fication of the compound VIIIa: yield 94%, m.p. 195.5–198.5°, $[\alpha]^{20}D$ +2.1 ± 1° (*c* 2, DMF).

N,N'-Bis(D-alanyl)-*meso*-diaminopimelylbis(L-alanine) (VII).—Bis(Z-L-Ala)-*meso*-DAP-bis(L-Ala) (VIIb) (180 mg., 0.25 mmole) was dissolved in aqueous methanol and a few drops of acetic acid. Hydrogenolysis was carried out with 5% palladized carbon catalyst in a stream of hydrogen. After 2 hr. the hydrogenation was complete and the catalyst was removed; filtrate and washings were concentrated under vacuum. The residue was redissolved in acetone and after evaporation was dissolved in a minimum amount of water and the free peptide was precipitated with ethanol. A gel-like precipitate was collected and dried: yield 93 mg. (81%) of hygroscopic white powder. After total hydrolysis of the product by 6 *N* hydrochloric acid (18 hr. at 110°) the amount of DAP and Ala was determined by a method previously described[9] and 0.036 μmole of DAP and 0.150 μmole of Ala were found, thus confirming the molecular ratio 1:4 for the constituents of this pentapeptide: m.p. >300°, $[\alpha]^{22}D$ −16.7 ± 1° (*c* 1.35, 0.1 *N* hydrochloric acid). A sample for analysis was dried at room temperature for 20 hr.

Anal. Calcd. for $C_{19}H_{34}N_6O_8 \cdot 2H_2O$ (510.5): C, 44.69; H, 7.50; N, 16.46. Found: C, 44.64; H, 7.62; N, 16.0.

N,N'-Bis(D-alanyl)-*meso*-diaminopimelylbis(D-alanine) (VIII).—This pentapeptide was prepared by the same procedure as the one described for the preparation of the enantiomorphic compound VII: yield 80%, m.p. >300°, $[\alpha]^{19}D$ +17.7 ± 1° (*c* 1.3, 0.1 *N* hydrochloric acid).

Acknowledgment.—The authors are pleased to express their thanks to Professor Edgar Lederer for his continued interest.

Oxidation of Aromatic Acids. V. Preparation of Salicylic Acids from Benzoic Acids

WARREN W. KAEDING[1] AND G. ROBERT COLLINS

Research Laboratories, Western Division, The Dow Chemical Company, Walnut Creek, California

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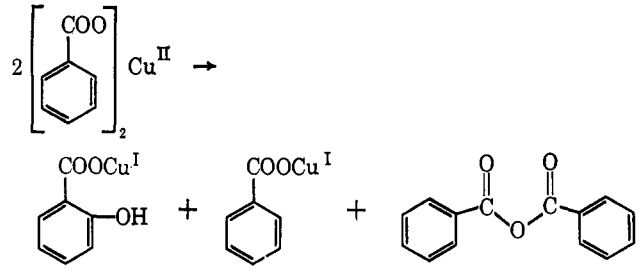
Salicylic acid was produced from benzoic acid by heating the cupric salt of the latter in a variety of aprotic media. Cupric ion was the oxidizing agent. This reaction has also been successfully used with a variety of substituted benzoic acids with at least one vacant *ortho* position. The use of air for the oxidation of benzoic acid to salicylic acid is discussed.

A previous paper of this series[2] has described a method for the preparation of salicylic acids from the corresponding benzoic acid by the thermal rearrangement of the basic cupric salt. This procedure has limited practical value for syntheses because of the necessity to prepare the basic salt and because of the low conversions to product. Free acid must also be rigorously excluded from the system to prevent the destruction of the basic salt.

On the other hand, the normal cupric salt can be prepared with ease by the reaction between the oxide, hydroxide, or carbonate of copper with benzoic acid. The thermal rearrangement of cupric benzoate in benzoic acid solution, in the presence of air and water, is being used for the large-scale industrial production of phenol.[3] Studies concerning the mechanism of this reaction have suggested that salicylic acid was a transient intermediate which rapidly decarboxylated during the oxidation of benzoic acid to phenol.[4] An interpretation of recent kinetic work on the mechanism of this reaction has suggested a bimolecular reaction between the salicylate anion and a proton.[5] Conditions were very favorable for this since the solvent, benzoic acid, provided a large source of protons and the catalysts and promoters facilitated the formation of salicylate anion.

