SYNTHESIS OF METHYLENE DIBENZOATE AND SOME OF ITS NITROGEN AND HALOGEN DERIVATIVES

by

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INTRODUCTION

Several years ago the National Institutes of Health initiated a gigantic program to find anticarcinoma agents. Their method of attacking the problem was to collect and test all known chemical compounds from any and every source, industrial or academic. It was through this routine screening process that methylene dibenzoate was obtained from the University of Illinois. The testing revealed that methylene dibenzoate has an inhibitory effect upon the growth of certain types of cancerous tissue, even though its structure is not related to other known anticarcinoma agents. It was thought that some nitrogen and halogen derivatives of methylene dibenzoate might be even more efficacious in the treatment of cancer, and the purpose of this research was to synthesize derivatives of methylene dibenzoate.

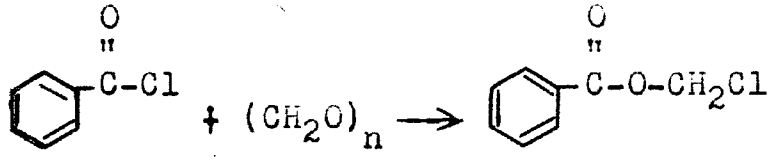
A search of the literature from 1900 to the present revealed only two references to methylene dibenzoate, and in one of these references (1) it was noted that methylene dibenzoate was obtained as a by-product in the preparation of chloromethylbenzoate. The chloromethyl ester and methylene dibenzoate (by-product) was prepared by refluxing benzoyl chloride with paraformaldehyde in the presence of anhydrous zinc chloride. The method of preparation recorded in the other reference (3) differed from the above method

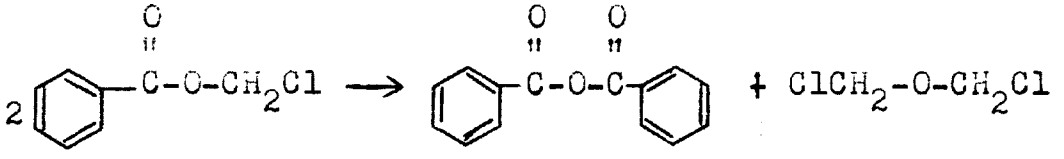
only in that benzoic anhydride was used as the starting material instead of benzoyl chloride. So, the first objective of this research was to find the optimum conditions necessary for preparing methylene dibenzoate itself and then the second objective was to prepare various substituted derivatives under these conditions or with modifications if necessary.

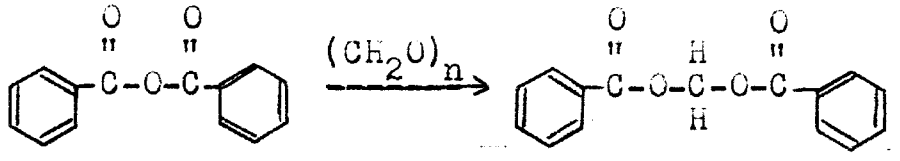
HISTORICAL

Methylene dibenzoate was first synthesized by Descudé (6) in 1902 by reacting benzoic anhydride with paraformaldehyde. It is a solid melting at 99°C and boiling at 225°C with decomposition. Dry ammonia reacts with the molten ester to give methylene bisbenzamide (3). Ulich and Adams (1) obtained methylene dibenzoate as a by-product in the preparation of chloromethyl benzoate and bromomethyl benzoate. They refluxed equal moles of the respective aromatic acid halides and paraformaldehyde in the presence of a small amount of anhydrous zinc chloride until the paraformaldehyde had disappeared.

It is possible that the following sequence of reactions occur in the presence of a little anhydrous zinc chloride. These are analogous to those proposed by Descudé (3) for acetyl chloride.







Vollweiler and Adams (2) found that the product resulting from the reaction of aromatic acid halides and aromatic aldehydes will decompose into the aldehyde, organic acid and halogen acid in the presence of water.

$$RCHXOCOR^1 + H_2O \longrightarrow RCHO + HX + R^1COOH$$

"The difference in rate of decomposition, however, is very marked. Some of the compounds, such as those formed from oxalyl bromide and furfural or benzoyl bromide and anisaldehyde decompose in air within a few seconds. On the other hand, the nitro-substituted benzoyl chlorides form addition products which are stable for a long time in cold water or even in dilute sodium carbonate solution. In general, the indications are that those substances which form with difficulty are more stable towards moisture or water."

EXPERIMENTAL PROCEDURE

Methylene dibenzoate -- One purpose of this research was to determine the optimum conditions for preparing methylene dibenzoate from benzoyl chloride and paraformaldehyde. A total of thirty-three runs were made (Table I) in which the catalyst, concentration of catalyst, and time of reflux were varied. All of the reactions were carried out in a 250 ml round-bottom flask fitted with a reflux condenser with heat supplied by a heating mantle. After refluxing, the solutions were allowed to stand at room temperature in a closed container for two weeks, because it was found from preliminary experiments that if the solution was vacuum distilled after refluxing the yield was reduced. At the end of the two-week period, the resulting crystals were separated by vacuum filtration and weighed.

It is known that the formation of esters without the aid of a catalyst is very slow even at elevated temperatures. The catalysts generally used for esterification of an organic acid with an alcohol are the strong mineral acids, hydrochloric and sulphuric, and some salts such as zinc chloride and aluminum chloride which are acids in the "Lewis" terminology. Four catalysts (anhydrous zinc chloride, anhydrous aluminum chloride, sulfuric acid and phosphorous oxychloride) were selected and used in

concentrations of 0.00033 to 0.0102 moles per mole of reactants.

