 3.53 (1H, d, $J=2$), 3.68—4.22 (2H, m), 4.51 (1H, d, $J=2$), 6.80—7.60 (9H, m). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.38; H, 5.41.

Ethyl *trans*-3-[4-(4-Chlorophenoxy)benzoyl]glycidate (**30**): mp 80—83 °C (from hexane–$Et_2O$). Yield 61.6%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1750, 1685. NMR $\delta$: 1.32 (3H, t, $J=7$), 3.69 (2H, d, $J=2$), 4.39 (2H, q, $J=7$), 4.40 (1H, d, $J=2$), 6.96 (2H, d, $J=9$), 7.25—7.45 (4H, m), 7.96 (2H, d, $J=9$). *Anal.* Calcd for $C_{18}H_{15}ClO_5$: C, 62.23; H, 4.36. Found: C, 62.00; H, 4.47.

Ethyl *trans*-3-[4-(3-Chlorophenoxy)benzoy]glycidate (**31**): Oil. Yield 64.2%. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1750, 1690. NMR $\delta$: 1.32 (3H, t, $J=7$), 3.66 (1H, d, $J=2$), 4.36 (1H, d, $J=2$), 4.39 (2H, q, $J=7$), 6.90—7.40 (6H, m), 8.02 (2H, d, $J=9$). *Anal.* Calcd for $C_{18}H_{15}ClO_5$: C, 62.23; H, 4.36. Found: C, 62.38; H, 4.65.

Ethyl *trans*-3-[4-(2-Chlorophenoxy)benzoy]glycidate (**32**): Oil. Yield 56.6%. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1750, 1685. NMR $\delta$: 1.32 (3H, t, $J=7$), 3.66 (1H, d, $J=2$), 4.36 (1H, d, $J=2$), 4.39 (2H, q, $J=7$), 6.95 (1H, d, $J=9$), 7.15—7.60 (5H, m), 8.00 (2H, d, $J=9$). *Anal.* Calcd for $C_{18}H_{15}ClO_5$: C, 62.23; H, 4.36. Found: C, 62.17; H, 4.65.

Ethyl *trans*-3-[4-(3,4-Dichlorophenoxy)benzoyl]glycidate (**33**): mp 78.0—79.5 °C (from hexane–$Et_2O$). Yield 39.6%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1750, 1675. NMR $\delta$: 1.32 (3H, t, $J=7$), 3.65 (1H, d, $J=2$), 4.28 (2H, q, $J=7$), 4.35 (1H, d, $J=2$), 6.80—8.20 (7H, m). *Anal.* Calcd for $C_{18}H_{14}Cl_2O_5$: C, 56.71; H, 3.70. Found: C , 56.43; H, 3.92.

Ethyl *trans*-3-[4-(4-Bromophenoxy)benzoyl]glycidate (**34**): mp 85—85.5 °C (from hexane–$Et_2O$). Yield 85.0%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1745, 1685. NMR $\delta$: 1.36 (3H, t, $J=7$), 3.70 (1H, d, $J=2$), 4.32 (2H, q, $J=7$), 4.41 (1H, d, $J=2$), 6.91—7.22 (4H, m), 7.55 (2H, d, $J=9$), 8.08 (2H, d, $J=9$). *Anal.* Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86. Found: C, 55.07; H, 4.00.

Ethyl *trans*-3-[4-(4-Methylphenoxy)benzoyl]glycidate (**35**): Oil. Yield 60.9%. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1750, 1690. NMR $\delta$: 1.32 (3H, t, $J=7$), 2.38 (3H, s), 3.66 (1H, d, $J=2$), 4.36 (1H, d, $J=2$), 4.39 (2H, q, $J=7$), 6.85—7.30 (6H, m), 7.98 (2H, d, $J=9$). *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.80; H, 5.69.

Ethyl *trans*-3-[4-(4-Methoxyphenoxy)benzoyl]glycidate (**36**): Oil. Yield 53.8%. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1750, 1690. NMR $\delta$: 1.30 (3H, t, $J=7$), 3.64 (1H, d, $J=2$), 3.85 (3H, s), 4.26 (2H, q, $J=7$), 4.33 (1H, d, $J=2$), 6.86—8.63 (8H, m). *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.50; H, 5.45.

