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

o-Methoxyphenylmalonic Acid and its Derivatives

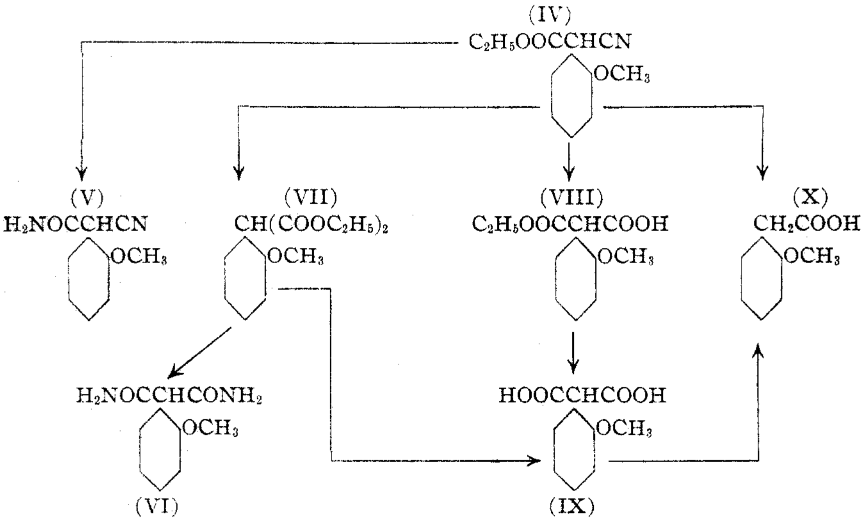
BY JOSEPH B. NIEDERL AND ROSLYN T. ROTH[1]

In a previous report of J. B. Niederl and coworkers,[2] the preparation of *p*-methoxyphenylmalonic acid and its derivatives was described and its general use in organic syntheses demonstrated. It was obvious that the preparation of its ortho isomer should be attempted. Unfortunately, due to the fact that in the diazotization of *o*-aminobenzyl cyanide not the phenolic product but rather the indazole compound is formed,[3] a similar reaction scheme as for the para acid could not be utilized for the ortho isomer. Instead, the following series of reactions had to be employed

$$
\begin{aligned}
&o\text{-}CH_3OC_6H_4CH_2OH\ (I) \xrightarrow{+HCl} \\
&\quad o\text{-}CH_3OC_6H_4CH_2Cl\ (II) \xrightarrow{+KCN} \\
&\qquad o\text{-}CH_3OC_6H_4CH_2CN\ (III) \xrightarrow{+\ \text{Claisen cond.}} \\
&\qquad\qquad o\text{-}CH_3OC_6H_4CH(CN)COOC_2H_5\ (IV)
\end{aligned}
$$

The ethyl *o*-methoxyphenylcyanoacetate (IV) was converted to the nitrile-amide (V) and the diester (VII). In the preparation of the latter compound, the monoethyl ester (VIII) was obtained as a by-product. On heating and saponification, it was converted into *o*-methoxyphenylacetic acid (X). The diester (VII) was converted into the diamide (VI) and the free dibasic acid (IX), which on heating also yielded *o*-methoxyphenylacetic acid (X). This latter acid was prepared by saponifying the *o*-methoxybenzyl cyanide (II) with alcoholic potassium hydroxide solution.[4]

The structural relationship of these compounds is as shown.



Experimental

***o*-Methoxybenzyl Chloride (II).**—Into a 500-cc. three-necked flask containing 100 g. of *o*-methoxybenzyl alcohol, a vigorous stream of dry hydrogen chloride was introduced. As soon as the temperature began to rise, the mixture was cooled externally with an ice–salt mixture, keeping the reaction temperature below 20°. Introduction of the gas was continued for about two hours, by which time the reaction was practically complete, as recognized by the attainment of constant weight or a fall of the temperature of the reaction mixture to about 2°. To the mixture was added crushed ice and ether. The ether extract was washed with water, 5% sodium carbonate solution and water. The washing was done rapidly to avoid hydrolysis. The ether was removed by distilling under reduced pressure, and the crude chloride was used directly for the preparation of the cyanide.

***o*-Methoxybenzyl Cyanide (III).**—The crude, freshly prepared *o*-methoxybenzyl chloride as prepared above was mixed with 100 cc. of ethyl alcohol and added dropwise over a period of an hour to a gently refluxing mixture of 46 g. of sodium cyanide in 42 cc. of water. Refluxing was continued for one and one-quarter hours (further refluxing decreased the yield due to the formation of high boiling and non-volatile products). The alcohol was removed from the reaction mixture under reduced pressure. The residue was dissolved in ether, the ether extract treated with water, then dried and distilled. The fraction boiling at 100–135° at 4 mm. was allowed to stand on ice for a week. Large prismatic crystals formed from which the oil was separated by placing the crystals on porous tile. The yield of crystals was 38 g.

In this process a large amount of *o*-methoxybenzyl ethyl ether always formed, due to interaction of the chloride with the ethyl alcohol used as solvent. Consequently,

---

[1] The material is taken from a portion of 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.

[2] Niederl, Roth and Plentl, THIS JOURNAL, **59**, 1901 (1937).

[3] Pschorr, *Ber.*, **43**, 2543 (1910).

[4] Pschorr, Wolfes and Buckow, *ibid.*, **33**, 166 (1900).

