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Lactone Carboxylic Acids. III. Reaction of Ethyl β-Alkylglycidates with Ethyl Malonate*

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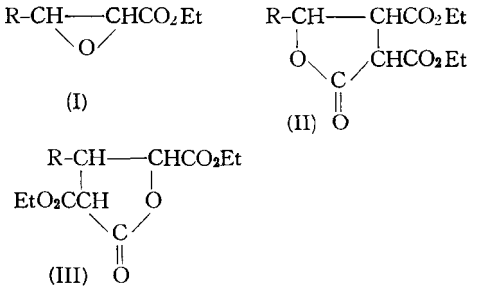
The ring opening of epoxide group in the reaction of ethyl β-alkylglycidates with sodiomalonate was observed mostly at the α-position of the glycidates. Ethyl β-ethylglycidate, however, on treatment with sodiomalonate gave ten percent of β-fission product, elucidated by NMR spectra. The reaction sequence provides a general preparative route to γ-alkylparaconic acids and their derivatives.

As to the orientation of ring opening of epoxide group in S_N2 reaction postulated by Parker[1] on ethyl β-alkylsubstituted glycidates, attack by nucleophilic reagents, i. e., ammonia[2], aniline[3–5], benzylamine[5], cyclohexylamine[5], and naphtylamine[5,6], has been shown to occur at β-position of the glycidates. On the other hand, there is a few evidences indicating that in the reaction of β, β-dialkylglycidates with sodiomalonates[7] or sodioacetoacetate[8], the epoxide ring opening occurs at the α-position. In a previous paper, we confirmed the α-attack by the carbanion of malonate[9]. Recently, Liwschitz[10] and Oh-hashi and Harada[11] reported that the reaction of sodium β-alkyl or β, β-dialkylglycidates with benzylamine took the alternative course to produce exclusively α-amino-β-hydroxy acids. Kaneko describes[12] that ammonia attacks the both sites of the oxiran ring. It seems that the latter results are incompatible with the manners of the reaction of ethyl β-substituted glycidates with amines[2–6]. In connection with the title reaction the condensation of ethyl β-tridecylglycidate with sodiomalonate has only been reported[13]. This paper describes the condensation of ethyl β-monoalkylglycidates (I) with sodiomalonate in ethanol and discusses the mode of the ring opening of epoxide group on the glycidates (I).

Results and Discussion

The synthesis of γ-alkyl-α, β-dicarbethoxybutyrolactones was carried out according to the previous paper[9] by the reaction of ethyl β-alkylglycidates with sodiomalonate (1 : 2 mole ratio). The structure of the reaction product may be expected to be II or III. In an effort to make these assignments, we attempted to hydrolyze the product to simpler derivatives.



As indicated in the flow sheet, the main product obtained was a neutral material (II or III) along with a small portion of an acidic one, in the ratio of fifteen to one. The structure of this acidic material (IV, R = C_6H_{13}) was proved by esterification with diazomethane to afford the lactone diesters (V, R = C_6H_{13}) and by decarboxylation at 230°C to give the lactone ester (VI, R = C_6H_{13}). The hydrolysis of the neutral portion derived from enanthaldehyde was carried out in 1 *N* alcoholic alkaline solution at room temperature to give a mixture of the acidic materials (IV and VII, R = C_6H_{13}) which was subject to decarboxylation to afford the lactone ester (VI, R = C_6H_{13}) and the lactone acid (VIII, R = C_6H_{13}).

The structure of the lactone acid (VIII, R = C_6H_{13}) was identical with the authentic specimen of γ-*n*-hexylparaconic acid prepared from the condensation of enanthaldehyde with sodium succinate by Fittig's method[14]. The infrared spectrum of the lactone ester (VI, R = C_6H_{13}) was

