[Contribution from the Department of Chemistry of Southern Methodist University]

A STUDY OF THE KOLBE-SCHMITT REACTION. II. THE CARBONATION OF PHENOLS

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An earlier report (1) has described the conversion of *p*-cresol into *p*-cresotinic acid by the Kolbe-Schmitt carbonation of the cresoxide (2), and also by the much more simple procedure of Marassé (3), which involves carbonation, under pressure and at elevated temperature, of a mixture of the cresol and anhydrous potassium carbonate. Because of the simplicity of the Marassé modification and the excellent results obtained with *p*-cresol in the previous study (1) we have applied this reaction to phenol and a group of representative substituted phenols. We are also reporting, for comparative purposes, our results when the Kolbe-Schmitt reaction was used.

In the carbonation of phenol by these two procedures we have observed the formation, in varying relative amount, of *o*-hydroxybenzoic acid (salicylic), *p*-hydroxybenzoic acid, and 4-hydroxyisophthalic acid. The relative amounts of the three acids will vary with reaction conditions, in particular reaction temperature, and is markedly different when sodium phenoxide is replaced by potassium phenoxide in the Kolbe-Schmitt method, and still different when the Marassé modification is employed.

It is generally stated in the literature (4) that the carbonation of sodium phenoxide leads to the formation of salicylic acid, while potassium phenoxide is by similar means converted primarily into *p*-hydroxybenzoic acid. Our studies indicate that the reaction cannot be adequately described in quite so simple a manner. The data shown in Table I are representative of over fifty carbonations. These results indicate that the carbonation of potassium phenoxide and the Marassé carbonation are roughly parallel, while the behavior of sodium phenoxide on carbonation is quite different. No reaction mechanism has been proposed which will explain these results (5).

We have extended the Marassé reaction to approximately 100 phenols that represent a wide variety of types. The results of typical carbonations are summarized in Table II. Yields from 70 to 80% are common when the phenol nucleus is substituted in the *para* position by *ortho-para*-directing groups. With the exception of phenol and the hydroxypyridines carbonation of phenols occurs on the carbon atom *ortho* to the phenolic hydroxyl. Based on the results with phenol it is conceivable that small amounts of the *para*-hydroxy acid could have been formed and escaped isolation. However, we were unable to rearrange the sodium

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TABLE I

CARBONATION OF PHENOL

TEMP., °C.	SALICYLIC ACID, %			*p*-HYDROXYBENZOIC ACID, %			4-HYDROXYISOPHTHALIC ACID, %		
	Na[a]	K	M	Na	K	M	Na	K	M
100	94[b, c]	46	49	4	54	51	2	0	0
150	97	54	57	2	44	42	1	2	1
200	96	79	76	2	16	20	2	5	4
250	95	67	63	1	1	1	4	32	36

[a] The symbols Na and K refer to the carbonation of sodium and potassium phenoxides, and M refers to the Marassé modification. [b] An ultraviolet spectrophotometric method of analysis, based on the work of Vaughn and Stearn, *Anal. Chem.*, **21,** 1361 (1949), the details of which will be published elsewhere, was used to determine the composition of the reaction mixtures. [c] The total over-all yields in many of the carbonations amounted to as much as 80% based on the quantity of mixed acids isolated. Varying the reaction time between 4 and 24 hours and the carbon dioxide pressure between 1200 and 2000 p.s.i. had little effect on the total yield or on the relative amount of the three acids formed.

salts of several *ortho*-hydroxy alkyl and halogen acids to the *para* isomers as is possible with sodium salicylate (6). When two *ortho* positions are available reaction takes place at the less hindered position. With the exception of certain very reactive phenols our chosen reaction conditions led to the formation of only mono acids.

