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Psychotropic Agents. IV.[1] Syntheses of β-Phenyl-γ-butyrolactone Derivatives

MAKOTO SATO,* AKIRA KOSASAYAMA and FUMIHIKO UCHIMARU

Research Institute, Daiichi Seiyaku Co., Ltd., 16-13, Kitakasai 1-chome, Edogawa-ku, Tokyo, 134, Japan

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β-Phenyl-γ-butyrolactones (IIIa—j) bearing several substituents on the phenyl ring were synthesized. Deamination of 4-amino-3-(2,4,6-trimethylphenyl)butyric acid (IV) with nitrous acid gave rearranged compounds, β-(2,4,6-trimethylbenzyl)-β-propiolactone (V) and 3-hydroxy-4-(2,4,6-trimethylphenyl)butyric acid (VI) together with the required β-(2,4,6-trimethylphenyl)-γ-butyrolactone (IIIj). Reaction of 2-phenyloxirane derivatives (IXh—j) with sodium diethylmalonate was found to be a convenient method for the preparation of β-phenyl-γ-butyrolactones (IIIh—j) substituted with electron-donating group on the phenyl ring.

Keywords——β-phenyl-γ-butyrolactones; β-propiolactone derivative; butenolides; 2-phenyloxiranes; deamination; rearrangement

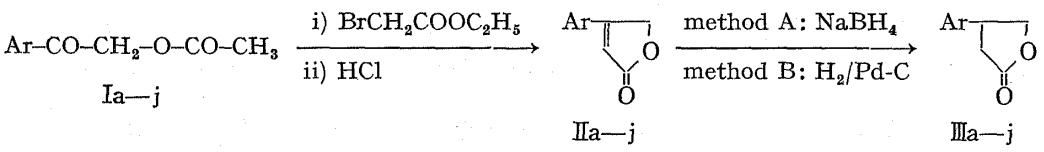
γ-Aminobutyric acid (GABA) and γ-hydroxybutyric acid (GHB), a normal brain metabolite, have been widely studied because of their neuropharmacological properties.[2,3a] It is known that their activities on the central nervous system occur at relatively high doses because of their restricted distribution in the central nervous system.[3] Our own research in this field led us to synthesize β-phenyl-γ-butyrolactones substituted with several substituents on the phenyl ring in order to obtain a much greater permeability through the blood-brain barrier.

In this paper we report syntheses of β-phenyl-γ-butyrolactones (IIIa—j) and a new rearrangement reaction of 4-amino-3-(2,4,6-trimethylphenyl)butyric acid (IV)[4] to β-(2,4,6-trimethylbenzyl)-β-propiolactone (V) observed in the deamination reaction of IV with nitrous acid.

In the first place β-phenyl-γ-butyrolactone derivatives (IIIe—i) were prepared in good yields by the Reformatsky reaction of ω-acetoxyacetophenones (Ie—i) according to the modified method of Linville *et al.*[5] followed by catalytic hydrogenation of the resulting $\Delta^{\alpha,\beta}$-butenolide derivatives (IIe—i), (Method B). Catalytic hydrogenation of IIa—d was not successful because of the formation of the dehalogenated compound (IIIe), but hydrogenation of IIa—d with $NaBH_4$ gave the desired γ-butyrolactone derivatives (IIIa—d) in good yields (Method A). The physical data for IIIa—i are listed in Table I. The yield of β-(2,4,6-trimethylphenyl)-$\Delta^{\alpha,\beta}$-butenolide (IIj) was extremely low in the Reformatsky reaction of ω-acetoxy-2,4,6-trimethylacetophenone (Ij), and β-(2,4,6-trimethylphenyl)-γ-butyrolactone (IIIj) could not be obtained by this method. The poor yield of IIj may be due to the steric effect of the *ortho*-substituents on the phenyl ring of Ij. The results of alternative approaches to the synthesis of IIIj are described below.