Ethyl *trans*-3-[4-(4-Isopropylphenoxy)benzoy]glycidate (**37**): Oil. Yield 50.3%. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1750, 1685. NMR $\delta$: 1.28 (6H, d, $J=7$), 1.34 (3H, t, $J=7$), 2.97 (1H, m), 3.70 (1H, d, $J=2$), 4.33 (2H, q, $J=7$), 4.42 (1H, d, $J=2$), 6.95—7.41 (6H, m), 8.06 (2H, d, $J=9$). *Anal.* Calcd for $C_{12}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.17; H, 6.34.

Ethyl *trans*-3-[4-(4-Chlorobenzyloxy)benzoy]glycidate (**41**): mp 92—93.5 °C (from hexane–$Et_2O$). Yield 31.2%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1750, 1670. NMR $\delta$: 1.32 (3H, t, $J=7$), 3.66 (1H, d, $J=2$), 4.29 (2H, q, $J=7$), 4.35 (1H, d, $J=2$), 5.10 (2H, s), 7.04 (2H, d, $J=9$), 7.36 (4H, s), 8.02 (2H, d, $J=9$). *Anal.* Calcd for $C_{19}H_{17}ClO_5$: C, 63.25; H, 4.75. Found: C, 62.97; H, 4.85.

**Method B**——A typical example is given to illustrate the general procedure.

Sodium *trans*-3-(4-Phenoxybenzoyl)glycidate (**21**), *cis*-3-(4-Phenoxybenzoyl)glycidic Acid and *trans*-3-(4-phenoxybenzoyl)glycidic Acid (**20**): A mixture of **8** (3.12 g), 15% aqueous $NaHCO_3$ solution (5.6 ml) and EtOH (50 ml) was refluxed for 2 h. After cooling of the mixture, $Et_2O$ (100 ml) was added. The precipitate was filtered off, washed with $Et_2O$, dried and recrystallized from EtOH to give **21** (2.45 g, 80%), mp 130—133 °C (dec.). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1680, 1632. NMR ($D_2O$) $\delta$: 3.55 (1H, d, $J=2$), 4.50 (1H, d, $J=2$), 6.70—7.60 (7H, m), 8.10 (2H, d, $J=9$). *Anal.* Calcd for $C_{16}H_{11}O_5Na$: C, 62.75; H, 3.62. Found: C, 62.54; H, 3.87. The filtrate was extracted with saturated $NaHCO_3$ solution. The aqueous layer was acidified with 10% HCl and extracted with AcOEt. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was recrystallized from hexane–$Et_2O$ to give colorless needles (*cis*-3-(4-phenoxybenzoyl)glycidic acid) (0.12 g, 5.0%), mp 120—123 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1760, 1737. NMR $\delta$: 3.94 (1H, d, $J=5$), 4.38 (1H, d, $J=5$), 6.95—7.70 (7H, m), 8.08 (2H, d, $J=9$), 8.95 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.44; H, 4.53. A solution of **21** (2.45 g) in $H_2O$ (30 ml) was acidified with 10% HCl, and extracted with AcOEt. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using hexane–acetone (10 : 1, v/v) as an eluent to give **20** as a colorless oil (2.20 g, 97%). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1755, 1700. NMR $\delta$: 3.72 (1H, d, $J=2$), 4.46 (1H, d, $J=2$), 6.99—7.65 (7H, m), 8.10 (2H, d, $J=9$), 9.00 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.26; H, 4.45.

The following compounds were similarly prepared.

*trans*-3-[4-(4-Chlorophenoxy)benzoyl]glycidic Acid (**38**): mp 155—157 °C (from hexane–$Et_2O$). Yield 79.8%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1725, 1685. NMR $\delta$: 3.76 (1H, d, $J=2$), 4.47 (1H, d, $J=2$), 6.96 (2H, d, $J=9$), 7.25—7.45 (4H, m), 7.98 (2H, d, $J=9$), 9.00 (1H, br s). *Anal.* Calcd for $C_{16}H_{11}ClO_5$: C, 60.30; H, 3.48. Found: C, 60.24; H, 3.68.

