Lactone Carboxylic Acids. V.[*1] A Way of Preparing a Lignans Skeleton

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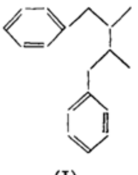
In a previous paper,1) we described the benzylation of γ,γ-dialkyl-α,β-dicarbethoxybutyrolactones at the α-position of the lactone ring, which is reminiscent of a synthetic route to lignans derivatives.2)

It is the aim of the present study to apply this method to the synthesis of compounds with a lignans skeleton (I) (see Scheme 2). The required materials, γ-aryl-α,β-dicarbethoxybutyrolactones (IIa, R=4-methoxy or 3,4-methylene dioxy), were prepared by the condensation of ethyl β-arylglycidates with sodiomalonate.3) In order to elucidate the course of the fission of the epoxy ring on the glycidates, the products (IIa or IIb) were converted into well-known compounds (VI),4) as is shown in Scheme 1.



(I)

The hydrolysis of II was carried out with an 1 N aqueous alcoholic potassium hydroxide solution;5) it gave *ca.* 70% yield of an acidic component

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[*1] Part II, III, and IV: *Memoirs of School of Engineering, Okayama Univ.*, **2**, 68, 74, 80 (1967).

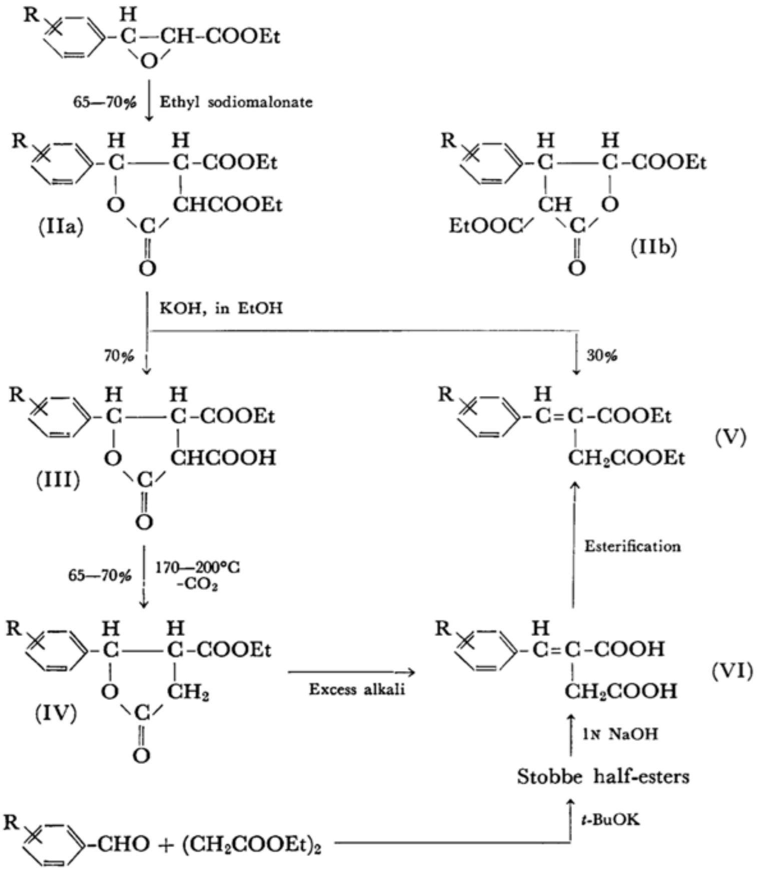
1) A. Takeda and S. Torii, This Bulletin, **40**, 1261 (1967).

2) W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955); F. M. Dean, "Naturally-occurring Oxygen Ring Compounds," Butterworths, London (1963), p. 29.

3) The reaction of ethyl β-phenylglycidate with sodiomalonate has previously been recorded; see G. V. Chelintsev and E. D. Osetrova, *J. Gen. Chem. USSR*, **7**, 2373 (1937).