It was found that if the refluxing time was increased to more than three hours (1) the yield of methylene dibenzoate was improved. Therefore, reflux periods of three, six, twelve and eighteen hours were conducted to determine the optimum conditions for the preparation of methylene dibenzoate. There were only three experiments that did not give the expected increase in yield, and these were obtained when sulfuric acid was used as the catalyst. There seemed to be a greater tendency toward decomposition in the presence of sulfuric acid than in the presence of the other catalysts.

EXPERIMENTAL DATA

Methylene dibenzoate:

1 mole benzoyl chloride

1 mole paraformaldehyde

0.0004 moles anhydrous zinc chloride

Refluxed for 6 hours.

Crude yield = 60% on the basis of C_7H_5OCl

Crude yield = 89% on the basis of $(CH_2O)_n$

Recrystallized 6 times from ethyl alcohol.

M.P. 98-99°C

Theory ($C_{15}H_{12}O_4$) %C = 70.30 %H = 4.72

Found %C = 70.22 %H = 4.82 (NIH)

Infrared spectrum of this compound shows it to be an ester (Figure 1).

Methylene ester of m-nitrobenzoic acid:

1 mole m-nitrobenzoyl chloride

1 mole paraformaldehyde

0.0004 moles anhydrous zinc chloride

Refluxed for 6 hours.

Crude yield = 66% on the basis of $C_7H_4NO_3Cl$

Crude yield = 96% on the basis of $(CH_2O)_n$

Recrystallized 6 times from ethyl alcohol and twice from benzene.

M.P. 39.5-40.5°C

Theory ($C_{15}H_{10}O_8N_2$) %C = 52.03 %H = 2.91

%N = 8.09

Found %C = 54.64 %H = 4.50 %N = 6.71

The infrared spectrum shows this compound to be an ester (Figure 2).

Methylene ester of 3,5-dinitrobenzoic acid:

0.217 moles 3,5-dinitrobenzoyl chloride

0.217 moles paraformaldehyde

0.0000734 moles anhydrous zinc chloride

Refluxed for 6 hours.

Solution completely solidified on cooling.

Recrystallized twice from ethyl alcohol and four times from benzene.

Yield after final recrystallization was 33% on the basis of $C_7H_3N_2O_5Cl$.

Yield after final recrystallization was 50% on the basis of $(CH_2O)_n$.

M.P. 89-90°C

Theory ($C_{15}H_8O_{12}N_4$) %C = 41.30 %H = 1.85 %N = 12.84

Found %C = 44.21 %H = 3.07 %N = 11.56 (NIH)

Infrared spectrum of this compound shows it to be an ester (Figure 3).

Methylene ester of p-nitrobenzoic acid:

0.501 moles p-nitrobenzoyl chloride

0.501 moles paraformaldehyde

0.00022 moles anhydrous zinc chloride

Refluxed for 6 hours.

The material solidified completely on cooling.

Recrystallized three times from ethyl alcohol and twice from benzene.

Yield after the final recrystallization was 31% on the basis of $C_7H_4NO_3Cl$.

Yield after the final recrystallization was 46% on the basis of $(CH_2O)_n$.

M.P. 239-40°C

Theory ($C_{15}H_{10}O_8N_2$) %C = 52.03 %H = 2.91 %N = 8.09

Found %C = 56.07 %H = 4.37 %N = 6.5

The infrared spectrum of this compound proved it to be an ester (Figure 4).

Product from o-chlorobenzoyl chloride:

0.571 moles o-chlorobenzoyl chloride

0.571 moles paraformaldehyde

0.00022 moles anhydrous zinc chloride

Refluxed for 6 hours.

Crude yield = 32% on the basis of $C_7H_4OCl_2$

Crude yield = 47% on the basis of $(CH_2O)_n$

Recrystallized from petroleum ether four times.

M.P. 141-2°C

Theory for methylene ester ($C_{15}H_{10}O_4Cl_2$)

%C = 55.41 %H = 3.10 %Cl = 21.81

Theory for acid ($C_7H_5O_2Cl$) %C = 53.69 %H = 3.22

%Cl = 22.65

Found %C = 53.58 %H = 3.54 %Cl = 22.47

Neutralization equivalent = 155

Negative hydroxamic acid test for ester linkage.

Product of p-chlorobenzoyl chloride:

1.143 moles p-chlorobenzoyl chloride

1.143 moles paraformaldehyde

0.00044 moles anhydrous zinc chloride

Refluxed for 6 hours.

Crude yield = 55% on the basis of $C_7H_4OCl_2$

Crude yield = 82% on the basis of $(CH_2O)_n$

M.P. decomposition started at approximately 195°C.

Theory for methylene ester ($C_{15}H_{10}O_4Cl_7$)

%C = 55.41 %H = 3.10 %Cl = 21.81

Theory for acid ($C_7H_5O_2Cl$) %C = 53.69 %H = 3.22

%Cl = 22.65

Found %C = 54.06 %H = 3.64 %Cl = 22.57

Neutralization equivalent = 155

Negative hydroxamic acid test for ester linkage.

The infrared spectrum of this compound proved it to be the acid (Figure 1).

Product of 3,4-dichlorobenzoyl chloride:

0.477 moles 3,4-dichlorobenzoyl chloride

0.477 moles paraformaldehyde

0.0002 moles anhydrous zinc chloride

Refluxed for 6 hours.

