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The Reaction between Ethylidenemalonic Ester and *o*-Methoxyphenylmagnesium Iodide

GUST.-AD. HOLMBERG

Institutet för organisk kemi, Åbo Akademi, Åbo, Finland

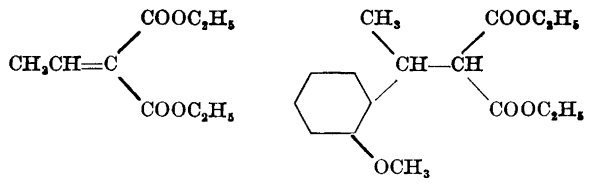
1-(*o*-Methoxyphenyl)ethylmalonic ester (II) and α-*o*-methoxybenzoyl-β-*o*-methoxyphenylbutyric ester (III) are formed in the reaction between ethylidenemalonic ester (I) and *o*-methoxyphenylmagnesium iodide. The latter reaction product has not been isolated as a pure compound, but its presence has been demonstrated by isolation of 1,3-di-*o*-methoxyphenyl-1-butanone (IV) (as its 2,4-dinitrophenylhydrazone) from the saponification products.

The identity of the isolated substances has been demonstrated by synthesis.

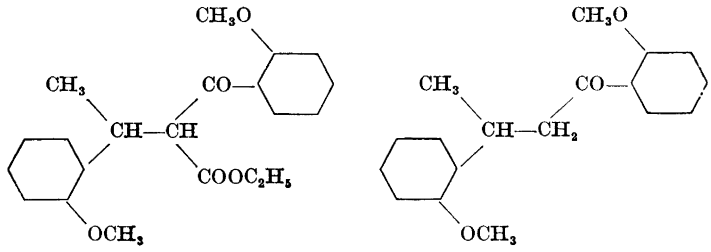
A preliminary examination of the reactions between ethylidenemalonic ester (I) and some aliphatic and aromatic Grignard reagents has shown that the main reaction seems to be 1,4-addition to the conjugated system [1].

When *o*-methoxyphenylmagnesium iodide was allowed to react with the unsaturated malonic ester, substances were found among the reaction products that could not have been formed by 1,4-addition only. The separation of the products was, however, difficult but some separation was attained by chromatography on alumina. The products were applied to the column in tetrachloromethane and the development and elution were performed successively with tetrachloromethane, ether, an ether-ethanol mixture and ethanol. The "normal" reaction product, 1-(*o*-methoxyphenyl)ethylmalonic ester (II), was eluted by tetrachloromethane. No pure product could be isolated from the ether fraction, but on saponification of the ether extract potassium carbonate and a neutral oil were obtained. The latter gave with 2,4-dinitrophenylhydrazine the 2,4-dinitrophenylhydrazone of 1,3-di-*o*-methoxyphenyl-1-butanone (IV).

This result indicates that the mixture of reaction products contains α-*o*-methoxybenzoyl-β-*o*-methoxyphenylbutyric ester (III), which is formed by 1,4-addition combined with a substitution of a methoxyphenyl group for an ethoxy group. Nothing can, of course, be concluded from the experimental results about the mechanisms leading to the above butyric ester.



I II



III IV

A similar double reaction between a Grignard reagent and an α,β-unsaturated ester has been reported by, *e.g.*, Kohler [2], who isolated α-benzhydrylpropiophenone as a by-product of the reaction between phenylmagnesium bromide and α-methylcinnamic ester.

When the ratio of the ethylidenemalonic ester to the Grignard reagent was 1:1.5, about 35 % of the ester had reacted to form 1-*o*-methoxyphenylethylmalonic ester. When the quantity of the Grignard reagent was increased so that the ratio was 1:2, about 50 % reacted in the same way. It was concluded from the quantity of potassium carbonate formed in the saponfication of the butyric ester derivative in the latter case that at least 19.6 % of the ethylidenemalonic ester had reacted twice with the Grignard reagent.

The identity of the reaction products was established by synthesis. 1-*o*-methoxyphenylethylmalonic ester was obtained in good yield by reacting methylmagnesium iodide with *o*-methoxybenzylidenemalonic ester. The same malonic and barbituric acids were obtained from this ester and the above ester. The malonic acid was decarboxylated to β-*o*-methoxyphenylbutyric acid, which was converted into the corresponding amide. This substance was dehydrated by a modification of a method of Stephens, Bianco, and Pilgrim [3] to form β-*o*-methoxyphenylbutyronitrile, which by a reaction with *o*-methoxyphenylmagnesium iodide gave 1,3-di-*o*-methoxyphenyl-1-butanone.

