[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

THE SYNTHESIS OF 6-FORMYLSALICYLIC ACID, ESTERS OF 6-BROMOMETHYLSALICYLIC ACID, AND RELATED SUBSTANCES

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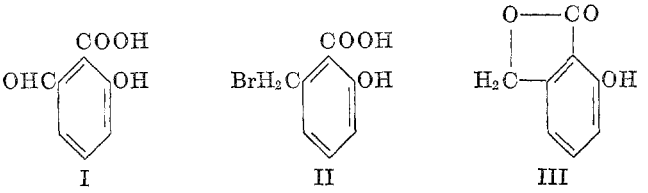
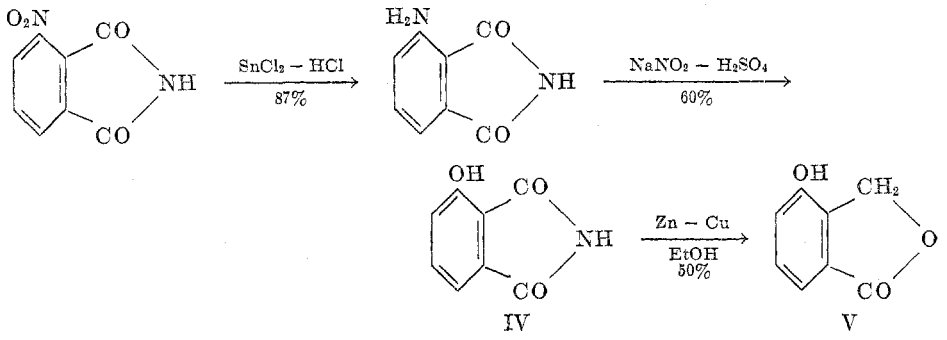
Received June 9, 1953

In the pursuit of another problem in synthesis we required 6-formylsalicylic acid (I) or 6-bromomethylsalicylic acid (II) (or esters thereof) as intermediates. Neither of these compounds is as yet reported in the literature.



Our first approach was based on the premise that the bromoacid II might be obtained from the corresponding lactone (III) which, in turn, might be accessible by reduction of 3-hydroxyphthalimide (IV). In fact, however, from the reduction of 3-hydroxyphthalimide (IV) only the isomeric lactone (V) was isolated, and it was identified by comparison with an authentic sample (1). This result is perhaps not surprising, since reduction, involving addition of electrons, should take place preferentially at the position of lowest electron density. Since salicylic acid is a stronger acid than *m*-hydroxybenzoic acid, the position *ortho* to the phenolic function in IV would appear to be the point of lowest electron density.

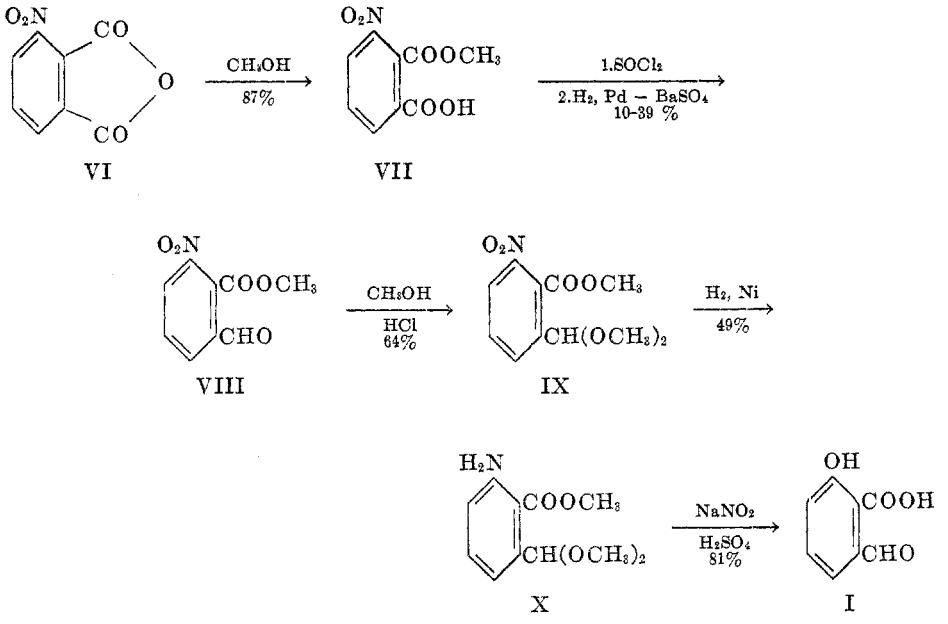
The sequence of reactions leading to 4-hydroxyphthalide (V) is shown in scheme A; the synthesis of the imide IV is essentially as described in the literature (2) and the reduction of the hydroxyphthalimide is patterned after that of the parent compound (3).



