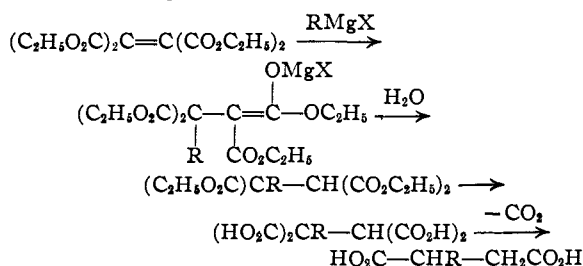


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The Action of Grignard Reagents on Ethyl Ethylenetetracarboxylate. A General Method for Preparation of Monoalkylated and Monoarylated Succinic Acids

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The addition of Grignard reagents to α,β -unsaturated carboxylic esters was studied intensively by Kohler and his co-workers.² The addition takes place either 1:2 or 1:4 depending on the character of the Grignard reagent and on the substituents in the unsaturated ester.³ Kohler noted that by substituting a cyano or another carboxylic ester group on the α -carbon atom, the addition of the Grignard reagent takes place exclusively 1:4. For instance, the reaction of benzal malonic ester with methylmagnesium iodide gives α -phenethyl malonic ester. When an excess of Grignard reagent is used the ester groups are not further attacked. It is the object of the present investigation to test whether the generalization made by Kohler can be equally well applied to the action of Grignard reagents on ethyl ethylenetetracarboxylate. If one mole of Grignard reagent adds 1:4 to ethyl ethylenetetracarboxylate, a general method for the preparation of mono-substituted succinic acids will be available. The reactions are given as follows



Bischoff⁴ has also made monoalkylated succinic acids from monoalkylated $\alpha,\alpha,\beta,\beta$ -ethanetetracarboxylic acid esters. The tetra-esters were obtained in poor yield by the alkylation of ethyl ethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate with an alkyl halide in the presence of sodium ethylate. The monoalkylated succinic acids were isolated as the final products by saponifying the crude esters. Arylated succinic acids could not be prepared by the method of Bischoff.

It was found that both aryl and alkylmagnesium bromide add to ethyl ethylenetetracarboxylate. When phenylmagnesium bromide was used, some coupling of the Grignard reagent with the formation of biphenyl was observed, while in the case of ethylmagnesium bromide, some reduction of ethyl ethylenetetracarboxylate took place.

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(2) Kohler and Heritage, *Am. Chem. J.*, **33**, 21, 153 (1905).

(3) Kohler and Johnstin, *ibid.*, **33**, 35 (1905); Kohler, *ibid.*, **36**, 529 (1906); Kohler and Reimer, *ibid.*, **33**, 333 (1905); Kohler, *ibid.*, **34**, 132 (1905).

(4) Bischoff and Rach, *Ann.*, **234**, 65 (1886).

The reduced compound was isolated as ethyl ethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate. In general the yields were good, varying from 56–79%. The saponification of the tetra-ester and the decarboxylation of the poly-acid were carried out by the usual methods. The yield was satisfactory in the case of ethyl phenylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate but poor in the case of ethyl methyl-ethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate. It is our hope to extend the present investigation and to improve the experimental conditions in order to make the method useful for general synthetic purposes when more material is available for the investigation. No attempt was made to isolate the tetracarboxylic acids in the pure state; they were decarboxylated directly. When ethyl phenylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate was saponified, an acid melting unsharply around 160° with decomposition was obtained. If the compound was heated at a temperature of 170° for some time until the decomposition ceased, the product melted sharply at 168°. This is the reported melting point of phenylsuccinic acid.^{5,6} The identity between the methylsuccinic acid synthesized by our method and an authentic specimen was established.

Although a number of methods⁷ for the preparation of monosubstituted succinic acids are available, the present method has the advantage of starting with readily prepared⁸ material. Certain monosubstituted succinic acids may be prepared by the present method that can be prepared only with great difficulty by any other method.

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Experimental

Ethyl Ethylenetetracarboxylate.—Ethyl ethylenetetracarboxylate was prepared as described by Corson and Benson.³

Ethyl α -Phenylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate.—In a 200-cc. 3-necked flask equipped with a dropping funnel, a mechanical stirrer through a mercury seal and a reflux condenser to the upper end of which was attached a calcium chloride tube, was placed 1.8 g. of magnesium shavings and 10 cc. of absolute ether. A mixture of 11.8 g. of bromobenzene in 15 cc. of absolute ether was added drop by drop through the funnel. When all the bromobenzene solution had been added, the mixture was refluxed for thirty minutes. A mixture of 4.7 g. of ethyl ethylene-

(5) Higson and Thorpe, *J. Chem. Soc.*, **89**, 1472 (1906).

(6) Lapworth and McRae, *ibid.*, **121** 1704 (1922).

(7) Markownikov and Lebedev, *Ann.*, **182**, 327 (1876); Higson and Thorpe, *J. Chem. Soc.*, **89**, 1455 (1906); Fittig, *Ann.*, **304**, 117, 127 (1899); Michael, *Ber.*, **29**, 1791 (1896).

(8) "Organic Syntheses," Coll. Vol. 11, p. 273 (1947).

tetracarboxylate dissolved in 40–50 cc. of absolute ether was dropped in through the funnel in thirty to forty minutes. The mixture was refluxed and stirred for an hour. The reaction flask was then cooled with ice water and 25 cc. of 25% ammonium chloride solution was added gradually. Stirring was continued for thirty minutes after all the ammonium chloride solution had been added. The ethereal layer was separated and the aqueous layer containing much solid matter was dissolved in a proper amount of 10% acetic acid and extracted several times with ether. The combined ethereal extracts were evaporated and the residue was then steam-distilled in order to remove most of the biphenyl formed during the reaction. The amount of biphenyl formed (m. p. 67–69°) varied from 0.6–1.2 g. The oil remaining in the distilling flask was extracted with ether and dried over sodium sulfate. The ether was removed and the residual oil was fractionated under reduced pressure. The fraction boiling at 208–210° (5 mm.) was collected. The yield was 4.2 g. (71%).