We attempted the deamination of 4-amino-3-(2,4,6-trimethylphenyl)butyric acid (IV)[4] with nitrous acid in 20% sulfuric acid for the purpose of obtaining IIIj according to the method of Genge *et al.*[6] Contrary to our expectation, the yield of IIIj was poor, and 3-hydroxy-4-(2,4,6-trimethylphenyl)butyric acid (VI) was obtained as a main product after treatment with 5% $NaHCO_3$ solution. The structure of VI was deduced from the molecular formula $C_{13}H_{18}O_3$ (mass spectrum and elemental analysis), the infrared (IR) spectrum, which was indicative of the presence of hydroxyl (3235 cm^{-1}) and carboxyl (1710 and 2650—2900 cm^{-1}) groups and also the nuclear magnetic resonance (NMR) spectrum, showing the presence of the methylene

Table I. Physical Data for γ-Butyrolactone Derivatives (IIIa—i)



No.	Ar	Method	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Br	Cl
IIIa	*p*-Br–C_6H_4–	A	69	78—78.5	Et_2O–Hx	$C_{10}H_9BrO_2$	49.82 (49.77	3.76 3.66	33.14 33.41)	
IIIb	*o*-Br–C_6H_4–	A	24	61—61.5	Et_2O–Pt E	$C_{10}H_9BrO_2$	49.82 (50.15	3.76 3.79	33.14 33.30)	
IIIc	*p*-Cl–C_6H_4–	A	95	53.5—55	Et_2O–Pt E	$C_{10}H_9ClO_2$	61.03 (61.23	4.60 4.53		18.02 18.29)
IIId	*o*-Cl–C_6H_4–	A	89	bp 144—155 (2 mmHg)	—	$C_{10}H_9ClO_2$	61.03 (61.14	4.60 4.55		18.02 17.91)
IIIe	C_6H_5–	B	96	47—48.5[b]	Et_2O–Pt E	$C_{10}H_{10}O_2$	74.05 (73.76	6.22 6.23)		
IIIf	*p*-C_6H_5–C_6H_4–	B	98	162.5—163.5	Ac	$C_{16}H_{14}O_2$	80.64 (80.83	5.92 5.80)		
IIIg	β-Naphtyl	B	77	117.5—118.5	Et_2O	$C_{14}H_{12}O_2$	79.22 (79.04	5.70 5.77)		
IIIh	*p*-CH_3–C_6H_4–	B	93	48.5—49.5	Et_2O–Pt E	$C_{11}H_{12}O_2$	74.97 (74.91	6.86 6.82)		
IIIi	*p*-$CH_3OC_6H_4$–	B	80	70.5—72.5	Et_2O–Pt E	$C_{11}H_{12}O_3$	68.73 (69.09	6.29 6.42)		
IIIj	Mesityl[c]									

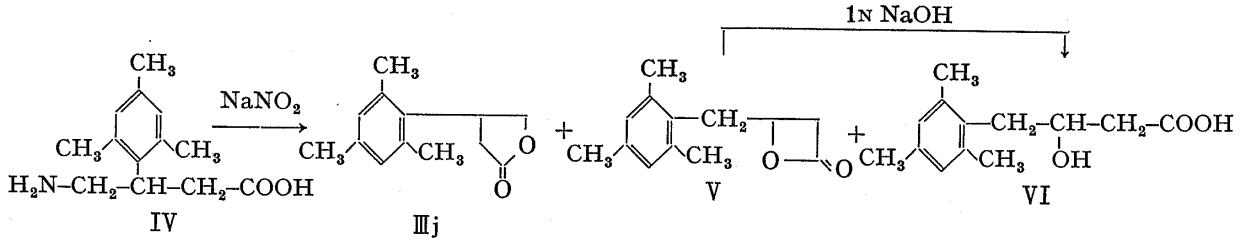
a) Et_2O, diethyl ether; Hx, hexane; Pt E, petroleum ether; Ac, acetone.
b) P.M.G. Bavin, D.P. Hansell and R.G.W. Spicketl, *J. Chem. Soc.*, **1964**, 4535. mp 47—48°C.
c) See "Experimental."

protons adjacent to the phenyl group [δ 2.60 (doublet, J=6.5 Hz)], methylene protons adjacent to the carboxyl [δ 2.88 (doublet, J=7.5 Hz)], and a methine proton neighboring the hydroxyl group [δ 4.0—4.5 (multiplet)]. When the methine proton (δ 4.0—4.5) was irradiated, the methylene protons (δ 2.06 and 2.88) were decoupled into two singlets. These NMR observations suggest the partial structure C–CH_2–CH–CH_2–C. On the basis of the above results, the product (VI) was presumed to be 3-hydroxy-4-(2,4,6-trimethylphenyl)butyric acid, and this was fully supported by the isolation of the intermediate of VI in the following experiment.