SCHEME A

[1] Reilly Fellow 1949–1951; National Institutes of Health Fellow 1951–1952. Part of this work was presented by D.E.R. as a dissertation to the University of Notre Dame in partial fulfillment of the requirements for the Ph.D. degree.

We next effected the synthesis of 6-formylsalicylic acid (I) as follows (Scheme B):

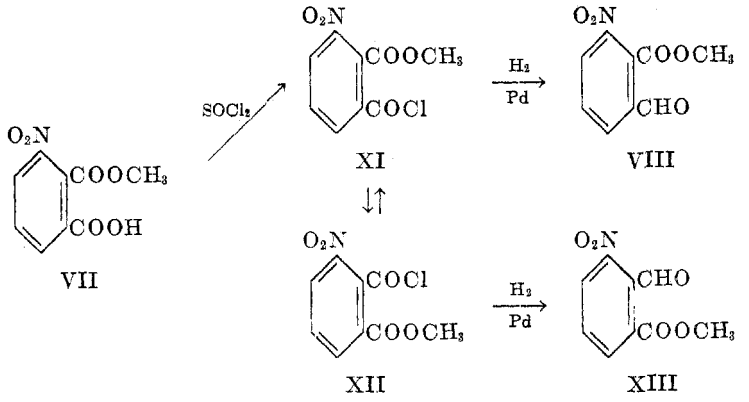


SCHEME B

The α-methyl ester of 3-nitrophthalic acid (VII) was prepared from the anhydride (VI) and was reduced to the corresponding aldehyde (VIII) by means of the Rosenmund method, in the way previously described for methyl acid phthalate (4). The 2-carbomethoxy-3-nitrobenzaldehyde (VIII) was then transformed to 6-formylsalicylic acid (I) *via* the dimethyl acetal (IX) and the dimethyl acetal of the corresponding aminoaldehyde (X) in a manner fashioned after the transformation of 3-nitrobenzaldehyde into 3-hydroxybenzaldehyde (5).

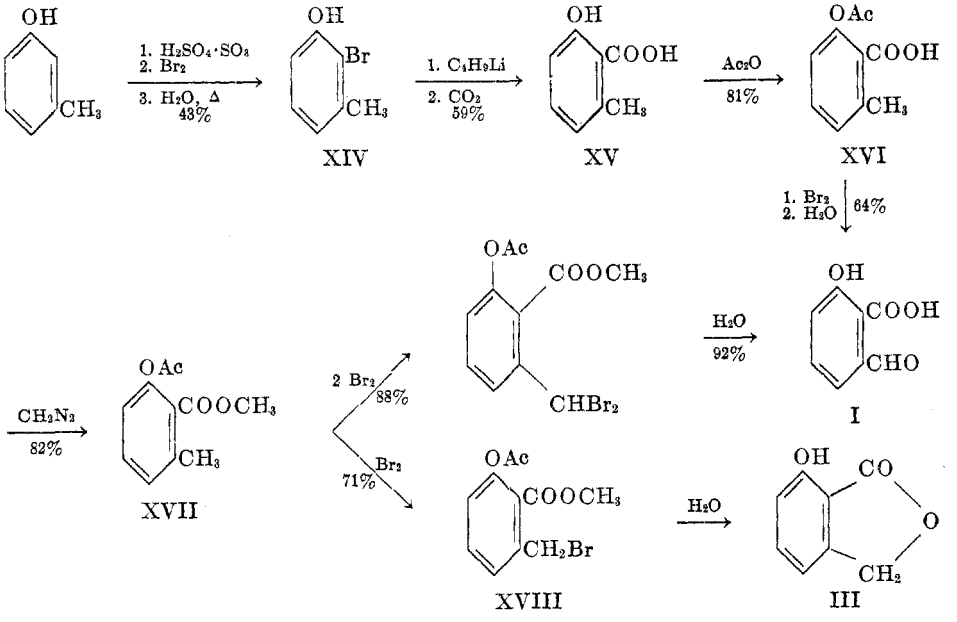
Scheme B suffers from two defects. One lies in the inconvenience in carrying out a Rosenmund reduction on a large scale and the low and fluctuating yields attained in it; the other centers around the fact that the transformation of VII into VIII does not determine the structure of VIII unequivocally. It has been shown (6) that the isomeric ester acid chlorides XI and XII are easily interconvertible, so that the Rosenmund reduction of VII instead of yielding VIII *via* XI might have produced XIII *via* XII (Scheme C).[2]

