

butyrate, ethyl ( $\beta$ -ethoxyethyl)-ethylmalonate,  $\alpha$ -ethyl- $\gamma$ -ethoxybutyric acid.

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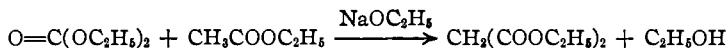
## THE CLEAVAGE OF DISUBSTITUTED MALONIC ESTERS BY SODIUM ETHOXIDE

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In the preceding paper the marked susceptibility of  $\beta$ -bromovinylethyl malonic ester and vinyl ethylmalonic ester to cleavage into the corresponding acetic esters and ethyl carbonate by means of alcoholic sodium ethoxide is pointed out. The isolation of  $\alpha$ -ethyl crotonamide from the attempted preparation of vinyl ethylbarbituric acid parallels the results reported by Dox and Thomas<sup>1</sup> in their unsuccessful attempts to prepare diphenylbarbituric acid from diphenylmalonic ester. That the susceptibility of the malonic ester to cleavage was the cause of the failure of the synthesis in the latter case is shown by an experiment performed in the present work in which diphenylmalonic ester was split quantitatively into diphenylacetic ester and ethyl carbonate in thirty minutes by refluxing with alcoholic sodium ethoxide. This cleavage is simply a reversal of the type of acetoacetic ester condensation which Lux<sup>2</sup> has applied to the synthesis of malonic ester from ethyl carbonate and ethyl acetate



If there is any analogy to the cleavage of the acetoacetic ester type, it would be expected from the work of Dieckmann<sup>3</sup> that the disubstituted malonic esters would be more readily cleaved by alcoholic sodium ethoxide than the monosubstituted or unsubstituted malonic esters. Experiments with diethyl- and monoethylmalonic esters reported in the experimental part of the paper indicate that such is the case.

It seemed likely that barbituric acids might be prepared from these more sensitive disubstituted malonic esters by condensing them with urea by means of dry, alcohol-free sodium ethoxide.<sup>4</sup> Preliminary experiments with diethylmalonic ester showed that such a condensation took place at 170°, the theoretical quantity of alcohol being distilled out of the reaction mixture in eight to ten minutes, and a yield of 55–65% of barbital obtained. Under similar conditions both vinyl ethylmalonic ester and diphenylmalonic

<sup>1</sup> Dox and Thomas, *THIS JOURNAL*, **45**, 1811 (1923).

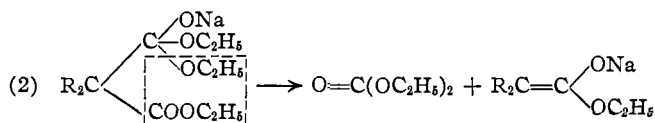
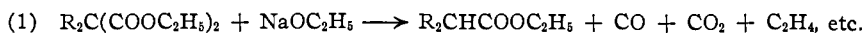
<sup>2</sup> Lux, *Ber.*, **62**, 1824 (1929).

<sup>3</sup> Dieckmann, *ibid.*, **33**, 2678 (1900).

<sup>4</sup> Cf. *Friedländer*, **7**, 655 (1903).

ester gave high yields of alcohol but in the case of the former ester a gummy, alkali-insoluble material was the main product obtained from the reaction mixture. The diphenylmalonic ester reaction yielded principally diphenylacetamide, the product obtained by Dox and Thomas from the reaction in alcoholic solution.

