Table II. Characteristic Infrared Absorptions of Substituted Aromatic and Aliphatic Sulfonic Esters

No.	Aromatic CH Stretch, Cm.$^{-1}$	Aliphatic CH Stretch, Cm.$^{-1}$	Aromatic C=C Stretch, Cm.$^{-1}$	$-SO_2-O$ Absorption, Cm.$^{-1}$	CH-out-of-Plane Deformation, Cm.$^{-1}$	Other Characteristic Absorption, Cm.$^{-1}$
1	3070	...	1640 1570 1470	1370 1180	910 820	C—Cl 700
2	3040	2940	1600 1570	1360 1170	825	O ‖ —C— 1650 NH 3340
3	3040	2900	1600 1550[a]	1360 1190	790 805 828	$-NO_2$ 1550[a] 1360
4	3070	2940	1580 1470	1360 1180	805 825	$-OCH_3$ 1070
5	3070	2940	...	1370 1200	805	...
6	...	2940	...	1360 1160	...	C—Cl 705
7	...	2940	...	1360 1160	...	C—Cl 680 720

[a] Absorptions for the NO_2 group fall in the same region as the absorption for aromatic C=C and $-SO_2-O$ functions. Therefore, definite assignments cannot be made.

nitrogen for 15 hours at 25° C. After filtering off the NaF, the filtrate was washed with 100 ml. of 5% hydrochloric acid, twice with saturated sodium carbonate solution, twice with cold water, dried (Na_2SO_4), filtered, and treated twice with Norit A. Ether was removed, leaving 89 grams (63%) of tan solid. On drying in vacuo at 50° C., this solid liquefied to an orange syrup.

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Carboxylation of Substituted Phenols in *N,N*-Dimethylamide Solvents at Atmospheric Pressure

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A series of substituted phenols were carboxylated at atmospheric pressure in the presence of strong base, in *N,N*-dimethylformamide, *N,N*-dimethylacetamide, and *N,N*-dimethylpropionamide solvents.

IN CONNECTION with recently increasing interest in substituted salicylic acids of demonstrable fibrinolytic (*33, 34*) and protein-bonding (*4, 31*) activity, and interest in substituted *p*-hydroxybenzoic acids as intermediates in the production of light-stabilizers for polyolefins (*7*), modified methods for the carboxylation of phenols were investigated recently. In the course of the present study, which centered on the use of certain amide solvents as reaction media, the authors learned of related work done by Hirao and coworkers on dimethylformamide and other nonprotonic high-boiling solvents (*10–15*). The present work on carboxylation of phenols with different and generally greater substitution than those studied by Hirao has led to observations which differ from those reported by the Japanese investigators for simpler phenols, and may thus contribute to a more general insight into the carboxylation process in the synthesis of aromatic hydroxy acids.

The reaction consists, essentially, of the treatment of the phenol with carbon dioxide at atmospheric pressure in a highly basic environment in an *N,N*-dimethylalkanoamide—e.g., dimethylacetamide—at temperatures typically in the range 165° to 180° C. The basic environment can be provided by first converting the phenol to the corresponding alkali metal phenoxide, or by adding sodium methoxide in slight excess to the mixture of the solvent and phenol. As an alternate to carbon dioxide, the carbox-

ylating agent can be a metal methyl carbonate—e.g., sodium methyl carbonate or magnesium methyl carbonate.

Optimum yields are obtained by carboxylating for at least two hours, in most cases.

The yield of carboxylated product is adversely affected by the presence of moisture in the reaction mixture, but the degree of sensitivity to moisture varies considerably with the individual phenol being carboxylated. This observation is consistent with the well-known fact that resorcinol can be carboxylated in aqueous alkaline solution at normal pressures, while phenol cannot.

The superiority in yield which was obtained using sodium metal and dry methanol, in place of commercial sodium methoxide, is probably a reflection of more water or sodium hydroxide in the latter.

The choices of alkali metals and solvents are not independent and can greatly affect yields. Solvents which are useful include dimethylformamide, dimethylacetamide, and dimethylpropionamide. Solvents which are unsuitable and afford zero or trivial yields were diethylacetamide, dimethylbenzamide, diethylformamide, *o*-dichlorobenzene, and nitrobenzene. The failure to obtain measurable product yields in reaction media comprising three of the six tested *N,N*-dialkylamides in some tests clearly indicates that the role of the solvent depends on factors other than the amide linkage per se. The failure of nitrobenzene as a solvent points up the differences between para-carboxylation of unsubstituted phenol, where Hirao and Hara (*11*) successfully used nitrobenzene, and para-carboxylation of 2,6-dialkylphenols. The latter are not carboxylated at all in nitrobenzene under the authors' experimental conditions, but are carboxylated in the preferred amide solvents.