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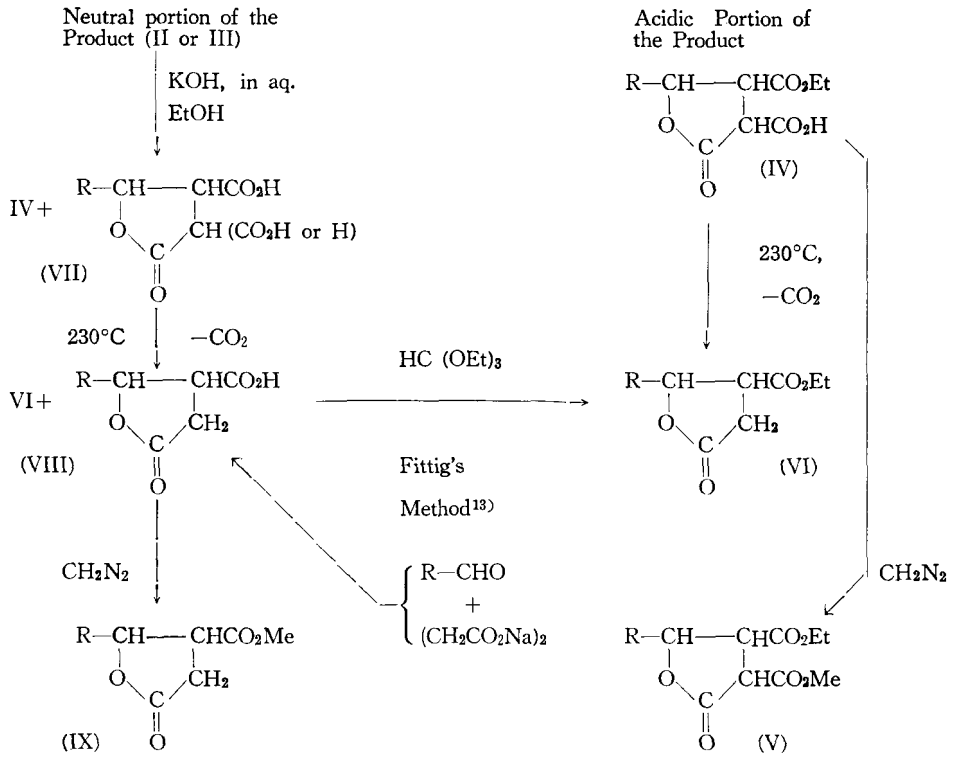
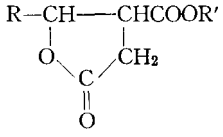


Table I. γ-Alkylpararaconic Acid Derivatives



Substituent		Yield	B. p. or m. p.	n_D^{20}	C, %		H, %	
R	R'	%	°C/mmHg		Found	Calcd.	Found	Calcd.
C_3H_7	C_2H_5	20	128—129/2	1.4502	59.98	59.76	8.05	8.23
C_6H_{13}	C_2H_5	28	145—146/1.5	1.4556	63.60	63.80	6.19	6.25
C_6H_{13}	CH_3	—	149/2	1.4534	63.14	63.14	8.83	8.85
C_6H_{13}	H	33	86 (lit.[14] m.p. 90) 178/1.5	—	—	—	—	—
C_9H_{19}	C_2H_5	18	154/3	1.4561	67.57	67.14	9.92	9.88
C_9H_{19}	H	27	95	—	65.60	65·47	9.44	9.54

Table II. Gas Chromatograph Data*)

Compounds		Column Temp., °C	Retention Time, min.
Ethyl	γ-*n*-Propylparaconate	195 (160)	4.5 (14.6)
Methyl	γ-*n*-Hexylparaconate	195	10.5
Ethyl	γ-*n*-Hexylparaconate	195	17.5
Ethyl	γ-*n*-Nonylparaconatc	220	50

*) The data were obtained with a Hitachi F6-D, Chromosorb W (NAW), Silicone SE-30, 1m long, 0.7 atm. N_2.

identical in every fine detail with that of ethyl γ-*n*-hexylparaconate which was further provided by the esterification of the authentic paraconic acid (VIII, R=C_6H_{13}) with ethyl orthoformate[15]. A number of the paraconic acids (VIII) and their esters (VI and IX), as shown in Table I, have been characterized by means of the IR spectra[9,16]. The volatile materials (VI and IX) have a single peak in gas chromatograph as shown in Table II. The typical IR spectra of II, IV, V, VI, VIII, and IX are shown in Figure 1.

