Lactone Carboxylic Acids. I. Synthesis of α, γ-Substituted Paraconic Acids

Akira TAKEDA and Sigeru TORII

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama

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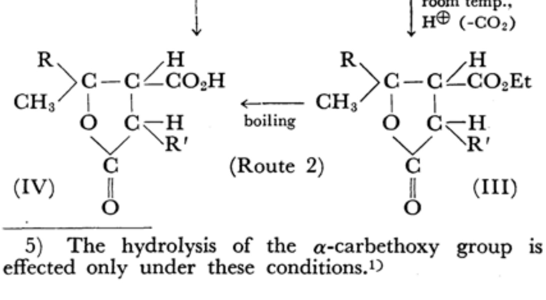
In a recent investigation¹⁾ we have reported that an *O*-acetyl compound is isolated when γ, γ-dimethyl-α, β-dicarbethoxybutyrolactone is treated with acetyl chloride in a benzene solution in the presence of sodium hydride. Although it has been reported²⁾ that the alkylation of α-carbethoxybutyrolactone affords *C*-alkylated derivatives, no similar attempt on α, β-dicarbethoxybutyrolactones¹,³,⁴⁾ has yet appeared in the literature. We found that α, β-dicarbethoxybutyrolactones (I) was alkylated at the α-position of the lactone ring with halides in the presence of sodium ethoxide.

The reactions of the lactone diesters with halides, *i. e.*, alkyl, alkenyl, and benzyl halides, in the presence of sodium ethoxide were carried out. The α-benzylated compounds (II) were obtained in 51—86% yields by fractional distillation, but the reaction of I with alkyl and alkenyl halides under the same conditions gave inferior yields. The hydrolysis of II in a 1 N alcoholic alkaline solution at room temperature⁵⁾ gave the corresponding ethyl α-substituted paraconates (III), as is shown in Table 2.

Upon treatment with an excess 1 N aqueous alkaline solution under reflux for 3—5 hr (Route 2),



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1) A. Takeda and S. Torii, *Memoirs of School of Engineering, Okayama Univ.*, **1**, 44 (1966).

2) a) R. Marburg, *Ann.*, **294**, 89 (1897); b) A. Michael and N. Weiner, *J. Am. Chem. Soc.*, **58**, 999 (1936); c) F. A. Berti, *Gazz. chim. ital.*, **84**, 420 (1954); d) P. C. Bhattacharyya, *J. Indian Chem. Soc.*, **42**, 463 (1965).

3) K. Sisido, S. Torii and M. Kawanisi, *J. Org. Chem.*, **29**, 904, 2290 (1964).

4) A. Haller and G. Blanc, *Compt. rend.*, **142**, 1471 (1906).

5) The hydrolysis of the α-carbethoxy group is effected only under these conditions.¹⁾

Table 1. α-Substituted lactone diesters (II)

R	R′	Yield %	Bp °C/mmHg	Mp °C	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Methyl	Benzyl	85	183—186/3	54	65.50	65.44	6.94	6.98
Ethyl	Benzyl	57	180/2.5	—	66.63	66.99	7.32	7.39
Isobutyl	Benzyl	51	175/1	—	67.67	67.73	7.74	7.73
Isoamyl	Benzyl	58	162/2	—	68.29	67.89	7.79	7.78
Methyl	*p*-Chlorobenzyl	56	196/2	65	59.60	59.74	6.06	6.22
Methyl	3, 4-Methylene-dioxybenzyl	70	215/2	—	61.21	61.31	6.17	6.43
Methyl	Allyl	23	142/2	—	60.39	60.22	7.43	7.52
Methyl	Methallyl	1>[a]	138—142/2	—	—	—	—	—
Methyl	*n*-Butyl	1—2	125—130/11	—	64.43	64.27	9.16	8.93

a) The infrared spectrum showed bands at 3100, 1655, and 906 cm^{-1} due to methallyl group.

