U.D.C. 547.586.3

2. **Zen-ichi Horii, Ichiya Ninomiya, and Yasumitsu Tamura**: Studies on Terramycin and Related Compounds. IX.* Synthesis of 3-(*o*-Carboxyphenyl)butyric Acid via the Reformatsky Reaction.

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In the previous paper,[1] we reported the synthesis of desoxyterracinoic acid from 3-(*o*-carboxyphenyl)butyric acid (V), which was prepared by the ring opening of 2-cyano-3-methyl-1-indanone (VI). This paper is concerned with another method for the preparation of this acid (V) via the Reformatsky reaction and with some informations on the structures of intermediates in this process.

When ethyl *o*-acetylbenzoate (Ia′) was subjected to the Reformatsky reaction with ethyl bromoacetate in dry benzene, the reaction product was ethyl 3-methyl-3-phthalideacetate (IIa), although the authors expected ethyl 3-hydroxy-3-(*o*-ethoxycarbonylphenyl)-butyrate (VIII) or its dehydrated product, i.e. ethyl 3-(*o*-methoxycarbonylphenyl)crotonate (VII). The structure of (IIa) was confirmed by its chemical properties and ultraviolet and infrared absorption spectra as described in the following sections. This abnormality in the Reformatsky reaction was also recognized in the case of ethyl *o*-formylbenzoate (Ib), which gave ethyl 3-phthalideacetate (IIb). The reaction product (IIa), on hydrolysis with 20% sodium hydroxide solution, afforded 3-(*o*-carboxyphenyl)crotonic acid (IIIa), and subsequent reduction with Raney nickel alloy in alkaline solution by the Papa and Schwenk procedure[2] gave 3-(*o*-carboxyphenyl)butyric acid (V). The over-all yield of (V) from (Ia′) was ca. 40%.

Structure of Ethyl 3-Methyl-3-phthalideacetate (IIa) and 3-(o-Carboxyphenyl)crotonic Acid (IIIa)

The product of the Reformatsky reaction of (Ia′) with ethyl bromoacetate remained unchanged after treating with phosphoryl chloride. Methyl *o*-acetylbenzoate (Ia) also gave the same product as that from the ethyl ester (Ia′). Both products presented analytical data that agreed with those for $C_{13}H_{14}O_4$(ethyl 3-methyl-3-phthalideacetate(IIa)). On alkaline hydrolysis, it gave a carboxylic acid, m.p. 150~151°, which was converted into an isomer of low melting point, m.p. 83.5~85°, on fusion. The former gave a positive permanganate test in acetone solution, but the latter was negative. From these chemical results, it was assumed that the former would have the structure of (IIIa) and the latter (IV), and the structural relation of these two compounds would be the same as the known example[3] of (IIb), (IIIb), and (IVb).

All these structures afforded by chemical treatment were also proved by means of the ultraviolet and infrared absorption spectra.

In the infrared spectra presented in Fig. 1, the dicarboxylic acids (IIIa and IIIb) exhibit intense bands at 1685 and 1690 cm^{-1} corresponding to the carbonyl group of aromatic and α,β-unsaturated carboxylic acid, and second bands at 1630 and 1648 cm^{-1} corresponding to the conjugated double bond. In the corresponding lactone-carboxylic acid derivatives, (IIa, IIb, and IVa), an absorption due to the double bond disappears and two strong bands appear at 1766, 1768, and 1770 cm^{-1}, corresponding to the carbonyl group of γ-lactone, and at 1715, 1718, and 1740 cm^{-1}, corresponding to the carbonyl group

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* Part VIII: J. Pharm. Soc. Japan, **76**, 739(1956).

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[1] Z. Horii, *et al.*: J. Pharm. Soc. Japan, **76**, 736(1956).

[2] E. Schwenk, *et al.*: J. Org. Chem., **9**, 175(1944); Org. Syntheses, **34**, 8(1954).

[3] S. Gabriel, *et al.*: Ber., **10**, 2203(1877).