It was evident from these results, as well as from the discrepancy in the yields of alcohol and barbital in the case of diethylmalonic ester, that sodium ethoxide itself will cleave these disubstituted malonic esters. An investigation in this direction showed that in the main two distinctly different types of reaction take place, (1) the decomposition of the malonic ester directly into the disubstituted acetic ester, carbon monoxide, carbon dioxide and relatively small amounts of ethylene, diethyl ether, alcohol, and the disubstituted acetic acids; (2) the cleavage of the malonic ester into ethyl carbonate and presumably the sodium enolate of the disubstituted acetic ester, although definite evidence of the presence of this latter compound was obtained only in the case of diphenylmalonic ester. These reactions which are probably preceded by the formation of the sodium ethoxide addition product with a carboxy group of the malonic ester may be illustrated as follows



The temperature necessary to bring about the above reactions as well as the extent to which each of them takes place is dependent upon the nature of the substituent R groups. The pertinent data obtained from the malonic esters studied are summarized in Table I. The nature and amounts of the gaseous products were determined only in the case of

TABLE I  
THE CLEAVAGE OF DISUBSTITUTED MALONIC ESTERS BY SODIUM ETHOXIDE

Substituents	Temp. of reaction, C.	Yield of ethyl carbonate, %	Yield of $R_2CHCOOC_2H_5$ , %	Yield of ether, %	Recovered malonic ester, %
Diethyl	220-230	16	67	8	12
Ethyl, isoamyl	220-230	12	66	9	5
Ethyl, methyl- <i>n</i> -propylcarbonyl	220-230	4	64	11	6
Phenyl, ethyl <sup>a</sup>	120 (24 mm.)	58	38	0	4
Vinyl, ethyl <sup>a</sup>	100 (14 mm.) <sup>b</sup>	38	..	0	35
Diphenyl <sup>a</sup>	100 (20 mm.)	90	0	0	0

<sup>a</sup> The reactions of these esters were run under diminished pressure in order that the ethyl carbonate might distil as it was formed.

<sup>b</sup> At this temperature and pressure the recovered vinyl ethyl malonic ester distilled over unchanged with the ethyl carbonate.

diethylmalonic ester and consequently are not included in this table. The amount of reaction (1) was determined by the yield of the disubstituted acetic ester which distilled out of or was extractable from the reaction mixture by ether. The amount of reaction (2) was determined by the yield of redistilled ethyl carbonate. Obviously, these values are minima and since some if not all of the diethyl ether, which was obtained in some cases, may have been formed from the ethyl carbonate,<sup>5</sup> the yields of ether are included in the data.

It is evident from the above data that the dialkylmalonic esters as a group react mainly according to reaction (1), while diphenylmalonic ester reacts entirely according to reaction (2). Phenylethylmalonic ester is, as might be expected, intermediate between these two extremes, showing considerable amounts of both types of reactions. Vinylethylmalonic ester appears to show only reaction (2) but since the volatility of this ester prevents any large amount of reaction from taking place no definite conclusions may be drawn on this point. It is significant that of the disubstituted malonic esters which were studied, those containing a double bond in the  $\beta,\gamma$ -position relative to the carbethoxy groups are cleaved by sodium ethoxide at a relatively low temperature and mainly into ethyl carbonate.

The preparative value of these reactions should be mentioned. Dialkylacetic esters may be prepared directly from the reaction of dry sodium ethoxide on dialkylmalonic esters in a few minutes and in quite good yields. Although the yields are somewhat higher when the dialkylmalonic ester is split to the dialkylacetic ester by alcoholic sodium ethoxide (see experimental part), special equipment is required for this reaction. The cleavage of diphenylmalonic ester by sodium ethoxide is a novel and most satisfactory method for the preparation of the sodium enolate of diphenylacetic ester in a pure state.<sup>6</sup> This enolate was characterized by its conversion (in 81% yields) into ethyl diphenylacetic ester<sup>6</sup> through reaction with ethyl iodide. No evidence of the existence of stable enolates of the other disubstituted acetic esters was obtained. It may be that the higher temperatures necessary for reaction caused their decomposition or polymerization in the cases of the dialkylmalonic esters. However, with ethylphenylmalonic ester it is seen from the above data that a considerable yield of ethyl carbonate was obtained and that the reaction temperature was but slightly higher than that required for diphenylmalonic ester. Attempts to demonstrate the presence of this enolate by benzylating it to

<sup>5</sup> Cf. Geuther, *Centr.*, 39, 635 (1868). The observation of Geuther that carbon dioxide, ethyl alcohol and sodium carbonate are formed by the decomposition of sodium ethyl carbonate explains the presence of small amounts of alcohol obtained in the above reactions. It is possible that some of the ether might be formed from the reaction of sodium ethoxide with sodium ethyl carbonate.