Crude yield = 65% on the basis of $C_7H_3OCl_3$

Crude yield = 97% on the basis of $(CH_2O)_n$

Recrystallized five times from benzene.

M.P. decomposition at 185°C

Theory for methylene ester ($C_{15}H_8O_4Cl_4$)

%C = 45.72 %H = 2.05 %Cl = 35.99

Theory for acid ($C_7H_4O_2Cl_2$) %C = 44.01 %H = 2.11

%Cl = 37.12

Found %C = 44.32 %H = 2.08 %Cl = 38.54

Neutralization equivalent = 190.5

Negative hydroxamic acid test for ester linkage.

Infrared spectrum of this compound proved it to be the acid (Figure 5).

Product of m-bromobenzoyl chloride:

0.456 moles m-bromobenzoyl chloride

0.456 moles paraformaldehyde

0.000169 moles anhydrous zinc chloride

Refluxed for 6 hours.

Crude yield = 66% on the basis of C_7H_4OBrCl

Crude yield = 99% on the basis of $(CH_2O)_n$

Recrystallized eight times from ethyl alcohol.

M.P. 157-8°C

Theory for methylene ester ($C_{15}H_{10}O_4Br_2$)

%C = 43.51 %H = 2.43 %Br = 38.60

Theory for acid ($C_7H_5O_2Br$) %C = 41.82 %H = 2.51

%Br = 39.75

Found %C = 41.45 %H = 2.61 %Br = 38.88

Neutralization equivalent = 198.8

Negative hydroxamic acid test.

Infrared spectrum of this compound proved it to be an acid.

Product of 1-naphthoyl chloride:

0.525 moles 1-naphthoyl chloride

0.525 moles paraformaldehyde

0.00018 moles anhydrous zinc chloride

Refluxed for 3½ hours (started to decompose).

Crude yield = 37% on the basis of $C_{11}H_7OCl$

Crude yield = 55% on the basis of $(CH_2O)_n$

Recrystallized once in glacial acetic acid and four times in benzene.

M.P. 163-4°C

Theory for methylene ester ($C_{23}H_{16}O_4$)

%C = 77.51 %H = 4.53

Theory for acid ($C_{11}H_8O_2$) %C = 76.73 %H = 4.68

Found %C = 76.99 %H = 4.36

Neutralization equivalent = 171.1

Negative hydroxamic acid test

Infrared spectrum of this compound proved it to be the acid (Figure 5).

Product of p-anisoyl chloride:

1.172 moles p-anisoyl chloride

1.172 moles paraformaldehyde

0.000426 moles anhydrous zinc chloride

Refluxed for 6 hours.

Recrystallized three times from ethyl alcohol and three times from benzene.

Yield after recrystallization was 24% on the basis of $C_8H_7O_2Cl$.

Yield after recrystallization was 36% on the basis of $(CH_2O)_n$.

M.P. 183-4°C

Theory for methylene ester ($C_{17}H_{16}O_6$)

%C = 64.55 %H = 5.10

Theory for acid ($C_8H_8O_3$) %C = 63.15 %H = 5.30

Found %C = 62.99 %H = 5.41

Neutralization equivalent = 155

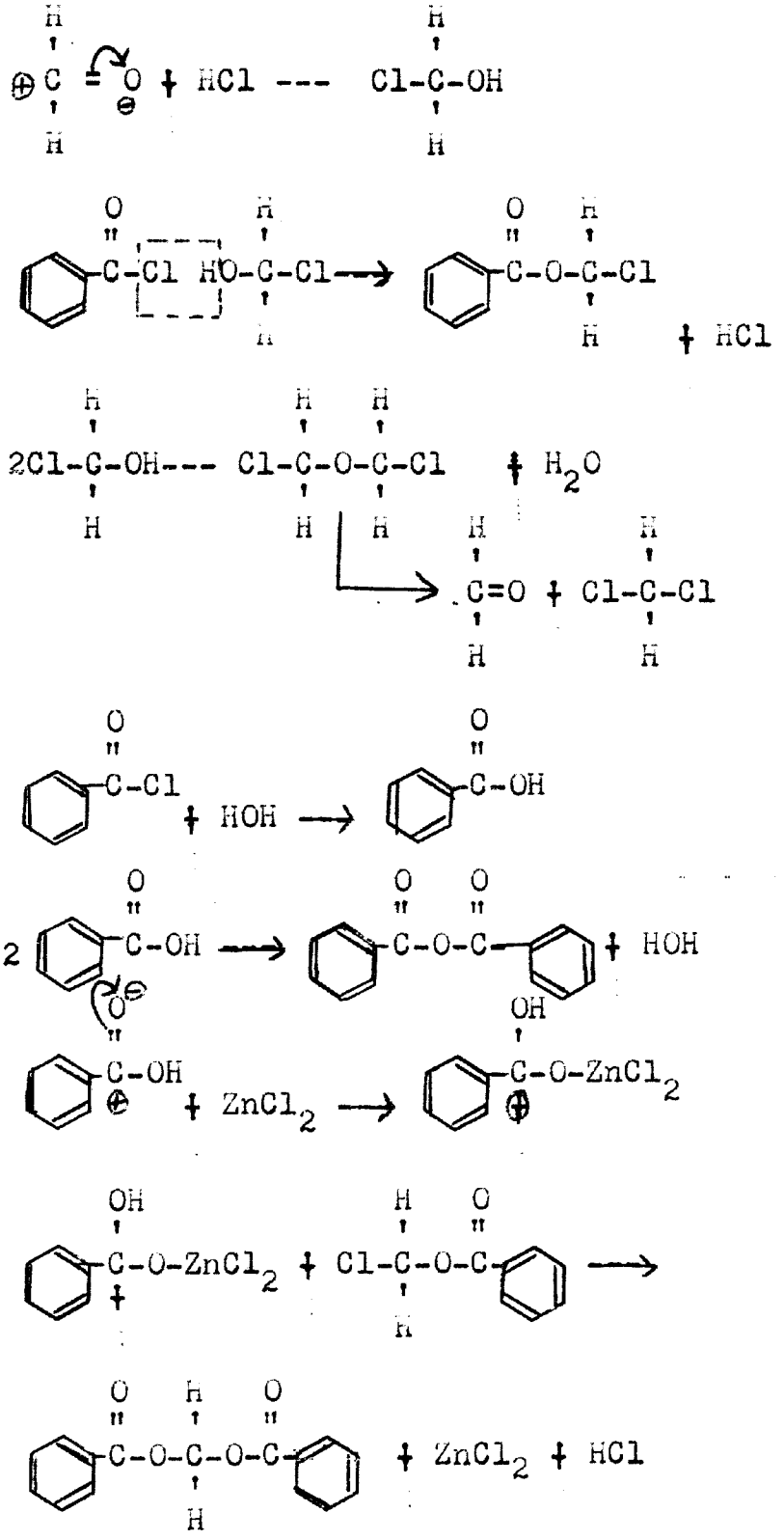
Negative hydroxamic acid test for ester linkage.