Table 2. α-Substituted lactone esters (III)

R	R′	Yield %	Bp °C/mmHg	Mp °C	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Methyl	Benzyl	63	156/2.5	—	69.54	69.56	7.30	7.35
Ethyl	Benzyl	54	180/2.5	—	70.32	70.27	7.64	7.60
Methyl	*p*-Chlorobenzyl	72	—	82	61.83	61.83	6.12	6.20
Methyl	3, 4-Methylene-dioxybenzyl	73	—	92	63.74	63.84	6.29	6.32
Methyl	Allyl	43	122—126/2.5	—	63.70	63.46	8.02	7.98

Table 3. α-Substituted paraconic acids (IV)

R	R′	Yield, % Route 1	Yield, % Route 2	Mp °C	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Methyl	Benzyl	90	55	179	67.73	67.58	6.50	6.64
Ethyl	Benzyl	63	—	118	68.68	68.60	6.92	6.64
Isobutyl	Benzyl	60	—	134	70.32	70.20	7.64	7.41
Methyl	*p*-Chlorobenzyl	90	62	208	59.47	59.78	5.34	5.50
Methyl	3, 4-Methylene-dioxybenzyl	0	32	175	61.64	61.70	5.52	5.42

the ethyl paraconates (III) underwent hydrolysis of the β-carbethoxy group to give paraconic acids (IV), along with dibasic acid of an unknown structure.[6] The acids (IV) are listed in Table 3. The acid-catalyzed hydrolysis[3] of II (Route 1) and III also gave IV, but no compound was characterized by the hydrolysis of the 3, 4-methylenedioxybenzyl derivative.

The structure of III ($R=CH_3$ and $R'=p\text{-}ClC_6H_4CH_2$) was established by infrared and NMR spectra, by elemental analysis, and by the conversion of the acid (IV) into the 3, 4-methylenedioxybenzyl ester. The infrared spectrum of IV showed a characteristic band[1,7] at 1735 cm^{-1} due to lactone and carboxylic carbonyls. The NMR peaks described in detail in the Experimental Section suggest that the coupling constant between H_α at 6.5 τ (quartet) and H_β at 7.2 τ (doublet) of 8.5 cps indicates a dihedral angle of near 180°[8] and a trans configuration of the two protons.[9] This structure appears to be sterically preferable.

Experimental

Microanalyses were carried out by Miss Teruko Nisi of our department. All melting points are uncorrected.

γ-Methyl-γ-ethyl-α, β-dicarbethoxybutyrolactone. Following the method described in the previous

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[6] The fission of the lactone ring seems to arise from prolonged hydrolysis with a large excess of alkali.

[7] C. Katsuta and N. Sugiyama, This Bulletin, **35**, 1194 (1962).

[8] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

[9] In the case of a β, γ-dicarboxybutyrolactone analogous coupling constant is observed; see "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, California (1963), No. 456.

papers,[2] a mixture of 13.6 g (0.2 mol) of sodium ethoxide, 37.5 g (0.25 mol) of diethyl malonate in 120 m*l* of anhydrous ethanol, and 15.8 g (0.1 mol) of ethyl β-methyl-β-ethylglycidate, bp 106°C/35 mmHg (lit.[10] bp 76°C/7 mmHg), was refluxed for 25 hr with stirring, and after addition of ice-water the reaction mixture was extracted with ether. The products obtained on evaporation of the ethereal solution were distilled *in vacuo* to give 15 g (59%) of the title compound, bp 143.5°C/2 mmHg, n_D^{17} 1.4450, λ_{max} 1785 (lactone $\nu_{C=O}$), 1740, and 1720 cm^{-1} (ester $\nu_{C=O}$). Found: C, 57.36; H, 7.59%. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

Similarly, 56% (based on ethyl β-methyl-β-isoamylglycidate, bp 144°C/47 mmHg) of γ-methyl-γ-isoamyl-α, β-dicarbethoxybutyrolactone was obtained, bp 147°C/1 mmHg, n_D^{17} 1.4449. Found: C, 61.11; H, 8.37%. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34%.

***p*-Chlorobenzylation of γ, γ-Dimethyl-α, β-dicarbethoxybutyrolactone (I).** To a mixture of 4.68 g (0.02 mol) of γ, γ-dimethyl-α, β-dicarbethoxybutyrolactone[3] (I, R=CH_3) and 1.34 g (0.02 mol) of sodium ethoxide in 10 m*l* of dry ethanol 3.2 g (0.02 mol) of *p*-chlorobenzyl chloride was added with stirring for 8 hr. The mixture was neutralized with dilute sulfuric acid, extracted with ether, washed with water, and dried over anhydrous sodium sulfate. Upon removing the solvent *in vacuo*, the residue was distilled off to give 4.1 g (56%) of γ, γ-dimethyl-α, β-dicarbethoxy-α-(*p*-chlorobenzyl)butyrolactone, bp 196°C/2 mmHg, mp 65°C, λ_{max} 1770 (lactone $\nu_{C=O}$) and 1733 cm^{-1} (esters $\nu_{C=O}$).

Several derivatives were prepared similarly. The results are summarized in Table 1.