On the other hand, if the two isomers (II and III) are present in the condensation products, the NMR peaks of the γ-methines of III may be expected to appear in a lower field than that of the γ-methines of II. The NMR spectra of A and B, as are given in Figure 2, showed the absorption due to γ-methine at 5.42—5.75τ (multiplet), and in the spectrum C the γ-methine peaks doubled with the absorption due to two methylene groups in the region of 5.5—6.1τ. The NMR spectra of A, B, and C, however, all show the absence of the peaks due to the γ-proton of the structure III, which would appear in the region of 5.0—5.5, whereas the γ-proton of the lactone diesters (III, R=C_2H_5) was measured as a doublet at 5.30 and 5.38τ, integrating for about a tenth proton. The former spectra reveal that the β-attack products (III) may be absent and the latter shows the presence of III mixed in II (about ten percent). From the above evidences the neutral lactone ester components (initially postulated II or III), prepared from alkanal higher than *n*-butanal, should have the structure II. A number of II obtained in this way are shown in Table III.

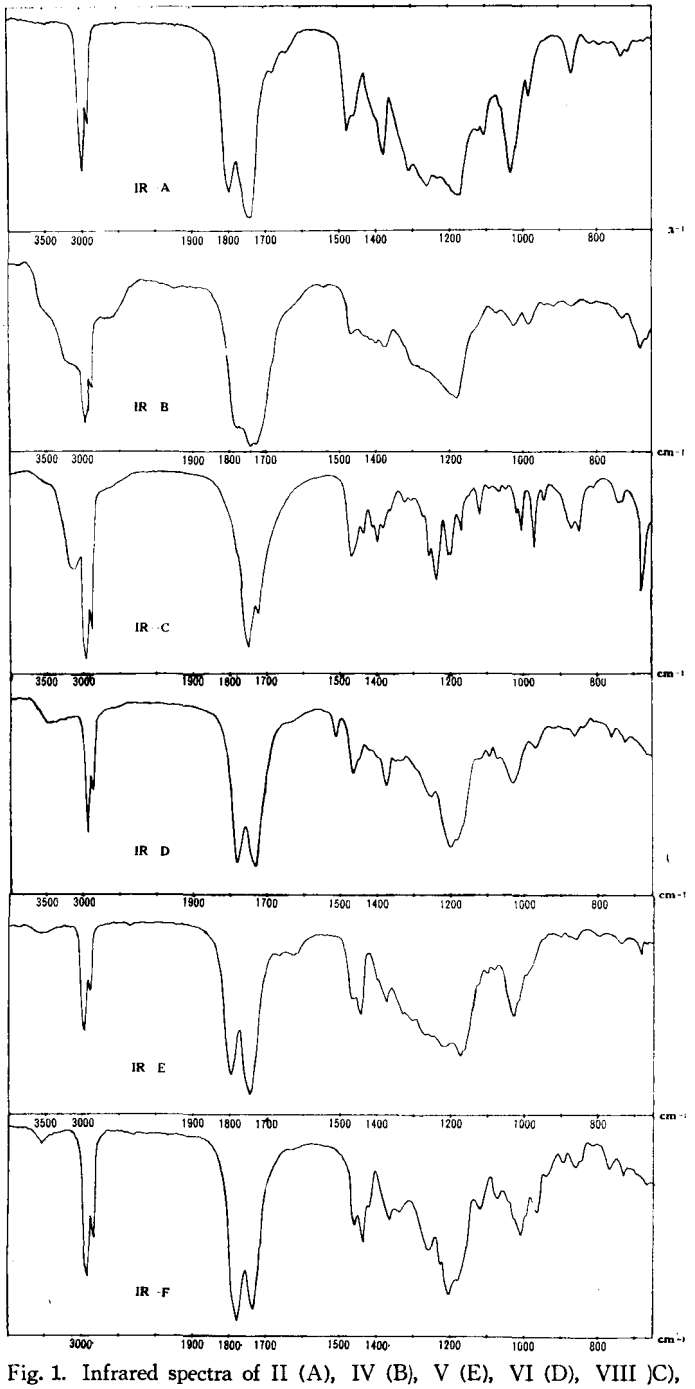


Fig. 1. Infrared spectra of II (A), IV (B), V (E), VI (D), VIII)C), and IX (F), (R=C_6H_{13}).