Infrared spectrum of this compound proved it to be the acid (Figure 6).

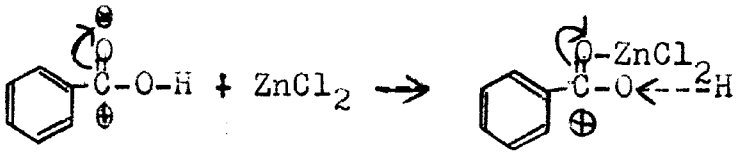
DISCUSSION OF RESULTS

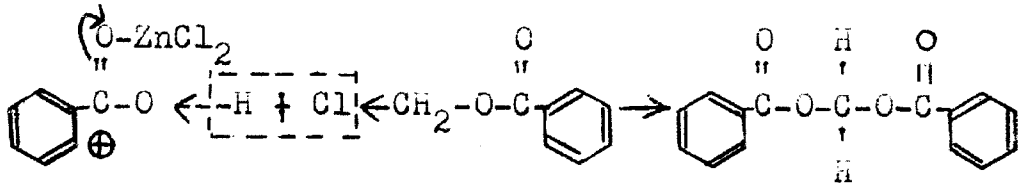
It was found that anhydrous zinc chloride in a concentration of 0.0004 moles per mole of reactants and a reflux time of six hours gave the maximum yield of methylene dibenzoate (Table I). If the reflux time was extended beyond six hours or if the concentration of the catalyst was increased, decomposition occurred. The same procedure was selected for preparing the substituted derivatives of methylene dibenzoate; although, they are not necessarily the optimum conditions for preparing these compounds.

A series of reactions has been suggested for benzoyl chloride and paraformaldehyde analogous to those proposed by Descudé (3) for acetyl chloride. "According to Descudé, chloromethyl acetate is the principal product formed by the exothermic reaction which takes place when a mixture of acetyl chloride and paraformaldehyde is treated with a little anhydrous zinc chloride. Small quantities of dichloromethyl ether and methylene diacetate are formed as by-products." Descudé does not suggest a mechanism for these reactions, but one mechanism that will explain the formation of the intermediate products is as follows:



The above is similar to a Gattermann reaction because of the formation of chloromethyl alcohol from paraformaldehyde and hydrochloric acid. In this reaction it is only necessary for a small amount of hydrochloric acid to be present in order to start the reaction. This small amount may be obtained from the hydrolysis of benzoyl chloride with a small amount of water, which would undoubtedly be present either in the paraformaldehyde or the anhydrous zinc chloride (which picks up water very readily from the atmosphere). The resulting chloromethyl alcohol can then condense with the benzoyl chloride to form chloromethyl benzoate (1) and hydrochloric acid which is liberated, making it available to react with more paraformaldehyde to form more chloromethyl alcohol. The formation of the dichloromethyl ether may be explained by the condensation of two molecules of chloromethyl alcohol to give the ether and water. The water thus obtained could be used to hydrolyze more benzoyl chloride to benzoic acid, liberating hydrochloric acid. Two molecules of benzoic acid thus obtained could be dehydrated to give water and benzoic anhydride; although, it is doubtful that this occurs to any great extent if at all. If it is assumed that the benzoic anhydride is not formed, the benzoic acid is free to react with the anhydrous zinc chloride as follows (7):