<sup>6</sup> Cf. the preparation of the potassium enolate from diphenylacetic ester by Staudinger and Meyer, *Helv. Chim. Acta*, 5, 656 (1922).

the known ethylphenylbenzylacetic ester gave no isolable quantities of the latter compound. It would seem that since the association of the disubstituted acetic ester enolate with ethyl carbonate is so apparent in the case of the diphenyl compound, their transitory existence must be assumed in the other instances. This assumption is substantiated by the fact that in these instances the extent of tar formation parallels the yield of ethyl carbonate.

### Experimental

**Materials Used.**—Sodium ethoxide was prepared by the reaction of powdered sodium with a 1% excess of absolute alcohol in dry ether.<sup>7</sup> The purity of the product was established by analysis for sodium. Diethylmalonic ester was purified by washing with hot 25% potassium hydroxide<sup>8</sup> and distillation. Monoethylmalonic ester, ethyl isoamylmalonic ester and ethyl methyl-*n*-propylcarbonylmalonic ester were kindly furnished by Mr. H. A. Shonle of The Lilly Research Laboratories, Indianapolis, Indiana. Ethyl phenylmalonic ester was supplied in liberal quantities by Dr. V. H. Wallingford of the Mallinckrodt Chemical Works, St. Louis, Missouri. Each of these esters was fractionated before use. Vinylethylmalonic ester is described in the preceding paper.

Diethylmalonic ester was prepared by the following modification of the procedure of Dox and Thomas.<sup>1</sup> To a cooled solution of 90 g. of oxomalonic ester in 270 g. of benzene was added 180 g. of 100% sulfuric acid (prepared by the addition of the calculated quantity of fuming sulfuric acid to the ordinary concentrated acid). The mixture was stirred and heated gradually in a water-bath to 65–70° and held at that temperature for seven hours. It was then poured onto ice, the benzene layer separated, and the acid aqueous solution extracted with benzene. The benzene extracts were combined, washed with water and sodium bicarbonate solution and then distilled. After removal of the benzene, 41 g. of diphenylmalonic ester, b. p. 192–194° (5 mm.), which solidified to a solid, m. p. 57–60°, was obtained. One recrystallization of this product from 175 cc. of alcohol gave 30 g. of product, m. p. 62–63°. The high purity of this product was proved by saponification of a 1-g. sample in an aqueous-alcoholic sodium hydroxide solution, followed by acidification with dilute sulfuric acid and absorption of the carbon dioxide evolved in ascarite. From 1 g. of the ester (m. p. 62–63°), 0.1418 g. of carbon dioxide (100.5%) was obtained. Material melting at 60–62° was found to be 98.3% pure by this method.

The procedure described by Dox and Thomas<sup>1</sup> was found in the present work to give a lower melting (58–59°) product.

**Barbituric Acid Synthesis with Dry Sodium Ethoxide.**—A mixture of 10 g. (1 mol) of diethylmalonic ester, 4.2 g. (1.7 mol) of urea and 9.5 g. (3 mols) of sodium ethoxide was heated in a two-necked 100-cc. flask, fitted with a mercury-seal stirrer and a condenser set for distillation, by an oil-bath to 170°. In twelve minutes 9.3 g. (109%) of ethyl alcohol had distilled out of the reaction mixture. The residue was decomposed with dilute hydrochloric acid and the diethylbarbituric acid recrystallized once from hot water. The yield was 5.55 g. (65%).

When this procedure was followed using vinylethylmalonic ester instead of diethylmalonic ester 101% of the calculated quantity of alcohol distilled out in ten minutes. The residue was only partially soluble in alkali, and this soluble portion gave a red gum on acidification. The major portion of the reaction was an alkali-insoluble

<sup>7</sup> Cf. Houben-Weyl, 1922, Vol. II, p. 578.