A modified deamination reaction reported by Genge *et al.*[6] was carried out, *i.e.*, when 4-amino-3-(2,4,6-trimethylphenyl)butyric acid hydrochloride (IV)[4] was treated with nitrous acid in 0.4 N AcOH solution, the desired β-(2,4,6-trimethylphenyl)-γ-butyrolactone (IIIj) (mp 74—74.5°C, 9.5%) was obtained together with two by-products, the compound VI (mp 121—125°C, 48%) mentioned above and a product (V) (mp 83—84°C, 11.4%). The structure of IIIj was supported by its elemental analysis and the spectral data [IR ν_{max}^{KBr} 1755 cm^{-1}: mass spectrum (MS) *m/e* 204 (M^+)]. The NMR spectrum of V showed three methyl groups [δ 2.27 (3H, singlet), 2.33 (6H, singlet)], a benzyl group [δ 3.16 (2H, doublet, J=6.5 Hz)], and ABX type proton signals on a β-propiolactone ring [δ 2.9—3.7 (2H, two double doublets, methylene protons) and δ 4.5—4.87 (1H, multiplet, methine proton)]. When the methine proton (δ 4.5—4.87) was irradiated, the signals at δ 3.16 and 2.9—3.7 were decoupled into a singlet and AB type quartet (J=17 Hz), respectively. The large geminal coupling constant[7] in the NMR spectrum and a carbonyl band at 1845 cm^{-1} in the IR spectrum supported the presence of the β-propiolactone moiety. The elemental analysis and the molecular weight (M^+ 204) provided an empirical formula of $C_{13}H_{16}O_2$. Hydrolysis of V with 1 N NaOH gave a hydroxy butyric

acid derivative (VI), whose IR spectrum was consistent with that of the sample obtained above. Consequently, the structure of V was determined as β-(2,4,6-trimethylbenzyl)-β-propiolactone. The formations of IIIj and V may well be accounted for by the intramolecular nucleophilic attack of the carboxylate ion on the phenonium ion (B) and the carbonium ions (A and C), as

Table II. Deamination of IV with Nitrous Acid



Experimental	Solvent	Products (%) IIIj	V	VI	Recovery of the starting material (IV·sulfate) (%)
Ex. 1[6]	20% H_2SO_4	1.5	Trace	16.8	43.3
Ex. 2	0.4 N CH_3COOH	9.5	11.4	48	—