As is mentioned in the introduction part the butyrolactones (II) separated from the reaction of ethyl β-di(or mono)-alkylglycidates with sodiomalonate have been produced as the result of α-fission of the glycidates (I)[7,9,13]. Although the results of the present investigation are not sufficiently definitive to warrant extended comment of the mode of the ring opening of I, they do, however, suggest that the bulkiness of the substituents at the

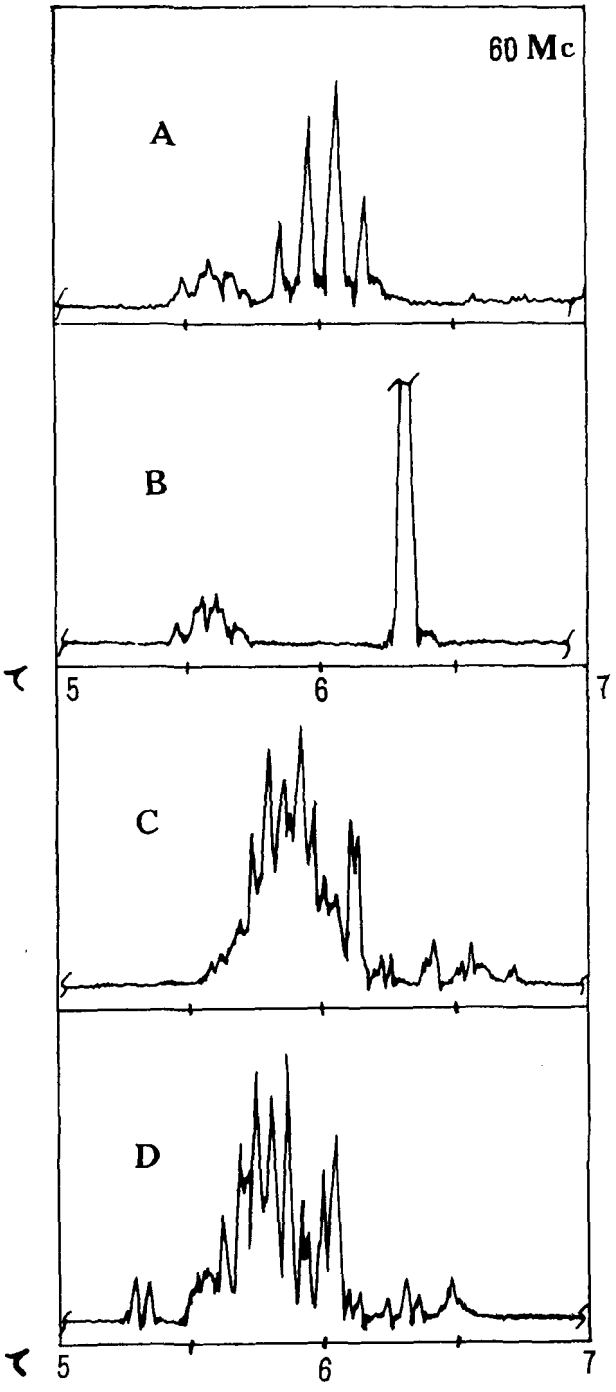


Fig. 2. NMR absorptions in the region of 5—7 τ in chloroform of ethyl γ-*n*-propylparaconate (A), methyl γ-*n*-hexylparaconate (B), γ-*n*-propyl-α, β-dicarbethoxybutyrolactone (C), and γ-ethyl-α, β-dicarbethoxybutyrolactone (D).

β-position of the glycidates may affect the course of the fission of the epoxides.

Experimental

All melting and boiling points are uncorrected.

NMR Spectra. — The spectra were taken with both a JNM-C-60 and a Hitachi H-60 high-resolution NMR spectrometers working at 60 Mc in chloroform, using tetramethylsilane as an internal reference.

