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THE SYNTHESIS OF 2-PROPOXY-5-METHYLBENZOIC ACID AND ITS REACTION WITH ZINC OXIDE

by

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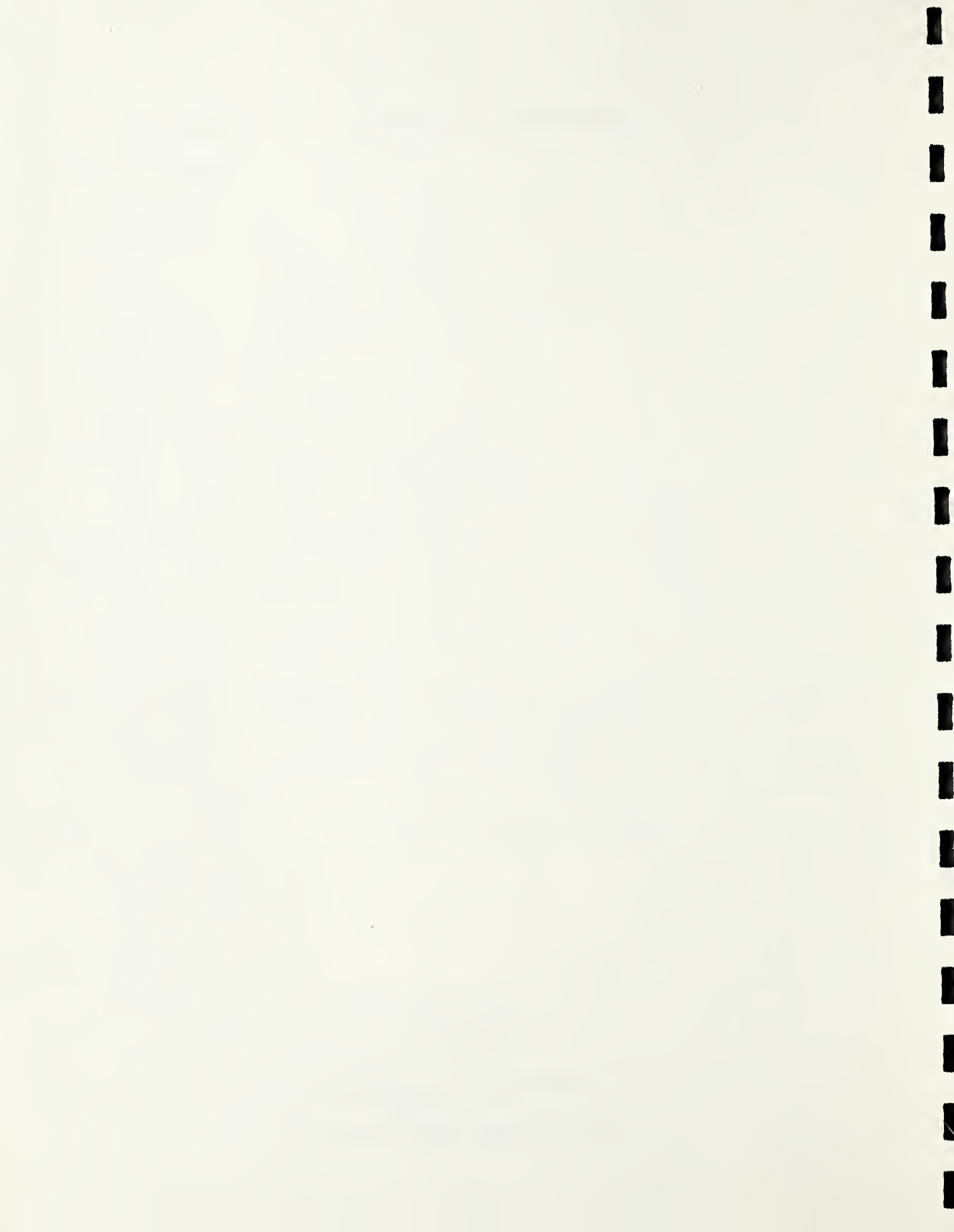
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THE SYNTHESIS OF 2-PROPOXY-5-METHYLBenZOIC

ACID AND ITS REACTION WITH ZINC OXIDE*

----- Abstract -----

In order to reduce the water solubility of o-ethoxybenzoic acid-eugenol-zinc oxide cements the reaction of zinc oxide with 2-propoxy-5-methylbenzoic acid has been studied. This compound has been synthesized in good yield by two routes. Mixtures of this compound and zinc oxide harden within 30 minutes. The water solubility of the resulting cements is unexpectedly high probably due to the incomplete reaction of the 2-propoxy-5-methylbenzoic acid with zinc oxide.