TABLE I

PHYSICAL CONSTANTS AND ANALYSES OF COMPOUNDS

Compound		M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
IV	Et. ester-nitrile	49	$C_{12}H_{13}NO_3$	65.80	66.10	5.94	5.65	6.39	6.40		
V	Nitrile-amide	142–143	$C_{10}H_{10}N_2O_2$	63.16	63.17	5.26	5.04	14.73	14.68		
VI	Diamide	204	$C_{10}H_{12}N_2O_3$	57.69	57.94	5.76	5.49	13.46	13.35		
VII	Diester[a]		$C_{14}H_{18}O_5$	63.16	63.30	6.77	6.64				
VIII	Monoethyl ester	86–87	$C_{12}H_{14}O_5$	60.51	60.66	5.89	5.89			238	235
IX	Free acid	142–143	$C_{10}H_{10}O_5$	57.15	57.30	4.76	4.91			105	106

[a] B. p. 133–135° (2 mm.); sp. gr. at 24°, 1.103; $n^{23°}\text{D}$ 1.5020.

substitution of the ethyl alcohol by other organic, water-soluble solvents (acetone, dioxane, etc.) was attempted, leading to the formation of non-volatile high polymeric residues. No cyanide could be obtained under these reaction conditions.

Since the above method would constitute a simplification in the synthesis of alkoxyphenylmalonic acids, this same reaction was applied to *p*-methoxybenzyl alcohol, but in this case no *p*-methoxybenzyl cyanide could be obtained at all, either the *p*-methoxybenzyl ethyl ether (ethyl alcohol as solvent), or the polymer formed (dioxane as solvent), while with acetone as solvent no reaction whatsoever took place.

***o*-Methoxyphenylmalonic Acid. Ethyl Ester-Nitrile (IV).**—A solution of 32 g. of the crystalline *o*-methoxybenzyl cyanide in 150 cc. of anhydrous ether was added dropwise, over a period of two and one-half hours, to a mixture of 5.1 g. of sodium shot, 20 cc. of ether, 26 g. of freshly dried and distilled ethyl carbonate. The mixture was allowed to stand overnight, and then after refluxing for two hours was acidified with ice-cold 25% sulfuric acid and extracted with ether. The ether extract was washed with water, 5% sodium carbonate solution, dried and distilled. The fractions from 150–175° (7 mm.) were collected. After standing, the lower fraction crystallized partly, and the higher fraction completely; yield 10 g. The ester-nitrile crystallized from alcohol in the form of large prisms.

In the preparation of the free *o*-methoxyphenylmalonic acid, 0.2 g. of the ester-nitrile in 10 cc. of ether was shaken for ten minutes with 8 cc. of 2% sodium hydroxide solution. Then the ether layer was removed and the ether allowed to evaporate. The residue thus obtained was unreacted ester-nitrile. Half of the alkaline solution, upon being acidified, yielded a mixture of acidic products. The other half of the alkaline solution, when allowed to stand overnight before being acidified, yielded the water-soluble *o*-methoxyphenylmalonic acid (IX).

***o*-Methoxyphenylmalonic Acid Amide-Nitrile (V).**—Six-tenths of 1 g. of the ester-nitrile (IV) was melted and shaken for five minutes with 20 cc. of concentrated ammonia. Nearly all dissolved, and the rest was removed by filtration immediately. The amide-nitrile crystallized out from the filtrate in long needles; yield 0.3 g. It was recrystallized from hot water; mixed m. p. with the *p*-isomer, 114–126°.

***o*-Methoxyphenylmalonic Acid Mono and Diethyl Esters (VII and VIII).**—A mixture of 4.45 g. of the ester-nitrile (IV), 7 cc. of ethyl alcohol, and 0.2 cc. of water 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, and then refluxed for one hour, and poured into water. The ether extract of this solution was washed with 5% sodium carbonate solution and water, dried with calcium chloride and distilled, the product being the diethyl ester (VII). Neutralization and extraction with ether of the sodium carbonate washings yielded 0.24 g. of the monoethyl ester (VIII) which crystallized on long standing and was recrystallized from hot water. The monoester was identified by heating to drive off the free carboxyl group and saponification of the ester group by 3% sodium hydroxide. On acidification, the *o*-methoxyphenylacetic acid was obtained, confirmed by a mixed melting point with the same acid prepared from *o*-methoxybenzyl cyanide.

***o*-Methoxyphenylmalonic Acid Diamide (VI).**—Three-tenths of a gram of the diethyl ester (VII) was shaken for several hours with 5 cc. of concentrated ammonia, filtered, and the filtrate allowed to evaporate at room temperature. The residue was recrystallized from absolute alcohol, in the form of flakes.

***o*-Methoxyphenylmalonic Acid (IX).**—An ether solution of 0.24 g. of the diethyl ester (VII) was shaken for three hours with 1 cc. of sodium hydroxide solution. On acidification and extraction with ether, 0.15 g. of the free acid was obtained. It was recrystallized from ether–petroleum ether mixture in the form of prisms. The acid on melting gave off carbon dioxide. The residue when heated to 150° gave *o*-methoxyphenylacetic acid; mixed m. p. with the *p*-isomer, 122°.

The authors desire to express their appreciation to Reed and Carnrick, Jersey City, N. J., for a fellowship grant.

Summary

1. The preparation of *o*- and *p*-methoxybenzyl cyanide was studied.

2. *o*-Methoxyphenylmalonic acid and several of its derivatives were prepared and characterized.

NEW YORK, N. Y. RECEIVED JUNE 10, 1938