[2] This possibility is rather remote, however, since XIII is reported in the literature (23) to melt at 145–146° while our compound melted at 95–95.5°. Cason and Smith (24) have recently shown that the interconversion XI $\rightleftharpoons$ XII requires the presence of Lewis acids.



SCHEME C

An unequivocal and quite convenient synthesis of 6-formylsalicylic acid was finally devised according to scheme D.



SCHEME D

In this scheme, experience on the photobromination of side-chains gained by the study of model compounds (7) was utilized. 2-Bromo-*m*-cresol (XIV) was readily synthesized by an improved version of the published method (8), *i.e.* sulfonation of *m*-cresol, followed by bromination and desulfonation by means of superheated steam. Direct sulfonation of *m*-cresol with fuming sulfuric acid was more convenient and gave better yields than the indirect method using

chlorosulfonic acid (9). Conversion of the bromo compound XIV to 6-methylsalicylic acid (XV) was effected by a halogen-metal interchange followed by carbonation (10). Acetylation of XV followed by photobromination of either the acetylated acid XVI or its methyl ester XVII and hydrolysis gave 6-formylsalicylic acid (I) in 13.7% over-all yield from *m*-cresol; the acid so obtained was identical in every respect with material prepared from 3-nitrophthalic anhydride by scheme B.

Treatment of the acetyl derivative XVI with diazomethane gave the methyl ester XVII which by photobromination was transformed to the methyl ester-acetate of the desired 6-bromomethylsalicylic acid (XVIII). The structure of XVIII was confirmed by conversion to the phthalide III, isomeric with but different from compound V.

The melting point of 7-hydroxyphthalide (III) (135–136.5°) so obtained agrees better with that (132°) of the same compound synthesized recently by Duncanson, Grove, and Zealley (11a) by cleavage of the corresponding methyl ether than with that (128–129°) of III prepared by Vène and Tirouflet (11b) by diazotization of 7-aminophthalide. The analysis of our sample (III) was not very satisfactory, but it gave a well-characterized acetate of correct analysis. It is possible that the discrepancy in melting point of the three different preparations is due to solvation.

EXPERIMENTAL[3]

4-Hydroxyphthalide (V). To 9.0 g. (0.14 mole) of acid-washed zinc dust were added solutions of 4.0 g. of sodium hydroxide in 20 ml. of water and 0.1 g. of the copper sulfate pentahydrate in 5 ml. of water. The rapidly stirred suspension was chilled to 3° and 8.0 g. of 3-hydroxyphthalimide (2, 12) was added over a period of 20 minutes. Stirring was continued at 0° for ten minutes, at room temperature for 40 minutes and finally on a steam-bath for 2½ hours. At the end of this period, ammonia evolution could no longer be detected. The reaction mixture was filtered and the residue was washed with hot water. The combined filtrates were acidified, boiled for 15 minutes, and cooled to room temperature. Crystals appeared at first, later an oil also precipitated. The crystals were collected and recrystallized from water (Norit) to give 3.5 g. (50%) of 4-hydroxyphthalide, m.p. 248–253°. Further recrystallization raised the melting point to 255–256° (slight dec.) and there was no depression on admixture of an authentic sample (1). Both samples had the same infrared spectrum in a Nujol mull. Our sample gave an acetyl derivative melting at 96–97°. Literature values: m.p. 255–256° for the parent compound (1), 96–97° for the acetate (13).