4) a) A. B. Kulkarni, A. L. Pandit, H. D. Shroff, B. D. Hosangadi, M. N. Katrak, A. B. Diwadkar and B. C. Ginde, *Indian J. Chem.*, **2**, 443 (1964); *Chem. Abstr.*, **62**, 7616e (1965). b) N. A. Babiyan, V. A. Mnatsakanyan, R. G. Arutyunyan, N. E. Akopyan, and O. L. Mndzhoyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **17**, 549 (1964); *Chem. Abstr.*, **62**, 11732 (1965). c) J. W. Cornforth, G. K. Hughes, and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 228 (1939).

5) In the case of the hydrolysis of γ,γ-dialkyl-α,β-dicarbethoxybutyrolactones, only acidic components, γ,γ-dialkyl-β-carbethoxy-α-carboxybutyrolactones, were isolated under these conditions; see A. Takeda and S. Torii, *Memoirs of School of Engineering, Okayama Univ.*, **1**, 44 (1966). On the other hand, the hydrolysis of α-benzylated γ,γ-dialkyl-α,β-dicarbethoxybutyrolactones gave exclusively neutral lactone derivatives, such as γ,γ-dialkyl-β-carbethoxy-α-benzylbutyrolactones.1)



Scheme 1

(III), a viscous yellow oil, and *ca.* 30% yield of a neutral component (V).

The acidic materials (III), when heated to 170—200°C, were converted into ethyl γ-arylparaconates (IV), which were then further hydrolyzed with reflux in a 1 N aqueous sodium hydroxide solution to give dibasic acids (VI).[4] The authentic samples of VI were prepared by the Stobbe condensation[6] of aromatic aldehydes with diethyl succinate and by the subsequent hydrolysis of the Stobbe half-esters.[4a]

The structure of the neutral materials (V) was readily confirmed by means of these spectral data in comparison with those of an authentic sample prepared by the esterification of VI. These facts reveal that the attack of the carbanion of malonate occurs exclusively at the α-position of the β-arylglycidates.[7]

The benzylation of IIa (R=4-methoxy) was carried out with the use of an equimolar amount of 4-chlorobenzyl chloride, as a model compound, in the presence of sodium ethoxide in dry ethanol.[1] The structure of the condensation product (VII, R=4-methoxy and R′=4-chloro), which was not distillable but which was condensed at 170—180°C/1—2 mmHg, was supported by its infrared spectrum, which showed enhanced peaks at 1513, 1490, and 835 cm^{-1} assignable to the *p*-chlorobenzyl group.

Without being purified further, VII was subjected to hydrolysis in an 1 N alcoholic potassium hydroxide solution to afford a 65% yield of acidic materials (VIII) and a 35% yield of neutral materials (IX). The structure of VIII (R=4-methoxy and R′=4-chloro), a sticky oil, was indicated by its infrared spectrum, which exhibited peaks at 3500—2400, 1770, 1735, and 1700 cm^{-1}, consistent with carboxylic acid, lactone, and ester groups respectively. The neutral material (IX, R=4-methoxy and R′=4-chloro) was purified by distillation and showed the expected combustion analytical results. Further proof of the structure of IX (R=4-methoxy and R′=4-chloro)