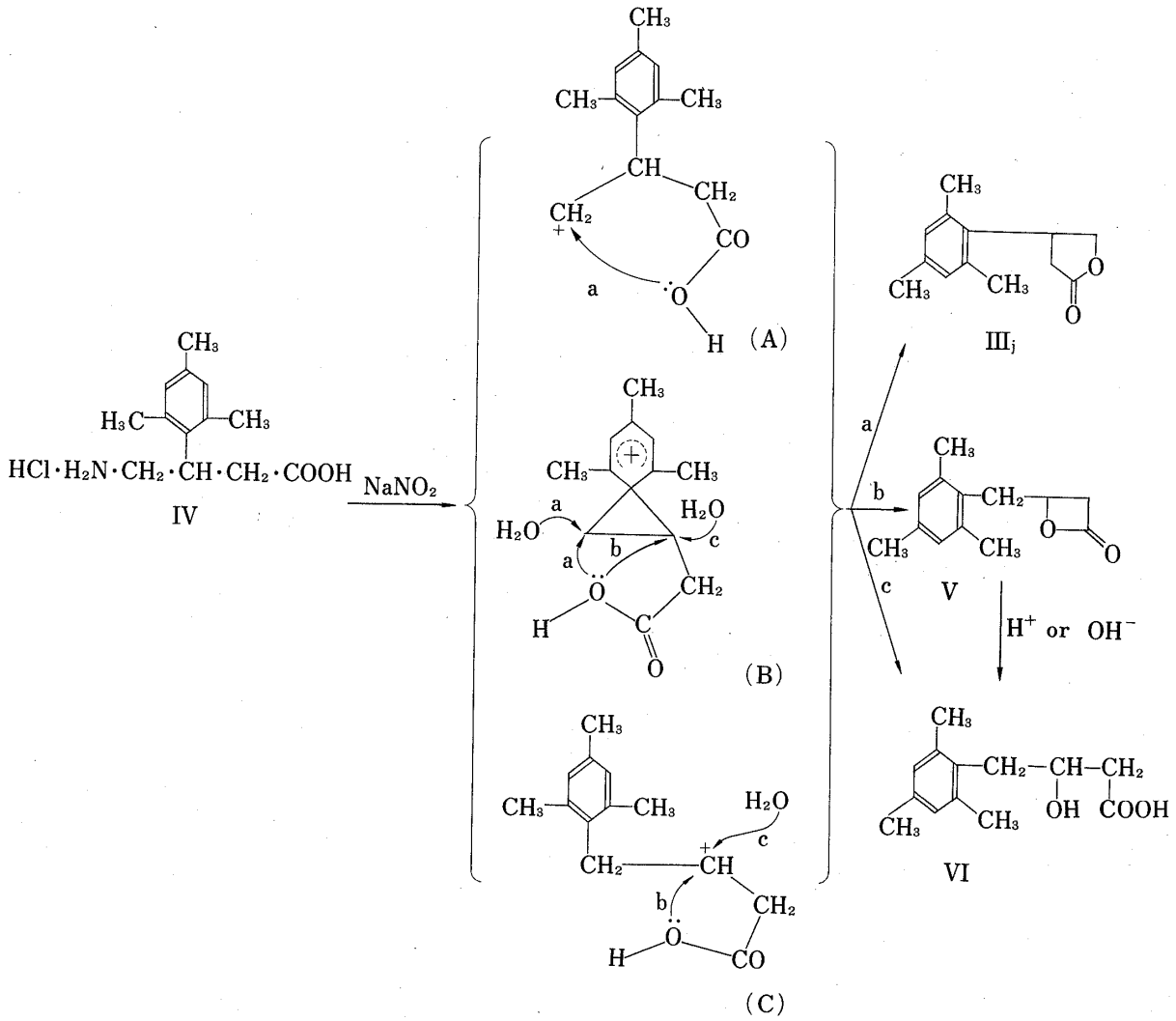


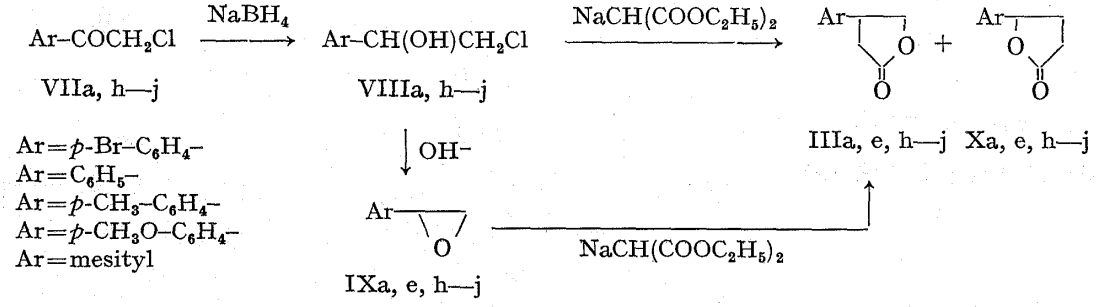
Chart 1

reported by Cram[8a] and Kirmse *et al.*[8b] Furthermore, the probable mechanisms of formation of VI were considered to be the nucleophilic attack of H_2O on the carbonium ion (A) and the phenonium ion (B) together with the hydrolysis of V (see Chart 1).

As the yield of the desired β-(2,4,6-trimethylphenyl)-γ-butyrolactone (IIIj) was extremely low in the above methods, we finally adopted the procedure reported by DePuy *et al.*[9] Reaction of 2-(2,4,6-trimethylphenyl)oxirane (IXj) with diethyl malonate gave IIIj (54%). Although gas–liquid chromatography of the crude reaction product suggested the presence of a small amount of γ-(2,4,6-trimethylphenyl)-γ-butyrolactone (Xj) in the ratio of IIIj: Xj = 97: 3, attempts to isolate the γ-isomer (Xj) from the reaction mixture were unsuccessful. The results were very different from those reported by DePuy *et al.*[9,10] It is interesting that the nucleophilic attack of diethyl malonate at the more hindered α-carbon atom of the oxirane ring of IXj is selective. This method was further adopted to obtain β-phenyl-γ-butyrolactones bearing several substituents on the phenyl ring, and the results are summarized in Table III. The starting materials (IXa, h—j) were obtained by $NaBH_4$ hydrogenation[11] of ω-chloroacetophenones (VIIa, h—j) followed by cyclization of the resulting chlorohydrin derivatives (VIIIa, h—j) with NaOH. In the ring-opening reaction of oxirane derivatives (IXa, e, h—j) with sodium diethylmalonate, the ratio of β-isomers (IIIa, e, h—j) and γ-isomers (Xa, e, h—j) was determined by gas–liquid chromatography; the data are listed in Table III. The β-isomers (IIIh—j) were easily isolated by one crystallization, although two isomers (IIIa and Xa) could not be separated by recrystallization. The separation of IIIa and Xa was achieved by recrystallization of the dicyclohexylamine salts of β- and γ-(4-bromophenyl)-γ-hydroxybutyric acid derived from the mixture of IIIa and Xa by alkaline hydrolysis, followed by cyclization of the separated β- and γ-aryl-γ-hydroxybutyric acids with dilute HCl.