2-Carbomethoxy-3-nitrobenzoyl chloride (XI). To 45 g. (0.2 mole) of 2-carbomethoxy-3-nitrobenzoic acid (VII) (6b, 12), m.p. 152.5–153° in a dry 200-ml. flask equipped with a reflux condenser protected by a calcium chloride tube was added 75 ml. of purified (14) thionyl chloride through the top of the condenser. The mixture was heated to gentle boiling on a steam-bath until gas evolution ceased (*ca.* 30 minutes). Excess thionyl chloride was then removed at reduced pressure and the residue was evaporated *in vacuo* three times with 50 ml. of dry benzene to remove all traces of thionyl chloride. The residue solidified on cooling. Recrystallization from benzene-petroleum ether (Norit) gave 47 g. (97%) of white crystals melting at 76–79°. Further recrystallizations raised the melting point to 78–79.5°.

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[3] Microanalyses by Micro-Tech Laboratories, Skokie, Illinois. All melting and boiling points are uncorrected. By "petroleum ether" is meant the fraction boiling in the 30–60° range.

Anal. Calc'd for $C_9H_6ClNO_5$: C, 44.37; H, 2.48; Cl, 14.56.
Found: C, 44.42; H, 2.47; Cl, 14.45.

The literature (15) reports a melting point of 95–97° for the above chloride.

2-Carbomethoxy-3-nitrobenzaldehyde (VIII). In a dry three-necked flask equipped with an inlet tube, efficient stirrer, and reflux condenser were placed 100 ml. of dry xylene and 1.0 ml. of Quinoline-S catalyst poison (16). In order to entrain all traces of water, dry hydrogen was passed through the boiling solution for ten minutes with the condenser water shut off. The hydrogen flow was then stopped momentarily and 3.0 g. of 5% palladium-barium sulfate catalyst (16) was added to the flask followed by a solution of crude 2-carbomethoxy-3-nitrobenzoyl chloride (XI) (m.p. 76–79°) freshly prepared from 30 g. of the corresponding acid (VII) in *ca.* 25 ml. of xylene. With the hydrogen flow and supply of condenser water reestablished, the suspension was stirred vigorously as long as hydrogen chloride was evolved (8–20 hours) while the flask was heated in an oil-bath at 170–180°. Higher temperatures and shorter reaction times led to a drop in yield. The flask was then cooled, the hydrogen flow stopped, and the catalyst removed by filtration. The xylene was removed at reduced pressure and the product was distilled at 0.5 mm., b.p. 158–160°, yield 5.2 g. (18.5%), m.p. 85–90°. Recrystallizations from benzene-petroleum ether raised the melting point to 95–95.5°.

Anal. Calc'd for $C_9H_7NO_5$: C, 51.68; H, 3.38.
Found: C, 51.91; H, 3.42.

On other occasions the melting point was found to be 102–103°; the material appears to be dimorphic.

The *semicarbazone* crystallized from dilute acetic acid melted at 221–222° (dec.).

Anal. Calc'd for $C_{10}H_{10}N_4O_5$: C, 45.12; H, 3.79.
Found: C, 45.45; H, 3.73.

The yield in the above preparation fluctuated rather widely, ranging from 10 to 40% in different instances.

2-Carbomethoxy-3-nitrobenzaldehyde dimethyl acetal (IX). Through a solution of 9 g. (0.043 mole) of the free aldehyde VIII (m.p. 100–102°) in 175 ml. of commercial absolute methanol, dry hydrogen chloride gas was passed until the weight had increased by one gram. The solution was left at room temperature for six days and then powdered sodium methoxide was added until the mixture was faintly alkaline. The precipitated sodium chloride was filtered and washed twice with 20-ml. portions of methanol. The combined filtrates were concentrated to *ca.* 25 ml. by distillation at reduced pressure. They were then recombined with the filtered sodium chloride and 80 ml. of water was added. The suspension was extracted with three 30-ml. portions of ether which were combined, dried over sodium sulfate, and concentrated at reduced pressure. The residue solidified to a homogeneous crystal mass weighing 9.5 g. (86%) and melting at 40–45°. Recrystallization from petroleum ether containing a small amount of benzene gave 7.0 g. (64%) of colorless needles, m.p. 49.5–50°.