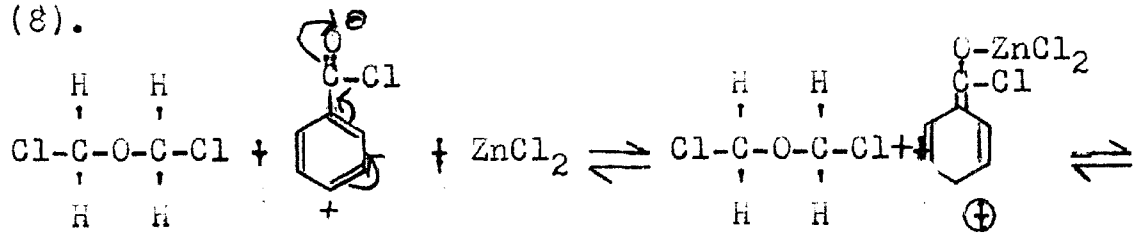


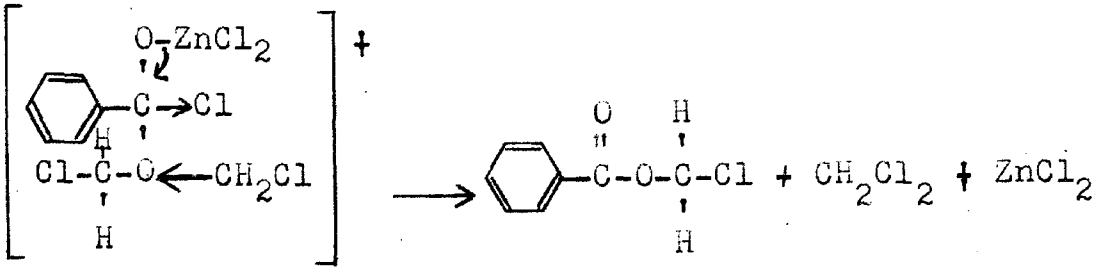


+ $ZnCl_2$

This will condense with the previously formed chloromethyl benzoate to give methylene dibenzoate and hydrochloric acid, and at the same time release the zinc chloride for reuse.

In order to explain the high yields, if calculated on the basis of paraformaldehyde, it is necessary for the dichloromethyl ether formed in a previous reaction to be cleaved with zinc chloride and benzoyl chloride to form more chloromethyl benzoate (8).





The reaction is induced by the electrophilic nature of the zinc chloride. The zinc chloride shares an electron pair belonging to the carbonyl oxygen atom. The resulting carbonium ion then attaches itself to an electron pair on the ether oxygen atom. This addition creates the electron displacements which result in the cleavage of the oxygen-carbon bond.

All of the derivatives of methylene dibenzoate except the nitro substituted compounds decomposed, on attempted purification by crystallization, to their respective acids. French and Adams (4) found that some of the esters formed by condensing an aromatic acid halide with an aromatic aldehyde decomposed very readily, depending on the substituents on the ring. French and Adams concluded that the more difficult the esters were to form, and the slower the reaction, the more stable they were once formed. Infrared spectra, elemental analyses, neutralization equivalents, and the hydroxamic acid test for esters were employed in the identification of the compounds.

The infrared spectra obtained on the crude products of anisoyl chloride, o-chlorobenzoyl chloride and m-bromobenzoyl chloride indicated that esters were present. After taking the crude products up in ethyl ether and shaking with sodium bicarbonate solution the ester band was still present but not as prominent as

in the crude product. On further purification the ester band at 1710-1735 cm^{-1} disappears completely and an acid band at 1670-1685 cm^{-1} (5) appears. (See curves in Figures 1,5,6). In every case the carbon, hydrogen and halogen analyses agree within acceptable limits to that calculated from theory for the free acid derived from the corresponding acid chloride. The analytical data for the nitro substituted compounds do not agree with the theoretical values for either the acid, the chloromethyl ester or the methylene ester. Therefore, it is assumed that the product is a mixture of the chloromethyl ester and the methylene ester of the respective compounds. The infrared spectra of the nitro compounds shows that they are esters, but the number of ester groups could not be determined. Thus, the only conclusion drawn is that the nitro substituted compounds contain an ester group, but the actual structure is not proposed.

Table I

Time of Reflux in Hours		$ZnCl_2$ in moles/mole of reactants		H_2SO_4 in moles/mole of reactants		$AlCl_3$ in moles/mole of reactants		$POCl_3$ in moles/mole of reactants	
		.00037	.0073	.00051	.0102	.00037	.0075	.00073	.0065
3/4	A	-	45	-	-	-	-	-	-
	B	-	68	-	-	-	-	-	-
3	A	23	35	35	30	2	3	0	0
	B	34	52	52	45	3	4	0	0
6	A	60	*18	33	*0	17	0	0	51
	B	89	27	49	0	25	0	0	75
12	A	13	*7%	*0	*34	15	18	2	40
	B	19	11	0	50	22	27	3	59
18	A	*0	*0	35	*0	43	34	-	-
	B	0	0	53	0	64	50	-	-

A-Per cent yield of methylene dibenzoate calculated on the basis of C_7H_5OCl.
B-Per cent yield of methylene dibenzoate calculated on the basis of $(CH_2O)_n$.
*-Partial decomposition.