If the thermal rearrangement of cupric benzoate were carried out in an aprotic medium, and if the decarboxylation mechanism suggested is valid, the proposed salicylic acid intermediate would be denied a proton and could not decarboxylate. When this theory was tested experimentally, salicylic acid was isolated as a major product of the reaction. Therefore, a new route is available for the preparation of salicylic acid, starting with benzoic acid. This reaction appears to be general and can also be utilized for the convenient preparation of a number of substituted salicylic acid derivatives.



Results

Salicylic acids were produced simply by heating a suspension of the cupric salt of the aromatic carboxylic acid in an aprotic media. The starting material was conveniently prepared *in situ* by the addition of basic cupric carbonate to a solution of the aromatic acid in the reaction medium. The thermal rearrangement appeared to occur as the cupric salt dissolved. The characteristic blue or blue-green color disappeared and was replaced by a solid with a dull copper to gold cast. The latter was a mixture of the cuprous salts of the starting acid and the salicylic acid produced by the thermal rearrangement. The results are summarized in Table I.

A variety of aprotic media was tested. Aliphatic hydrocarbons appeared to be inert. A high-boiling mineral oil which was a mobile liquid at room temperature was convenient because the reaction could be carried to completion at atmospheric pressure. Cyclo-

(1) To whom inquiries should be sent: Mobil Chemical Co., Metuchen, N. J.

(2) W. W. Kaeding and A. T. Shulgin, *J. Org. Chem.*, **27**, 3551 (1962).

(3) (a) W. W. Kaeding, R. O. Lindblom, and R. G. Temple, *Ind. Eng. Chem.*, **53**, 805 (1961); (b) W. W. Kaeding, *Hydrocarbon Process, Petrol. Refiner*, **43**, No. 11, 175 (1964).

(4) W. W. Kaeding, Proceedings, 6th World Petroleum Congress, 1963, Section II, paper 30.

(5) W. W. Kaeding, *J. Org. Chem.*, **29**, 2556 (1964).

TABLE I

PRODUCTION OF SALICYLIC ACIDS FROM THE CORRESPONDING BENZOIC ACIDS

Run no.	R	mmoles	Medium[a]	Cu(II),[b] mmoles	Temp., °C.	Time heated, min.	mmoles	Recov. starting acid,[c] mmoles	Material balance,[d] %	Conversion,[e] %	Yield,[f] %
1	H	410	DPO	436	250	25	98	293	95	24	84
2	H	164	DPO	349	230	30	66	88	94	40	87
3	H	2050	DPO	1020[g]	230	90	590	1332	94	29	82
4	H	32.7	CH	16.3[h]	250	15	4.8	26.7	96	15	80
5	H	32.7	B	16.3[h]	250	13	2.7	29.8	99	8	93
6	H	32.7	T	16.3[h]	250	10	2.7	30.1	100	8	100
7	H	164	MO	349	250	40	36	125	98	22	92
8	H	162	MO	81[h]	250	25	24[i]	129	95	15	73
9	*o*-CH_3	184	MO	436	215	30	35	141	96	19	82
10	*m*-CH_3	114	DPO	57[h]	250	28	5	104	96	4	50
11	*p*-CH_3	368	DPO	786	260	90	152	150	82	41	70
12	*p*-*t*-Bu	168	MO	349	250	50	31	112	85	18	55
13	*o*-NO_2	150	DPO	436	240	15	0[j]				
14	*m*-NO_2	150	MO	436	255	20	2	139	94	1	18
15	*p*-NO_2	150	DPO	436	255	35	29	121	100	19	100
16	*p*-CN	130	CH	65[h]	250	10	0[j]				
17	*p*-OMe	164	DPO	436	215	20	43	102	88	26	70

[a] DPO, diphenyl oxide; DPM, diphenylmethane; CH, cyclohexane; B, benzene; T, toluene; MO, mineral oil. [b] Added as basic cupric carbonate to a solution of the organic acid in the reaction medium. [c] Includes acid recovered by treatment of esters and anhydrides with base. [d] Identified moles of aromatic rings recovered × 100/moles of starting acid. [e] Moles of salicylic acid × 100/moles of starting benzoic acid. [f] Moles of salicylic acid × 100/(moles of starting benzoic acid − moles of recovered benzoic acid). [g] Air bubbled through reactor at a rate of 4000 cc./min. for 1.4 hr. [h] Cupric salt of the acid prepared by independent synthesis. [i] CO_2 produced, 1.6 mmoles. [j] Color test with $FeCl_3$ indicated the presence of salicylic acid but the amount was too small for recovery of pure sample. Extensive decarboxylation.

hexane was also used, with pressure apparatus, and has the advantage of being easy to separate from the less volatile reaction products.