----- 1. INTRODUCTION

In a previous investigation [1] the reaction of various compounds containing groups capable of forming chelates with metals was studied. o-Ethoxybenzoic acid-eugenol-zinc oxide mixtures were found to harden rapidly to cementitious products having greatly improved compressive strength and density compared to the conventional zinc oxide-eugenol cements used in restorative dentistry. However, the best value for the 24-hour solubility and disintegration test [3] for these products was 2.5% even on incorporation of a silicone. Later studies by Phillips and Love [2] showed that various formulations con-

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taining o-ethoxybenzoic acid-eugenol and zinc oxide had solubility and disintegration values as low as 1.2%. These investigators also reported that the inflammatory reaction of selected formulas to the connective tissue of the rat was mild and the tissue tolerance was superior compared with zinc phosphate cements.

It was the purpose of the present study to investigate ways to reduce the water solubility by modifying the structure of the benzoic acid derivative. It was thought that introduction of hydrophobic groups such as alkyl groups substituted in the benzene ring or increase in the length of the ether substituent in the side chain might result in decreased solubility. Suitable compounds should be symmetrically or asymmetrically trisubstituted benzoic acid derivatives since previous studies with eugenol isomers [4] had shown that vicinal substituted compounds do not react readily with zinc oxide, probably due to the steric hindrance of the neighboring group to the formation of a zinc chelate. Furthermore, a desirable compound should be a liquid at or near room temperature to avoid the use of solvents which will modify the setting reaction with zinc oxide. From the few compounds which meet these requirements 2-propoxy-5-methylbenzoic acid (PMBA) was selected. This compound has been reported [⁵4] in a study of the effect of different alkoxy groups on the anomalous reactivity of

o-alkoxyphenylmagnesium bromide Grignard reagents with carbon dioxide.

2. EXPERIMENTAL

2.1 Synthesis of 2-Propoxy-5-methylbenzoic Acid

The route employed by Holmberg [5] in obtaining 5-propoxy-2-methylbenzoic acid did not appear to be well adapted for a large scale synthesis due to lack of availability of intermediates as well as the large amount of 2, 2'-dipropoxy-5,5'-dimethylbenzophenone by-product which is formed in the Grignard reaction.

The following two routes were therefore investigated and route 2 was found to be more suitable. (See Figure 1).

p-Cresotinic acid (2-hydroxy-5-methylbenzoic acid) was prepared by carbonation of p-cresol according to the procedure of Cameron, Jeskey and Baine [6]. Dry powdered potassium cresoxide was placed in a pressure bomb and carbon dioxide was admitted until a pressure of 10 atm. was obtained. The bomb was heated for 24 hours at 175°C, cooled, and the material was purified as described previously.

2.2 Route 1

2.2.1 Propylation of p-Cresotinic Acid

52.9 g (0.35M) of p-cresotinic acid were mixed with 42g (0.75M) of KOH and 122 g (0.73M) of propyl iodide in an 800 ml pressure bomb heated to 145°C and kept overnight at this

temperature. The reaction mixture was dissolved in hot water, the solution extracted with ether, and the ether solution shaken with 5% NaOH. After evaporation of the ether 45.0 g of liquid remained. Vacuum distillation of the residue gave two fractions.

Fraction 1, propyl 2-hydroxy-5-methylbenzoate, distilled approximately at $77-79^{\circ}\text{C}^{\text{a}}/4$ mm. The colorless liquid had a b.p. of $266-268^{\circ}\text{C}$, $n_{\text{D}}^{25} = 1.5122$ and gave a positive ferric chloride test for phenol.

Yield: 28.9 g (43%).