The carbonation of the aminophenols is of interest because of the importance of *p*-aminosalicylic acid (7) in the treatment of tuberculosis. This acid was formed in 51% yield from *m*-aminophenol by the Marassé procedure. Because of the structural similarity of *m*-aminophenol and resorcinol, it seemed reasonable that this phenol, like resorcinol (8) might carbonate in aqueous solution. Ordinarily the yields by the Marassé method are substantially reduced in the presence of water. On carbonation of *m*-aminophenol in sodium bicarbonate solution at 120° and 12 hours under a carbon dioxide pressure of 1500 p.s.i. a 45% yield of *p*-aminosalicylic acid was obtained. Attempts to carbonate *o*- and *p*-aminophenols have thus far been unsuccessful. Acetylation and benzoylation of the amino groups of all three isomeric aminophenols gave derivatives which carbonated smoothly.

The presence of *meta*-directing groups in some cases appears to inhibit the reaction, but in other cases does not interfere. We have successfully carbonated vanillin, *p*-hydroxypropiophenone, *p*-hydroxybenzophenone and 2-amino-4-nitrophenol, whereas no acids were obtained with the three isomeric nitrophenols.

In Table III we have listed, for comparative purposes, the maximum yields of *o*-hydroxy acids obtained from those phenols which were carbonated by the Kolbe-Schmitt procedure. For the most part the Marassé method, although requiring higher temperatures, gave greater yields than the Kolbe-Schmitt. The Marassé procedure has the further advantage in that it eliminates the time consuming preparation and isolation of extremely hydroscopic phenoxides.

TABLE II

CARBONATION OF PHENOLS; MARASSÉ PROCEDURE[a]

PHENOL	o-HYDROXY ACID, YIELD, %	PHENOL	o-HYDROXY ACID, YIELD, %
A. Alkyl Phenols		D. Halogen Phenols	
Phenol (for reference)	70	*o*-Fluoro-	69 (200°)
o-Cresol	70	*m*-Fluoro-	72
m-Cresol	85	*p*-Fluoro-	77 (225°)
p-Cresol	85	*o*-Chloro-	72
m-Ethyl-	83	*m*-Chloro-	68
p-*tert*-Butyl-	90 (200°)	*p*-Chloro-	83
p-Benzyl-	69	*o*-Bromo-	64
o-Cyclohexyl-	55	*m*-Bromo-	51
2,5-Dimethyl-	25	*p*-Bromo-	79
3,4-Dimethyl-	59	*o*-Iodo-	31 (125°, 8 hrs.)
3,5-Dimethyl-	74	*m*-Iodo-	35 (125°, 8 hrs.)
B. Hydroxy Phenols and Derivatives		*p*-Iodo-	6 (125°, 8 hrs.)
Catechol[b]	72 (225°)	2,4-Dichloro-	45 (200°)
Resorcinol[c]	65 (125°, 8 hrs.)	2,4-Dibromo-	38
Hydroquinone[d]	49 (200°, 8 hrs.)	2-Bromo-4-*tert*-butyl-	46
o-Methoxy-	47 (200°)	E. Miscellaneous Phenols	
m-Methoxy-	61 (200°)	Vanillin	57
p-Methoxy-	90 (150°)	*p*-Hydroxyazobenzene	42
Pyrogallol	62 (130°)	*alpha*-Naphthol	63
2-Methoxy-4-methyl-	69 (200°)	*beta*-Naphthol	23 (200°)
C. Amino Phenols and Derivatives		*o*-Hydroxydiphenyl-[e]	90
m-Amino-	51	*p*-Hydroxydiphenyl-[e]	23
o-Acetamido-	11	2-Amino-4-nitro-	20
m-Acetamido-	25	*p*-Hydroxypropiophenone	25
p-Acetamido-	71 (200°, 8 hrs.)	*p*-Hydroxybenzophenone	39 (200°, 8 hrs.)
o-Benzamido-	7	4,4′-Dihydroxybenzophenone	54 (250°)
m-Benzamido-	58	2-Hydroxypyridine[e]	0 (250°, 8 hrs.)
p-Benzamido-	80 (230°, 8 hrs.)	3-Hydroxypyridine[f]	28 (8 hrs.)
m-Diethylamino-	51	8-Hydroxyquinoline	21 (200°)
p-Benzylamino-	12		

