The base was liberated from the hydrochloride and distilled as a colorless viscous oil, which failed to crystallize; b. p. 198–200° (0.5 mm.); $n^{25}\mathrm{D}$ 1.5643.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.53; H, 6.77; N, 4.29.

Acknowledgment.—The authors wish to thank Mr. E. F. Shelberg and the members of the Microanalytical Department for the microanalyses and Mr. Morris Freifelder for his assistance in the hydrogenation experiments.

Summary

A new synthesis of N-(3-methoxybenzyl)-N-methyl-3-methoxy-4,5-methylenedioxyphenethylamine is reported and additional physical data for this compound and its intermediates are described.

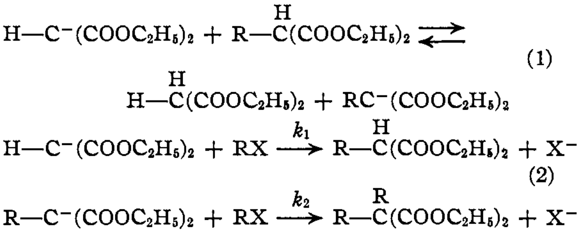
NORTH CHICAGO, ILLINOIS RECEIVED JANUARY 13, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Alkylation of Malonic Ester

BY RALPH G. PEARSON

The relative amounts of mono- and dialkylation obtained in the reaction of equivalent amounts of malonic ester, sodium alcoholate and an alkyl halide depends on two factors: first, the relative acidities of the substituted and unsubstituted malonic esters; and, secondly, the rates of reaction of the two ester anions with the alkyl halide



$$\mathrm{H{-}C^{-}(COOC_2H_5)_2 + R{-}\overset{H}{C}(COOC_2H_5)_2 \rightleftarrows H{-}\overset{H}{C}(COOC_2H_5)_2 + RC^{-}(COOC_2H_5)_2} \qquad (1)$$

$$\mathrm{H{-}C^{-}(COOC_2H_5)_2 + RX \xrightarrow{k_1} R{-}\overset{H}{C}(COOC_2H_5)_2 + X^{-}} \qquad (2)$$

$$\mathrm{R{-}C^{-}(COOC_2H_5)_2 + RX \xrightarrow{k_2} R{-}\overset{R}{C}(COOC_2H_5)_2 + X^{-}}$$

Presumably the effect of an alkyl group is acid weakening so that the equilibrium in (1) lies well to the left. The effect of an alkyl group on the rate of (2) is not known for malonic ester.

This paper presents the results of attempted measurements of the acid ionization constants of malonic ester and ethylmalonic ester in absolute ethanol, and of the rates of reaction of the sodium salts with ethyl bromide in the same medium. These quantities were determined for malonic ester but the acidity of ethylmalonic ester proved too low for either measurement to be made accurately.

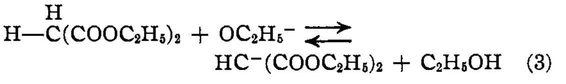
Experimental

Diethyl malonate was purified by two fractionations through a ten-plate column, $n^{25}\mathrm{D}$ 1.4112, d^{25}_{4} 1.0490. Ethyl diethylmalonate was made by standard procedures[1] and repeatedly fractionated, $n^{25}\mathrm{D}$ 1.4141, d^{20}_{4} 0.9982. C. P. ethyl bromide was fractionated and a constant-boiling, middle-fraction taken. Ethyl alcohol was dried by the method of Manske[2] and protected from moisture as far as possible. Solutions of sodium ethoxide were made by dissolving freshly cut sodium metal in dry alcohol and analyzed by titration. Both the acidities and the rates of reaction were measured by utilizing the large changes in electrical resistance that occur when malonic ester is converted to its sodium salt and when the sodium salt reacts with ethyl bromide. Selected volumes of the reactants were mixed at the reaction temperature, placed in a conductivity cell and thermostated at 25.0 ± 0.02°. Measurements of the resistances were made with a Jones-Josephs bridge.

The solutions of sodium ethoxide were not stable and were prepared fresh for each run. Ethyl bromide stock solutions in alcohol were alcoholyzed very slowly and could be kept for several days in the cold room.

Calculations and Results

The method of obtaining acid ionization constants is similar to that of Goldschmidt[3] who measured the hydrolysis of salts of weak acids in ethanol. Resistances of solutions containing a fixed concentration of sodium ethoxide and varying amounts of malonic ester were measured. The resistance increased with the concentration of malonic ester because of the replacement of ethoxide ion by the less mobile malonic ester anion. Because of the weak acidity of the ester this change is not complete for any solution experimentally available. However, if R_0 is the resistance when the malonic ester concentration is zero and R the resistance when the concentration is c then a plot of $R/(R - R_0)$ against $1/c$ gives a straight line which can be extrapolated to $1/c$ equal to zero. This gives a value of R_∞ which is the resistance of a hypothetical solution of infinite ester concentration and in which all of the sodium ethoxide has been converted to sodiomalonic ester. From values of R_∞, R_0 and R the fraction of ethoxide ion converted to ester anion can be found for any solution (by assuming the ionic conductivities are additive) and the concentration equilibrium constant K_1 for (3) determined.



$$\mathrm{H{-}\overset{H}{C}(COOC_2H_5)_2 + OC_2H_5^{-} \rightleftarrows HC^{-}(COOC_2H_5)_2 + C_2H_5OH} \qquad (3)$$

The experimental and calculated results are given in Table I. The effect of malonic ester on a neutral electrolyte, potassium iodide, was also checked. The relatively small increase in resistance for the latter is due to viscosity effects and a correction of the same magnitude was applied to the measured resistances with sodium ethoxide before calculations were made. Table II gives

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[1] "Organic Syntheses," Coll. Vol. I, (1941), p. 250.