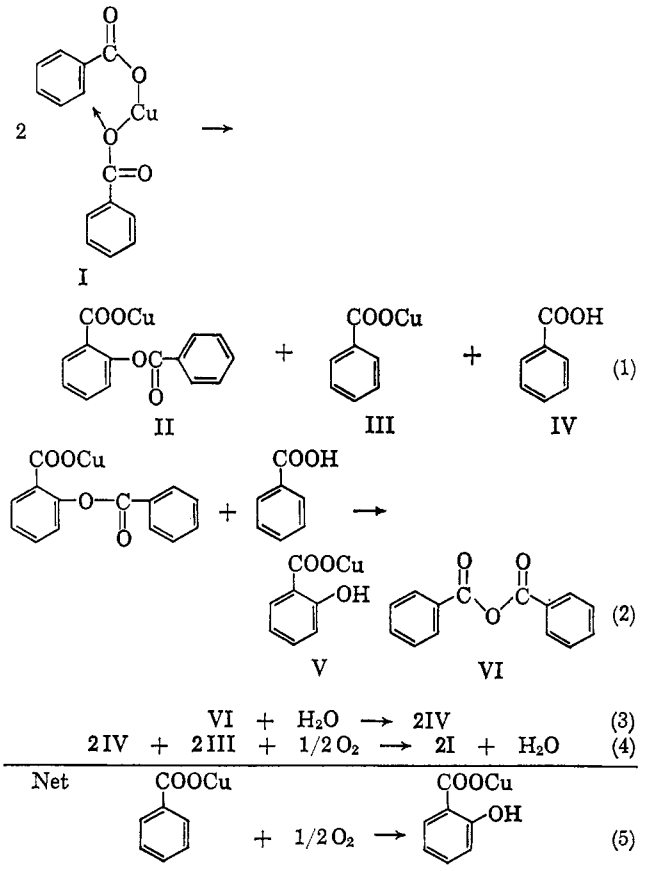
A number of aprotic aromatic compounds were also successfully utilized for the reaction media. A competing reaction, involving the solvent, also occurred, the nature of which will be discussed in a subsequent paper.

Discussion

A reaction sequence for the oxidation of benzoic acid to salicylic acid with cupric ion is proposed. The initial thermal rearrangement of cupric benzoate is shown by eq. 1. *o*-Benzoyloxybenzoic acid (II, free acid) was isolated and positively identified, in certain reaction mixtures, in molar quantities approaching one-quarter that of salicylic acid.

This is the first time that it has been possible to isolate this important intermediate which has been used to explain the oxidative attack at a position on the aromatic ring *ortho* to the carboxyl group. This has been demonstrated repeatedly when the corresponding molten benzoic acid was used as the solvent.[6-9] In the latter protic reaction medium, decarboxylation was rapid to give (in the absence of water) the corresponding phenyl benzoate as the principal reaction product.

Hydrolysis of the ester produced the corresponding phenol. Both *o*- and *p*-toluic acids gave *m*-cresol as the principal oxidation product while *m*-toluic acid gave a mixture of *o*- and *p*-cresols.[4]



The principal salts isolated from the reaction mixture were cuprous benzoate and cuprous salicylate, as indicated by their infrared spectra, powder X-ray diffraction patterns, and elemental analyses. To account for this, a reaction between the free benzoic acid, liberated during the initial thermal rearrange-

(6) W. Schoo, J. V. Veenland, J. A. Bigot, and F. L. J. Sixma, *Rec. trav. chim.*, **80**, 134 (1961).
(7) W. W. Kaeding, *J. Org. Chem.*, **26**, 3144 (1961).
(8) W. G. Toland, *J. Am. Chem. Soc.*, **83**, 2507 (1961).
(9) W. Schoo, J. V. Veenland, and T. J. DeBoer, *Rec. trav. chim.*, **82**, 954 (1963).