No satisfactory theory is available concerning the relevance of the solvent structure to the mechanism of the reaction. However, the amide linkage in the solvent apparently can be rendered less effective by either steric factors (increased size of the N-alkyl groups) or by electronic effects (substitution of C-alkyl by C-aryl groups). Further experimentation is now in progress to elucidate the mechanism.

The compounds prepared by the authors' carboxylation procedures are described in Table I.

All compounds previously unknown to the literature, and those for which observed melting points were substantially different from those previously reported, were subjected to elemental analysis, acidimetric titration, and spectrophotometric examination (in both ultraviolet and infrared).

In the case of single-ring compounds, the only structural possibilities considered were those resulting from carboxylation ortho or para to the hydroxyl group. For most of the compounds only one possibility exists, and thus the carboxylated product presented no ambiguity in identification.

In cases where the 2- and 4- positions with respect to the hydroxyl group were available as carboxylation sites, previously unknown compounds were assigned structures based on definitive and characteristic differences between the infrared spectra and the ultraviolet spectra, respectively, of substituted salicylic acids and substituted *p*-hydroxybenzoic acids.

In the ultraviolet spectra, the substituted salicylic acids exhibited three λ_{max} values, typically at 212–16, 236–48, and 312–28 mμ, respectively. The *p*-hydroxybenzoic acids had two λ_{max} values, typically at 212 and 250–62 mμ, respectively.

In the case of fused ring systems (hydroxynaphthoic acids and hydroxyquinoline carboxylic acids), some additional confirmation of structure was sought. The identities of the hydroxynaphthoic acids were established by observing mixed melting points with authentic samples.

Table I. Carboxylation of Substituted Phenols in Amide Solvents

Phenol	Acid	Method[a]	Yield, %	M. P., °C., Recryst. Solvent	
				Observed	Literature
2-*tert*-Butyl 6-methylphenol	3-*tert*-Butyl 4-hydroxy-5-methylbenzoic acid	I	96	184.5–6	172 (*9*)
3-*N,N*-Diethylaminophenol	4-*N,N*-Diethylaminosalicylic acid	III	94	132 (decomp.) (methanol)	142–5 (*6*)
3-*N,N*-Dimethylaminophenol	4-*N,N*-Dimethylaminosalicylic acid	III	94	140 (decomp.) (methanol)	129 (*27*)
2,6-Di-*tert*-butyl phenol	3,5-Di-*tert*-butyl 4-hydroxybenzoic acid	I	93[b]	218–19 (benzene)	218–19 (*3*)
4,6-Di-*tert*-butyl resorcinol	3,5-Di-*tert*-butyl γ-resorcylic acid	II	92	179 (decomp.) (heptane)	
2,4-Di-*tert*-butyl phenol	3,5-Di-*tert*-butyl salicylic acid	I	86	164 (heptane)	
4-Methylphenol	5-Methylsalicylic acid	IV	82	152–3 (aq. methanol)	151 (*26*); 152.5 (*30*)
2-*tert*-Butyl 4-methylphenol	3-*tert*-Butyl 5-methylsalicylic acid	III	80	198–200 (heptane)	
4-Methoxyphenol	5-Methoxysalicylic acid	IV	77	144–6 (heptane)	145–6 (*25*)
2,6-Diisopropylphenol	3,5-Diisopropyl-4-hydroxybenzoic acid	II	72	146–7 (benzene)	147 (*9*)
4-(1,1,3,3-Tetramethylbutyl)phenol	5-(1,1,3,3-Tetramethylbutyl)-salicylic acid	III	70	161–2 (toluene)	
2-*tert*-Butyl 5-methylphenol	3-*tert*-Butyl 6-methylsalicylic acid	I	67	185–6.5 (toluene)	184 (*22*)
4-Chlorophenol	5-Chlorosalicylic acid	II	66	176–7 (benzene)	172 (*18*); 173 (*23*)
2,6-Dimethylphenol	3,5-Dimethyl-4-hydroxybenzoic acid	II	58	223–4 (methanol)	222–4 (*24*)
8-Hydroxyquinoline	8-Hydroxy-7-quinolinecarboxylic acid	III	57	268 (decomp.) (2-propanol)	237–50 (*29*)
1-Naphthol	1-Hydroxy-2-naphthoic acid	II	50	200 (decomp.) (aq. methanol)	197 (*2*)
3-Methoxyphenol	4-Methoxysalicylic acid	II	32	158–61[c]	159 (*5*)
2-Naphthol	2-Hydroxy-1-naphthoic acid	II	22	151.5 (decomp.)	156–7 (*32*)
4-*N*-Nonanoylaminophenol	5-*N*-Nonanoylaminosalicylic acid	II	22	206.5–7.5 (methanol)	
8-Hydroxyquinaldine	8-Hydroxy-2-methyl-7-quinolinecarboxylic acid	III	21	215 (methanol)	207 (*17*)
3-*tert*-Butyl phenol	4-*tert*-Butyl salicylic acid	II	17	140 (heptane)	