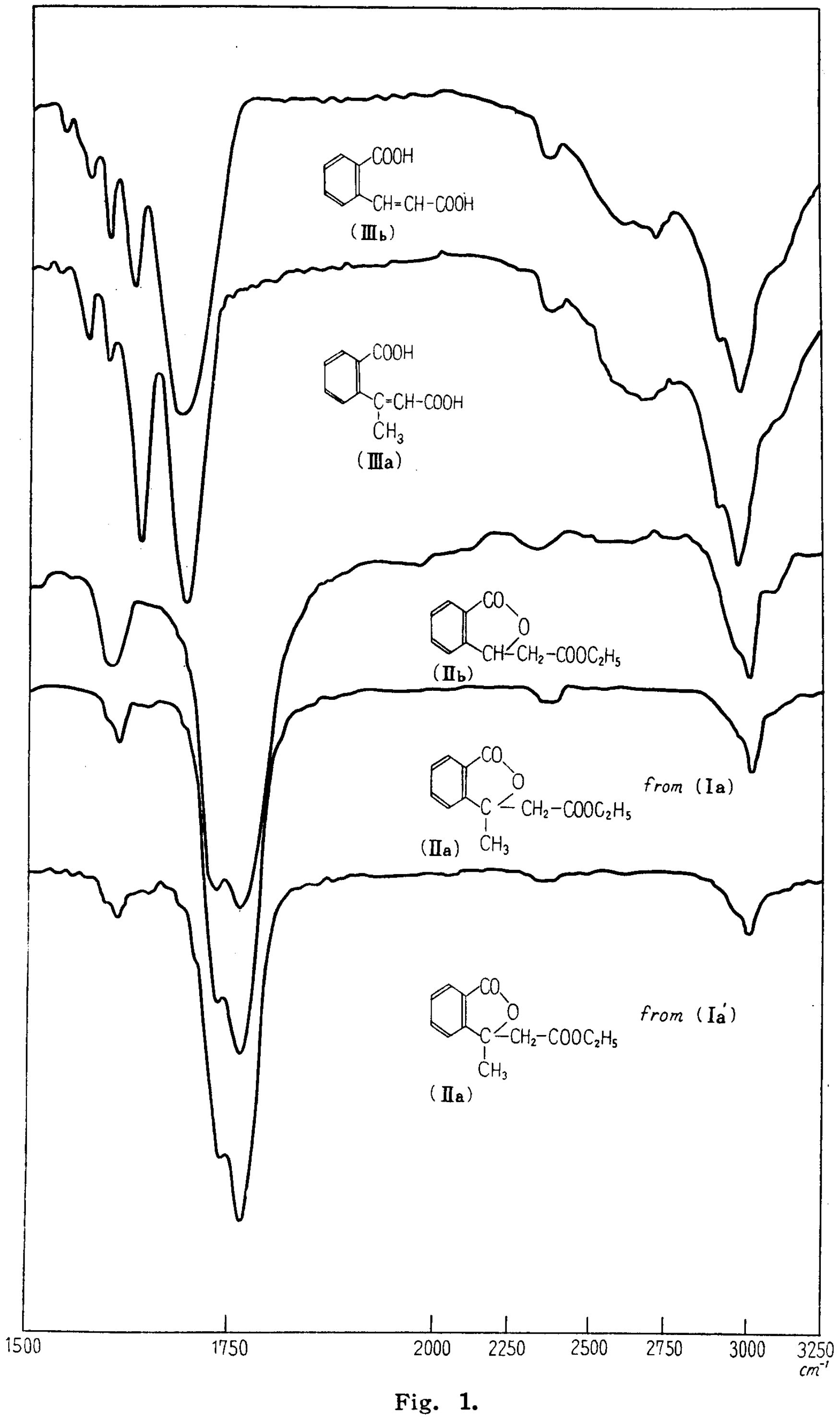
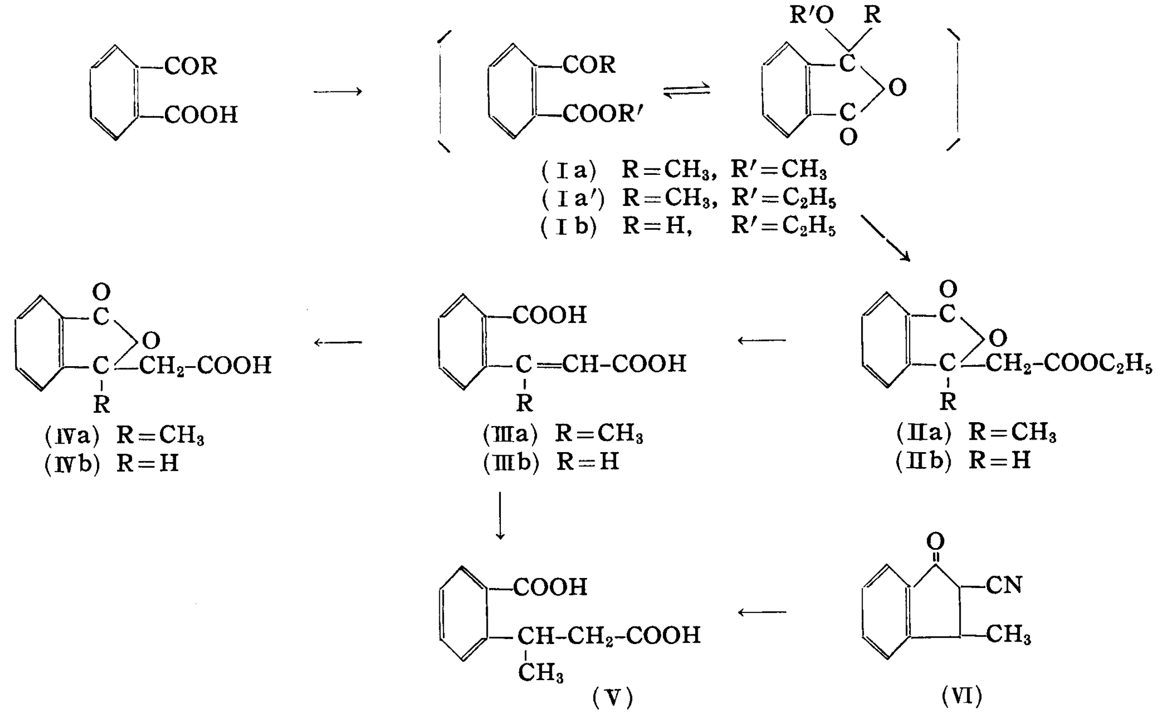