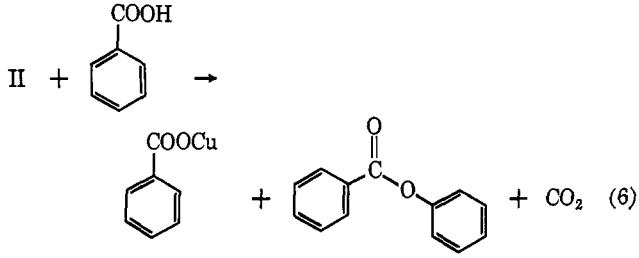
ment (eq. 1), and the cuprous salt of benzoylsalicylic acid (II) is proposed (eq. 2). The presence of sufficient quantities of benzoic anhydride to support this reaction was demonstrated.

The early paper of Bamdas and Shemyakin[10] reported the isolation of salicylic acid (14% yield) and benzoic anhydride by the dry distillation of cupric benzoate. Their proposed mechanism did not show an oxidation–reduction reaction involving the metal. The work reported here indicates that cupric ion, present as the salt of benzoic acid, was the oxidizing agent for the production of salicylic acid. In order to increase the 25% theoretical conversion of benzoic acid, predicted by eq. 1, additional cupric carbonate usually was added. The free acid liberated rapidly reacted with it to form more cupric salt which subsequently rearranged to product. This procedure always resulted in a higher conversion to product but with a decreased efficiency in the utilization of total oxidizing power supplied to the system by the cupric ion.

For example, when pure cupric benzoate was heated in cyclohexane (run 4, Table I), only a 15% conversion was realized. With runs 1 and 2, however, over a 100% excess of basic cupric carbonate was used. The conversion to salicylic acid was increased to 24 and 40%.

In benzoic acid solution, however, cuprous benzoate could be rapidly converted to the higher oxidation state with air[3] (eq. 4). This reaction also occurred in this system, even though the concentration of free acid was very low by comparison. The water produced by the oxidation appeared to hydrolyze the anhydride effectively to the free acid (eq. 3). In this manner, relatively high degrees of conversion to salicylic acid could be achieved, with air acting as the principal oxidizing agent as shown in the over-all net reaction (eq. 5).

The formation of a small amount of free benzoic acid (eq. 1) might be expected to provide protons for a decarboxylation reaction.[5] Phenol would be produced from salicylic acid while benzoylsalicylic acid would give phenyl benzoate (eq. 6).



The amount of carbon dioxide produced was usually not measured since a large volume was generated initially by the formation of cupric benzoate *in situ* from the reaction between benzoic acid and basic cupric carbonate. However, when cupric benzoate previously synthesized was used, only 1.6 mmoles of carbon dioxide was produced starting with 81 mmoles of cupric benzoate (run 8, Table I). Analysis of the reaction products by vapor phase chromatography has indicated that phenyl benzoate rather than free phenol was present, lending support to the reaction path shown by eq. 6.

(10) F. M. Bamdas and M. M. Shemyakin, *Zh. Obshch. Khim.*, **18**, 324 (1948).

Substituted benzoic acids may also be converted to their corresponding salicylic acid derivatives (Table I). A limited number of experiments has indicated that the salicylic acid yield was poor when electron-withdrawing substituents were present in the *ortho* or *meta* position of the starting benzoic acid, while alkyl or alkoxy substituents did not appear to have an adverse effect.

The cyclic mechanism proposed for this reaction (eq. 1) indicates that the hydroxy group will be located *ortho* to the carboxyl group. This isomer was the only one isolated as a pure compound for all of the derivatives tested. This is in contrast to the well-known Kolbe[11] method where a *para* orientation may occur. The presence of traces (<1% of *m*- and *p*-hydroxybenzoic acid in the product mixture, starting with benzoic acid, was suggested by the appearance of small peaks in the appropriate places in the vapor phase chromatograms of the methyl esters.

The reaction described here offers a unique advantage for the production of 6-substituted salicylic acid derivatives which cannot be prepared by the carbonation of the corresponding phenol. The synthesis of 6-methylsalicylic acid from *o*-toluic acid (run 9) is an example. The reaction temperature exerted a critical influence on the production of 6-methylsalicylic acid. This product could be recovered only when the temperature was kept below 215°. Phthalide was the principal oxidation product isolated at a reaction temperature of 250–260°.