[a] Unless otherwise indicated the reaction was carried out for a period of four hours at 175° under a carbon dioxide pressure of 1200 to 2000 p.s.i. In some cases where very small yields were obtained, these conditions were modified as indicated. No attempt was made to determine the optimum conditions for a maximum yield from any phenol. All yields are based on the total amount of acids isolated. [b] At 225°, eight hours, gave an 81% yield of 2,3-dihydroxybenzene-1,4-dicarboxylic acid. [c] At 200°, four hours, gave a 74% yield of 4,6-dihydroxybenzene-1,3-dicarboxylic acid. [d] At 225°, eight hours, gave a 14% yield of 2,5-dihydroxybenzene-1,4-dicarboxylic acid. [e] Substitution occurred *para* to the hydroxyl group to give a 45% yield of 6-hydroxynicotinic acid. No *ortho*-hydroxy acid was isolated even at lower temperatures. [f] Carbonation occurred at the 2-position to give a 28% yield of 3-hydroxypicolinic acid and at the 6-position to give a 21% yield of 5-hydroxypicolinic acid. No 3-hydroxyisonicotinic acid was isolated.

TABLE III

Carbonation of Phenols; Kolbe-Schmitt Procedure[a]

PHENOL	TEMP., °C.	YIELD, %
Phenol	125	79
o-Cresol	125	44
m-Cresol	125	70
p-Cresol	125	78
p-*tert*-Butyl—	150	74
m-Fluoro—	175	59
p-Fluoro—	175	44
o-Chloro—	150	64
m-Chloro—	175	68
p-Chloro—	150	69
o-Bromo—	175	64
m-Bromo—	175	80
p-Bromo—	175	5
p-Iodo—	175	0
2,4-Dichloro—	200	59
2-Bromo-4-*tert*-butyl—	200	58

[a] All carbonations were carried out for a period of eight hours under a carbon dioxide pressure of 1200 to 2000 p.s.i. using 0.05 mole of the sodium salt of the phenol.

EXPERIMENTAL

The apparatus and general experimental procedure have been described previously (1). All reagents and apparatus were thoroughly dried, but otherwise no special precautions need be observed. Anhydrous potassium carbonate should be dried at 400° for several hours. Most of the runs were made with 0.03 to 0.1 mole of phenol. In several cases (the cresols) one-mole quantities of the phenols were used with equally good results (70–80%).

Sodium salts of most of the phenols were prepared by mixing equimolecular amounts of sodium ethoxide and phenol dissolved in ethanol and evaporating to dryness. Using alcohol as a solvent rather than water had the advantage of permitting reaction with both components in solution. The excess alcohol was much easier to remove than the water. Before carbonation the phenoxides were dried overnight in a vacuum oven at 60–70° (5 mm.).

The acids formed were identified by determination of the melting points and neutral equivalents. In the case of the dihydroxy phenols where both mono- and di-carboxylic acids were formed, the components were separated by fractional crystallization from water, the monocarboxylic acids being much more soluble than the dicarboxylic acids. The relative amounts of mono- and di-carboxylic acid were calculated from the neutral equivalents of the mixtures.

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SUMMARY

The results obtained by the carbonation of phenol and certain substituted phenols by the Kolbe-Schmitt procedure and the Marassé modification are compared with respect to the yield of hydroxy acid formed under various experimental conditions. Sodium phenoxide, regardless of reaction temperature, gives almost exclusively salicylic acid. Potassium phenoxide forms variable amounts

of the *ortho* and *para* isomers with substantial amounts of 4-hydroxyisophthalic acid, depending on the temperature. Our results indicate that the carbonation of potassium phenoxide and the Marassé carbonation are roughly parallel. Substituted phenols containing *ortho-para*-directing groups carbonate in good yield by either procedure to give *ortho* hydroxy acids. *Meta*-directing groups reduce the yield or completely inhibit the reaction.

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