EXPERIMENTAL

o-*Methoxybenzylidenemalonic ester.* The yield of this substance [4] from the reaction between *o*-methoxybenzaldehyde and malonic ethyl ester in the presence of piperidine was improved and the reaction time shortened to 5 h by adding a small quantity of *o*-methoxybenzoic acid (1 g/100 g malonic ester) to the reaction mixture. The yield of material boiling at 207—209°/11 mm was 84 %. Before the ester was used in the following synthesis, it was twice recrystallized from ligroin.

1-(o-Methoxyphenyl) ethylmalonic ester. A solution of *o*-methoxybenzylidenemalonic ester (27.8 g) in dry ether (100 ml) was gradually added with cooling to a Grignard reagent prepared from magnesium (2.88 g) and methyl iodide (17.04 g) in dry ether (55 ml). During this addition two layers usually formed. Only when the cooling was less effective, the addition resulted in a homogeneous solution, which, however, separated into two layers on cooling. When the addition was complete, the reaction mixture was stirred for 20 minutes before it was poured into a mixture consisting of hydrochloric acid (70 ml), water (100 ml) and ice (about 100 g). After shaking, the organic phase was washed with water and a dilute potassium carbonate solution. The acid water solution was extracted once more with ether and this ether was also washed with water and potassium carbonate before it was combined with the main portion. After drying with sodium sulphate, the ether was evaporated and the residue distilled under reduced pressure. The yield of the ester, b.p. 183—183.5°/10 mm, was 89 % (26.19 g). (Found: C 65.10; H 7.57. Calc. for $C_{16}H_{22}O_5$: C 65.29; H 7.53.)

The same percentage yield was obtained from a larger batch (0.3 mole).

1-(o-Methoxyphenyl) ethylmalonic acid. 1-*o*-Methoxyphenylethylmalonic ester (37.66 g) was saponified with a solution of potassium hydroxide (38 g) in a mixture of water (40 ml) and ethanol (450 ml) during 5 h on a boiling water bath. The mixture was then kept in a refrigerator over night. The crystals (37.08 g) of potassium 1-*o*-methoxyphenylethylmalonate monohydrate were filtered off. (Found: H_2O 5.37. Calc. for $C_{12}H_{13}O_5K_2 \cdot H_2O$: 5.42.) This salt was dissolved in water (200 ml) and the solution acidified. The precipitated 1-*o*-methoxyphenylethylmalonic acid (25.04 g) melted at about 170° with evolution of gas. (Found: C 60.39; H 5.93. Calc. for $C_{12}H_{14}O_5$: C 60.50; H 5.92.)

The alkaline ethanolic filtrate was evaporated on a boiling water bath. The crystals that had formed on cooling were filtered and washed with ether. They were dissolved in water and the solution acidified. In this way a further quantity (3.56 g) of the malonic acid was obtained. The total yield of the acid was 93.8 %.

β-(o-Methoxyphenyl)butyric acid. 1-*o*-Methoxyphenylethylmalonic acid (28.5 g) was decarboxylated by heating in an oil bath at 170—180° for 15 min. The residue (23.0 g) was distilled under reduced pressure. In this way, pure *β-o*-methoxyphenylbutyric acid, b.p. 180—181°/15 mm, was obtained in a yield of 94.5 % (21.9 g). On standing and treatment with ligroin, the acid solidified and melted at 49—50°. The melting and boiling points correspond well with those reported by Lauer and Hansen [5], who prepared the acid by another method.

β-(o-Methoxyphenyl) butyramide. A mixture of *β-o*-methoxyphenylbutyric acid (22.8 g), thionyl chloride (20 ml) and benzene (40 ml) was heated on a boiling water bath for half an hour. The solvent and the excess of thionyl chloride were then distilled off (finally under reduced pressure). The residue, crude *β-o*-methoxyphenylbutyryl chloride, was dissolved in benzene (75 ml). This solution was gradually added to benzene (125 ml) through which dry ammonia was led at such a rate that an excess of ammonia was present during the whole addition. The flask was at the same time cooled with cold water. Next day the mixture was filtered and the solid material dissolved in boiling water. When the solution cooled, crystals of *β-o*-methoxyphenylbutyramide (16.45 g) separated. After recrystallization from water the substance melted at 127—128°. (Found: N 7.37. Calc. for $C_{11}H_{15}NO_2$: N 7.25.)