[2] Manske, THIS JOURNAL, **53**, 1106 (1931).

[3] Goldschmidt, *Z. physik. Chem.*, **99**, 116 (1921).

the results of resistance measurements with ethylmalonic ester.

TABLE I

ACIDITY OF MALONIC ESTER IN ETHANOL AT 25°

0.0279 *M* Sodium Ethoxide		0.0240 *M* Potassium Iodide	
Malonic ester, molar	Resistance, ohms	Malonic ester, molar	Resistance, ohms
0.0000	3606	0.0000	2890
.0099	3976	.0793	2935
.0199	4386	.1585	2963
.0793	6260		
.1585	8192		
∞	13910 (calcd.)	$K_1 = 22 \pm 1$	

TABLE II

ACIDITY OF ETHYL MALONIC ESTER AT 25°
0.0287 *M* Sodium Ethoxide

Ethyl malonic ester, molar	Resistance, ohms[a]
0.0000	3437
.0457	3474
.0914	3537
.1828	3649

$K_2 \sim 0.3$

[a] These values are extrapolated back to time of mixing, since the resistance increases slowly due to hydrolysis of the ester.

Kinetic studies were made on solutions containing 12–30-fold excess ethyl bromide and at least fourfold excess of malonic ester over sodium ethoxide. Under these conditions pseudo first-order kinetics were obtained. Figure 1 shows the results of plotting log $((R - Re)/R)$ against the time, where R is the resistance at time $= t$ and Re is the resistance at the completion of the reaction. The linearity confirms first-order kinetics.[4] Because of the incompleteness of reaction (3) the slope also varies with the ratio of malonic ester to sodium ethoxide. Any free ethoxide ion will also react with ethyl bromide to give ether.

$$OC_2H_5^- + C_2H_5Br \xrightarrow{k_3} C_2H_5OC_2H_5 + Br^-$$

So that the total appearance of bromide ion is given by

$$d(Br^-)/dt = k_1 \text{ [ester anion][ethyl bromide]} + k_3 \text{ [ethoxide ion][ethyl bromide]} \quad (4)$$

From (3)

$$\text{[ester anion]/[ester][ethoxide ion]} = K_1 \quad (5)$$

also

$$\text{[ester anion]} + \text{[ethoxide ion]} = (a - x)$$

where a is the initial concentration of ethoxide ion and x is the concentration of bromide ion. So that

$$\text{[ethoxide ion]} = (a - x)/[1 + K_1\text{[ester]}]$$
$$\text{[ester anion]} = (a - x)\,K_1\text{[ester]}/[1 + K_1\text{[ester]}] \quad (6)$$

and (4) becomes

$$\frac{dx}{dt} = \frac{k_1K_1\text{[ester]} + k_3}{[1 + K_1\text{[ester]}]}\text{[ethyl bromide]}\,(a - x) \quad (7)$$

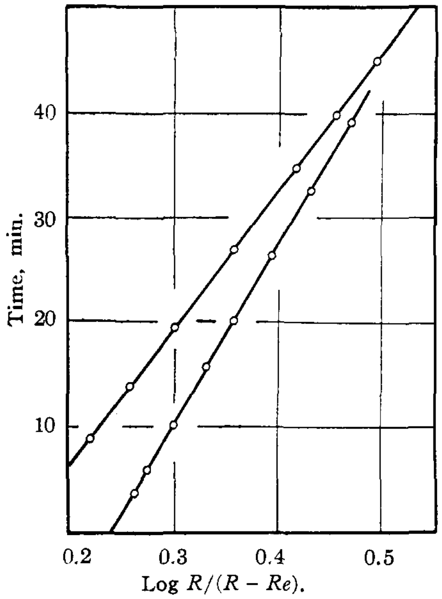

Fig. 1.—Upper curve: 0.0445 *M* sodium ethoxide, 0.298 *M* malonic ester, 0.526 *M* ethyl bromide; lower curve: 0.0282 *M* sodium ethoxide, 0.153 *M* malonic ester, 0.482 *M* ethyl bromide.

Hence the observed second order rate constant obtained by multiplying the slope by 2.303 and dividing by the concentration of ethyl bromide is equal to

$$k_{obs.} = [k_1K_1\text{[ester]} + k_3]/[1 + K_1\text{[ester]}] \quad (8)$$

The value of k_3, the rate constant for the reaction of ethoxide ion with ethyl bromide, was obtained by direct measurement. Putting in the previously measured value of K_1, one can obtain k_1 from (8) for various values of the concentration of ester.[5] Table III summarizes the results obtained. The constancy of k_1 is sufficiently good to justify the value of K_1 used.