Anal: Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_3$: C, 68.02; H, 7.27.

Found^b: C, 68.2 ; H, 7.4.

I. R. spectrum^c: Absorption bands at the respective wavelengths indicate the presence of the following groups:

3.16 μ (-OH), 5.95 μ (ester carbonyl for salicylates), doublet at 6.15 μ and 6.24 μ (possible conjugation of carbon to oxygen double bond with aromatic ring), 8.30 μ (phenol) and 12.11 μ (unsymmetrically trisubstituted benzene).

Fraction 2, propyl 2-propoxy-5-methylbenzoate, distilled at $100-108^{\circ}\text{C}/4$ mm. Colorless liquid, b.p. 302°C , $n_{\text{D}}^{28} = 1.5022$, gave a negative ferric chloride test for phenol, a negative

^a All b.p. are uncorrected.

^b Carbon and hydrogen analyses were done by E. Deardorff of the Analytical Section, National Bureau of Standards.

^c I. R. Spectra were determined by Miss M. Katharyn Wharton, Textile Section, National Bureau of Standards.

Tollens and 2,4-dinitrophenylhydrazine tests.

Yield: 12.2 g (15%).

Anal: Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53.

Found: C, 70.6; H, 8.4.

I. R. spectrum: The presence of the following groups is indicated: benzoyl, alkoxy and unsymmetrically trisubstituted benzene.

The propyl ester of p-cresotinic acid was converted to the propoxy ether as follows: 2.9 g (0.125 M) sodium in 60 ml of absolute ethanol and an excess (27.0 g, 0.159 M) of propyl iodide were added to 24.2 g (0.125 M) of the ester. The solution was refluxed until it was no longer alkaline to litmus. After evaporating off the alcohol in a vacuum the residue was dissolved in ether and the solution was extracted with 5% NaOH. On evaporation of the ether 22.7 g (77%) of liquid remained. Upon purification by vacuum distillation propyl 2-propoxy-5-methylbenzoate was obtained which was identical with the product obtained in the propylation of p-cresotinic acid with respect to b.p., n_D and infra-red absorption.

2.2.2 Hydrolysis of Propyl 2-propoxy-5-methylbenzoate

10 g of the sample and 35 ml of 10% KOH in 50% ethanol were refluxed for $4\frac{1}{2}$ hours and the ethanol and propanol were distilled off. The residue was acidified with HCl, extracted with ether and the ether evaporated off. After vacuum

distillation at approximately 4 mm the liquid had a b.p. of 257°C, $n_D^{27} = 1.527$ Yield: 6.5 g (79%). I. R. spectrum confirmed the presence of -OH, COOH, ether and unsymmetrically trisubstituted benzene groups.

2.3 Route 2

In order to avoid the tedious separation of the products of the propylation of 2-hydroxy-5-methylbenzoic acid an improved synthesis of 2-propoxy-5-methylbenzoic acid was developed. The 2-hydroxy-5-methylbenzoic acid is converted to the ethyl ester which is reacted with propyl iodide. The resulting ethyl 2-propoxy-5-methylbenzoate on hydrolysis gives PMBA.

2.3.1 Ethyl 2-hydroxy-5-methylbenzoate

13 g (0.085 M) of p-cresotinic acid was refluxed with 39 ml (0.67M) of absolute alcohol and a small amount of H₂SO₄ as catalyst for 8 hours. The excess alcohol was distilled off, the ester washed with water and 5% NaHCO₃, dried over anhydrous Na₂SO₄, and distilled at 94-95°C/4 mm. The liquid had a b.p. of 235°C, $n_D^{25} = 1.5190$.

Yield: 10.8 g (70%).

Anal: Calcd. for C₁₀H₁₂O₃: C, 66.7; H, 6.73.

Found: C, 66.9; H, 7.0.