Fig. 1.

of aliphatic carboxylic acid. The ultraviolet spectra (Fig. 2 and Table I) indicated that all the four lactonecarboxylic acid derivatives (IIa, IIb, IVa, and IVb), exhibit the same absorption curves having maxima at 227, 273, and 280 mμ, but two dicarboxylic acids, (IIIa and IIIb), show rather different absorptions. The result from the ultraviolet spectra is consistent with that from the infrared spectra, except that, in the former case, an absorption at 267 mμ present in (IIIb) becomes less distinct in (IIIa). This difference may be ascribed to the steric hindrance of resonance by the β-substituted methyl group in (IIIb). Therefore, it is shown from these experiments that the method is valuable



(Ia) $R=CH_3$, $R'=CH_3$
(Ia′) $R=CH_3$, $R'=C_2H_5$
(Ib) $R=H$, $R'=C_2H_5$

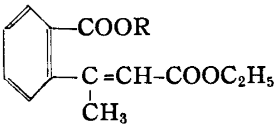
(IVa) $R=CH_3$
(IVb) $R=H$

(IIIa) $R=CH_3$
(IIIb) $R=H$

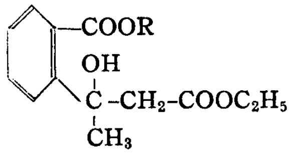
(IIa) $R=CH_3$
(IIb) $R=H$

(V)

(VI)

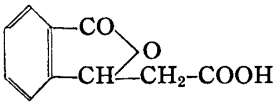
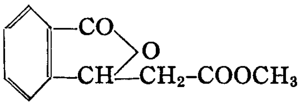
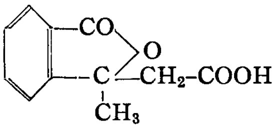
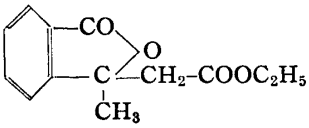
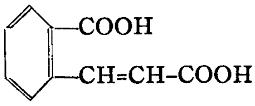
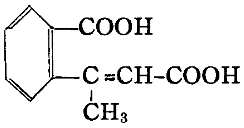