Experimental Section

Rearrangement of Cupric Salts of Aromatic Acids in Aprotic Media. Method A.—This technique was used for media with relatively high boiling points which were suitable for reactions at atmospheric pressure.

The tubular reactors were constructed of Pyrex with a length to diameter ratio of approximately 10:1 and operating volumes of 350 and 1500 cc. The top section had four openings which led to an air condenser, removable thermowall, and gas inlet tubes which extended to the bottom of the reactor, with ball-joint seals, and a device to permit the addition of solids. Agitation was achieved by nitrogen or air bubbling through the reaction vessel. The reflux condenser could be connected to Dry Ice, calcium chloride, and Ascarite traps.

Run 7, Table I, will be described to illustrate the method. The reactor was filled with 259 g. of mineral oil and 20 g. (0.164 mole) of benzoic acid. When the temperature reached 210°, 20 g. of basic cupric carbonate (BCC), 55.5% Cu, was carefully added to the solution to generate the cupric benzoate *in situ* which separated as a finely divided blue solid. The addition was complete in 10 min. during which time the temperature had reached 255°. At this point the blue color of the viscous slurry faded and was replaced by a dull copper-colored solid. After 10 min. at 255–260°, a second 20-g. portion of BCC was added over a 5-min. period and heating was continued for 15 min. The slurry was cooled, diluted with ether, and filtered to give 44 g. of a dull copper-colored solid. Treatment of this solid with a dry ether–HCl solution decomposed the organic copper salts by the formation of the corresponding copper chlorides and free aromatic acids.

The ether filtrate was extracted with 40 ml. of water to remove HCl and traces of soluble copper and then with excess, saturated aqueous sodium bicarbonate solution. Acidification of the latter, followed by extraction with methylene chloride, produced 17.3 g. of an ivory-colored solid, labeled "acids from the copper(I) salts," which was a mixture of salicylic acid, 28.3% (method C), and benzoic acid, 71.7% (by difference).

The original ether–mineral oil filtrate was extracted with sodium bicarbonate in a similar manner to give 2.78 g. of an

(11) A. S. Lindsay and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).

acid mixture, labeled "soluble acids," which was benzoic acid containing 2.2% by weight of salicylic acid.

The remaining organic phase was heated with 100 ml. of strong aqueous KOH solution for several hours to decompose and extract any aromatic acids which may have been present as esters or anhydrides. Only 0.15 g. of benzoic acid was recovered in this manner. A total of 4.96 g. (0.036 mole) of salicylic acid, 92% yield, add 15.25 g. (0.125 mole) of benzoic acid were recovered.

Mineral oil was an unsatisfactory medium when the starting acid was not soluble prior to the generation of the cupric salt at a temperature of 200°. In this case, diphenyl oxide (diphenyl ether) was used. A reaction with the solvent, however, consumed a certain amount of the oxidizing power of the cupric salt.

In a similar manner (run 3), 118 g. of BCC was added to a solution of 250 g. of benzoic acid dissolved in 1275 g. of diphenyl oxide at 190°. The temperature was raised to 230° for a period of 10 min. Nitrogen was used for agitation. At this point, air was substituted for nitrogen at a rate of 4000 cc./min. for a period of 1.4 hr. The slurry was cooled, diluted with ether, and filtered to give 167 g. of dull copper-colored solid.

Anal. Calcd. for $C_7H_5CuO_2$: Cu, 34.4. Calcd. for $C_7H_5CuO_3$: Cu, 31.7. Found: Cu, 38.3.

Powder X-ray diffraction patterns contained bands which were characteristic of a mixture of cuprous oxide, cuprous benzoate, and cuprous salicylate. The infrared spectrum was characteristic of a mixture of cuprous salicylate contaminated with cuprous benzoate. Authentic samples were prepared by reducing the cupric salts of benzoic acid and salicylic acid with boiling phenol in a nitrogen atmosphere.[12] Compounds recovered from the cuprous salt mixture were 76 g. (0.55 mole) of salicylic acid and 27.1 g. (0.22 mole) of benzoic acid.