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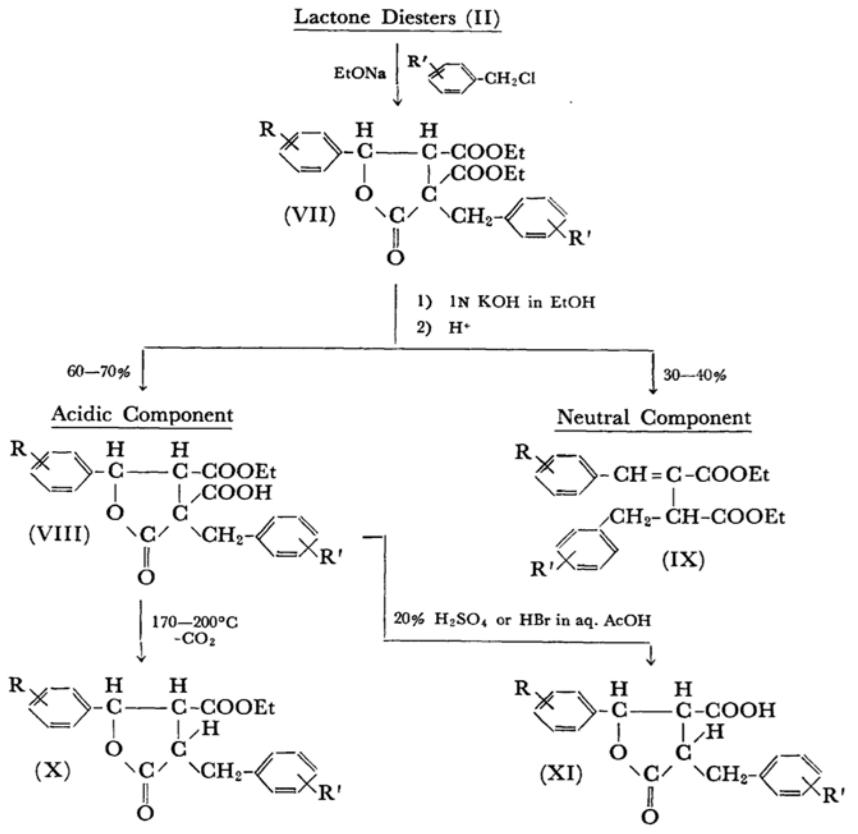
6) W. S. Johnson and G. H. Daub, "Organic Reactions," Vol. VI, John Wiely and Sons, New York, N. Y. (1951), p. 1.

7) Detailed studies of the ring opening of the epoxide group upon the reaction of ethyl β-alkyl- and β,β-dialkylglycidates with sodiomalonate have been reported; see A. Takeda, Y. Kariya and S. Torii, *Memoirs of School of Engineering, Okayama Univ.*, **2**, 74 (1967); K. Sisido, S. Torii, and M. Kawanisi, *J. Org. Chem.*, **29**, 904 (1964).



Scheme 2

was given by the following evidence. The absorption spectrum of IX (R=4-methoxy and R′=4-chloro), when carefully compared with that of V (R=4-methoxy), showed enhanced peaks at 1513 and 840—820 cm^{-1} due to the newly-introduced *p*-chlorobenzyl group. A Beilstein test was positive also.

Experimental

The microanalyses were performed by Miss Teruko Nisi of our department. All melting and boiling points are uncorrected.

Reaction of Ethyl β-(4-Methoxyphenyl)glycidate with Sodiomalonate. Following the method described in the previous paper,[1] to a mixture of 13.6 g (0.2 mol) of sodium ethoxide and 37.6 (0.25 mol) of diethyl malonate in 120 m*l* of anhydrous ethanol, 22.2 g (0.1 mol) of ethyl β-(4-methoxyphenyl)glycidate, bp 158°C/3 mmHg (lit.[8] bp 187—191°C/18 mmHg), were added. The mixture was refluxed for 25 hr with stirring, extracted with ether after the addition of ice water, and dried over anhydrous sodium sulfate. Upon the distillation of the residue *in vacuo*, there were obtained 22.5 g (67% based on the glycidate) of the γ-(4-methoxyphenyl)-α,β-dicarbethoxybutyrolactone (IIa, R=4-methoxy), bp 215—225°C/2 mmHg, ν_{max} (cm^{-1}) 1790 (lactone $\nu_{C=O}$) and 1735 (ester $\nu_{C=O}$). Found: C, 61.02; H, 6.04%. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99%.