γ-Butyrolactones (IIIi, j) were also obtained by reaction of chlorohydrins (VIIIi, j) with diethyl malonate by the use of two equivalent amounts of alkali under reaction conditions similar to those reported by DePuy *et al.*[9] As the ratio of the two isomers in the reaction

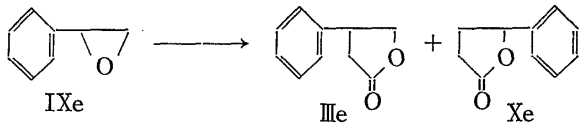
Table III. The Ratios of the Two Isomeric Lactones (III, X) in the Reaction of 2-Phenyloxirane Derivatives with Diethyl Malonate



	Starting material	Ratio of isomeric lactones		Retention time (min)[a]		Column temperature (°C)
		β-Isomer	γ-Isomer	β-Isomer	γ-Isomer	
IXa	p-Br-C_6H_4	IIIa 48	Xa 52	52	38	190
IXe	C_6H_5	IIIe 60	Xe 40	30	24	160
IXh	p-CH_3-C_6H_4	IIIh 71	Xh 29	37	32	160
IXi	p-CH_3O-C_6H_4	IIIi 89	Xi 11	65	57	180
VIIIi	p-CH_3O-C_6H_4-$CHCH_2Cl$ (OH)	IIIi 88	Xi 12			
IXj	Mesityl	IIIj 97	Xj 3	53	45	170
VIIIj	Mesityl-$CHCH_2Cl$ (OH)	IIIj 95	Xj 5			

a) Conditions of gas-liquid chromatography: column, 5% PEG succinate (2 m); carrier gas, N_2 at 40 ml/min.

TABLE IV. Solvent Effect in the Reaction of 2-Phenyloxirane with Diethyl Malonate



IXe IIIe Xe

Solvent	Ratio of the isomeric lactones	
	β-Isomer (IIIe)	γ-Isomer (Xe)
CH_3OH	68	32
C_2H_5OH	60	40
$CH_2(COOC_2H_5)_2$	34	66
$C_2H_5OC_2H_5$	18	82

was similar to that of the products in the ring-opening reaction of IXi, j with diethyl malonate, the intermediates of the reaction seemed to be 2-phenyloxirane derivatives (IXi, j). These results are similar to those of the reaction of 2-bromo-1-phenylethanol with sodium phenolate reported by Guss *et al.*[12] In the ring-opening reaction of 2-phenyloxirane with diethyl malonate, the ratio of the isomers (IIIe and Xe) was affected by the solvent used, and the results are shown in Table IV.

The data in Tables III and IV suggest that electron-donating groups on the phenyl ring of 2-phenyloxirane derivatives (IX) and polar solvents enhance the reactivity of the 2-position of 2-phenyloxiranes (IX) in the ring-opening reactions of IX. Accordingly, this procedure is a convenient method for the synthesis of β-phenyl-γ-butyrolactones bearing electron-donating groups on the phenyl ring, and these results are considered to be additional examples of the "modified S_{N2} reaction" in the ring-opening of oxiranes reported by Parker *et al.*[13]

Pharmacological studies of β-phenyl-γ-butyrolactones are in progress and the details will be published elsewhere.

Experimental

The following instruments were used. IR spectra, a Hitachi type EPI-G2 infrared spectrometer; NMR (tetramethylsilane as an internal standard), a Hitachi R-20B spectrometer (60 MHz) and a JEOL JNM-4H-100 spectrometer (100 MHz) (Japan Electron Optics Lab., Tokyo, Japan); mass spectra, a Hitachi RMS-4 mass spectrometer (direct inlet, at 70 eV); gas-liquid chromatography, a Hitachi gas chromatograph (K-53) with a hydrogen flame detector; melting points, a Yanagimoto melting point apparatus (Type MP-1). All melting points are uncorrected.

General Procedure for the Synthesis of β-Phenyl-γ-butyrolactone (IIIa—d) (Method A)——$NaBH_4$ (380 mg, 10 mmol) was added portionwise to a solution of butenolide (IIa—d) (5 mmol) in CH_3OH (200 ml), and the mixture was heated under reflux for 15 min. After cooling, the reaction mixture was acidified with 10% HCl (10 ml) and concentrated. To the residue was added 1 N NaOH (100 ml), and the mixture was stirred for 30 min at room temperature. The mixture was washed with $CHCl_3$ (100 ml), and the aqueous layer was acidified with 4 N HCl (60 ml) and stirred at 80°C for 30 min. The reaction mixture was extracted with benzene, and the extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was dissolved in benzene and passed through silica gel (20 g). The eluate was concentrated to give a colorless oil, which was recrystallized from a suitable solvent. The physical data for IIIa—d are listed in Table I.