TABLE III

RATE OF ALKYLATION OF MALONIC ESTER

Ethyl bromide, *M*	Malonic ester, *M*	Sodium ethoxide, *M*	$k_{obs.}$	k_1 liters/ mole-min.
0.690	0.521	0.0270	0.0343	0.0370
.526	.298	.0445	.0335	.0384
.713	.201	.0301	.0306	.0371
.482	.153	.0282	.0280	.0358
.393	.0780	.0192	.0232	.0355
.552	.0000	.0467	.0051[a]	....
.691	.195[b]	.0292	.0308	.0375

[a] This value of $k_{obs.}$ is simply equal to k_3, Taylor [*J. Chem. Soc.*, 1514 (1935)] found the second order rate constant for ethyl bromide at 25° to be 0.0036 with sodium hydroxide and 0.0046 with potassium hydroxide both in absolute ethanol. [b] This run also contained 0.166 molar ethylmalonic ester.

It was not possible to measure the rate of reaction of ethylmalonic ester anion with ethyl

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(4) Pearson, THIS JOURNAL, 69, 3100 (1947).

(5) The value of the ester concentration is that of free ester, correcting for that used up in salt formation.

TABLE IV

RATE OF ALKYLATION OF ETHYLMALONIC ESTER

Ethyl bromide, M	Ester, M	Sodium ethoxide, M	$k_{obs.}$	k_2K_2
0.552	0.000	0.0467	0.0051	....
.694	.148	.0303	.0067	0.0108
.675	.288	.0310	.0089	.0132

bromide exactly because of the low concentration of ester anion formed. However, it was possible to show that the addition of ethylmalonic ester to a solution of sodium ethoxide and ethyl bromide increases the rate of liberation of bromide ion as determined by titration with standard silver nitrate.[6] The appearance of bromide ion followed first-order kinetics and the rate constants were determined for varying concentrations of ester. If we set $k_{obs.} \simeq k_2K_2[\text{ester}] + k_3$, the product k_2K_2 can be evaluated. The results are shown in Table IV.

Discussion

The acid ionization constant for malonic ester may be found by multiplying K_1 by the ion product of ethanol at 25°, 7.28×10^{-20}, as found by Danner.[7] Although the conductance data on ethylmalonic ester do not allow a precise value of the acidity to be calculated, one can estimate, by assuming that the value of R_∞ is the same for ethylmalonic ester and malonic ester, that the value of K_2 is between 0.2 and 0.4. The acid ionization constants are 1.6×10^{-18} and about 2×10^{-20} for malonic and ethylmalonic ester, respectively. The effect of the alkyl group is to lower the acidity 50–100-fold. Although the rate constant k_2 was not found, it is almost as instructive to compare the ratio k_1K_1/k_2K_2 since for equal concentrations of the two esters it will be this ratio which determines the amounts of monoalkylation and dialkylation. The ratio is about 70 to 1 in favor of monoalkylation in this particular case. For other alkyl halides the ratio might be quite different of course. The results of Conrad and Bruckner[8] indicate that the rate of alkylation is increased by an alkyl substituent. These workers measured the rate constants for the alkylation of acetoacetic ester and its α-substituted derivatives with ethyl iodide and found the rate sequence to be benzyl > methyl > ethyl > H > phenyl with the α-ethyl ester some four times faster than the unsubstituted ester.

One concludes then that even though the equilibrium in (1) is favorable only to monoalkylation, still considerable dialkylation may occur near the end of a synthesis where the concentration of malonic ester is low and that of alkylmalonic ester is high. If an excess of malonic ester over sodium ethoxide is used, the dialkylation should be greatly reduced.[9] This is indicated also by the last entry in Table III which shows that the presence of an equal amount of ethylmalonic ester does not affect the rate of alkylation of unsubstituted malonic ester. If dialkylation is desired, the reaction medium should preferably be an aprotic solvent because of the failure of the monoalkylated ester to form salts in alcohol.

Acknowledgment.—The author wishes to thank Mr. James Tucker for some of the resistance measurements described.

Summary

The acidity and rate of alkylation of malonic ester in dry ethanol were measured. Similar measurements on ethylmalonic ester could not be made because of its weak acidity, but a quantity proportional to the product of acid ionization constant and rate constant for alkylation was determined.

EVANSTON, ILLINOIS RECEIVED SEPTEMBER 27, 1948

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[6] The alcohol must be freshly dried or a slow hydrolysis of the ester by traces of water destroys the sodium ethoxide.

[7] Danner, THIS JOURNAL, **44**, 2832 (1922).

[8] Conrad and Bruckner, *Z. physik. Chem.*, **99**, 116 (1921).

[9] (a) Cohen, Marshall and Woodman, *J. Chem. Soc.*, **107**, 887 (1915); (b) Leuchs, *Ber.*, **44**, 1507 (1911); (c) Grigsby, Hind, Chanley and Westheimer, THIS JOURNAL, **64**, 2606 (1942).