[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

Para-Methoxyphenylmalonic Acid and its Derivatives[1]

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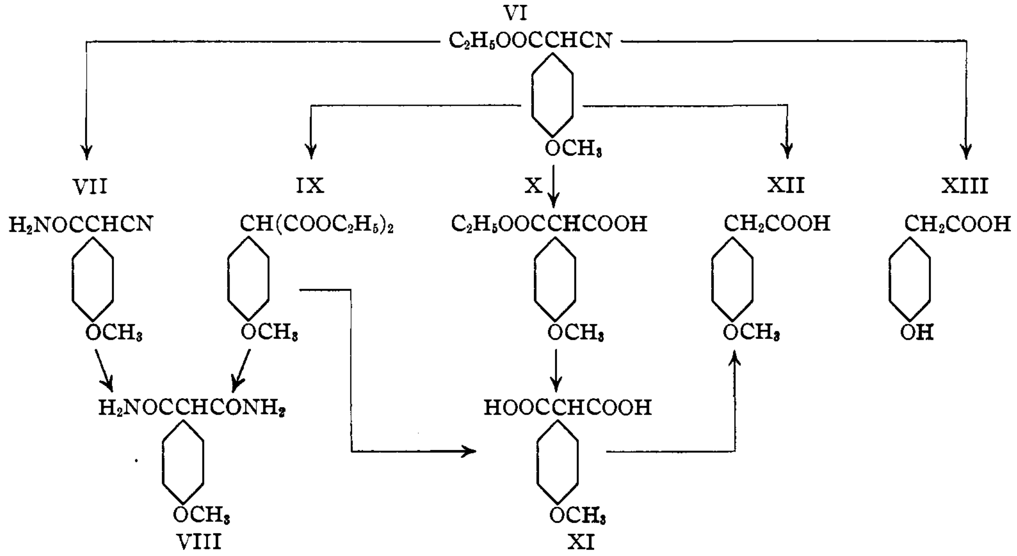
While the chemistry of phenylmalonic acid and its derivatives appears to be rather well studied, the preparation of its phenolic derivatives seems to be limited to that of the methyl ethyl ester of *p*-hydroxyphenylethylmalonic acid and its methyl ether,[3] which, since no reactive hydrogen is present, are not suitable for further alkylation reactions. The object of the present investigation was to prepare suitable derivatives of the *p*-hydroxyphenylmalonic acid which would contain such a reactive hydrogen atom, replaceable by metallic sodium, for use in synthesis. Ethyl *p*-methoxyphenylcyanoacetate (VI) was prepared by the following series of reactions: $C_6H_5CH_2CN$ (I) $\longrightarrow$ *p*-$NO_2C_6H_4CH_2CN$ (II) $\longrightarrow$ *p*-$NH_2C_6H_4CH_2CN$ (III) $\longrightarrow$ *p*-$HOC_6H_4CH_2CN$ (IV) $\longrightarrow$ *p*-$CH_3OC_6H_4CH_2CN$ (V) $\longrightarrow$ *p*-$CH_3OC_6H_4CH(CN)COOC_2H_5$ (VI). The ethyl *p*-methoxyphenylcyanoacetate (VI) was converted by usual methods to the following compounds: *p*-$CH_3OC_6H_4CH(CN)CONH_2$ (VII) and *p*-$CH_3OC_6H_4CH(COOC_2H_5)_2$ (IX); *p*-$CH_3OC_6H_4CH(COOH)COOC_2H_5$ (X) was formed as a by-product in the preparation of the last compound. The di-ester (IX) was converted into the diamide (VIII) and the free dibasic acid (XI). *p*-Methoxyphenylacetic acid (XII) was obtained from the original ester-nitrile (VI) by acid hydrolysis and from the *p*-methoxyphenylmalonic acid (XI) on heating. Hydrolysis with hydrobromic acid of the original ester-nitrile (VI) resulted in the formation of *p*-hydroxyphenylacetic acid (XIII). The last two compounds (XII and XIII) were identified conclusively by quantitative analysis and mixed melting points with standard samples. The structural relationship of these compounds is as follows



The ethyl *p*-methoxyphenylcyanoacetate (VI) was alkylated readily with methyl iodide and ethyl bromide, yielding the corresponding *p*-methoxyphenylalkyl cyanoacetic acid esters (XIV, XVI), which were converted to the corresponding cyanoacetamides (XV, XVII).