*cis*-3-[4-(4-Chlorophenoxy)benzoyl]glycidic Acid (**46**): mp 148—152 °C (from hexane–acetone). Yield 4.1%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1765, 1743. NMR ($d_6$-acetone) $\delta$: 3.88 (1H, d, $J=5$), 4.44 (1H, d, $J=5$), 7.12 (2H, d, $J=9$), 7.17 (2H, d, $J=9$), 7.52 (1H, d, $J=9$), 8.16 (2H, d, $J=9$), 9.78 (1H, br s). *Anal.* Calcd for $C_{16}H_{11}ClO_5$: C, 60.30; H, 3.48. Found: C, 60.21; H, 3.71.

*trans*-3[4-(4-Bromophenoxy)benzoy]glycidic Acid (**39**): mp 148—151 °C (from hexane–$Et_2O$). Yield 80.7%. IR

$\nu_{max}^{KBr}$ $cm^{-1}$: 1725, 1680. NMR ($d_6$-acetone) $\delta$: 3.63 (1H, d, $J$=2), 4.56 (1H, d, $J$=2), 7.11 (2H, d, $J$=9), 7.62 (2H, d, $J$=9), 8.15 (2H, d, $J$=9), 10.75 (1H, br s). *Anal.* Calcd for $C_{16}H_{11}BrO_5$: C, 52.92; H, 3.04. Found: C, 52.65; H, 3.24.

*trans*-3-(Benzyloxybenzoyl)glycidic Acid (**40**): mp 123—127 °C (from hexane–acetone). Yield 85.6%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1750, 1650. NMR ($d_6$-acetone) $\delta$: 3.63 (1H, d, $J$=2), 4.55 (1H, d, $J$=2), 5.25 (2H, s), 7.02 (2H, d, $J$=9), 7.39 (5H, s), 7.40 (1H, br s), 8.02 (2H, d, $J$=9). *Anal.* Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.25; H, 4.93.

*trans*-3-[4-(4-Chlorobenzyloxy)benzoyl]glycidic Acid (**42**): mp 138—142 °C (from hexane–acetone). Yield 93.8%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730, 1630. NMR ($d_6$-acetone) $\delta$: 3.63 (1H, d, $J$=2), 4.65 (1H, d, $J$=2), 5.25 (2H, s), 7.04 (2H, d, $J$=9), 7.37 (4H, s), 7.40 (1H, br s), 8.02 (2H, d, $J$=9). *Anal.* Calcd for $C_{17}H_{13}ClO_5$: C, 61.37; H, 3.74. Found: C, 61.38; H, 4.09.

**Method C**——A typical example is given to illustrate the general procedure.

Methyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**22**): A mixture of **8** (3.12 g), MeOH (3 ml), benzene (30 ml) and a few drops of conc. $H_2SO_4$ was refluxed for 5 h. The mixture was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using hexane–acetone (10 : 1, v/v) as an eluent to give **22** as an oil (2.20 g, 73.8%). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1747, 1682. NMR $\delta$: 3.66 (1H, d, $J$=2), 3.80 (3H, s), 4.38 (1H, d, $J$=2), 6.90—7.50 (7H, m), 8.05 (2H, d, $J$=9). *Anal.* Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.15; H, 4.82.

The following compounds were similarly prepared.

Isopropyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**23**): Oil. Yield 89.3%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1740, 1682. NMR $\delta$: 1.30 (6H, d, $J$=6), 3.67 (1H, d, $J$=2), 4.36 (1H, d, $J$=2), 5.14 (1H, m), 6.90—7.50 (7H, m), 8.04 (2H, d, $J$=9). *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.70; H, 5.69.

*n*-Pentyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**24**): Oil. Yield 92.1%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1764, 1682. NMR $\delta$: 0.60—1.90 (9H, m), 3.64 (1H, d, $J$=2), 4.27 (2H, t, $J$=6), 4.41 (1H, d, $J$=2), 7.00—7.53 (7H, m), 8.10 (2H, d, $J$=9). *Anal.* Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.89; H, 6.37.

Cyclopentyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**28**): Oil. Yield 88.1%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1740, 1680. NMR $\delta$: 1.30—2.10 (8H, m), 3.64 (1H, d, $J$=2), 4.36 (1H, d, $J$=2), 5.36 (1H, m), 6.90—7.50 (7H, m), 8.04 (2H, d, $J$=9). *Anal.* Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found; C, 71.31; H, 5.94.

Benzyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**29**): Oil. Yield 93.9%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1742, 1680. NMR $\delta$: 3.73 (1H, d, $J$=2), 4.40 (1H, d, $J$=2), 5.26 (2H, s), 6.90—8.10 (14H, m). *Anal.* Calcd for $C_{23}H_{18}O_5$: C, 73.78; H, 4.85. Found: C, 73.74; H, 4.98.

**Method D**——A typical example is given to illustrate the general procedure.

Allyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**25**): Allyl chloride (4.24 g) and **21** (3.06 g) were dissolved in DMF (30 ml), then heated to 90 °C under stirring for 1 h. After cooling, the mixture was poured into $H_2O$ and extracted with $Et_2O$. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using hexane–acetone (20 : 1, v/v) as the eluent to give **25** as an oil (2.27 g, 70.1%). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1745, 1680. NMR $\delta$: 3.75 (1H, d, $J$=2), 4.45 (1H, d, $J$=2), 5.42 (2H, m), 5.95 (1H, m), 7.00—7.45 (7H, m), 8.10 (2H, d, $J$=9). *Anal.* Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.18; H, 5.03.

The following compounds were similarly prepared.

Propargyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**26**): mp 100—101 °C (from hexane–acetone). Yield 59.5%. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2120, 1755, 1690. NMR $\delta$: 2.58 (1H, t, $J$=3), 3.77 (1H, d, $J$=2), 4.46 (1H, d, $J$=2), 4.86 (2H, d, $J$=3), 7.00—7.52 (7H, m), 8.08 (2H, d, $J$=9). *Anal.* Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.62; H, 4.62.

2-Isopentenyl *trans*-3-(4-Phenoxybenzoyl)glycidate (**27**): Oil. Yield 71.9%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1745, 1683. NMR $\delta$: 1.76 (6H, br s), 3.70 (1H, d, $J$=2), 4.38 (1H, d, $J$=2), 4.74 (2H, d, $J$=7), 5.42 (1H, t, $J$=7), 6.90—7.50 (7H, m), 8.10 (2H, d, $J$=9). *Anal.* Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.37; H, 5.78.

**Method E**——*trans*- and *cis*-3-[4-(4-Chlorophenoxy)benzoyl]glycidic Acid (**38** and **46**): A 30% $H_2O_2$ solution (50 ml) was added dropwise to a stirred and ice-cooled mixture of *trans*-3-[4-(4-chlorophenoxy)benzoyl]acrylic acid[7] (30.0 g), acetone (400 ml), MeOH (150 ml) and 8% NaOH (110 ml). The stirring was continued at room temperature for 1 h and at 45 °C for an additional 1 h. Acetone was removed under reduced pressure at room temperature, then the residue was poured into ice-water. The mixture was acidified with 10% HCl and extracted with $Et_2O$. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was recrystallized from hexane–acetone to give **38** (16.1 g, 50.9%). The filtrate was concentrated and recrystallized from hexane–acetone to give **46** (1.2 g, 3.8%).

**Preparation of the Diphenylethers**——A typical example is given to illustrate the general procedure.

4-Chlorodiphenylether: A mixture of sodium *p*-chlorophenoxide (117 g), bromobenzene (163 g), $CuCl_2$ (10 g) and pyridine (500 ml) was refluxed for 10 h. Pyridine was removed under reduced pressure. A solution of NaOH (18 g) in $H_2O$ (300 ml) was added to the residue, and the mixture was extracted with hexane. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated, followed by fractional distillation to afford a colorless oil (134 g, 84.0%), bp 150 °C (8 mmHg).