<sup>8</sup> Michael, *J. prakt. Chem.*, **72**, 551 (1905).

resinous material. From 5 g. of diphenylmalonic ester 68% of the expected alcohol was obtained in twelve minutes. From the residue 0.62 g. of diphenylacetic acid and 1.31 g. of diphenylacetamide, m. p. 168–169°, were isolated.

**The Cleavage of Substituted Malonic Esters with Alcoholic Sodium Ethoxide. 1. Diphenylmalonic Ester.**—To a solution of 0.46 g. (1 atom) of sodium in 50 cc. of absolute alcohol was added 6.24 g. (1 mol) of diphenylmalonic ester. After refluxing this solution for thirty minutes, the alcohol was removed under diminished pressure, the residue treated with water and then extracted with ether. After drying, the ether extract was distilled; 4.33 g. (81%) of ethyl diphenylacetate, b. p. 186–189° (20 mm.), m. p. 60–61°, was obtained. This product showed no depression of melting point when mixed with an authentic specimen.

**2. Diethylmalonic Ester.**—A solution of 11.5 g. (1 atom) of sodium in 200 cc. of absolute alcohol and 108 g. (1 mole) of diethylmalonic ester were placed in the brass liner of a steel bomb and heated for six hours at 250° under an initial hydrogen pressure of 1000 pounds. The contents of the bomb were then filtered with suction and the solid material (sodium carbonate or sodium ethyl carbonate) was washed with ether. These washings were added to the filtrate. Fractionation of this solution yielded 58.9 g. (82%) of ethyl diethylacetate, b. p. 147–150°, and 12 g. (11%) of unchanged diethylmalonic ester.

**3. Monoethylmalonic Ester.**—When the above procedure was repeated using 94 g. of monoethylmalonic ester and 2 equivalents of sodium ethoxide, 30 g. (52%) of ethyl butyrate and 19.5 g. (21%) of the unchanged malonic ester were obtained.

**The Cleavage of Disubstituted Malonic Esters by Dry Sodium Ethoxide.**—The experiments with the dialkylmalonic esters were all carried out in the same manner except that the nature and amounts of the gaseous products of the reaction were determined only in the case of diethylmalonic ester. A description of the procedure used for the latter compound will suffice for this type.

A mixture of 108 g. (1 mole) of diethylmalonic ester and 34 g. (1 mole) of sodium ethoxide was placed in a 500-cc. Claisen flask, fitted with a mercury-seal stirrer and connected to a distillate receiver. This receiver was connected through a trap surrounded by a mixture of ice and hydrochloric acid to a graduated carboy filled with a saturated salt solution which served as a gas receiver. The flask was immersed in an oil-bath which was heated rapidly to 220–230° and kept at that temperature for thirty minutes. During this time 70 g. of distillate and 6 liters of gas were collected. The receiver was then changed, the stirrer in the reaction flask replaced by a solid stopper and a vacuum applied to the reaction flask. An additional 14 g. of distillate was thereby collected. An analysis of the collected gas showed that yields of 14% of ethylene and 25% of carbon monoxide had been obtained. Fractionation of the combined distillates through a Widmer column gave the following products: 3.0 g. (8%) ether, b. p. 35–38°; 1.45 g. ethyl alcohol, b. p. 77–79°; 9.5 g. (16%) ethyl carbonate, b. p. 126–128°; 48.2 g. (67%) ethyl diethylacetate, b. p. 147–150°; 12 g. (12%) diethylmalonic ester. The residue in the reaction flask on acidification yielded large quantities of carbon dioxide and a small amount of diethylacetic acid. A quantitative determination of the carbon dioxide on a smaller run showed that it was formed to the extent of 35% of the theoretical.

Ethyl  $\alpha$ -ethyl- $\beta$ -methylcaproate (I) and ethyl  $\alpha$ -ethyl- $\beta$ -methylcaproate (II), which were obtained from ethylisoamylmalonic ester and ethylmethyl-*n*-propylcarbonylmalonic ester, respectively, as well as the acid (III) obtained from the saponification of (II), are new compounds. Their properties and analyses are given in Table II.