Attempts to shorten the synthesis of the initial *p*-hydroxyphenylmalonic acid or any of its derivatives (methyl ether, etc.) included the following studies: (a) direct condensation of ethyl malonate with phenol, (b) rearrangement of phenoxymalonic acid and several of its derivatives, and (c) solvent exchange reactions, *i. e.*, the action of metallic sodium and carbon dioxide upon a mixture of *p*-cresyl methyl ether and amyl

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(2) Some of the material is taken from the thesis presented by Roslyn T. Roth to the faculty of the Graduate School of New York University in partial fulfilment for the degree of Doctor of Philosophy.

(3) Bousquet and Adams, THIS JOURNAL, **52**, 224 (1930).

TABLE I

PHYSICAL CONSTANTS AND ANALYSES OF COMPOUNDS

	Compound		M. p. or b. p., °C.	Mm.	Sp. gr. 24°	n^{23}_D	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	p-Methoxyphenylmalonic acid												
VI	Et ester nitrile	B	152–153	2	1.148	1.5175	$C_{12}H_{13}NO_3$	65.80	66.03	5.94	5.84	6.39	6.38
VII	Nitrile amide	M	144–145				$C_{10}H_{10}N_2O_2$	63.16	63.01	5.26	4.74	14.73	14.51
VIII	Diamide	M	190–191				$C_{10}H_{12}N_2O_3$	57.69		5.76		13.46	13.23
IX	Diester	B	152–153	2.5	1.115	1.4995	$C_{14}H_{18}O_5$	63.16	63.45	6.77	7.05		
X	Monoethyl ester	M	77–78				$C_{12}H_{14}O_5$	60.51		5.89	N. eq.,	238	246
XI	Free acid	M	137–138				$C_{10}H_{10}O_5$	57.15	57.43	4.76	5.03		
											N. eq.,	105	106
	p-Methoxyphenylmethylmalonic acid												
XIV	Et ester nitrile	B	136–138	0.5	1.143	1.5106	$C_{13}H_{15}NO_3$	66.95	67.04	6.43	6.30	6.00	6.02
XV	Nitrile amide	M	143–144				$C_{11}H_{10}N_2O_2$	65.34		4.95		13.46	13.50
	p-Methoxyphenylethylmalonic acid												
XVI	Et ester nitrile	B	142–143	0.5	1.139	1.5090	$C_{14}H_{17}NO_3$	68.01	68.15	6.88	6.66	5.66	5.90
XVII	Nitrile amide	M	138				$C_{12}H_{14}N_2O_2$	66.05		6.42		12.83	12.61

chloride according to A. A. Morton and I. Hechenbleikner.[4] In this last reaction the 5-methyl-2-methoxybenzoic acid was formed. Thus in none of these reactions did the formation of the desired *p*-hydroxyphenylmalonic acid or its derivatives take place.

Experimental

***p*-Methoxyphenylmalonic Acid Ethyl-ester-nitrile (VI). Preparation.**—To a mixture of one atomic weight equivalent of cut clean sodium or sodium dust in 300 cc. of anhydrous ether was added 1 mole of freshly distilled diethyl carbonate and the mixture thoroughly stirred. One mole of *p*-methoxybenzyl cyanide (V) was then added slowly through a separatory funnel. The mixture was left standing overnight, refluxed for about two hours, cooled, acidified with ice-cold 25% sulfuric acid, extracted with ether, and the ether extracts washed with 5% sodium carbonate solution to remove the small amount of anisic acid which is formed as a by-product. The ether was evaporated and the remaining oil fractionally distilled; yield, 50–55%.