The following compounds were similarly prepared. 3-Chlorodiphenylether; bp 110 °C (1.5 mmHg), 73.0%. 2-Chlorodiphenylether; oil, 43.2%. 3,4-Dichlorodiphenylether; bp 150 °C (3 mmHg) [lit.[8] bp 160—163 °C (7 mmHg)], 23.4%. 4-Methyldiphenylether; bp 131 °C (8 mmHg) [lit.[9] bp 110—111 °C (2 mmHg)], 57.9%. 4-Methoxydiphenylether; oil [lit.[10] bp 168—170 °C (15 mmHg)], 50.0%. 4-Isopropyldiphenylether; bp 150 °C (11 mmHg) [lit.[9] bp 150 °C (7 mmHg)], 64.6%. 3-Acethyldiphenylether; oil, 48.3%. 2-Acethyldiphenylether; oil [lit.[11] bp 132—138 °C

(3 mmHg)], 19.1%.

α-Haloacetophenone were prepared by methods F and G.

**Method F**——A typical example is given to illustrate the general procedure.

4-Phenoxyphenacyl chloride;[12] Chloroacetyl chloride (13.3 g) was added to a stirred and ice-cooled solution of diphenylether (20.0 g) and $AlCl_3$ (15.7 g) in $CS_2$ (118 ml). After being stirred at room temperature for 6 h, the mixture was poured into ice-water, and the whole was acidified with conc. HCl and extracted with AcOEt. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was recrystallized from hexane–acetone to give colorless needles (17.4 g, 60.0%), mp 53—54 °C (lit.[12] mp 56—57 °C).

The following compounds were similarly prepared.

4-(4-Chlorophenoxy)phenacyl chloride; mp 73—75 °C (from hexane–acetone), 70.0%. 4-(3-Chlorophenoxy)-phenacyl chloride;[13] oil. 67.0%. 4-(2-Chlorophenoxy)phenacyl chloride;[13] oil. 50.2%. 4-(3,4-Dichlorophenoxy)-phenacyl chloride; mp 82.5—83 °C (from hexane–acetone) 75.1%. 4-(4-Bromophenoxy)phenacyl chloride; mp 61—62.6 °C (from hexane–acetone), 85.2%. 4-(4-Methylphenoxy)phenacyl chloride; mp 60—61.5 °C (from hexane–acetone), 45.8%. 4-(4-Methoxyphenoxy)phenacyl chloride; oil, 59.0%. 4-(4-Isopropylphenoxy)phenacyl chloride; oil, 48.8%.

**Method G**——A typical example is given to illustrate the general procedure.

2-Phenoxyphenacyl Bromide: Bromine (5.00 g) was added to a stirred and ice-cooled solution of 2-phenoxyacet-ophenone (5.90 g) in AcOH (15.0 ml). After being stirred for 30 min at room temperature, the mixture was poured into ice-water and extracted with AcOEt. The extract was washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using hexane–acetone (10 : 1, v/v) as the eluent to give a colorless oil (7.70 g, 95.2%).

The following compounds were similarly prepared.

3-Phenoxyphenacyl bromide;[14] oil. 79.0%. 4-Benzyloxyphenacyl bromide; mp 89—91.5 °C (from hexane–$Et_2O$) (lit.[15] mp 83—84 °C), 52.2%. 4-Phenethyloxyphenacyl bromide; oil, 57.7%. 4-(4-Chlorobenzoyl)phenacyl bromide; mp 106.5—107 °C (from hexane–$Et_2O$), 65.5%.

Ethyl *trans*-3-(4-Phenoxy)phenyl Glycidate (**43**): A portion of 60% NaH (1.40 g) was added to a stirred solution of 4-phenoxybenzaldehyde (5.27 g) and ethyl bromoacetate (5.90 g) in DMF (40 ml), and the mixture was stirred for 30 min at room temperature, then washed with $H_2O$, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel using hexane–$Et_2O$ (5 : 1) as an eluent to give **43** as an oil (2.64 g, 34.9%). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1745. NMR $\delta$: 1.31 (3H, t, $J$=7), 3.48 (1H, d, $J$=2), 4.04 (1H, d, $J$=2), 4.25 (2H, q, $J$=7), 6.80—7.50 (9H, m). *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.82; H, 5.84.

## References and Notes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