Similarly, a 60% yield [based on ethyl β-(3,4-methylenedioxyphenyl)glycidate, bp 157—160°C/2.5 mmHg, lit.[8] bp 205—210°C/17 mmHg] of γ-(3,4-methylenedioxyphenyl)-α,β-dicarbethoxybutyrolactone, (IIa, R=3,4-methylenedioxy), bp 215°C/0.5 mmHg, ν_{max} (cm^{-1}) 1790 (lactone $\nu_{C=O}$) and 1730 (esters $\nu_{C=O}$) was obtained. Found: C, 58.45; H, 5.08%. Calcd for $C_{17}H_{18}O_8$: C, 58.29; H, 5.18%.

Hydrolysis of γ-(4-Methoxyphenyl)-α,β-dicarbethoxybutyrolactone (IIa, R=4-methoxy). A mixture of 2.8 g (0.05 mol) of potassium hydroxide with a trace of water and 4.5 g (0.013 mol) of IIa (R=4-methoxy) in 70 m*l* of ethanol was stirred for 2 days, neutralized to pH 6.5—7.0 with dilute sulfuric acid, and extracted with ether. The ethereal solution was then extracted several times with a saturated sodium bicarbonate solution, washed with water, dried over anhydrous magnesium sulfate, and evaporated. The distillation of the residual oil gave a *ca.* 30% yield of a neutral substance (V, R=4-methoxy), bp 183—186°C/0.5 mmHg (lit.[9] bp 285°C/4 mmHg), ν_{max} (cm^{-1}) 1730 and 1700 (esters $\nu_{C=O}$), which was identical with the authentic sample prepared by the esterification of the Stobbe half-ester.[4a]

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[8] K. W. Rosenmund and H. Dornsaft, *Ber.*, **52** 1734 (1919).

[9] F. G. Baddar, L. S. El-Assal, N. A. Doss and A. H. Shehab, *J. Chem. Soc.*, **1959**, 1016.

The alkaline extracts were acidified with dilute sulfuric acid. The organic layer was taken up in ether, washed with a saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The concentration of the ethereal solution gave a *ca.* 70% yield of III (R=4-methoxy), viscous oil, ν_{max} (cm^{-1}) 1785 (lactone $\nu_{C=O}$), 1730 (ester $\nu_{C=O}$), and 3500—2400, 1700 (COOH).

III (R=4-methoxy) was heated to 170—230°C for 30 min and then taken up in ether. The organic layer was washed with a saturated sodium bicarbonate solution and water, and dried over sodium sulfate. The distillation of the extract gave a 65—70% yield (based on III, R=4-methoxy) of ethyl γ-(4-methoxyphenyl)-paraconate, pale yellow oil, ν_{max} (cm^{-1}) 1785 (lactone $\nu_{C=O}$) and 1735 (ester $\nu_{C=O}$).

Found: C, 63.80; H, 6.25%. Calcd for $C_{14}H_{16}O_5$: C, 63.60; H, 6.19%.

In a similar manner, a 60—63% yield (based on III, R=3,4-methylenedioxy) of ethyl γ-(3,4-methylenedioxyphenyl)paraconate, bp 160°C/0.5 mmHg, ν_{max} (cm^{-1}) 1790 (lactone $\nu_{C=O}$) and 1730 (ester $\nu_{C=O}$) was obtained.

Found: C, 60.46; H, 5.37%. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07%.

By acidifying the alkaline extracts with dilute sulfuric acid, III (R=4-methoxy) was recovered unaffected.