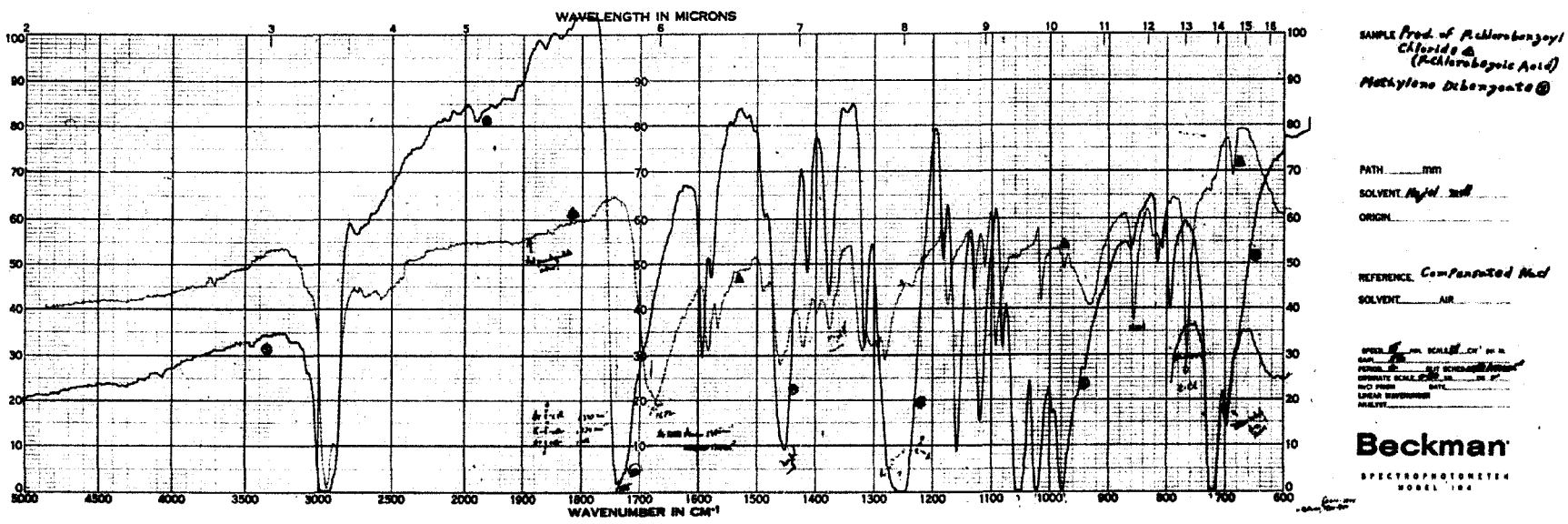

WAVELENGTH IN MICRONS
WAVENUMBER IN CM⁻¹
SAMPLE Prod. of P-Chlorobenzoyl Chloride & (P-Chlorobenzoic Acid)
Methylene Dibenzoate ②
PATH mm
SOLVENT Mujol
ORIGIN
REFERENCE Compensated Mull
SOLVENT AIR
Beckman
SPECTROPHOTOMETER
MODEL IR4