(VII) $R=CH_3$ or C_2H_5

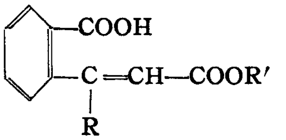


(VIII) $R=CH_3$ or C_2H_5

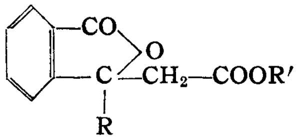
TABLE I. Ultraviolet Absorption Spectra

		λmax		λmax		λmax	
		mμ	log ε	mμ	log ε	mμ	log ε
	(IVb)	227	4.017	273	3.229	280	3.224
		227	4.023	273	3.205	280	3.199
	(IVa)	228	3.994	273	3.170	280	3.158
	(IIa)	228	3.998	273	3.184	280	3.176
	(IIIb)	222	4.306	267	4.136		
	(IIIa)	220	4.289				

for the verification of each structure of the tautomerism represented by the general formulae :



and



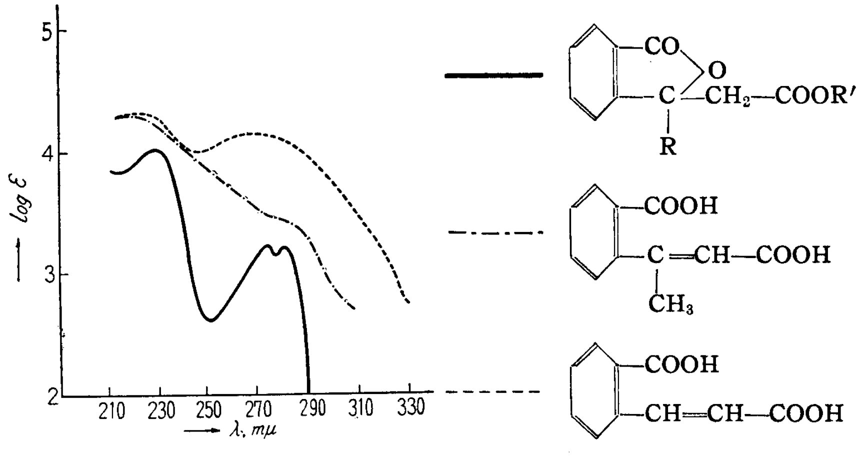


Fig. 2

Experimental

The Reformatsky Reaction of Ethyl *o*-Acetylbenzoate (**Ia′**)—In a reaction vessel were placed 12 g. of activated Zn dust and 1.5 g. of dried Cu powder. A solution of 15 g. of ethyl *o*-acetylbenzoate and 22 g. of ethyl bromoacetate in 120 cc. of dry benzene was placed in a separatory funnel. A small amount of this solution was added to the Zn-Cu powder and the flask was warmed until the reaction started. The mixture was then stirred and the rest of the solution was introduced at such a rate that gentle refluxing occurred. Stirring was continued for 4 hrs. After cooling, the reaction mixture was decomposed with 20% H_2SO_4 under vigorous stirring. The benzene layer was separated and the aqueous acid layer was extracted with a small amount of benzene. The combined extracts were washed with 10% Na_2CO_3 solution and water. After drying over anhydrous Na_2SO_4, the solvent was removed and the residue was distilled under a diminished pressure. Ethyl 3-methyl-3-phthalideacetate, was obtained as a viscous yellow oil, b.p$_{2.5}$ 173~273.5°. The yield was 11.5 g. (59%). *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.64; H, 6.02. Found : C, 66.40; H, 6.06. This was unaffected by heating with $POCl_3$ in dry benzene for 2 hrs. and showed b.p$_9$ 196~198°. *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.64; H, 6.02. Found : C, 66.48; H, 5.91.

The Reformatsky Reaction of Methyl *o*-Acetylbenzoate (**I a**)—The reaction of methyl *o*-acetylbenzoate, b.p$_{16.5}$ 154~156°, prepared from *o*-acetylbenzoic acid and MeOH in the presence of conc. H_2SO_4 was carried out as above and methyl 3-methylphthalide-3-acetate, was obtained as a viscous yellow oil, b.p$_2$ 168~169°. The yield was 63%. *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.21; H, 6.01.

Infrared spectrum of this product was identical with that of the product from (Ia′) as shown in Fig. 1.

The Reformatsky Reaction of Ethyl *o*-Formylbenzoate (**Ib**)—Ethyl *o*-formylbenzoate, b.p$_{17}$ 162~165°, m.p. 66~68°, was treated under the same condition as for (Ia′) and a viscous pale yellow liquid, b.p$_2$ 172~175°, was obtained. The yield was 61%. This was crystallized from AcOEt-petr. benzine mixture to colorless needles, m.p. 73.5~75°. Admixture with the sample of ethyl 3-phthalideacetate, m.p. 74°, prepared by Roth's method[4] gave no depression.