Anal. Calc'd for $C_{11}H_{12}NO_6$: C, 51.97; H, 4.75.
Found: C, 52.15; H, 5.06.

In later experiments it was found convenient to prepare the acetal from crude (undistilled) 2-carbomethoxy-3-nitrobenzaldehyde (VIII). In this case the acetal (IX) was distilled for purification, b.p. 200–208°/2–4 mm., the over-all yield of recrystallized material from 2-carbomethoxy-3-nitrobenzoic acid (VII) being 24%.

2-Carbomethoxy-3-aminobenzaldehyde dimethyl acetal (X). The nitro compound IX (6.0 g., 0.023 mole) was dissolved in 75 ml. of commercial absolute methanol and reduced with hydrogen at room temperature and 60 p.s.i. pressure in the presence of 1 g. of commercial (Harshaw Chemical Co.) Raney nickel catalyst. The calculated amount of hydrogen was taken up in three hours. After removal of the catalyst by filtration and the solvent by distillation at reduced pressure, the residue was taken up in 100 ml. of ether and dried over magnesium sulfate. Filtration followed by concentration *in vacuo* gave the amino compound as a pale-colored viscous residue weighing 5.0 g. which could not be made to crystal-

lize. The material was distilled with considerable loss at 138–140° (0.08 mm.); the distillate weighed 2.6 g. (49%) and had n_D^{20} 1.5480–1.5485.

6-Formylsalicylic acid (XI). The above amino acetal X (2.5 g., 0.011 mole) was slowly added to 20 ml. of 6 *N* sulfuric acid at 0° with stirring. Solution was complete in somewhat less than one hour. A solution of 0.77 g. of sodium nitrite in 5 ml. of water was then added to the amine salt over a period of 15 minutes at 0°. The resulting diazonium salt solution was slowly warmed to 80° on a water-bath and maintained at that temperature until nitrogen evolution was complete (*ca.* 1 hour). The warm solution was filtered and the filtrate allowed to deposit crystals in the refrigerator overnight. The solid was collected and dried; it melted at 110–115° and weighed 1.5 g. (81%). Recrystallization from water (Norit) gave colorless needles of what appeared to be a hydrate, m.p. 117–117.5°. Recrystallization from benzene raised the melting point to 137.5–138.5°.

Anal. Calc'd for $C_8H_8O_4$: C, 57.83; H, 3.64.
Found: C, 57.56; H, 3.80.

The material gave a purple-red color with ferric chloride in alcoholic solution.

2-Bromo-m-cresol (XIV). The following modification of the published procedure (8) was found most satisfactory as to yield and convenience. *m*-Cresol (270 g., 2.5 moles) was placed in a 3-l. three-necked flask equipped with a Hershberg stirrer and the flask was placed in an ice-bath. A mixture of 180 ml. of 65% fuming sulfuric acid and 1035 ml. of 16% fuming sulfuric acid was then added at such a rate that the temperature did not exceed 70°. After all the acid was added, the reaction mixture was maintained at 50–55° for a total of 18–24 hours by means of a Glascol mantle. There was then added 400 g. (2.5 moles) of bromine over a period of 3 days in 50-g. portions at room temperature. The flask was then placed in an ice-bath again and 1500 ml. of water was added cautiously. The solution so formed was then added slowly[4] to the still-pot of a superheated-steam-distillation assembly and the product was entrained by means of steam heated to 160–170° with the still-pot at 180–190°. The product was collected in the first three or four liters of distillate and the steam-distillation was discontinued when a solid began to appear in the condenser.[5] The distillate was extracted with ether, the extract dried with sodium sulfate, filtered and concentrated, first at atmospheric pressure and finally *in vacuo*. The oily product was dissolved in petroleum ether and chilled in a Dry Ice-acetone bath to yield crystals which upon recrystallization from petroleum ether weighed 156.5 g. and melted at 59.5–60.5°. By concentration of the mother liquors and recrystallization of the material so obtained a second crop weighing 51.5 g. and melting at 58–59.5° was obtained, the total yield being 43%. A sample crystallized to constant melting point melted at 61–62° which is also the melting point reported in the literature (18).