Organic acids ("soluble acids") (49 g.) were recovered by extraction of the ether filtrate with sodium bicarbonate solution. Analysis indicated the presence of 8.9 g. (0.037 mole) of *o*-benzoyloxybenzoic acid and 40.1 g. (0.33 mole) of benzoic acid.

Treatment of a portion of the remaining filtrate with base indicated the presence of a total of 90.3 g. (0.74 mole) of benzoic acid and 7 g. (0.075 mole) of phenol.

Isolation of *o*-Benzoyloxybenzoic Acid.—The carboxylic acids recovered from the ether solution of run 3 ("soluble acids") reacted with an amount of bromine equivalent to 10.4 wt. % calculated as salicylic acid. The infrared spectrum indicated that the major component was benzoic acid with distinctive, isolated peaks of an impurity at 5.75, 5.90, and 13.35 μ. These bands are characteristic of *o*-benzoyloxybenzoic acid, rather than salicylic acid.

A 20-g. sample of the mixture was extracted with 750 ml. of water near the boil. The clear, hot water solution was decanted from about 1.5 g. of a yellow organic phase. The latter was recrystallized from 150 ml. of hexane. As the solution cooled, a yellow oil layer was deposited (0.1 g.). The warm hexane solution was decanted to a clean flask. Two crops of pale yellow crystals were deposited, 0.1 and 0.15 g., which melted at 115–123°. Their infrared spectra were identical with that of an authentic sample of *o*-benzoyloxybenzoic acid, m.p. 132.5°.[13] The presence of some salicylic acid in this fraction could not be ruled out, although it would appear to be a minor component by comparison with the *o*-benzoyloxybenzoic acid. The latter was included with the salicylic acid for the tabulation of data in Table I.

Authentic samples of *o*-, *m*-, and *p*-benzoyloxybenzoic acid were prepared, according to the method of Einhorn, Rothlauf, and Seuffert,[13] and converted to their methyl esters according to method D. This treatment resulted in a cleavage of the original ester bond to produce equal molar amounts of methyl benzoate and the corresponding methyl hydroxybenzoate. Emergence times at 185° with the column described in method D were methyl benzoate, 2.2 min.; methyl *o*-hydroxybenzoate, 2.6 min.; methyl *m*-hydroxybenzoate, 4.0 min.; and methyl *p*-hydroxybenzoate, 4.4 min. With run 3, small peaks appeared with emergence times which corresponded to the methyl esters of *m*- and *p*-hydroxybenzoic acids. The results in Table II were obtained with an analysis of the soluble acid portion, A, and the acids recovered from the cuprous salts, B, utilizing method D.

TABLE II

	Methyl benzoate, %	Methyl hydroxybenzoate, %		
		ortho	*meta*	*para*
A	85.2	10.2	0.05	0.32
B	26.9	72.2	0.9	0.00

Method B.—This procedure was utilized with media which had boiling points at atmospheric pressure which were less than the desired temperature of reaction. In this instance, the reactants were sealed, under vacuum, at Dry Ice temperature, in heavy-walled glass bombs having a volume of approximately 50 cc. Three of these bombs separated by a metal divider were placed in the metal bomb of a 1000-cc. Parr high-pressure hydrogenation apparatus for heating. Approximately 100 ml. of the medium used for the run was placed in the Parr bomb to equalize the pressure on the walls of the glass bombs.

Run 4, Table I, will be described in more detail to illustrate the method. The glass bomb was filled with 5.0 g. (0.0163 mole) of cupric benzoate purified by recrystallization from acetone[2] and 25 ml. of spectral grade cyclohexane. After heating for 10 min. at 250°, the bomb was slowly cooled in the heater and removed from the metal Parr bomb after standing overnight. Large white crystals (identified as pure cuprous benzoate by the infrared spectra) and a finely divided copper-colored solid were present in a clear, very pale blue liquid. The pressure was less than atmospheric when the bomb was opened at room temperature. The contents were poured on a weighed sintered glass funnel and washed with ether leaving a 2.91-g. residue.

Anal. Found: Cu, 36.03.

This residue on the filter funnel was treated with a dry ether–HCl solution to decompose the salts in a manner similar to that described previously, leaving 1.56 g. of solids, primarily cuprous chloride. After thoroughly washing the filter cake with ether, the solvent was evaporated, leaving 1.84 g. of an almost white solid. The infrared spectrum indicated a mixture of benzoic and salicylic acids.