General Procedure for the Synthesis of β-Phenyl-γ-butyrolactone (IIIe—i) (Method B)——A mixture of butenolide (IIe—ı) (0.2 mol) and 10% Pd-C (13 g) in AcOEt (200 ml) was subjected to catalytic hydrogenation at ordinary temperature and pressure. After the theoretical amount of H_2 had been absorbed, the catalyst and the solvent were removed. The residue was recrystallized from a suitable solvent. The physical data for IIIe—i are listed in Table I.

Deamination of 4-Amino-3-(2,4,6-trimethylphenyl)butyric Acid (IV)[4] with Nitrous Acid——(ex. 1) Deamination of IV according to the method of Genge *et al.*[6]: An ice-cooled solution of $NaNO_2$ (276 mg, 4 mmol) in H_2O (2 ml) was added to a suspension of IV (664 mg, 3 mmol) in 20% H_2SO_4 (4 ml) with stirring. Next, 20% H_2SO_4 (4 ml) was added, and then the mixture was extracted with Et_2O after heating on a water-

bath for 1 h. The aqueous layer was concentrated to recover colorless prisms of the starting material (IV-sulfate) (351 mg, 43.3%), mp 181—183°C. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). *Anal.* Calcd for $C_{13}H_{19}NO_2 \cdot 1/2H_2SO_4$: C, 57.76; H, 7.46; N, 5.18. Found: C, 57.58; H, 7.36; N, 5.19. The organic layer was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC on a silica gel plate developed in $CHCl_3$ to give colorless crystals of β-(2,4,6-trimethylphenyl)-γ-butyrolactone (IIIj) (9 mg, 1.5%) mp 74°C. IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O). MS *m/e*: 204 (M^+).

The 5% $NaHCO_3$ soluble fraction was acidified with dilute HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was recrystallized from Et_2O–hexane to afford colorless needles of 3-hydroxy-4-(2,4,6-trimethylphenyl)butyric acid (VI) (112 mg, 16.8%): mp 121—123°C. *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.01; H, 7.98. IR ν_{max}^{KBr} cm^{-1}: 3235 (OH), 2900—2650, 1710 (COOH). MS *m/e*: 222 (M^+). NMR (δ in $CDCl_3$): 2.27 (3H, s, *para* methyl), 2.34 (6H, s, *ortho* dimethyl), 2.60 (2H, d, J=6.5 Hz, $-C\underline{H}_2-C_6H_2(CH_3)_3$, 2.88 (2H, d, J=7.5 Hz, $-C\underline{H}_2COOH$), 4.0—4.5 (1H, m, $>C\underline{H}-OH$), 6.90 (2H, s, aromatic protons).

(ex. 2) Deamination of IV with Nitrous Acid in 0.4 N Acetic Acid: An ice-cooled solution of $NaNO_2$ (1.40 g, 20.3 mmol) was added dropwise to a solution of 4-amino-3-(2,4,6-trimethylphenyl)butyric acid hydrochloride (IV)[4] (3.30 g, 12.8 mmol) in 0.4 N CH_3COOH (125 ml) over a period of 5 min with stirring at 5°C, and the mixture was stirred for 30 min at 5°C then for another 30 min at 25°C. Then, the reaction mixture was heated on a water-bath for 90 min. After cooling, the mixture was extracted with Et_2O. The organic layer was washed with 10% Na_2CO_3 solution, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (30 g) using benzene–petroleum ether (5: 1) and benzene. The fraction eluted with benzene–petroleum ether (5: 1) was concentrated, and the residue was recrystallized from Et_2O–hexane to afford colorless crystals of β-(2,4,6-trimethylbenzyl)-β-propiolactone (V) (300 mg, 11.4%), mp 83—84°C. *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.29; H, 7.51. IR ν_{max}^{KBr} cm^{-1}: 1845 (C=O). MS *m/e*: 204 (M^+). NMR (δ in $CDCl_3$): 2.27 (3H, s, *para* methyl), 2.33 (6H, s, *ortho* dimethyl), 3.16 (2H, d, J=6.5 Hz, $(CH_3)_3C_6H_2-C\underline{H}_2$), 2.9—3.7 (2H, two dd, J=6, 17 Hz, $O-C\underline{H}-C\underline{H}_2-C=O$), 4.5—4.87 (1H, m, $-O-C\underline{H}-CH_2-C=O$), 6.9 (2H, s, $(CH_3)_3-C_6\underline{H}_2-$).