I. R. spectrum: The principle bands are the same as those for the propyl ester.

2.3.2 Ethyl 2-propoxy-5-methylbenzoate

10.8 g (0.060 M) of the ethyl ester dissolved in 21.6 g benzene was refluxed overnight in the presence of 21.0 g of freshly precipitated and dried silver oxide and 32.4 g (0.19 M) propyl iodide. The liquid was decanted from the remaining solid and the benzene was distilled off. The residue was extracted with ether, the ether solution washed with 10% NaOH and dried. The liquid remaining after evaporation of the solvent distilled at 133°C/6 mm. The colorless liquid decomposed before reaching the b.p., $n_D^{27} = 1.5033$.

Yield: 10.4 g (78%).

Anal: Calcd. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.16.

Found: C, 70.3; H, 8.1.

I. R. spectrum: The spectrum is very similar to that of the propyl ester. All absorption bands occur at approximately the same wavelengths as those found for the propyl ester.

2.3.3 Hydrolysis of Ethyl 2-propoxy-5-methylbenzoate

The procedure is similar to that described for the hydrolysis of the propyl ester described in route 1. 7.3 g of ester were refluxed for 8 hrs. with 10% KOH in 50% ethanol.

Yield of purified product: 5.0 g (78%), $n_D^{27} = 1.5269$.

Anal: Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3.

Found: C, 67.9; H, 7.5.

The infra-red absorption spectra of the products obtained by routes 1 and 2 were identical.

2.4 Reaction With Zinc Oxide

In order to study the reaction of PMBA with zinc oxide and to determine the physical properties of the resulting products, the consistency and setting times of mixes of varying compositions and their solubility and disintegration and crushing strength were measured. Standard consistencies of the slurries as well the solubilities and disintegration and crushing strength were determined according to American Dental Association Specification No. 9 [3].

Standard consistencies of slurries are given in Table 1. Considerable difficulties were encountered in preparing these mixes since PMBA and PMBA- eugenol solutions do not wet readily the zinc oxide particles. Incorporation of wetting agents especially oleic acid alleviated this problem somewhat. The setting times of mixes of standard consistency of PMBA and PMBA-eugenol solution with zinc oxide were measured at 37°C and 100% relative humidity as described previously [1]. The mixes of PMBA with zinc oxide harden completely in 30 minutes (Table 1). Mixes containing PMBA and up to 50% eugenol harden somewhat faster. A solution containing 80.9% PMBA, 14.3% eugenol and 4.8% oleic acid and sets in 15 minutes.

The large water solubility and disintegration obtained in duplicate determinations for slurries of standard consistency

were quite unexpected and disqualify these materials for possible clinical applications. The increased solubility of the higher homologues of o-ethoxybenzoic acid can possibly be explained due to the (1) decreased reactivity of the PMBA resulting in an incomplete reaction with zinc oxide or (2) formation of a somewhat water soluble zinc salt instead of a chelate compound.

Compressive strength was determined after immersion of the molded specimens in water at 37°C for 23 hours. The specimens were then crushed at a rate of 500 lb/in² ± 10%^{/MIN.}. The crushing strength values averaged around 1500 lb/in². The low values may be caused by the large water solubility which will weaken the cement on immersion in water prior to measuring crushing strength.

3. CONCLUSIONS

2-propoxy-5-methylbenzoic acid (PMBA) zinc oxide mixtures harden without accelerators. The resulting cements show unexpectedly high water solubility which would limit any possible clinical applications. The use of PMBA or other homologues of o-ethoxybenzoic acid which are liquids at room temperature does not look promising. The possibility of employing solid chelating agents dissolved in eugenol or o-ethoxybenzoic acid to obtain satisfactory cements is being actively investigated.

Acknowledgments:

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Table 1

Physical Properties of PMBA-Eugenol-Zinc Oxide Mixtures

Temperature: 37°C

Relative Humidity: 100%

| <u>Composition</u> | <u>Standard Consistency</u> | <u>Setting Time</u> | <u>Solubility and Disintegration</u> |
|---|-----------------------------|---------------------|--------------------------------------|
| | P/L (g/ 0.4 ml) | Min. | % |
| 100% PMBA | 2.3 | 30 | |
| 85% PMBA + 15% Eug. | 3.0 | 20 | 11.8 |
| 66.7% PMBA + 33.3% Eug. | 2.7 | 30 | |
| 50% PMBA + 50% Eug. | 3.1 | 23 | |
| 25% PMBA + 75% Eug. | 3.4 | >30 | |
| 10% PMBA + 90% Eug. | 3.1 | >30 | |
| 80.9% PMBA + 14.3% Eug. +4.8% oleic acid | 3.0 | 15 | 10.7 |