β-(o-Methoxyphenyl)butyronitrile. *β-o*-Methoxyphenylbutyramide (19.76 g) was dissolved in pyridine (90 ml), and benzenesulphonyl chloride (31.0 g) was added. After the exothermic reaction was over, the reaction flask was placed in warm water for 20 min. The mixture was then poured into water and the oil taken up in ether. The ether solution was shaken with dilute hydrochloric acid and potassium bicarbonate solution and finally dried with sodium sulphate. After evaporation of the ether, the residue was distilled under reduced pressure. The yield of *β-o*-methoxyphenylbutyronitrile, b. p. 148—149°/10.5 mm, was 81.5 % (14.60 g). (Found: N 8.03. Calc. for $C_{11}H_{13}NO$: N 7.99.)

2,4-Dinitrophenylhydrazone of 1,3-di-o-methoxyphenyl-1-butanone. A solution of *β-o*-methoxyphenylbutyronitrile (7.80 g) in dry ether (50 ml) was gradually added with cooling to a Grignard reagent prepared from magnesium (1.60 g) and *o*-iodoanisole (15.64 g) in dry ether (50 ml). During the addition, the reaction mixture separated into two layers. After all the nitrile had been added, the mixture was kept for one hour at room temperature. When it was then poured into an excess of dilute hydrochloric acid, a substance

(probably the ketimino hydrochloride) insoluble in both ether and water separated. Steam was led through the reaction mixture for one hour in order to hydrolyze the formed ketimine. The remaining oil was taken up into ether, in which it was readily soluble, and the ether solution washed with dilute sodium hydroxide. After drying with sodium sulphate, the ether was evaporated. An oil (11.06 g) remained in the flask.

A sample of this oil (1.36 g) was treated with 2,4-dinitrophenylhydrazine (0.53 g) in dilute ethanolic sulphuric acid. The quantity of hydrazine was intentionally chosen small in order to facilitate the later purification of the reaction product. On boiling yellow crystals (1.13 g) of 2,4-dinitrophenylhydrazone of 1,3-di-*o*-methoxyphenyl-1-butanone separated from the solution. After recrystallization from ethanol, the hydrazone melted at 158—159°. (Found: N 11.92. Calc. for $C_{24}H_{24}N_4O_6$: N 12.06.)

1,3-Di-*o*-methoxyphenyl-1-butanone was isolated from the above oily reaction product. It boiled at 219—221°/8.5 mm, but was not qute pure.

5-(1'-o-Methoxyphenylethyl)barbituric acid. Urea (1.44 g) and 1-*o*-methoxyphenylethylmalonic ester (5.88 g) were added to a sodium ethoxide solution prepared from sodium (0.55 g) and absolute ethanol (30 ml). The mixture was boiled for 8 h on a boiling water bath. The precipitate formed was filtered, washed with a small amount of absolute ethanol, and dissolved in water. The dihydrate of the barbituric acid (3.05 g) precipitated on adding hydrochloric acid. The ethanol was distilled off from the ethanolic filtrate, the residue treated with water and ether, and impure dihydrate of the barbituric acid (1.40 g) precipitated with acid from the aqueous phase. The crude products were repeatedly recrystallized from aqueous ethanol. The dihydrate melts at 92—94° on rapid heating and at 154—155° on slow heating. (Found: N 9.29; H_2O 12.24. Calc. for $C_{13}H_{14}N_2O_4 \cdot 2\,H_2O$: N 9.39; H_2O 12.08.) When the dihydrate is boiled with benzene or heated on a Kofler Heizbank at 70°, the anhydrous barbituric acid is formed. It melts sharply at 154—155°. (Found: N 10.60. Calc. for $C_{13}H_{14}N_2O_4$: N 10.68.) When the anhydrous barbituric acid is recrystallized from aqueous ethanol, the dihydrate is formed.