Hydrolysis. (a) With Ammonium Hydroxide Solution.—One gram of the ester-nitrile (VI) was dissolved in 8 cc. of concd. ammonium hydroxide solution. After standing for about one hour the *p*-methoxylphenylmalonic acid amide-nitrile (VII) crystallized out: yield, approx. 80%. The compound was recrystallized from 50% alcohol. The amide nitriles of *p*-methoxymethyl- (XV) and *p*-methoxyethylphenylmalonic acids (XVII) were prepared in a similar manner.

(b) With Sodium Hydroxide Solution.—Treatment of an ether solution of the cyanoacetate (VI) with 6% or 3% sodium hydroxide resulted, on neutralization, in a mixture of hydrolysis products involving the cyano and acetate groups. On long standing of the alkaline mixture the chief product was *p*-methoxyphenylmalonic acid (XI).

(c) With Alcoholic Hydrogen Chloride.—A mixture of 5.3 g. of the cyanoacetate (VI), 8 cc. of ethyl alcohol, and 0.25 cc. of water was placed in a flask provided with a reflux condenser and a gas inlet tube of fine bore. The mixture was treated with dry hydrogen chloride, first while cold, then for fifteen minutes while refluxing and then while being cooled in an ice–salt bath. It was allowed to stand overnight, refluxed for one hour, and poured into water. The ether extract of this solution was washed with sodium carbonate and water and then dried with calcium chloride and distilled, the product being the diethyl ester (IX).

Neutralization and extraction with ether of the sodium carbonate solution used to wash the ether extract of the diethyl ester yielded 0.1 g. of the *p*-methoxyphenylmalonic acid monoethyl ester (X) which was recrystallized from ether and petroleum ether. Saponification of this monoester with 3% sodium hydroxide solution yielded after neutralization the free *p*-methoxyphenylmalonic acid (XI).

***p*-Methoxyphenylmalonic Acid Diethyl Ester (IX). (a) With Sodium Hydroxide Solution.**—An ether solution of the di-ester was shaken for two hours with 3% sodium hydroxide. On neutralization, extraction and evaporation of the ether at room temperature, *p*-methoxyphenylmalonic acid (XI) was obtained which was recrystallized from ether and petroleum ether.

(b) With Ammonium Hydroxide Solution.—Eight-tenths gram of the di-ester (IX) was shaken with 10 cc. of ammonium hydroxide for six hours, only undissolved ester was removed by filtering, and the solution allowed to stand overnight, after which time 0.2 g. of the diamide (VIII) crystallized out in long needles. It was recrystallized from 30% alcohol.

(c) With Hydrobromic Acid.—Eighty-seven hundredths gram of the ester (IX) was refluxed for six hours with a mixture consisting of 10 cc. of hydrobromic and 5 cc. of glacial acetic acids. The reaction mixture was then poured into water and extracted with ether: 0.42 g. of *p*-hydroxyphenylacetic acid (XIII) was obtained.

***p*-Methoxyphenylmalonic Acid (XI). Heating.**—*p*-Methoxyphenylmalonic acid (XI) was heated to 150° in a test-tube. Carbon dioxide was given off. The residue consisted chiefly of the *p*-methoxyphenylacetic acid (XII).

***p*-Methoxyphenylmethyl (XIV) and *p*-Methoxyphenylethylmalonic Acid Ester-Nitrile (XVI).**—The usual pro-

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(4) Morton and Hechenbleikner, THIS JOURNAL, 58, 2599 (1936).

cedure was followed. Metallic sodium was dissolved in absolute alcohol, the malonic ester nitrile added and the mixture refluxed for a few minutes with the alkyl halides, methyl iodide and ethyl bromide, respectively.