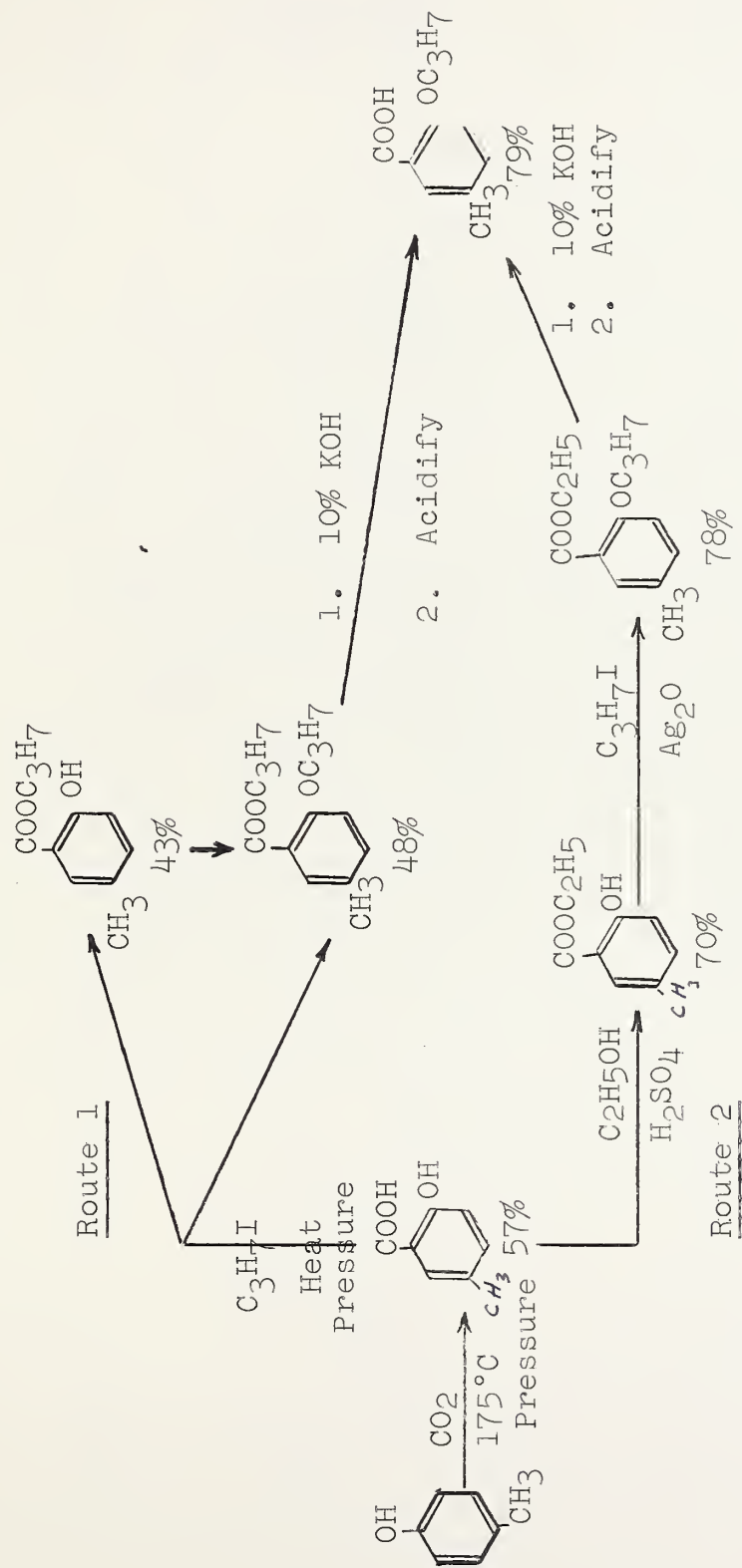


Figure 1. Synthesis of 2-Propoxy-5-methylbenzoic Acid.

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