Figure 1

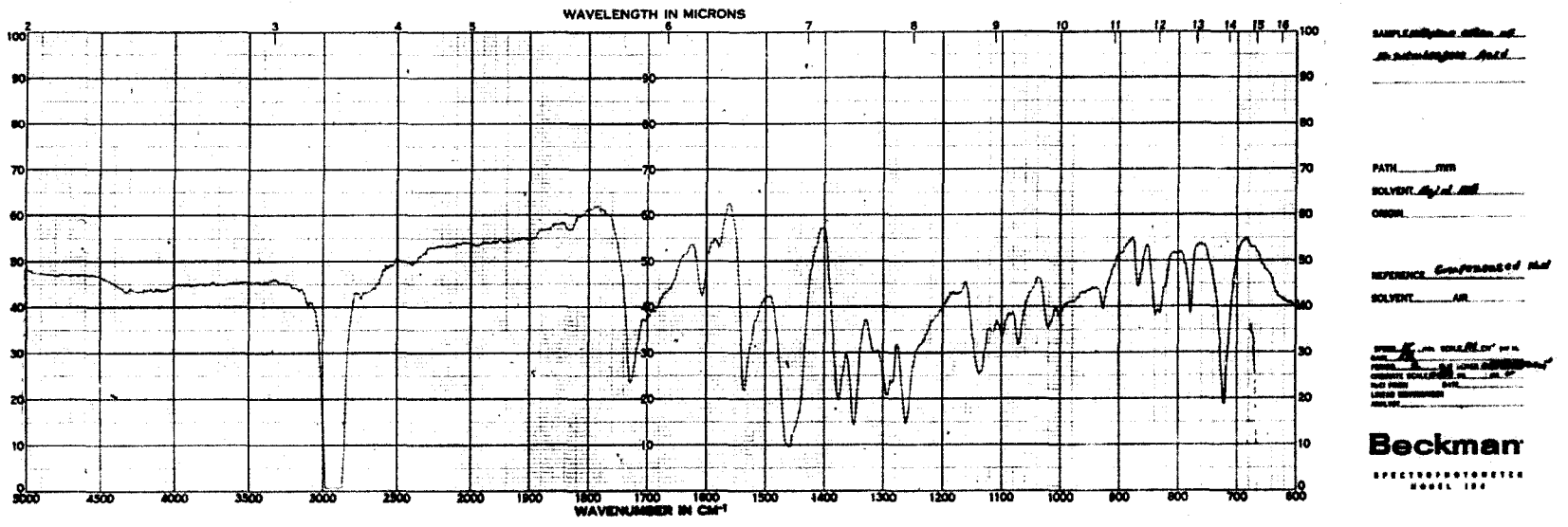


Figure 2

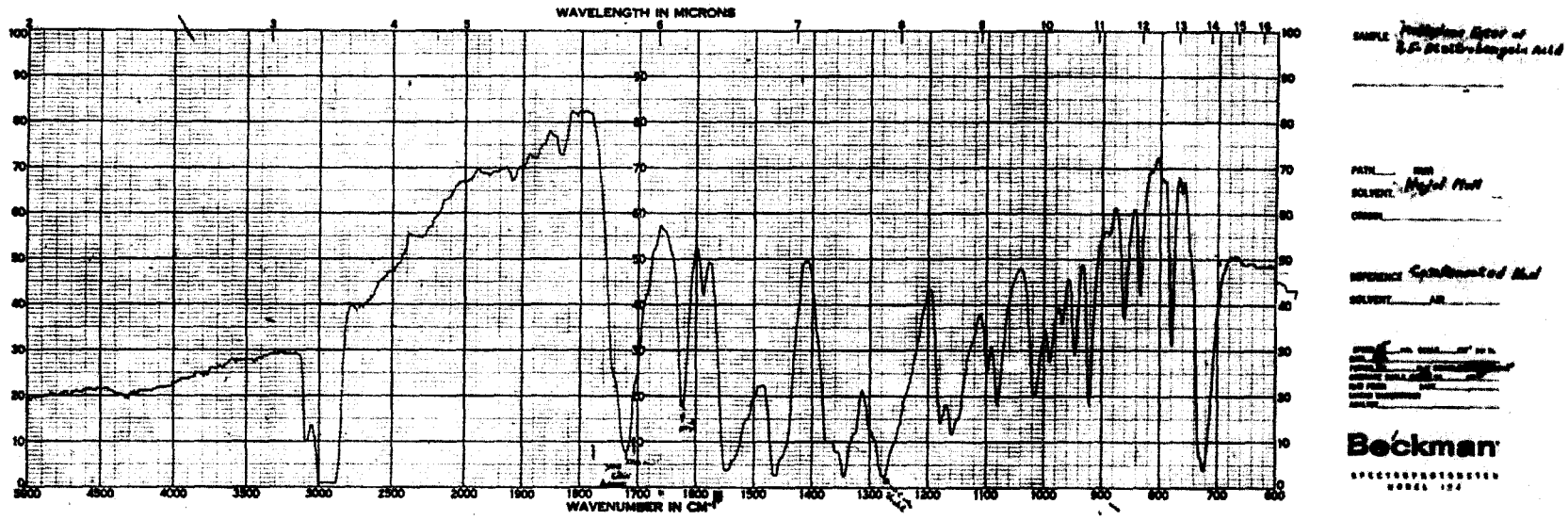


Figure 3

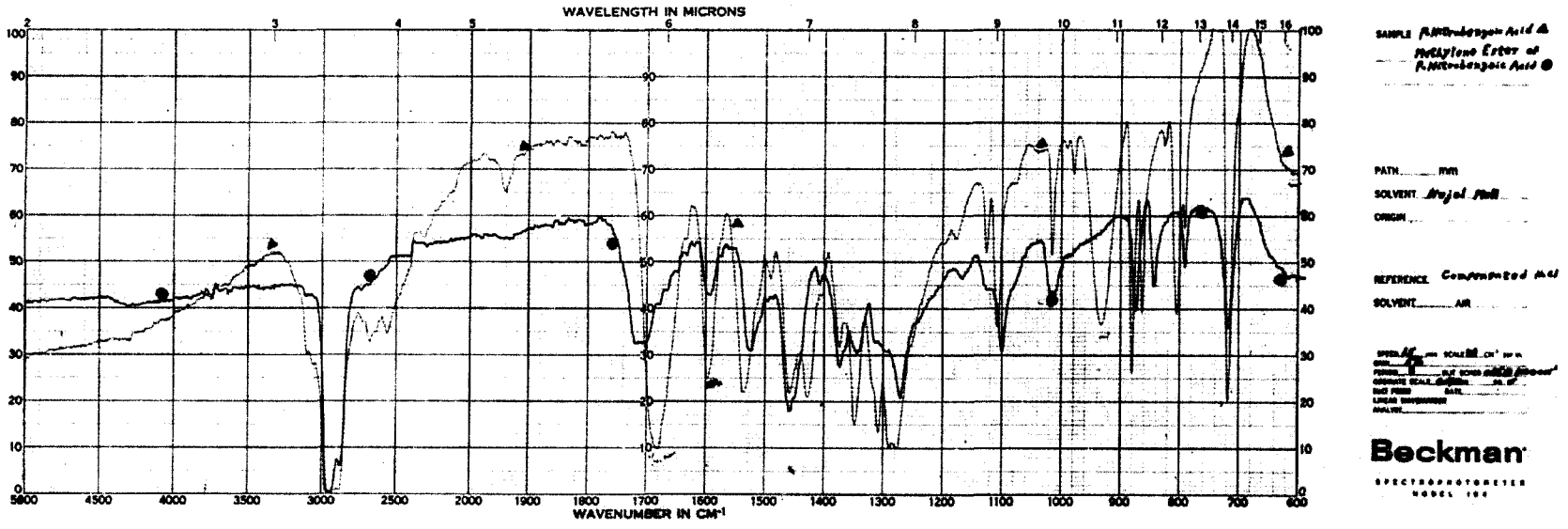

WAVELENGTH IN MICRONS
WAVENUMBER IN CM-1
SAMPLE
PATH
SOLVENT
ORIGIN
REFERENCE
SOLVENT
AIR
Beckman

Figure 4

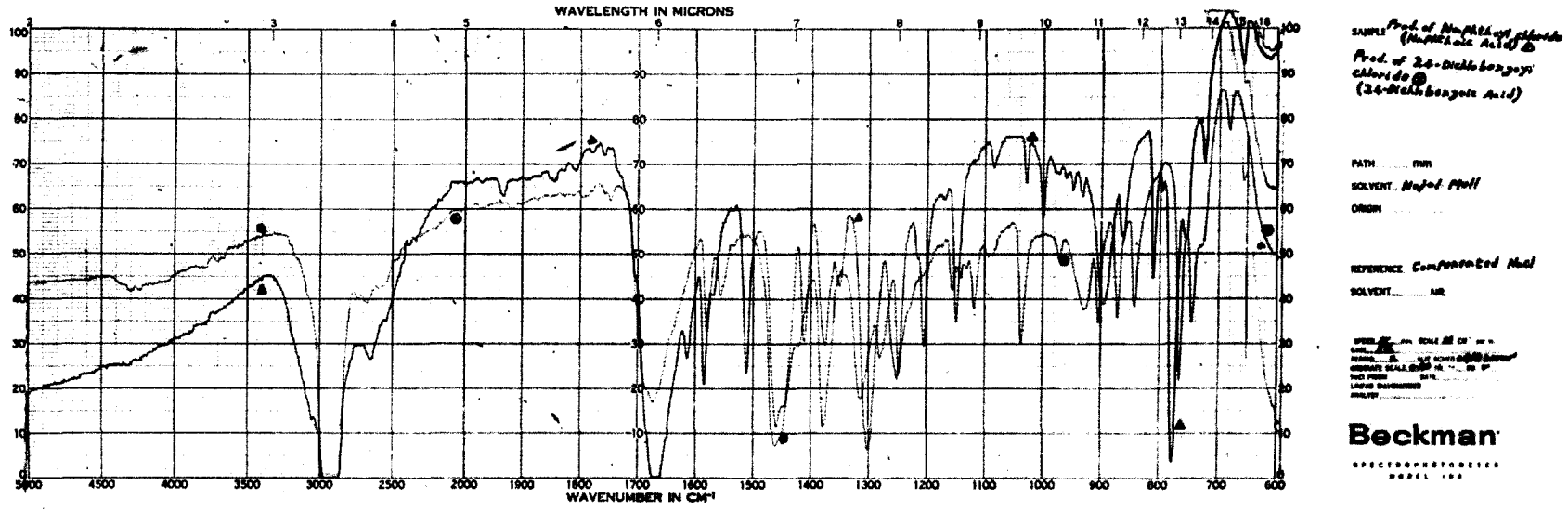

WAVELENGTH IN MICRONS
WAVENUMBER IN CM-1
SAMPLE Prod. of Naphthalene Sulfonyl Chloride (Naphthalic Acid) Prod. of 2,4-Dichlorobenzoyl chloride (2,4-Dichlorobenzoic Acid)
PATH mm
SOLVENT Nujol Mull