The alcoholic solution was filtered and the alcohol evaporated under reduced pressure. The residue was suspended in water and extracted with ether. The ether extract was dried, the ether evaporated and the remaining oil fractionally distilled.

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Summary

1. *p*-Methoxyphenylmalonic acid and several of its derivatives were prepared and characterized.

2. Its use in general alkylation reactions has been demonstrated.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

The Thermodynamics of Aqueous Sodium Bromide Solutions from Electromotive Force Measurements[1]

BY HERBERT S. HARNED AND CHESTER C. CRAWFORD

The electromotive forces of the cells

$$\text{Ag-AgBr} \mid \text{NaBr}\ (m) \mid \text{Na}_x\text{Hg} \mid \text{NaBr}\ (0.1) \mid \text{AgBr-Ag} \qquad (1)$$

have been obtained at 25° by Harned.[2] In this communication, a more extensive series of measurements of these cells, covering the ranges of temperature and concentration from 0 to 40° and 0.1 to 4 *M* has been obtained. From the results, the activity coefficient, relative partial molal heat content and the relative partial molal heat capacity of sodium bromide in aqueous solutions have been calculated.

Experimental Results

With minor variations, the cell technique was the same as that employed by Harned.[2] Large amalgam droppers were employed so as to facilitate measurement at different temperatures. Four cells were measured at each concentration and at 5° intervals from 0 to 40° inclusive. These were corrected slightly so that all results were obtained at round concentrations. The silver[3]-silver bromide electrodes were made according to the method of Keston[3] by heating a mixture of silver bromate and oxide.

The electromotive forces have been expressed by the equation

$$E = E_{25} + a(t - 25) + b(t - 25)^2 \qquad (2)$$

Values of E_{25}, a and b are contained in Table I. In the last column of the table, the average values of the deviations between the observed results and those calculated by equation (2) are given. The third column contains the results at 25° obtained by Harned.[2] The agreement of these with present results is good, particularly since Harned employed silver-silver bromide electrodes prepared by electrolysis. Smoothed values of b which are useful for the computation of the relative partial molal heat capacity are given in the next to last column of the table.

TABLE I

ELECTROMOTIVE FORCES OF THE CELLS

$\text{Ag-AgBr} \mid \text{NaBr}\ (m) \mid \text{Na}_x\text{Hg} \mid \text{NaBr}\ (0.1) \mid \text{AgBr-Ag}$

AT 25° AND CONSTANTS OF EQUATION (2). VALID FROM 0 TO 40°

m	E_{25}	E_{25}[2]	$a \times 10^4$	$-b \times 10^6$	$-b' \times 10^6$	Δ, mv.
0.2	0.03276	0.0327	1.08	0.45	0.35	0.14
.3	.05202	....	1.77	.55	.55	.15
.5	.07657	.0769	2.63	.93	.93	.07
.7	.09327	....	3.29	1.30	1.25	.06
1	.11163	.1118	4.20	1.50	1.50	.05
1.5	.13373	.1333	5.25	1.80	1.76	.05
2	.15069	.1507	6.06	2.03	2.02	.05
2.5	.16511	.1650	6.74	2.33	2.28	.08
3	.17757	.1776	7.31	2.50	2.35	.07
3.5	.18865	.1884	7.72	2.83	2.81	.08
4	.19871	.1988	9.12	3.15	3.07	.15

The computations required concentrations in moles per liter of solution, c. These may be computed accurately from the molalities by the equation

$$c/m = d_0 + A'm + B'm^2 \qquad (3)$$

in which d_0 is the density of water, and A' and B' are isothermal constants. Values of d_0, A' and B' computed from density data by the method of least squares are given in Table II.

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(1) This contribution contains material from a dissertation presented by Chester C. Crawford to the Graduate School of Yale University in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, June, 1937.

(2) Harned, THIS JOURNAL, **51**, 416 (1929).

(3) Keston, *ibid.*, **57**, 1671 (1935).