Anal. Found: salicylic acid, 29.35; benzoic acid, 70.65 (by difference).

The original cyclohexane–ether filtrate was heated to 75° under aspirator vacuum to remove the volatile components. A pale blue solid remained, 1.97 g., which gave a titration value for salicylic acid of 7.5%. A further analysis was made utilizing an Aerograph A-90-P2 gas chromatograph manufactured by the Wilkins Instrument Co. A 5-ft., 3/8-in. aluminum column with 5% SE 30 silicone substrate on 40–65-mesh Chromosorb W, HMDS, with a helium carrier gas, at a temperature of 165°, was used. Salicylic acid was not volatile under these conditions and a correction was made for this for the final analysis. Retention times after injection and corrected mole per cents of constituents based on peak areas were as follows: benzoic acid, 0.9 min., 49.5%; phenyl benzoate, 3.3 min., 7.9%; and benzoic anhydride, 9.6 min., 42.6%. The individual volatile components were isolated from the chromatograph and identified by a comparison of their infrared spectra with those of authentic samples. The components recovered, in summary, were salicylic acid, 0.67 g. (80% yield); benzoic acid, 2.21 g.; phenyl benzoate, 0.14 g.; and benzoic anhydride, 0.79 g.

Analysis of Salicylic Acid in the Presence of Benzoic Acid. Method C.—The weight of sample was selected to contain 30–50 mg. of salicylic acid. A 30.0-ml. aliquot of 0.100 *N* $Br^- - BrO_3^-$ solution and enough 50% NaOH solution to dissolve the solids were added to the sample. The alkaline solution was allowed to stand for 15 min. This treatment was sufficient to hydrolyze all of the *o*-benzoyloxybenzoic acid present. The solution was acidified with 2–3 ml. of concentrated HCl and allowed to stand for 15 min. to complete the bromination. An excess of KI and 100 ml. of water were added and the iodine liberated was titrated with 0.100 *N* thiosulfate solution to the starch–iodine end point. Three moles of bromine was consumed (to produce carbon dioxide and tribromophenol) for every mole of salicylic acid present. Known samples of various mixtures of benzoic and salicylic acids and *o*-benzoyloxybenzoic acid were analyzed by this method with a maximum error of 1%. This procedure could also be used for many substituted salicylic acid mixtures. The method was always checked for accuracy by titrating known mixtures of the pure starting acid and corresponding salicylic acid derivative.

(12) W. W. Kaeding, *J. Org. Chem.*, **28**, 1063 (1963).
(13) A. Einhorn, L. Rothlauf, and R. Seuffert, *Ber.*, **44**, 3309 (1911).

Analysis of Acid Fraction. Method D.—A modification of the procedure of Metcalfe and Schmitz[14] was used. A 0.1- to 5.0-g. sample of acid was refluxed on the steam bath for 1 hr. with a 10–15-fold weight excess of BF_3–methanol reagent (125 g. of BF_3 in 1 l. of dry methanol). At the end of this period, the condenser was disconnected and the bulk of the volatile solvent was allowed to boil away (15–20 min.). The concentrate was diluted with methylene chloride and extracted with water and then saturated sodium bicarbonate solutions. If a precipitate occurred when the latter was acidified, the conversion to ester was incomplete and a quantitative determination could not be made.

After removal of the solvent, the methyl esters were separated and analyzed with a vapor phase chromatograph utilizing a 0.25-in., 20-ft. aluminum column packed with 5% SE-30 silicone oil on 60–80-mesh Chromosorb W. Helium was used as the carrier gas at a flow rate of 300 cc./min. The various components were trapped as they emerged and identified by a comparison of their infrared spectra with those of authentic samples. Known mixtures of acid were used to determine the relation between the peak area and mole fraction of the various components. A representative comparison of results obtained with methods C and D is shown in Table III.

Isolation of Pure Salicylic Acids. Method E.—A countercurrent extraction method has been described.[2] The salicylic acid forms a highly colored complex with aqueous ferric chloride from which the corresponding starting benzoic acid derivative can be extracted with methylene chloride. The stability or water solubility of this complex, and consequently the success of the separation technique, varied considerably with the various ring substituents on the salicylic acid. Strong electron-withdrawing groups appeared to weaken the complex. Hydrophobic groups, such as *t*-butyl, appeared to reduce the water solubility of the salicylic acid complex. As a result, larger volumes of the aqueous phase were used. It was also discovered that the aqueous complex could be decomposed with acid. This greatly facilitated the final isolation of product.