[a] Method I uses sodium and ethanol or methanol as the source of base; Method II uses commercial sodium methoxide; Methods III and IV use KOH, with subsequent removal of water of reaction from phenolate formation. The amide solvent in I, II, and IV is *N,N*-dimethylacetamide; in III it is *N,N*-dimethylformamide. For additional details, see illustrations in the experimental section. [b] When Method I was modified by replacement of *N,N*-dimethylacetamide by other amide solvents, the following yields were recorded: in *N,N*-dimethylpropionamide, 56%; in *N,N*-dimethylformamide, 10%; in *N,N*-dimethylbenzamide, 2%; in *N,N*-diethylformamide, 0%. [c] The product was purified by solution in sodium carbonate, and reprecipitation with hydrochloric acid, after either activated charcoal or solvent treatment to remove impurities.

In the case of 8-hydroxyquinoline-7-carboxylic acid, the authors had no access to authentic samples. The compound prepared by Schmitt and Engelmann (*29*) by carboxylation of 8-hydroxyquinoline had a lower melting point, but gave a similar violet color with ferric chloride. Baine *et al.* (*1*) also carboxylated 8-hydroxyquinoline, but did not assign a structure to the product. Subsequently, Lindsey and Jeskey (*19*), in a review article, referred to both Baine's product and Schmitt's as 8-hydroxyquinoline-2-carboxylic acid. This latter compound is known, and its synthesis and properties have been described by Irving and Pennington (*16*). It melts at 211° C. (57° below the authors' compound), and it gives a green color with ferric salts. It is evident that this is not the authors' compound, and that Schmitt's and possibly Baine's have been misidentified. Since carboxylation on the pyridine ring is much less probable than on the benzene ring, the only other isomeric product which might be considered is 8-hydroxyquinoline-5-carboxylic acid. This compound is also known (*20, 21*) and gives a green ferric ion test. The authors' product has the characteristic suppression of hydroxyl absorption in the 3500 $cm.^{-1}$ region of the spectrum, which is associated with hydrogen bonding. This is a common feature of salicylic acids. The *p*-hydroxy acids absorb strongly in this region.

In support of structural assignments generally, the *o*-hydroxy acids have a characteristic carbonyl absorption at about 1675 $cm.^{-1}$, while the *p*-hydroxy acids have the corresponding absorption at 1690 $cm.^{-1}$.

Carboxylation did not occur at sites adjacent to a tertiary butyl group or a dialkylamino group, presumably for steric reasons. When 3-*tert*-butyl phenol was carboxylated, the only observed product was 4-*tert*-butyl salicylic acid. In the case of 3,5-di-*tert*-butyl phenol, in which any possible carboxylation would have to be adjacent to a tertiary butyl group, no carboxylation was observed. When 4,6-di-*tert*-butyl resorcinol was carboxylated, the only carboxylation site not adjacent to a tertiary butyl group was the position between the two hydroxyl groups. The indicated disubstituted γ-resorcylic acid was, in fact, obtained in high yield.

EXPERIMENTAL SECTION

Analyses. Melting points are uncorrected. All acids were titrated for the acid value—i.e., the number of milligrams of potassium hydroxide neutralized by a 1-gram sample of acid. Infrared spectra were obtained on a Perkin-Elmer Model 337 (grating-type) spectrophotometer. Ultraviolet spectra were obtained in a Beckman DB spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Syntheses. The carboxylic acids were prepared by Methods I to V, detailed illustrations of which are given below. The preparation of 4,6-di-*tert*-butyl resorcinol, required as an intermediate in the synthesis of 3,5-di-*tert*-butyl γ-resorcylic acid, is described separately.