Ethyl γ, γ-Dimethyl-α-(*p*-chlorobenzyl)paraconate (III, R=CH_3 and R′=*p*-$ClC_6H_4CH_2$). A mixture of 1.6 g (0.04 mol) of sodium hydroxide with a trace of water and 7.16 g (0.02 mol) of II (R=CH_3 and R′=*p*-$ClC_6H_4CH_2$) in 35 m*l* of ethanol was stirred for 7 hr at 30—40°C and then neutralized to pH 7—6.5 with dilute sulfuric acid. The organic layer was taken up in ether, washed with saturated sodium chloride solution, and extracted with saturated sodium bicarbonate solution. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. Removing the solvent *in vacuo*, the residue was solidified. Recrystallization from *n*-hexane gave 4.1 g (72%) of III (R=CH_3 and R′=*p*-$ClC_6H_4CH_2$), mp 82°C, λ_{max} 1773 (lactone $\nu_{C=O}$) and 1730 cm^{-1} (ester $\nu_{C=O}$), $\tau_{TMS}^{CCl_3H}$ 8.8 (CH_3, triplet), 8.7, 8.4 (*gem*-CH_3), 7.2 (C-H_β, doublet, *J*=8.5 cps), 6.9 (Ph-CH_2, doublet, *J*=4 cps), 6.5 (C-H_α, quartet, *J*=8.5 and 4 cps), 5.9 (Me-CH_2, quartet), 2.8 (Ph-H).

All the compounds listed in Table 2 were prepared by an essentially similar procedure.

γ, γ-Dimethyl-α-(*p*-chlorobenzyl)paraconic Acid (IV, R=CH_3 and R′=*p*-$ClC_6H_4CH_2$). Route 1. A mixture of 2.86 g (0.01 mol) of III (R=CH_3 and R′=*p*-$ClC_6H_4CH_2$) or 3.58 g (0.01 mol) of II (R=CH_3 and R′=*p*-$ClC_6H_4CH_2$) with 60 m*l* of 20%[2] hydrobromic acid in aqueous acetic acid was refluxed for 4—5 hr. When the solvent was removed *in vacuo*, there was obtained the title compound IV in a quantitative yield, mp 208°C, mixed melting point with the compound obtained by Route 2 was 207°C. The infrared spectrum shows the characteristic absorption of the paraconic acid at the carbonyl region,[2] *i. e.*, 1735 cm^{-1}.

Route 2. A mixture of 20 m*l* of 1 N sodium hydroxide solution and 2.86 g (0.01 mol) of III (R=CH_3 and R′=*p*-$ClC_6H_4CH_2$) was refluxed for 6 hr and neutralized with dilute sulfuric acid. The organic layer was extracted with ether and benzene (3: 1), and the extract was washed with water, dried over anhydrous sodium sulfate and evaporated to give 1.4 g (62%) of white solid, mp 207°C (from benzene). The infrared spectrum was identical with that of the specimen prepared by Route 1.

New paraconic acids (IV) prepared by both Route 1 and Route 2 are shown in Table 3.

3, 4-Methylenedioxybenzyl γ, γ-Dimethyl-α-(*p*-chlorobenzyl)paraconate. To a mixture of 1.14 g (0.0075 mol) of piperonyl alcohol and 1.06 m*l* (0.0083 mol) of dimethylaniline in 10 m*l* of dry ether, γ, γ-dimethyl-α-(*p*-chlorobenzyl)paraconyl chloride, prepared from 4.5 g (0.015 mol) of IV (R=CH_3 and R′=*p*-$ClC_6H_4CH_2$) and 2 m*l* of thionyl chloride in 10 m*l* of dry benzene, was added portionwise under reflux for 6 hr. The mixture was hydrolyzed with water and taken up in ether. The organic layer was washed with sodium bicarbonate solution, with water and dried over anhydrous sodium sulfate. After the solvent was removed *in vacuo*, the residue was solidified. Recrystallization from *n*-hexane afforded 5.4 g (84%) of the title 3, 4-methylenedioxyphenyl paraconate, mp 95—96°C, λ_{max}^{Nujol} 1775 (lactone $\nu_{C=O}$), 1734 (ester $\nu_{C=O}$), 1610, 1595, 1505, 1490, 1250, 1040, 935 cm^{-1} (3, 4-methylenedioxyphenyl). Found: C, 63.45; H, 5.15%. Calcd for $C_{22}H_{21}O_6Cl$: C, 63.38; H, 5.07%.

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[10] a) V. F. Martynov and I. B. Belov, *Zh. Obshch. Khim.*, **32**, 2341 (1962); b) Z. S. Kagan, *Isv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 317.