TABLE III

Run no.	% salicylic acid, Method C	% salicylic acid, Method D
2[a]	69.5	69.6
3[a]	73.7	73.1
3[b]	10.4	10.2
8[a]	29.2	30.8

[a] Acids isolated from the ether-insoluble Cu(I) salt fraction. [b] Acids isolated from the ether-soluble fraction.

To specifically illustrate the improved method, the work-up of run 17 will be described. A 7.5-g. sample of the mixture of acids obtained from the decomposition of the insoluble cuprous salts was dissolved in 400 ml. of methylene chloride. This was agitated with 1500 ml. of 0.33 *M* aqueous $FeCl_3$ solution. After separation of the organic phase, the purple-black aqueous complex was extracted with three 250-ml. portions of methylene chloride, filtered, and made acid with gaseous HCl. The purple color was replaced by the characteristic orange color of the ferric chloride. After cooling to room temperature, fine needles of *p*-methoxysalicylic acid separated. The slurry was extracted with methylene chloride to give 2.2 g. of the product, m.p. 160° after recrystallization from water. A second extraction of the methylene chloride phases, reduced in volume to 400 ml., in a similar manner, gave 1.21 g. of product. The identity of all of the salicylic acid derivatives was established by a comparison of the physical properties or infrared spectra with those of authentic samples.

Acknowledgment.—We are indebted to Mrs. Veda M. Brink for assistance with the experimental work, Mr. H. O. Kerlinger for advice and help with the analytical problems, and Mr. M. D. Yeaman for assistance with the interpretation of the X-ray diffraction patterns.

(14) L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

Oxidation of Aromatic Acids. VI. Reaction of Cupric Salts of Carboxylic Acids with Aromatic Aprotic Compounds

WARREN W. KAEDING,[1] H. O. KERLINGER, AND G. ROBERT COLLINS

Research Department, The Dow Chemical Company, Walnut Creek, California

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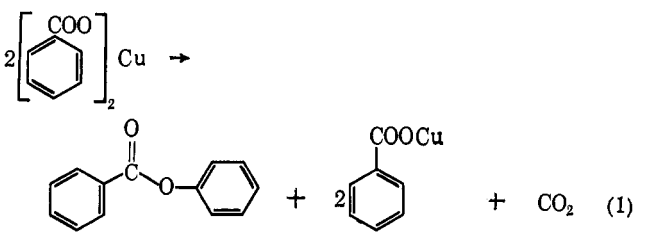
Cupric salts of carboxylic acids have been used to oxidize a variety of aprotic aromatic compounds. Ring hydrogen atoms were replaced by the acyloxy group of the salt [$2(RCOO)_2Cu + R'C_6H_5 \rightarrow R'C_6H_4OCOR + 2RCOOCu + RCOOH$]. The ratios of isomers produced with a variety of monosubstituted benzene derivatives was approximately 1:2:1 for *ortho–meta–para* positions, respectively. The proposed mechanism is discussed in terms of single-electron transfers by a pair of cupric ions.

When cupric benzoate is heated with a variety of aprotic, aromatic compounds, a two-electron oxidation–reduction reaction occurs. The electrons are transferred to a pair of cupric ions which are converted to the cuprous form. The aromatic compound is oxidized by the replacement of a ring hydrogen atom with the acyloxy group of the salt.

There are two different aromatic compounds in this system, the benzoate ion of the copper salt and the aromatic substrate (solvent). Each competes for the oxidizing power of cupric ion. Since distinctive compounds are usually produced, the relative amount of reaction by each path may be determined by an analysis of the reaction products.

Only one aromatic species is present where benzoic acid is used as the solvent. The product of reaction in this case is phenyl benzoate[2] (eq. 1). A simple



(1)

hydrolysis will liberate the phenol. This reaction provides the basis for a commercial process for the production of phenol from toluene *via* benzoic acid,[3,4] and will be referred to as the *phenol reaction*.

(1) To whom inquiries should be sent: Mobil Chemical Co., Metuchen, N. J.

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