The fraction eluted with benzene was concentrated, and the residue was recrystallized from Et_2O–hexane to give colorless prisms of β-(2,4,6-trimethylphenyl)-γ-butyrolactone (IIIj) (250 mg, 9.5%), mp 74—74.5°C, which were identical with a sample prepared in (ex. 1) as judged by comparison of IR spectra. *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.23; H, 7.70.

The 10% Na_2CO_3 soluble fraction was acidified with dilute HCl and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated. The residue was recrystallized from Et_2O–hexane to give colorless needles of 3-hydroxy-4-(2,4,6-trimethylphenyl)butyric acid (VI) (1.25 g, 48%), mp 121—125°C, which were identical with a sample obtained in (ex. 1) as judged by comparison of IR spectra. *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.93; H, 7.90.

Hydrolysis of β-Propiolactone Derivative (V)——A mixture of (V) (51 mg, 0.25 mmol), 1 N NaOH (2 ml) and EtOH (5 ml) was allowed to stand for 1 h at room temperature, then the ethanol was removed by distillation. The residue was acidified with dilute HCl and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was recrystallized from Et_2O–hexane to give colorless needles (49 mg, 88%), mp 122—123°C, which were identical with an authentic sample (VI) obtained as described above, as judged by comparison of IR spectra.

2-(4-Bromophenyl)oxirane (IXa)——Prepared by hydrogenation of VIIa (11.1 g, 0.04 mol) with $NaBH_4$ according to the procedure of Nash[11] followed by cyclization of the resulting 1-(4-bromophenyl)-2-chloroethanol with 4 N NaOH. Yield 5.36 g (67.8%), bp 82—91°C (2 mmHg).

2-(4-Methylphenyl)oxirane (IXh)——Prepared from VIIh (11.5 g, 0.086 mol) as described for IXa. Yield 5.54 g (47.1%), bp 60°C (1.5 mmHg).

2-(4-Methoxyphenyl)oxirane (IXi)——Prepared from VIIIi (9.23 g, 0.05 mol) as described for IXa. Yield 3.75 g (49.9%), bp 93—95°C (2 mmHg).

2-(2,4,6-Trimethylphenyl)oxirane (IXj)——Prepared from VIIj (9.9 g, 0.05 mol) as described for IXa. Yield 7.0 g (86.4%), bp 72—75°C (1 mmHg).

2-Chloro-1-(4-methoxyphenyl)ethanol (VIIIi)——$NaBH_4$ (15.7 g, 0.415 mol) was added portionwise to a cold (2°C) solution of 4-methoxyphenacyl chloride (30.87 g, 0.166 mol) in CH_3OH (2 l) over a period of 2 h with stirring. The reaction mixture was further stirred for 3 h at ice-bath temperature, neutralized with dilute HCl solution, concentrated *in vacuo* and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to give a pale yellow oil (29.8 g, 96.2%), which was used for the next step without further purification. IR ν_{max}^{neat} cm^{-1}: 3420 (OH).

2-Chloro-1-(2,4,6-trimethylphenyl)ethanol (VIIIj)——Prepared from VIIj (59 g, 0.3 mol) as described for VIIIi. Yield 58.2 g, (97.6%), a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 3420 (OH).

β-(2,4,6-Trimethylphenyl)-γ-butyrolactone (IIIj)——(ex. 1): Sodium metal (300 mg, 13 mmol) was dissolved in a solution of diethyl malonate (2.0 g, 12.5 mmol) in EtOH (10 ml). The reaction mixture was heated under reflux and 2-(2,4,6-trimethylphenyl)oxirane (IXj) (1.5 g, 9.3 mmol) was added over a period of 30 min with stirring. The solution was refluxed for 4 h, then cooled. Next, 17% KOH solution (5 ml) was added to the reaction mixture. It was allowed to stand overnight at room temperature, then concen-

trated, acidified with 35% H_2SO_4 (4 ml), refluxed for 10 min, and extracted with Et_2O. The extract was concentrated, and the residue was heated at 130°C for 1 h to give an oily product. The gas-liquid chromatographic data for the crude product are listed in Table III. The oily substance was purified by distillation, bp 142—147°C (0.05 mmHg). Yield 1.1 g (54%). The distillate crystallized as needles after standing for several hours. Recrystallization of the product from Et_2O–hexane gave colorless needles of IIIj (700 mg, mp 74—74.5°C), which was identified by comparison (mixed melting point test and IR spectra) with a sample synthesized by deamination of 4-amino-3-(2,4,6-trimethylphenyl)butyric acid (IV) according to the procedure of Genge *et al.*[6]