Hydrolysis of Ethyl γ-(4-Methoxyphenyl)paraconate (IV, R=4-Methoxy). A mixture of 2.76 g (0.01 mol) of ethyl γ-(4-methoxyphenyl)paraconate (IV, R=4-methoxy) and 4.0 g (0.1 mol) of sodium hydroxide in 100 m*l* of water was refluxed for 10 hr. After it had then cooled to room temperature, the solution was neutralized with dilute sulfuric acid and extracted with ether. The organic layers were washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. After the solvent had then been removed *in vacuo*, the residual solid was recrystallized to give VI (R=4-methoxy), mp 192°C (lit. mp 202.3°C[4a] and 187—188°C[4b]), whose infrared spectrum was identical with that of the specimen prepared by the hydrolysis of the corresponding Stobbe half-ester.[4a]

***p*-Chlorobenzylation of γ-(4-Methoxyphenyl)-α,β-dicarbethoxybutyrolactone (IIa, R=4-Methoxy).** Into a mixture of 6.72 g (0.02 mol) of γ-(4-methoxyphenyl)-α,β-dicarbethoxybutyrolactone (IIa, R=4-methoxy) and 1.34 g (0.02 mol) of sodium ethoxide in 10 m*l* of dry ethanol, 3.2 g (0.02 mol) of 4-chlorobenzyl chloride were stirred over a 14-hr period. The mixture was then neutralized with dilute sulfuric acid, extracted with ether, washed with water, and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was distilled. The forerun fraction which was distilled below 170°C/2 mmHg was removed. The residual high-boiling fraction, ν_{max} (cm^{-1}) 1790 (lactone $\nu_{C=O}$), 1735—1720 (esters $\nu_{C=O}$), with enhanced absorption bands at 1610, 1513, 1490, and 835 (4-chlorobenzyl group), which were decomposed as the distillation continued, was hydrolyzed with an excess 1 N alcoholic potassium hydroxide solution at 30—40°C for 20 hr and then neutralized to pH 6.5—7.0 with dilute sulfuric acid. The organic layer was taken up in ether, washed with a saturated sodium chloride solution, and extracted with a saturated sodium bicarbonate solution. The ethereal extract was washed with water and dried over anhydrous sodium sulfate. After the solvent had been removed *in vacuo*, the distillation of the residue gave 2.5 g (30% based on IIa) of diesters (IX, R=4-methoxy and R′=4-chloro), bp 170—175°C/0.05 mmHg, ν_{max} (cm^{-1}) 1730 (esters $\nu_{C=O}$), enhanced absorption bands at 1605, 1513, 840, and 820, due to the 4-chlorobenzyl group, in comparison with that of V (R=4-methoxy).

Found: C, 65.92; H, 6.52%. Calcd for $C_{23}H_{25}ClO_5$: C, 66.26; H, 6.04%.

The alkaline extracts were neutralized with dilute sulfuric acid to pH 6.5—7.0. The organic layer was taken up in ether, washed with a saturated sodium chloride solution and with water, and dried over anhydrous magnesium sulfate. Upon removing the solvent *in vacuo*, there was obtained 5.04 g of a viscous oil (VIII, R=4-methoxy and R′=4-chloro), ν_{max} (cm^{-1}) 1770 (lactone $\nu_{C=O}$), 1730 (ester $\nu_{C=O}$), 3400—2400, 1700, 930—900 (COOH).

The viscous oil (VIII), when heated to 170—220°C, gave a 30% yield of the lactone ester (X, R=4-methoxy and R′=4-chloro), bp 195—200°C/2 mmHg, ν_{max} (cm^{-1}) 1790 (lactone $\nu_{C=O}$) and 1735 (ester $\nu_{C=O}$).

Found: C, 64.90; H, 5.59%. Calcd for $C_{21}H_{21}ClO_5$: C, 64.83; H, 5.44%.

The viscous oil (VIII), when boiled with excess 20% sulfuric acid for 8 hr or with an excess 1 N sodium hydroxide solution for 4 days, gave a 45% yield of lactone acid (XI, R=4-methoxy and R′=4-chloro), mp 130°C, ν_{max} (cm^{-1}) 1770 (lactone $\nu_{C=O}$), and 1730 and 1705 (carboxylic acid $\nu_{C=O}$).

Found: C, 63.29; H, 4.94%. Calcd for $C_{19}H_{17}ClO_5$: C, 63.24; H, 4.76%.