Anal. Calcd. for $C_{22}H_{20}O_8$: C, 60.9; H, 6.5. Found: C, 61.1; H, 6.2.

Saponification of Ethyl α -Phenylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate.—Forty cc. of 25% potassium hydroxide was refluxed with 1.7 g. of ethyl phenylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate in an oil-bath until the oil had disappeared completely (twelve hours). The aqueous solution was once extracted with ether in order to remove all traces of biphenyl remaining in the ester, then cooled in ice water and acidified with 20% sulfuric acid. An amorphous solid separated. It was filtered and dried on a steam-bath and then pulverized. The white powder was heated in dilute sulfuric acid until complete solution occurred. The solution was combined with the former filtrate and extracted several times with ether. After drying and removing the ether a crystalline substance (0.96 g.) was obtained. The crude acid was crystallized from hot water using a little charcoal. A yield of 0.82 g. of crystals was obtained. It decomposed at about 160°.

Phenylsuccinic Acid.—The acid obtained above was placed in a small glass tube and heated in a sulfuric acid bath keeping the temperature at 170–175° while the carbon dioxide evolved briskly. When the evolution of gas had ceased, 0.77 g. (86% based on the tetra-ester) of crude phenylsuccinic acid was obtained. After one crystallization from water, the pure acid was obtained as fine needles weighing 0.73 g., m. p. 168° (Thorpe reported 168°; Lapworth reported 167°).⁸

Anal. Calcd. for $C_{16}H_{16}O_4$: neut. equiv., 97. Found: neut. equiv., 96.

Ethyl α -Methylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate.—The procedure was similar to that used for the preparation of ethyl phenyl-ethanetetracarboxylate. From 4.7 g. of ethyl ethylenetetracarboxylate 3.8 g. (79%) of ethyl methyl ethanetetracarboxylate was obtained as a slightly yellowish oil boiling at 165–166° (5 mm.).

Anal. Calcd. for $C_{16}H_{24}O_8$: C, 54.2; H, 7.2. Found: C, 54.4; H, 7.8.

Methylsuccinic Acid.—In a 150-cc. 2-necked round-bottomed flask, which was fitted with a reflux condenser and a mechanical stirrer, 2.4 g. of ethyl methylethane-tetracarboxylate and 40 cc. of 20% potassium hydroxide were heated under reflux with stirring for seven hours. The solution was acidified and then extracted with ether.

The aqueous layer was further extracted with ether in a continuous extraction apparatus. The ethereal extracts were combined and dried. After the solvent had been removed, an oil was obtained which was then heated at a temperature 150–160° until no more carbon dioxide was evolved. The residue was dissolved in water, decolorized, and evaporated to dryness. The residual oil solidified slowly in the desiccator. It was crystallized from a mixture of petroleum ether and chloroform. The pure acid was obtained as beautiful crystals, m. p. 110–111° (Boettinger reported 112.5°; Bone and Sprankling reported 110°).⁹ The melting point was not depressed by mixing with an authentic specimen.

Ethyl α -Ethylethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate.—The procedure was similar to that used in the previous experiment. The Grignard reagent was prepared from 6.5 g. of ethyl bromide and 1.4 g. of magnesium shavings and allowed to react with 4.2 g. of ethyl ethylenetetracarboxylate. The crude product was obtained as a yellowish oil. The oil was allowed to stand for a few days. The crystals which separated were filtered and washed with a small amount of cold alcohol. On further standing a second crop of crystals was obtained. The process was repeated until no more crystals separated. The total amount of crystals weighed about 1.8 g., m. p. 76°. The melting point was not depressed by mixing with ethyl ethane- $\alpha,\alpha,\beta,\beta$ -tetracarboxylate. The oil, freed from the reduced compound, was fractionated under reduced pressure. The fraction boiling at 180–183° (6 mm.) was collected. The product was of pale yellow color and weighed 2.6 g. (56%).

Anal. Calcd. for $C_{18}H_{20}O_8$: C, 55.5; H, 7.5. Found: C, 54.8; H, 7.9.

Ethylsuccinic Acid.—The saponification of the ester was similar to that of the ethyl methylethanetetracarboxylate. The decarboxylation was carried out at a temperature of 150–160° for thirty minutes. The product was decolorized in hot water. On evaporation, 0.37 g. (36% of the theoretical amount based on the tetra-ester) of oil remained. The oil solidified completely on standing. It was crystallized from chloroform-petroleum ether mixture, and the pure ethyl succinic acid melting at 96–98° (Huggenberg reported 98°; Polk reported 97°)¹⁰ was obtained as fine crystals.

Anal. Calcd. for $C_8H_{10}O_4$: neut. equiv., 73. Found: neut. equiv., 73.

Summary

1. The mode of addition of both aryl and alkylmagnesium bromide to ethyl ethylenetetracarboxylate has been shown to take place exclusively 1:4.

2. A general method for the preparation of monosubstituted succinic acids has been described and phenyl-, methyl- and ethyl-succinic acids were synthesized in this way.

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(9) Boettinger, *Ber.*, **11**, 1352 (1878); Bone and Sprankling, *J. Chem. Soc.*, **75**, 860 (1899).

(10) Huggenberg, *Ann.*, **192**, 149 (1879); Polk, *ibid.*, **242**, 122 (1887).