6-Methylsalicylic acid (XV). *n*-Butyllithium was prepared by the standard method (19) from 39.6 g. (5.70 g.-atoms) of lithium covered with 200 ml. of dry ether and an ethereal solution of 312 g. (2.28 moles) of butyl bromide in a 2-l. three-necked flask. To the undecanted solution was added 109 g. (0.58 mole) of 2-bromo-*m*-cresol (XIV) in 300 ml. of ether at such a rate as to maintain gentle reflux. This took about 3–4 hours. The solution was then boiled gently for another hour, allowed to cool, and poured with stirring over about 350 g. of solid carbon dioxide. The suspension was stirred manually from time to time for about an hour; then excess lithium and lithium salts were cautiously decomposed with water and finally dilute hydrochloric acid was added to make the solution strongly acidic. The organic

[4] It was found advisable to start the flow of steam first and then to add the solution to be distilled slowly from a separatory funnel. When all the material was placed in the still-pot at the beginning, boiling was liable to be quite violent and in one case led to loss of material.

[5] This material appears to be tetrabromo-*m*-cresol; it melted at 193° and its acetate melted at 165–166°. The literature (17) reports 193–194° as the melting point of the tetrabromo-compound and 165–166° as the melting point of its acetate. By stopping the steam distillation at the appropriate point, the tedious fractional distillation of the crude product was avoided.

material was extracted with two 400-ml. portions of ether which were cleared with 100 ml. of water; the acid was then extracted from the ether layers by means of three 300-ml. portions of 5% sodium bicarbonate solution. Acidification of the combined aqueous bicarbonate layers with concentrated hydrochloric acid led to precipitation of the desired acid and also some valeric acid. The solution was chilled in the refrigerator overnight and the crystals were collected, washed with cold water, and dried in a vacuum desiccator. Material so obtained weighed 52.5 g. (59%) and melted at 160–161°. Recrystallization from ether-petroleum ether raised the melting point to 170–171°; Lit. (20) (a) 172°, (b) 168°.

The *methyl ester* was formed in poor yield (25%) by the standard method of esterification employing methanol and sulfuric acid (14); the use of ethylene dichloride as a solvent (21) gave even lower yields. Crystallized from petroleum ether the ester melted at 30.5–31°.

Anal. Calc'd for $C_9H_8O_4$: C, 60.00; H, 4.48.

Found: C, 59.52; H, 4.49.

2-Acetoxy-6-methylbenzoic acid (XVI). The method described (14) for acetylsalicylic acid was followed. Crude 6-methylsalicylic acid (52.2 g., 0.34 mole, m.p. 164–165°), 105 ml. of acetic anhydride, and 4 drops of concentrated sulfuric acid were placed in a 1-l. Erlenmeyer flask and warmed on a water-bath with swirling until solution was effected. After 30 minutes the mixture was chilled to effect crystallization. It was then diluted with 800 ml. of water and left in the refrigerator overnight. If lumps formed they were broken up and the material was collected, washed with water, and dried; it weighed 48.8 g. and melted at 121–122°. Another 5.2 g. were recovered by concentration of the mother liquor for a total yield of 81%. Recrystallization from ether petroleum ether raised the melting point to 128.5–130°; lit. (20) m.p. 123–124°.

The *methyl ester* XVII was prepared by treatment of the acid XVI with diazomethane in the usual manner. After one crystallization from ether petroleum ether the material melted at 39–41° and was obtained in 82% yield. The analytical sample melted at 41.5–42.5°.

Anal. Calc'd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81.

Found C, 63.62; H, 5.88.

Alternatively, the methyl ester could be prepared in 92% yield by acetylation of methyl 6-methylsalicylate with acetic anhydride according to Chattaway (22). However, because of the above mentioned difficulty in preparing methyl 6-methylsalicylate, the route from XV to XVII *via* XVI is preferred.