(ex. 2): Sodium metal (16.6 g, 0.72 mmol) was dissolved in a solution of diethyl malonate (57.66 g, 0.36 mol) and 2-chloro-1-(2,4,6-trimethylphenyl)ethanol (VIIIj) (58 g, 0.292 mol) in CH_3OH (700 ml) while the temperature was kept below 20°C by ice-cooling. The reaction mixture was stirred at room temperature for 22 h, then 17% KOH (150 ml) was added and the whole was refluxed for 1 h, and concentrated. The residue was acidified with 25% H_2SO_4 (150 ml) and the mixture was refluxed for 30 min. The reaction mixture was worked up as in (ex. 1). Yield 16.7 g (28.3%), mp 72.5—74°C.

β-(4-Methylphenyl)-γ-butyrolactone (IIIh)——Prepared from IXh (2.74 g, 0.02 mol) as described for IIIj. Recrystallization from Et_2O–petroleum ether gave 790 mg (22.4%) of colorless plates, mp 48.5—49.5°C, which were identified by comparison (mixed melting point test and IR spectra) with an authentic sample prepared by method B (see Table I).

β-(4-Methoxyphenyl)-γ-butyrolactone (IIIi)——(ex. 1): The title compound was prepared from IXi (3.75 g, 0.025 mol) as described for IIIj. Recrystallization from Et_2O–petroleum ether gave 1.2 g (25.3%) of colorless plates, mp 71—72.5°C, which were identified by comparison (mixed melting point test and IR spectra) with an authentic sample prepared by method B (see Table I).

(ex. 2): The title compound was prepared from VIIIi (109.8 g, 0.588 mol) as described for IIIj. Recrystallization from Et_2O gave 63.04 g (55.8%) of colorless plates, mp 70.5—72°C.

β-(4-Bromophenyl)-γ-butyrolactone (IIIa) and γ-(4-Bromophenyl)-γ-butyrolactone (Xa)——Prepared from IXa (13.74 g, 0.069 mol) as described for IIIj. Distillation of the crude product gave 11.87 g of a colorless oil, bp 135—137°C (0.02 mmHg). A mixture of the oily product and 1 N NaOH (100 ml) was heated at 100°C for 40 min. After cooling, the reaction mixture was washed with AcOEt, and the aqueous layer was neutralized with 1 N HCl and extracted with AcOEt. The organic layer was dried over Na_2SO_4, filtered, and dicyclohexylamine (10.9 g, 0.06 mol) was added to the filtrate. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from $CHCl_3$–petroleum ether to give 4.58 g of colorless powder, mp 157—158.5°C. *Anal.* Calcd for $C_{10}H_{11}BrO_3 \cdot C_{12}H_{23}N$: C, 60.01; H, 7.78; Br, 18.14. N, 3.18; Found: C, 60.29; H, 7.75; Br, 18.02.; N, 3.28 A mixture of the powdery product, CH_3OH (40 ml) and 10% HCl (100 ml) was heated on a water bath for 1 h, then the reaction mixture was concentrated and extracted with Et_2O. The extract was washed with water, dried over Na_2SO_4 and concentrated to afford a colorless oil. Recrystallization from Et_2O–hexane gave 1.94 g (11.7%) of colorless crystals (IIIa), mp 77—78.5°C, which were identified by comparison (IR spectra) with an authentic sample prepared by method A (see Table I).

The combined mother liquor of the dicyclohexylamine salt was concentrated, and the residue was recrystallized from $CHCl_3$–petroleum ether to afford 4.3 g of colorless powder, mp 140—142°C. The powdery product was worked up as described above for the preparation of IIIa to give the title compound (Xa) (530 mg, 3.2%), mp 81.5—82.5°C.[14] *Anal.* Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.14. Found: C, 49.80; H, 3.85; Br, 33.17. IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O).

β-Phenyl-γ-butyrolactone (IIIe) and γ-Phenyl-γ-butyrolactone (Xe)——Reaction of 2-phenyloxirane (IXe) with diethyl malonate according to the method of DePuy *et al.* was carried out in several solvents. The ratios of the two isomers (IIe and Xe) were determined by gas-liquid chromatography, and the data are summarized in Table IV.

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