In the case of diphenylmalonic ester 12.4 g. (1 mole) of the ester and 2.7 g. (1 mole) sodium ethoxide were placed in a 100-cc. two-necked flask connected by one neck

TABLE II  
 PHYSICAL PROPERTIES AND ANALYSES

Compound	Formula	B. p., °C.	$d_{25}^{25}$	$n_D^{25}$	$M_D$		Analyses %		C, H Found	
					Calcd.	Found	Calcd.	%	Found	%
I <sup>a</sup>	C <sub>11</sub> H <sub>22</sub> O <sub>2</sub>	197-198	0.8560	1.41481	54.60	54.59	70.90	11.91	70.70	11.78
II	C <sub>11</sub> H <sub>22</sub> O <sub>2</sub>	197-198	.8671	1.41885	54.60	54.36	70.90	11.91	70.95	11.97
III	C <sub>9</sub> H <sub>18</sub> O <sub>2</sub>	230-232	.9087	1.43015	45.23	45.16	68.29	11.47	68.19	11.40

<sup>a</sup> This ester was also characterized by conversion to the corresponding amide, m. p. 109-110°. Tiffeneau, *Bull. soc. chim.*, **33**, 183 (1923), reports this amide as melting at 106-108°.

to a distillate receiver surrounded by solid carbon dioxide-ether mixture and carrying in the other neck a stirrer fitted with machined conical bearings which allowed for its operation under diminished pressure. The flask was heated in an oil-bath for forty minutes at 100° under 20 mm. pressure. The distillate was ethyl carbonate which on redistillation boiled at 125-126° and weighed 4.25 g. (90%). The residue in the reaction flask was insoluble in ether, but was decomposed by ether containing dry hydrogen chloride into sodium chloride and pure diphenylacetic ester, m. p. 60-61°.

Vinylethylmalonic ester (10.7 g.) and an equivalent of sodium ethoxide after ten minutes at 100° and 14 mm. pressure gave a distillate which upon fractionation was separated into 2.23 g. (38%) of ethyl carbonate and 3.82 g. (35.4%) of unchanged vinylethylmalonic ester. The organic portion of the residue was entirely polymerized material from which nothing definite could be isolated.

Ethylphenylmalonic ester (66 g.) reacted readily at 120° with an equivalent of sodium ethoxide and after thirty minutes under 24 mm. pressure a distillate was obtained which on redistillation gave 17.2 g. (58%) of ethyl carbonate. The temperature of the oil-bath was then raised to 200°, whereupon 24.7 g. of distillate came over. Fractionation of this distillate yielded 18.4 g. (38%) of ethyl  $\alpha$ -phenylbutyrate, b. p. 117-119° (17 mm.), and 2.5 g. (4%) of ethylphenylmalonic ester.

Alkylation Experiments with the Ester Enolates.—The residue remaining after the distillation of ethyl carbonate from the above described reaction of diphenylmalonic ester and sodium ethoxide at 100° was treated with 25 cc. of ethyl iodide and refluxed for fifteen hours. This reaction mixture was then taken up in ether, washed with water, dried and distilled. The yield of ethyl ethyldiphenylacetate, b. p. 186-188° (15 mm.), was 8.66 g. (81%). Two grams of this ester yielded on saponification 1.7 g. (95%) of ethyl diphenylacetic acid,<sup>6</sup> which after one recrystallization melted at 173-174°.

The red, viscous residue that remained after the reaction of ethylphenylmalonic ester with sodium ethoxide at 120° was treated with an excess of benzyl chloride instead of raising the temperature to remove any undistilled ethyl  $\alpha$ -phenylbutyrate as described above. This mixture was heated under reflux for sixteen hours at 160-170°. When the reaction product was fractionated 15 g. (31%) of ethyl  $\alpha$ -phenylbutyrate, 22 g. of higher boiling material and 24 g. of tar were obtained. However, saponification of the higher boiling material gave no trace of  $\alpha$ -phenyl- $\alpha$ -benzylbutyric acid which has been described<sup>9</sup> as a solid melting at 140°.