3-(*o*-Carboxyphenyl)crotonic Acid (**IIIa**)—6.3 g. of (IIa) was boiled with 100 cc. of 20% NaOH solution for 5 hrs. After cooling, the mixture was extracted with ether, acidified carefully under ice cooling, the separated crystals were filtered, washed with water, and dried. A further crop was obtained from AcOEt extract of the mother liquor. 3-(*o*-Carboxyphenyl)crotonic acid (IIIa) formed white crystals from AcOEt, m.p. 150~151°. The yield was 4.0 g. (72%). *Anal.* Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.87. Found : C, 63.88; H, 4.95. The material gave a positive permanganate test in acetone.

3-Methyl-3-phthalideacetic Acid (**IVa**)—(IIIa) was fused in an oil bath (ca. 160°) for a while.

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[4] R. Roth : Ber., **47**, 1597(1914).

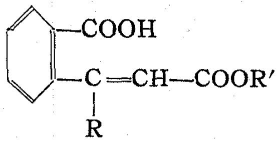
After cooling, the solid obtained was recrystallized from AcOEt-petr. benzine to colorless platelets, m.p. 83.5~85°. This substance gave a negative permanganate test in acetone. *Anal.* Calcd. for $C_{11}H_{14}O_4$: C, 64.07; H, 4.89. Found: C, 63.61; H, 4.86.

3-(*o*-Carboxyphenyl)butyric Acid (V)—A solution of 2 g. of (IIIa) in 60 cc. of 10% NaOH was heated under stirring at 90° in a water bath. Raney Ni alloy was then added to the solution in small portions over a period of 90 mins. The solution was heated for additional 1 hr. After cooling, the precipitated Ni was filtered and washed with water. The combined aqueous layer was acidified with conc. HCl and the solid obtained formed white crystals from water, m.p. 147.5~149.5°. An admixture with the sample of β-(*o*-carboxyphenyl)butyric acid, m.p. 148~150°, prepared by th ring-opening of 2-cyano-3-methyl-1-indanone, gave no depression of the melting point. The yield was 1.9 g. (95%). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.27; H, 5.85.

Summary

The Reformatsky reaction of ethyl *o*-acetylbenzoate (II) with ethyl bromoacetate gave ethyl 3-methylphthalide-3-acetate (IIIa) as the product, which was led to 3-(*o*-carboxyphenyl)butyric acid (I) via 3-(*o*-carboxyphenyl)crotonic acid (IVa).

The structures of (IIIa) and (IVa) were established by means of their chemical properties and the ultraviolet and infrared absorption spectra, and it was shown that the method was valuable for the verification of each structure of the tautomerism represented by the following general formulae:



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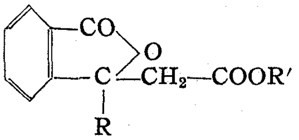

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3. Masao Tomita and Tatsuhiko Nakano: Studies on the Alkaloids of Rutaceous Plants. I. Alkaloids of *Phellodendron amurense* Rupr. (1).

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto**)

In view of the recent report concerning the isolation of N-methylisocorydine of the aporphine type from *Fagara coco* (Gill) Engl.[1] and Xanthoxylum spp.[2] of the Rutaceae family, there seems to be a possibility that some of Rutaceous plants may yield other quaternary alkaloids besides those of the berberine type since so far only berberine type of alkaloids are known throughout the family.

Our attention was first directed to *Phellodendron amurense* Rupr. (Japanese name "Kihada") when it was noted that Murayama and Shinozaki,[3] and Takada[4] in an investigation of this plant reported only the presence of berberine-type alkaloids.

The methanol extract of the plant material, after removal of berberine-type alkaloids as the hydrochlorides, was treated by the modification of the previously reported procedure.[3] After purification by reineckate precipitation there was isolated a basic substance as the picrate crystallizing in orange-yellow microscopic pillars, m.p. >300°. It gave analytical values corresponding to $CH_5N_3 \cdot C_6H_3O_7N_3$, and contains no methoxyl nor N-methyl group. The styphnate formed orange-yellow microscopic pillars, $CH_5N_3 \cdot C_6H_3O_8N_3$,

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[1] J. Comin, V. Deulofeu: J. Org. Chem., **19**, 1774(1954).

[2] J. R. Cannon, G. K. Hughes, E. Ritchie, W. C. Taylor: Australian J. Chem., **6**, 86(1953).

[3] Y. Murayama, K. Shinozaki: J. Pharm. Soc. Japan, **530**, 299(1926).

[4] Y. Murayama, J. Takada: *Ibid.*, **550**, 1035(1927).