1-(o-Methoxyphenyl)ethylmalonic p-nitrobenzyl ester. 1-*o*-Methoxyphenylethylmalonic acid was characterized by preparing its *p*-nitrobenzyl ester, m. p. 144—145°, according to Reid [6]. (Found: N 5.58. Calc. for $C_{26}H_{24}N_2O_9$: N 5.51.)

Action of o-methoxyphenylmagnesium iodide on ethylidenemalonic ester. When 0.1 mole of ethylidenemalonic ester was allowed to react with 0.15 mole of *o*-methoxyphenylmagnesium iodide as previously described [1], no pure substance could be isolated by distillation under reduced pressure. Only impure 1-*o*-methoxyphenylethylmalonic ester was obtained in a yield of about 35 %. If the ratio of the ester to the Grignard reagent was changed to 1:2, a yield corresponding to about 50 % was obtained. The impurities seem to result from the pyrolysis of other reaction products than 1-*o*-methoxyphenylethylmalonic ester.

In order to obtain a sufficiently large quantity of the reaction product mixture, ethylidenemalonic ester (52.46 g) in dry ether (85 ml) was gradually added, with cooling, to a Grignard reagent prepared from magnesium (13.56 g) and *o*-iodoanisole (132 g) in dry ether (260 ml). The molar ratio of the ester to the Grignard reagent was thus 1:2. After the addition had been completed, the mixture was stirred for 20 min. The two layers formed were then poured into a mixture of hydrochloric acid, water and ice. After shaking, the organic phase was washed with water and potassium carbonate solution. After drying with sodium sulphate and evaporating the ether, an oil (105 g) was obtained.

After preliminary experiments the following separation method was considered most effective.

A sample of the oil (10.80 g) was dissolved in tetrachloromethane (50 ml). The solvent was then distilled off in order to remove any ether remaining in the oil. The residue was again dissolved in tetrachloromethane (50 ml) and this solution was transferred to a large chromatographic column consisting of standardized alumina (200 g; Riedel-de Haën A.G.) and tetrachloromethane. The chromatogram was developed with tetrachloromethane (650 ml) and the elution was performed first with ether (300 ml), then with ether and ethanol (1:1; 300 ml) and finally with ethanol (600 ml). After the solvents had been evaporated, it was found that the tetrachloromethane fraction contained 48.8 % (5.28 g) of the original oil, the ether fraction 35.4 % (3.83 g), the ether-ethanol fraction 6.6 % (0.71 g) and the ethanol fraction 1.7 % (0.18 g). The substance lost was 7.4 % (0.80 g).

When the combined tetrachloromethane fractions from two runs (22.03 g of the original oil in all) were worked up, a substance (8.61 g) boiling at 186—189°/12 mm was

obtained. The substance was in every respect identical with 1-*o*-methoxyphenylethylmalonic ester. The amount corresponds to a yield of about 49 % calculated on ethylidenemalonic ester. The forerun (1.36 g) in the distillation had a smell of anisole, but was not examined further.

Experiments conducted to separate the substances in the ether fraction chromatographically were not successful. A sample (17.81 g) of the combined residues was therefore examined in the following way. It was dissolved in ethanol (100 ml) and the solvent distilled off to drive away any remaining ether. The substance was then dissolved in ethanol (300 ml), a solution of potassium hydroxide (20 g) in water (20 ml) added, and the mixture heated on a boiling water bath. After 4 h it was cooled and kept for one night in a refrigerator. The mixture was filtered and the solid substance dissolved in water. By titrimetric analysis it was found that the substance was potassium carbonate (3.65 g in all). The ethanol was evaporated from the alkaline ethanolic filtrate and the residue treated with ether and water. After the evaporation of the solvent from the ether phase, an oil (8.51 g) was obtained. When this oil was treated with 2,4-dinitrophenylhydrazine, an impure hydrazone (8.00 g) was formed. After several recrystallizations from ethanol it melted at 158—159° and was identical with the above-mentioned 2,4-dinitrophenylhydrazone of 1,3-di-*o*-methoxyphenyl-1-butanone. On acidification of the aqueous phase, a resinous substance (5.70 g) was obtained. No pure substance has yet been isolated from it.

The ether-ethanol and the ethanol chromatographic fractions yielded no pure substance.

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