### Summary

The cleavage of certain substituted malonic esters by alcoholic sodium ethoxide and by dry sodium ethoxide is reported. It is shown that with the former reagent these esters are cleaved smoothly into the substituted acetic esters. With the latter reagent the disubstituted malonic esters

<sup>9</sup> Blondeau, *Ann. chim.*, [10] **3**, 5 (1924).

undergo in the main two types of cleavage, (1) into the disubstituted acetic esters and simpler decomposition products and (2) into ethyl carbonate and the sodium enolate of the disubstituted acetic esters. The nature of the substituent groups determines the readiness and manner in which these malonic esters are cleaved.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY]

## THE CONDENSATION OF CERTAIN PHENOLS WITH SOME ALIPHATIC ALDEHYDES<sup>1</sup>

BY WILTON C. HARDEN AND E. EMMET REID

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Recently there have been many studies of the bactericidal power of series of substituted phenols and phenol derivatives. Johnson and his co-workers.<sup>2</sup> Dohme, Cox and Miller<sup>3</sup> and Leonard<sup>4</sup> have studied the alkyl resorcinols. Other reports in this field have been made by Hampil,<sup>5</sup> Schaffer and Tilley,<sup>6</sup> Rettger and his co-workers,<sup>7</sup> and Klarmann.<sup>8</sup>

The bactericidal properties of the alkyl phenols have been studied by Schaffer and Tilley,<sup>6</sup> Rettger, Plastridge and Valley,<sup>9</sup> and the alkyl cresols by Coulthard, Marshall and Pyman.<sup>10</sup> Klarmann and his collaborators<sup>11</sup> have made an extensive investigation of the mono ethers of dihydric phenols, and recently Read and Miller<sup>12</sup> have reported on certain substituted phenols.

The present investigation is concerned with several series of di-(hydroxy-phenyl)-alkyls of the general type

$$\text{HO} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \text{X} \quad \text{Y} \\ \diagdown \quad \diagup \end{array} \text{C} \begin{array}{c} \text{H} \\ | \\ \text{R} \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \text{Y} \quad \text{X} \\ \diagdown \quad \diagup \end{array} \text{OH}$$

These

were all prepared by the Baeyer reaction<sup>13</sup> which has been used by

<sup>1</sup> From the Ph.D. dissertation of Wilton C. Harden, Johns Hopkins University, 1932.

<sup>2</sup> Johnson and Hodge, *THIS JOURNAL*, **35**, 1014 (1913); Johnson and Lane, *ibid.*, **43**, 348 (1921).

<sup>3</sup> Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926).

<sup>4</sup> Leonard, *J. Am. Med. Assoc.*, **83**, 2205 (1924).

<sup>5</sup> Hampil, *J. Infectious Diseases*, **43**, 25 (1928).

<sup>6</sup> Schaffer and Tilley, *J. Bacteriology* **12**, 303 (1926); **14**, 259 (1927).

<sup>7</sup> Rettger, Valley and Plastridge, *Zentr. Bakt. Orig.*, **110**, 80 (1929).

<sup>8</sup> Klarmann, *THIS JOURNAL*, **48**, 791 (1926); **48**, 2358 (1926); Klarmann and Von Wovern, *ibid.*, **51**, 605 (1929).

<sup>9</sup> Rettger, Plastridge and Valley, *Zentr. Bakt. Orig.*, [I] **111**, 287 (1929).

<sup>10</sup> Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).

<sup>11</sup> Klarmann, *THIS JOURNAL*, **53**, 3397 (1931); **54**, 298 (1932); **54**, 1204 (1932).

<sup>12</sup> Read and Miller, *ibid.*, **54**, 1195 (1932).

<sup>13</sup> Baeyer, *Ber.*, **5**, 280, 1096 (1872).