Methyl 2-acetoxy-6-bromomethylbenzoate (XVIII). A solution of 5.15 g. (0.035 mole) of methyl 2-acetoxy-6-methylbenzoate (XVII), m.p. 41–42° in 70 ml. of carbon tetrachloride was placed in a 500-ml. two-necked flask equipped with a reflux condenser and separatory-funnel and exposed to a 500-watt tungsten lamp. While the solution was boiled gently, a solution of 4 g. (0.025 mole) of bromine in 80 ml. of carbon tetrachloride was added at such a rate that a slight pink color persisted until the reaction was complete; the total reaction time being about 15 minutes. The reaction mixture was cooled to *ca.* 60° and petroleum ether was added until the solution became slightly turbid. Crystals formed on chilling in an acetone-Dry Ice bath; they were collected and dried, weighed 5.96 g. (84%) and melted at 82–84°. Recrystallization from ether-petroleum ether gave 5.0 g. (71%) of product melting at 99–100°.

Anal. Calc'd for $C_{11}H_{11}BrO_4$: C, 46.01; H, 3.86.

Found: C, 46.41; H, 4.07.

2-Acetoxy-6-bromomethylbenzoic acid was similarly prepared from 2-acetoxy-6-methylbenzoic acid (XVI) (*cf.* 7) in 73–82% yield, m.p. 101.5–102° (dec.) (capillary inserted in block at 97°) after recrystallization from ether-petroleum ether.

Anal. Calc'd for $C_{10}H_9BrO_4$: C, 43.98; H, 3.32.

Found: C, 43.94; H, 3.50.

Treatment of this acid with diazomethane gave a compound identical with the above-described methyl ester XVIII.

7-Hydroxyphthalide (III). This material was obtained either by basic hydrolysis of 2-acetoxy-6-bromomethylbenzoic acid or by acid hydrolysis of methyl 2-acetoxy-6-bromo-

methylbenzoate (XVIII) in the manner described earlier (7) for the parent compounds. The material first appeared in a solvated form melting around 115°, but recrystallization from benzene-petroleum ether raised the melting point to 135–136.5°.

Anal. Calc'd for $C_8H_6O_3$: C, 63.99; H, 4.03.
Found: C, 64.64; H, 4.10.

Vène and Tirouflet (11) report a melting point of 128–129°.

The *acetate* prepared by the method described before (14) melted at 108–109°.

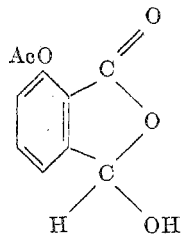
Anal. Calc'd for $C_{10}H_8O_4$: C, 62.50; H, 4.20.
Found: C, 62.66; H, 4.23.

6-Formylsalicylic acid (I) *from 2-acetoxy-6-methylbenzoic acid* (XVI). The photodibromination (7) of 10.2 g. (0.0526 mole) of XVI in 120 ml. of carbon tetrachloride using 16.8 g. (0.0105 mole) of bromine in 80 ml. of the same solvent was complete after 3¾ hours. The bromination product precipitated as a gum when petroleum ether was added to the reaction mixture and could not be induced to crystallize. The crude material was boiled under reflux for 90 minutes with a solution of 5 ml. of concentrated hydrochloric acid in 70 ml. of water and 25 ml. of glacial acetic acid. There was considerable darkening of the reaction mixture, so 4 g. of Norit was added and boiling was continued for 15 minutes. The solution was filtered and chilled, and the crystals were collected, dried, and recrystallized from benzene to give 3 g. (34%) of material melting at 136–137°, which did not depress the melting point of a sample of 6-formylsalicylic acid obtained according to Scheme B as described above. The two samples had identical infrared spectra. From the mother liquors, another 2.6 g. (30%) of less pure material was recovered.

The *acetyl derivative* was prepared with acetic anhydride using a drop of sulfuric acid as a catalyst (14). It melted at 110–111° after recrystallization from benzene-petroleum ether and did not depress the melting point of material similarly obtained by Scheme B. The two samples had identical infrared spectra.

Anal. Calc'd for $C_{10}H_8O_3$: C, 57.69; H, 3.88.
Found: C, 57.88; H, 4.20.

The infrared spectrum of the compound indicated that it exists in the pseudo form (XX), since the carbonyl bands appeared at 5.63 μ (lactone) and 5.72 μ (acetate). This may explain why an attempted esterification of the compound with diazomethane was unsuccessful; only starting material was recovered.