Reaction of Ethyl β-Hexylglycidate with Diethyl Malonate. — A mixture of 6.8 g. (0.10 mole) of sodium ethoxide, 17.6 g. (0.11 mole) of diethyl malonate in 30 ml. of anhydrous ethanol, and 10.0 g. (0.05 mole) of ethyl β-hexylglycidate (lit[17]. b. p. 122—123°C/7 mmHg) was refluxed for 30 hr. The mixture was acidified and taken up in ether. The ether layer was washed with a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated. Distillation of the residue yielded 11.4 g. (73% based on the glycidate) or γ-hexyl-α, β-dicarbethoxybutyrolactone (II, R = C_6H_{13}), b. p. 179—180°/2 mmHg, IR: 1795 (lactone ν C=O) and 1742 cm^{-1} (ester ν C = O). Other lactone diesters (II) prepared similarly are shown in Table I.

The alkaline extracts were acidified to pH 7—6.5 and extracted with ether. The ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo. There was obtained 0.7 g. (5%) of an acidic material. IR: 1789 (lactone ν C = O) and 1740 cm^{-1} (ester ν C = O). This unstable acidic material (IV, R = C_6H_{13}), after esterification with diazomethane, was converted into the corresponding γ-*n*-hexyl-β-carbethoxy-α-carbomethoxybutyrolactone (V, R = C_6H_{13}), b. p. 153.5°C/2 mmHg, n_D^{20} 1.4776. IR: 1790 (lactone ν C=O) and 1741 cm^{-1} (ester ν C=O). Found: C, 59.86; H, 7.93. Calcd. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05.

Similarly, γ-*n*-propyl-β-carbethoxy-α-carbomethoxybutyrolatone boiled at 137—138°C/2 mmHg. Found: C, 55.77; H, 7.10. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02%.

γ-*n*-Nonyl-β-carbethoxy α-carbomethoxybutyrolactone boiled at 151°C/2 mmHg. Found: C,

Table III. γ-Alkyl-α, β-dicarbethoxybutyrolactones (II)

Substituent	B. p.	n_D^{20}	Yield	C, %		H, %	
R	°C/mmHg		%	Found	Calcd.	Found	Calcd.
C_2H_5	145/3*)	1.4481	78	55.80	56.07	7.03	6.94
n-C_3H_7	162/2	1.4490	77	57.34	57.46	7.40	7.38
n-C_6H_{13}	179-180/2	1.4510	72	61.15	61.45	8.26	8.13
n-C_9H_{19}	190-198/2	1.4540	71	64.02	64.18	9.05	9.20

*) This compound is a mixture of II and III in the ratio of nine to one.

63.09; H, 8.62. Calcd. for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83%.

Hydrolysis of the Lactone Diesters (II, R = C_6H_{13}) with 1*N* Alcoholic Potassium Hydroxide Solution. — A mixture of 12.5 ml. of 1*N* potassium hydroxide solution and 1.0 g. (0.003 mole) of II (R = C_6H_{13}) was stirred for 10 hr. at room temperature and then acidified to pH 7—6.5 with dilute sulfuric acid. The reaction mixture was extracted with ether and washed with water. Then, the ethereal solution was extracted with sodium bicarbonate solution. The alkaline extracts were neutralized with dilute sulfuric acid. The organic layer was extracted with ether, washed with water, and dried over anhydrous sodium sulfate. The products obtained on evaporation of the ethereal solution were heated to 230°. During this treatment evolution of carbon dioxide was observed. After the decarboxylation subsided, the reaction mixture was cooled to room temperature. From the ethereal solution of the mixture, acidic material was removed with sodium bicarbonate solution. The residual ethereal layer was washed with water, dried and evaporated. On distillation of the crude neutral material, there was obtained 0.25 g. (28%) of ethyl γ-*n*-hexylparaconate (VI, R = C_6H_{13}), b. p. 145—146°C/1.5 mmHg, which was identified with the authentic specimen prepared from Fittig's method[14].

The alkaline extracts were neutralized, and the product was taken up in ether. On evaporation of the solvent, there was obtained 0.3 g. (33%) of γ-*n*-hexylparaconic acid (VIII, R = C_6H_{13}), m. p. 86°C. The results of melting point, IR, and NMR agreed well with those of the authentic sample[14]. This γ-*n*-hexylparaconic acid treated with diazomethane was converted into methyl γ-*n*-hexylparaconate, b. p. 149°C/2 mmHg, n_D^{20} 1.4534, in quantitative yield. IR: 1782 (lactone ν C=O) and 1736 cm^{-1} (ester ν C=O). Microanalyses along with physical constants are listed in Table I.

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