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THE KOLBE-SCHMITT REACTION. I. VARIATIONS IN THE CARBONATION OF *p*-CRESOL

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In order to carry out a certain study made in our laboratory some time ago it became necessary to prepare several aromatic hydroxy acids. The possibility of employing the traditional Kolbe-Schmitt reaction (1) suggested itself early in this work. Upon an examination of the literature one is faced with a wide variation in possible procedures (2, 3, 4, 5, 6). By far the most simple technique reported consists in heating the phenol with potassium carbonate and carbon dioxide under pressure, a procedure apparently first used by Marassé (7). It was evident that, while a large number of compounds have been prepared by the Kolbe-Schmitt reaction, no general study of the relative merits of these several modifications has been reported.

In this paper we attempt to show the effect of variations in temperature, reaction time, carbon dioxide pressure, and the particular alkali metal or compound thereof on the yield of *p*-cresotinic acid (2-hydroxy-5-methylbenzoic acid) prepared from *p*-cresol. This particular phenol was selected for study since the possibility of forming more than one acid is remote. No attempt has been made to interpret the results of our study to support any of the theories related to the mechanism of this reaction (8), but it is felt that further work using a wide variety of different phenols may justify this.

The procedure mentioned under reference (7) was chosen for this preliminary work since it did not involve the initial preparation and isolation of an extremely hygroscopic metallic cresoxide. The number of operations involved in the reaction was thereby reduced to a minimum, thus making the comparison of yields under different conditions more valid. Table I shows the variation in yield of *p*-cresotinic acid at various temperatures and pressures when the reaction is carried out for different lengths of time. The examples that appear in the table are typical of those resulting from several hundred runs made during this study and all reported yields have been checked by duplicate runs. Details concerned with the control of temperature and pressure are described under Experimental.

From the results shown in Table I (Part A) it is evident that no appreciable amount of acid (less than 1%) will be formed at a temperature lower than 100° regardless of the pressure and time of reaction. A very high yield of product may be secured at a temperature of 125° while operating for eight hours at a pressure of 250 p.s.i. or more. The amount of acid formed is satisfactory at pressures as low as 100 p.s.i. when operating at the higher temperatures. A large increase in temperature, pressure, and reaction time do not result in a significant increase in yield.

Based on further studies made along these lines several points of general interest may be noted:

(a) A 2:1 molar ratio of potassium carbonate/*p*-cresol gave yields of product in general as high as did a ratio of 3:1. Reducing the ratio below this level usually served to decrease the yield.

(b) No *p*-cresotinic acid was formed when potassium carbonate was replaced by sodium carbonate, sodium bicarbonate, lithium carbonate, or the carbonates of magnesium or calcium. When potassium bicarbonate, cesium carbonate or rubidium carbonate was used the reaction proceeded normally except that yields were lower than with potassium carbonate (being of the order of 20%).

TABLE I

YIELD OF *p*-CRESOTINIC ACID UNDER VARIOUS REACTION CONDITIONS

PART A—HIGH PRESSURES

RUN NO.	TEMP., °C.	TIME, HRS.	PRESSURE, P.S.I.	YIELD, %
1	100	24	1420	0
2	110	8	1480	13
3	125	2	1240	40
4	125	4	1400	68
5	125	8	1310	84
6	175	4	1540	85
7	250	4	1580	82

PART B—LOW PRESSURES

RUN NO.	TEMP., °C.	TIME, HRS.	PRESSURE, P.S.I.	YIELD, %
8	125	8	250	79
9	125	8	100	43
10	125	8	15 (1 atm)	5
11	175	8	250	87
12	175	8	100	78
13	175	8	15 (1 atm)	29

(c) When *p*-cresol was mixed with potassium carbonate and heated to 250° for 24 hours without carbon dioxide no *p*-cresotinic acid was isolated. Negative results were also obtained when the reaction vessel was filled with nitrogen and heated under the same conditions at 1300 p.s.i.

(d) The addition of as little as one ml. of water to the reaction mixture may decrease the yield by as much as one-half.

(e) Attempts to prepare *p*-cresotinic acid by dissolving potassium carbonate in water, adding *p*-cresol, and refluxing the mixture in an atmosphere of carbon dioxide were unsuccessful. When glycerol was used instead of water yields of the order of 5% were secured.

(f) The reaction was also carried out in the traditional manner, that is, by heating the dry sodium, potassium or lithium cresoxides with carbon dioxide under pressure. The yield of *p*-cresotinic acid is lower when prepared from the metallic cresoxide by the traditional Kolbe-Schmitt procedure than when it is made by reacting *p*-cresol with potassium carbonate and carbon dioxide under pressure. Judging from our results there is nothing to be gained by preparing the cresoxide from the metal rather than the metallic hydroxide. The yield of product is generally largest when prepared from sodium cresoxide, somewhat less when the potassium salt is used, and lowest by far with the lithium salt.