XX

Methyl 6-formylsalicylate. A warm solution of 10 g. of silver nitrate in 30 ml. of water was added with stirring to a warm solution of 8.96 g. (0.054 mole) of 6-formylsalicylic acid in 31.73 g. (0.027 mole) of potassium carbonate and 40 ml. of water. The reaction mixture was warmed on the steam-bath for 30 minutes, cooled, and the silver salt filtered, triturated with a mixture of 50 ml. of ethanol and 50 ml. of ether, collected, and dried in a vacuum desiccator. The dry salt was boiled under reflux for five hours with a solution of 8 g. of methyl iodide in 50 ml. of absolute ether while the suspension was stirred mechanically. As the reaction proceeded, the aspect of the solid changed to that of silver iodide which was filtered at the end of the reaction period and washed with 25 ml. of ether. The combined ethereal filtrates were successively washed with 25 ml. of a 5% sodium bicarbonate solution

and 25 ml. of water, dried over magnesium sulfate, and concentrated *in vacuo*. The solid residue (8.4 g.) was crystallized from ether-petroleum ether to give 7 g. (72%) of material melting at 53–55°. Further recrystallization raised the melting point to 65–66°.

Anal. Calc'd for $C_9H_8O_4$: C, 60.00; H, 4.48.

Found: C, 59.52; H, 4.49.

The material gave a violet color with ferric chloride in alcohol solution. Attempts to acetylate the material by the Chattaway procedure (22) led to hydrolysis of the ester function and yielded 2-acetoxy-6-formylsalicylic acid which did not depress the melting point of material obtained by other routes (see above).

Methyl 2-acetoxy-6-dibromomethylbenzoate. Photodibromination (7) 10 g. (0.048 mole) of methyl 2-acetoxy-6-methylbenzoate (XVII), m.p. 41–42°, in 100 ml. of carbon tetrachloride was effected with 15.4 g. (0.096 mole) of bromine in 90 ml. of carbon tetrachloride. The product was precipitated by the addition of petroleum ether and chilling in Dry Ice-acetone; it weighed 15.4 g. (88%) and melted at 68–69°. Recrystallization from benzene-petroleum ether raised the melting point to 69–70°.

Anal. Calc'd for $C_{11}H_{10}Br_2O_4$: C, 36.09; H, 2.75.

Found: C, 35.61; H, 3.01.

Hydrolysis of this material with dilute hydrochloric acid (7) gave the hydrate of 6-formylsalicylic acid, m.p. 116–117° which upon recrystallization from benzene melted at 137.5–139°; the yield in this hydrolysis was 92%.

Acknowledgment. One of us (D.E.R.) is indebted to the National Institutes of Health for financial assistance in the form of a fellowship.

SUMMARY

6-Formylsalicylic acid (I) has been prepared in 15.5% over-all yield from *m*-cresol *via* 2-bromo-*m*-cresol (XIV), 6-methylsalicylic acid (XV), 2-acetoxy-6-methylbenzoic acid (XVI), and 2-acetoxy-6-dibromomethylbenzoic acid.

Methyl 2-acetoxy-6-bromomethyl benzoate (XVIII) and 7-hydroxyphthalide (XIX) were also obtained from the methyl ester of 2-acetoxy-6-methylbenzoic acid (XVII).

An alternative but less convenient route to 6-formylsalicylic acid using 3-nitrophthalic anhydride (VI) as a starting material proceeded *via* the α-methyl ester of 3-nitrophthalic acid (VII), 2-carbomethoxy-3-nitrobenzaldehyde (VIII) and its acetal (IX), and 2-carbomethoxy-3-aminobenzaldehyde dimethyl acetal (X).

The reduction of 3-hydroxyphthalimide (IV) with the zinc-copper couple in base was found to give rise mainly to 4-hydroxyphthalide (V).

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(1) We are indebted to Dr. C. A. BUEHLER, Department of Chemistry, The University of Tennessee for an authentic sample of 4-hydroxyphthalide prepared by the method of BUEHLER, HARRIS, SHACKETT, AND BLOCK, *J. Am. Chem. Soc.*, **68,** 574 (1946).

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