Method I. 3,5-Di-*tert*-Butyl Salicylic Acid. In a 500-ml., three-necked reaction flask equipped with a thermometer, stirrer, condenser, and drying tube, 6.9 grams of metallic sodium (0.3 gram-atom) was dissolved in 200 ml. of anhydrous alcohol. To the solution, 20.6 grams of 2,4-di-*tert*-butyl phenol (0.1 mole) was added and carbon dioxide was passed into the solution until 10.0 grams (0.228 mole) had been absorbed. Following the addition of 50 ml. of *N,N*-dimethylacetamide, the solvents were distilled until the pot temperature reached 180° C. The reaction mixture was stirred at 180° C. for 1.5 hours, cooled to 90° C., and dissolved in 250 ml. of water. The aqueous solution was washed twice with 50-ml. portions of toluene to remove unreacted phenol and then acidified to pH 1 with concentrated aqueous HCl. The solids were filtered, water-washed, and dried in vacuo to give 21.5 grams (86%) of crude product. Crystallization from *n*-heptane (Nuchar) gave white crystals melting at 164° C.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; acid value, 224. Found: C, 71.97; H, 8.89; acid value, 223.

Analogous procedures were used for the preparation of the following compounds.

3-*tert*-Butyl 4-Hydroxy-5-methylbenzoic Acid. Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75; acid value, 270. Found: C, 69.33; H, 7.79; acid value, 269.

3,5-Di-*tert*-Butyl 4-Hydroxybenzoic Acid. Calcd. acid value, 224; found, 224. It showed no depression of mixed melting point with an authentic sample. It gave an infrared spectrum identical to the reference sample.

3-*tert*-Butyl 6-Methylsalicylic Acid. Calcd. acid value, 270; found, 269. Infrared spectrum was identical to Sadtler spectrum 23209 (*28*).

Method II. 3,5-Diisopropyl-4-hydroxybenzoic Acid. (Apparatus as in Method I). Carbon dioxide was passed into a mixture of 35.6 grams of 2,6-diisopropylphenol (0.2 mole), 150 ml. of *N,N*-dimethylacetamide, and 16.2 grams of fresh sodium methoxide (0.3 mole), and the gas flow continued throughout the subsequent reaction period. The mixture was heated, distilling dimethylacetamide until the temperature reached 180° C. After stirring at 180° C. for 1.5 hours, the mixture was cooled to 90° C., the CO_2 stream was discontinued, and 300 ml. of water was added. The mixture was washed with toluene (2 × 50 ml.) and acidified to pH 1 with concentrated aqueous HCl. The solids were filtered, washed, and dried in vacuo to give 31.9 grams (72%) of crude product. Crystallization from benzene (Nuchar) gave white crystals melting at 146–7° C.

Anal. Calcd. acid value, 252.5; found, 253.

By analogous procedures, the following compounds were prepared.

5-*N*-Nonanoylaminosalicylic Acid. Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.52; H, 7.85; N, 4.78; acid value, 191. Found: C, 65.67; H, 7.97; N, 4.65; acid value, 187.

4-*tert*-Butyl Salicylic Acid. Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26; acid value, 289. Found: C, 68.14; H, 7.41; acid value, 287.

5-Chlorosalicylic Acid. Calcd. acid value, 326; found, 325.

3,5-Dimethyl-4-hydroxybenzoic Acid. Calcd. acid value, 338; found, 335.

1-Hydroxy-2-naphthoic Acid. Calcd. acid value, 298; found, 292. Mixed melting point with authentic sample gave no depression.

4-Methoxysalicylic Acid. Calcd. acid value, 334; found, 326.

2-Hydroxy-1-naphthoic Acid. Calcd. acid value, 298; found, 294. Mixed melting point with authentic sample gave no depression.

In the preparation of 3,5-di-*tert*-butyl γ-resorcylic acid by Method II, the solid obtained on acidification was a 1 to 1 molecular complex of the desired acid with *N,N*-dimethylacetamide. The complex was decomposed by stirring for 1 hour at 95° C. with about 10 times its weight of 5% HCl, cooling, filtering, drying, and recrystallizing from heptane. Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; acid value, 211. Found: C, 67.87; H, 8.39; acid value, 211.

Method III. 8-Hydroxy-7-quinolinecarboxylic Acid. A mixture of 29.0 grams of 8-hydroxyquinoline (0.22 mole), 13.2 grams of KOH (Tech. 90%, 0.21 mole), and 100 ml. of toluene was heated at reflux, collecting the water of reaction in a Dean-Stark trap. After the theoretical amount of water was collected, the solution was cooled slightly, 100 ml. of *N,N*-dimethylformamide was added, and the toluene distilled. At 145° C., a stream of CO_2 was passed into the solution and continued throughout the reaction. Distillation of the solvents was continued until the temperature reached 160° C. After stirring at 160° for 2 hours,

the mixture was cooled, the CO_2 stream discontinued, and 250 ml. of water added. A small amount of insoluble material was removed, and the aqueous solution was acidified to pH 4.7 with concentrated HCl. The precipitate was filtered, washed with water, and dried in vacuo to give 26.5 grams (56.8%) of crude product. After recrystallization from isopropyl alcohol, the pale yellow crystals melted with decomposition at 268° C.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41; acid value, 296.5. Found: C, 63.41; H, 3.70; N, 7.38; acid value, 293.