It should be stated at this point that the authors found the regular Kolbe-Schmitt procedure to be unpredictable as to yield of product. It was not uncommon to observe no product formation at all under conditions which on a previous run had led to a good yield. Apparently the preparation of the cresoxide is not always reproducible, in spite of observing every precaution in isolating and drying the compound.

EXPERIMENTAL

Apparatus. Any of the commercial pressure reactors designed for hydrogenation studies may be used for these carbonations. It was not necessary to employ agitation in any form. Temperatures were automatically controlled to within ±5°. It was necessary to replace gaskets and small connection tubes frequently. Gaskets formed from copper or aluminum were found to be satisfactory. Stainless steel valves and tubing are desirable but not essential.

Preparation of potassium carbonate/p-cresol mixtures. The anhydrous potassium carbonate (fine granular) and freshly distilled *p*-cresol were used in a molar ratio of 3:1 or 2:1. Practically all of the runs were made with 0.05 mole (5.1 g.) of the cresol, but satisfactory results were obtained when using amounts of cresol as small as 0.01 mole. About one-half of the carbonate was placed in a Pyrex test tube of suitable size (20 × 200 mm.), the cresol added, and then the remainder of the carbonate. The two compounds may be mixed thoroughly or not mixed at all with little difference in yield obtained. All reagents and apparatus should be thoroughly dry, but otherwise no special precautions need be observed.

Preparation of sodium, potassium, and lithium cresoxides. Method A. About 400 ml. of dried toluene was placed in a one-liter three-neck flask and 0.25 mole of the metal was added. When lithium cresoxide was prepared the metal was hammered into thin wafers and trimmed into small places before being placed in the reaction flask. The flask was fitted with a Herschberg stirrer (9), reflux condenser, and a dropping-funnel. The metal (except lithium) was melted by bringing the toluene to a gentle reflux under stirring, and *p*-cresol (0.25 mole dissolved in 100 ml. of toluene) was added over a period of thirty minutes. The material in the flask became very viscous as the reaction progressed, and stirring under reflux was continued for two to three hours after all the cresol had been added.

The product was allowed to cool and the metallic cresoxide separated from toluene by suction filtration. The cresoxide was dried in a casserole by careful warming on a hot-plate, powdered by grinding gently with a pestle, and finally heated in a vacuum-oven (10–15 mm.) at 60° overnight.

Method B. p-Cresol (0.25 mole) and the metallic hydroxide (0.25 mole) were mixed in a casserole with 100 ml. of water. The solution was stirred constantly as it was rapidly evaporated to dryness on a hot-plate. Constant stirring was necessary to avoid charring the cresoxide. When the product appeared to be dry it was powdered in the casserole and dried further under the same condition as employed in Method A above.

Reaction procedure. The Pyrex tube containing the material to be studied was placed in the pressure reactor and carbon dioxide admitted from a commercial cylinder with no purification, following which the reactor was heated to the desired temperature. When operating at low pressures it was advisable to determine by preliminary blank runs the proper starting pressure so that when the desired temperature was reached it would not be necessary to reduce the pressure by venting the reactor, since this would inevitably be accompanied by loss of cresol and a marked decrease in the yield of product. Minor variations in pressure that appear in Table I were due to variations in the starting tank pressure. Best yields of product were secured when a considerable excess of carbon dioxide was used. At no point in any of our reactions were sudden increases in pressure noted that might constitute an explosion hazard.

At the end of the reaction the apparatus was allowed to cool, vented, and the tube removed. The reaction product was usually a hard cake having a light yellow to brown color. The cake was dissolved in hot water and filtered to remove tarry material. The filtrate was then extracted with ether to remove unreacted cresol, boiled with charcoal, cooled and filtered. No effort was made to recover any unreacted cresol. The filtrate was acidified with concentrated hydrochloric acid and the precipitated *p*-cresotinic acid was thoroughly dried in an oven at 60°. Melting points and neutral equivalents were determined on all products isolated in all of the runs.

All yields of *p*-cresotinic acid are reported on a crude basis. This is felt to be justified since the melting point of practically every product was 149 ±1° (uncorrected), as compared with that of 152° for a carefully purified sample. The neutral equivalent of the products was 152 ± 1; calculated value, 152.

Further studies being pursued related to the preparation of aromatic hydroxy acids by the carbonation of phenols are: the application of the reaction to amino- and nitro-phenols, and the effect of reaction conditions on the relative amounts of isomeric products formed.

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SUMMARY

The modification proposed by Marassé for the preparation of aromatic hydroxy acids was shown to be superior to the Kolbe-Schmitt procedure when *p*-cresol was used as a starting material. The variation in yield of product with changes in temperature, pressure, and reaction time is tabulated.

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