ORIGIN
REFERENCE Compensated Mull
SOLVENT AIR
Beckman
SPECTROPHOTOMETER
MODEL 1R4

Figure 5

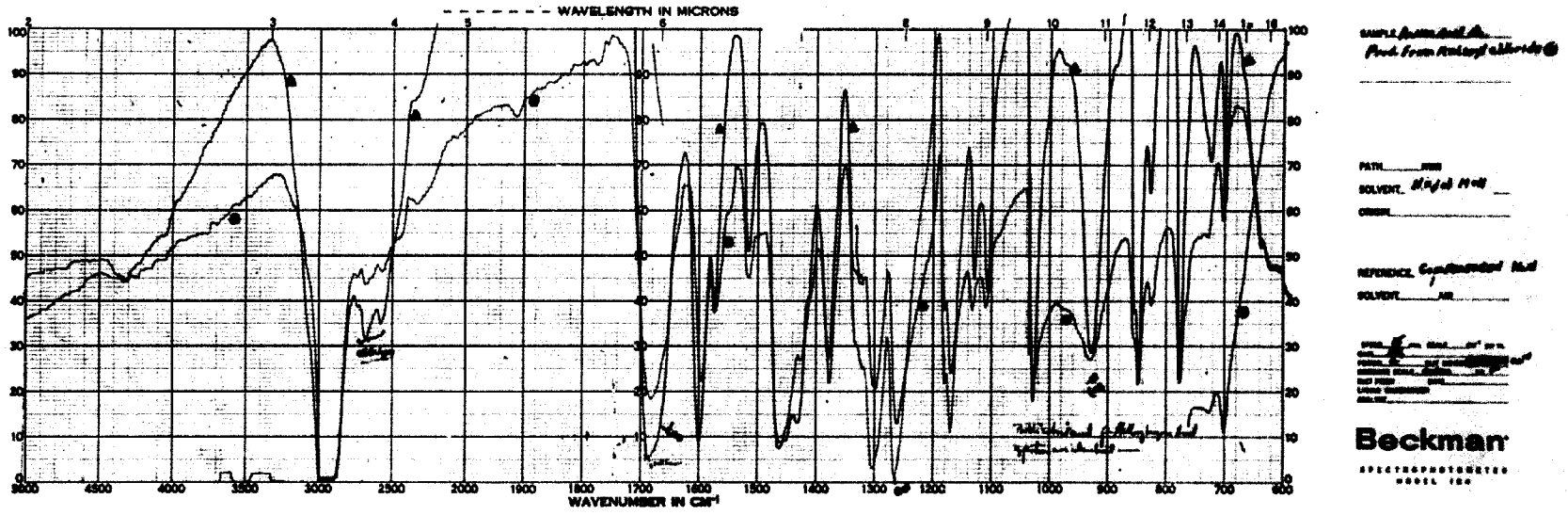


Figure 6

SUMMARY

1. Anhydrous zinc chloride is the preferred catalyst for forming the methylene esters of benzoic acid.
2. A catalyst concentration of 0.0004 moles per mole of reactants, and a reflux time of six hours is optimum.
3. Methylene esters formed from some substituted benzoyl chlorides are unstable.

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