By analogous procedure, 8-hydroxy-2-methyl-7-quinoline carboxylic acid was prepared. Calcd. acid value, 276; found, 275.

The following were also prepared by this procedure, except that no filtration was required prior to acidification.

4-*N*,*N*-DIMETHYLAMINOSALICYLIC ACID. Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73; acid value, 310. Found: C, 59.73; H, 6.14; N, 7.71; acid value, 307.

3-*tert*-BUTYL 5-METHYLSALICYLIC ACID. Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75; acid value, 270. Found: C, 69.22; H, 7.75; acid value, 269.

5-(1,1,3,3-TETRAMETHYLBUTYL)SALICYLIC ACID. Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; acid value, 224. Found: C, 71.97; H, 8.89; acid value, 225.

4-*N*,*N*-DIETHYLAMINOSALICYLIC ACID. Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.70; acid value, 268. Found: C, 63.04; H, 7.30; N, 6.68; acid value, 267.

Method IV. 5-METHOXYSALICYLIC ACID. A mixture of 24.8 grams of *p*-methoxyphenol (0.2 mole), 13.2 grams of KOH (Tech. 90%, 0.21 mole), and 100 ml. of toluene was heated, and the theoretical amount of water removed by a Dean-Stark trap. The solution was cooled slightly, 100 ml. of *N*,*N*-dimethylacetamide was added, and the toluene distilled. At 160° C., a stream of CO_2 was passed into the solution and continued throughout the reaction. Distillation of solvents was continued until the temperature reached 180° C. After stirring at 180° C. for 2 hours, the mixture was cooled to 90° C., the CO_2 stream discontinued, and 200 ml. of water added. The mixture was extracted twice with 50-ml. portions of toluene and acidified to pH 1 with concentrated HCl. The precipitate was filtered, washed with water, and dried to give 26.0 grams (77.4%) of crude product. After crystallization from toluene, the white crystals melted at 145–6° C. Calcd. acid value, 334; found, 334.

By an analogous procedure, 5-methylsalicylic acid was prepared. Calcd. acid value, 369; found, 368.

Method V. 3,5-DI-*tert*-BUTYL 4-HYDROXYBENZOIC ACID. To a methanolic solution of methyl magnesium carbonate—prepared by saturating a solution of 3.7 grams of Mg (0.15 gram-atom) in 150 ml. of anhydrous methanol with carbon dioxide—was added 20.6 grams of 2,6-di-*tert*-butyl phenol (0.1 mole) and 50 ml. of *N*,*N*-dimethylacetamide. The mixture was heated, allowing the solvents to distill until a pot temperature of 180° C. was reached. After heating at 180° C. for two hours, the mixture was cooled and diluted with 200 ml. of water. After acidification with concentrated HCl, the oily precipitate was dissolved in 100 ml. of toluene. The solution was extracted twice with 10% aqueous sodium carbonate—2 × 50 ml. Following acidification of the combined extracts, the product was filtered, water-washed, and dried to give 12.0 grams of 3,5-di-*tert*-butyl 4-hydroxybenzoic acid (48% yield), melting at 218–19° C. (benzene).

Preparation of 4,6-Dibutyl Resorcinol. A mixture of 55.0 grams of resorcinol (0.5 mole), 0.5 gram of *p*-toluenesulfonic acid, and 100 ml. of heptane was heated to 95° C. in a 500-ml. reaction flask equipped with stirrer, thermometer, gas inlet tube, and condenser. Isobutylene was then passed into the mixture, maintaining a slight positive pressure. After two hours, 61.0 grams of isobutylene (1.09 mole) had been absorbed and the reaction was stopped. The hot solution was treated with 2.0 grams of activated carbon, filtered, and cooled in an ice bath. The white crystals were filtered, washed with a little cold heptane, and dried in vacuo at 60° C. The yield of white crystals, melting at 113–16° C., was 76.0 grams (68.5%). After two recrystallizations from heptane, the melting point was 123° C. (lit. 122–3° C.) (*8*).

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