REACTION OF ANHYDROSEPEDONIN WITH ALKALI

SYNTHESIS OF A DEGRADATION PRODUCT AND SOME RELATED DIMETHYLHYDROXYBENZOIC ACIDS[1]

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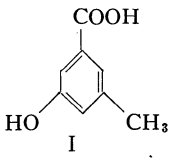
ABSTRACT

Two products have been isolated from the reaction of anhydrosepedonin with alkali and identified as 3-hydroxy-5-methyl benzoic acid and 3,4-dimethyl-5-hydroxybenzoic acid. The structure of the latter compound was established by unambiguous synthesis. In the course of this work the remaining *o*- and *m*-hydroxybenzoic acids derived from *o*-xylene were also prepared.

Sepedonin, a metabolic product of the fungus *Sepedonium chrysospermum*, was first isolated as the anhydro derivative by Divekar and Raistrick (1). From its chemical properties these authors suspected that their product might be a substituted tropolone, several examples of which are already known among the secondary metabolites of fungi. Subsequent studies in this laboratory have shown that treatment of anhydrosepedonin with alkali under conditions expected to cause rearrangement of a tropolone to a benzoic acid derivative (2) affords a small amount of product with the properties of a phenolic acid.

Difficulty was encountered in obtaining sufficient material from the reaction mixture for adequate purification and characterization of the components. However, analytical and spectroscopic evidence suggested the presence of a dimethyl *o*- or *m*-hydroxybenzoic acid. Attempts to synthesize these compounds were therefore begun. Subsequently paper chromatographic examination showed the product to be a mixture of phenolic acid and tropolone derivatives. Partition chromatography on a cellulose column allowed two of the former to be separated and isolated in a pure form. These compounds had similar ultraviolet and infrared spectra and differed only in the number of C-methyl substituents. The simpler of the two was identified by comparison with a synthetic specimen as 3-hydroxy-5-methylbenzoic acid (I).



I

On biogenetic grounds it was considered likely that the two methyl substituents of the second compound were vicinal. It was compared with the isomeric dimethylhydroxybenzoic acids synthesized by the routes outlined (III–IX, XI–XVII) and found to be indistinguishable from 3,4-dimethyl-5-hydroxybenzoic acid. The derived acetates and methyl ethers of the two compounds were also identical. The acid has previously been known as a degradation product of camphor, resulting from the action of warm sulphuric acid on dicamphorylic acid (3). The orientation of the substituents was established at

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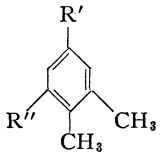
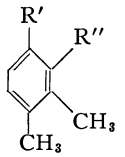
that time by decarboxylation to 2,3-xylenol, and by oxidation of the methyl ether to 6-methoxy-2-methylterephthalic acid, but does not appear to have been confirmed by synthesis.



	R′ =	R″ =		R′ =	R″ =
II	NO_2	NO_2	XII	NO_2	CN
III	NH_2	NO_2	XIII	NO_2	COOH
IV	CN	NO_2	XIV	NO_2	$COOCH_3$
V	COOH	NO_2	XV	NH_2	$COOCH_3$
VI	$COOCH_3$	NO_2	XVI	OH	$COOCH_3$
VII	$COOCH_3$	NH_2	XVII	OH	COOH
VIII	$COOCH_3$	OH	XVIII	$OCOCH_3$	COOH
IX	COOH	OH	XIX	$CONH_2$	NO_2
X	COOH	$OCOCH_3$	XX	NO_2	$CONH_2$
XI	NO_2	NH_2			

The synthetic route used in the present work employed *o*-xylene as starting material. Nitration under suitable conditions gave mainly the dinitro derivatives in which each of the nitro groups can be selectively reduced to give the corresponding nitroxylidines. From these substances a series of *o*- and *m*-hydroxybenzoic acids containing two vicinal methyl substituents may be conveniently prepared by replacement of the amino and nitro with carboxyl and hydroxyl groups, respectively.

The three dimethylsalicylic acids derived from *o*-xylene were also prepared by other methods. 3,4-Dimethylsalicylic acid (XXXII), which has not been previously described, was obtained in good yield by carbonation (4) of 2,3-xylenol. When this reaction was applied to 3,4-xylenol, 4,5-dimethylsalicylic acid (XXXV) was the sole product. Earlier workers (4, 5) have observed a similar result which is evidently due to steric factors. Use of 3,4-xylenol in the Tiemann–Riemer reaction, on the other hand, is reported (6) to yield a mixture of 4,5- and 5,6-dimethylsalicylaldehydes (XXXVI and XXXI) which can be oxidized to the corresponding acids by fusion with alkali. Separation of the two aldehydes is difficult and Hunsberger and co-workers (5) in attempting to repeat Clayton's synthesis were able to obtain only one of them in pure condition. This was presumed to be the 5,6-derivative since 4,5-dimethylsalicylaldehyde was prepared by an alternative route and proved to be different. We have found, as did Auwers (7), that the main product from the Tiemann–Riemer reaction on 3,4-xylenol is the cyclohexadienone (XXXVII). Only a small amount of the mixture of aldehydes was obtained but these were separated



	R′ =	R″ =		R′ =	R″ =
XXI	NO_2	NO_2	XXVIII	OH	$COOCH_3$
XXII	NO_2	NH_2	XXIX	OH	COOH
XXIII	NO_2	CN	XXX	$OCOCH_3$	COOH
XXIV	NO_2	$CONH_2$	XXXI	OH	CHO
XXV	NO_2	COOH	XXXII	COOH	OH
XXVI	NO_2	$COOCH_3$	XXXIII	COOH	$OCOCH_3$
XXVII	NH_2	$COOCH_3$	XXXIV	$COOCH_3$	OH

and each obtained in a pure form. Oxidation of one of them gave 4,5-dimethylsalicylic acid in good yield. The other under more vigorous conditions afforded a little 5,6-dimethylsalicylic acid, the identity of which was established by comparison with a sample synthesized from 3-amino-4-nitro-*o*-xylene (XXII–XXIX).

Isolation of the two related hydroxybenzoic acids from the action of alkali on anhydrosepedonin provides strong evidence that this compound has a tropolone structure. It is, moreover, of interest that such a tropolone would have hydroxyl and carbon substitution at the same positions on the ring as found in stipitatonic acid, a tropolone derivative isolated from *Penicillium stipitatum* (8). Since anhydrosepedonin has a molecular formula $C_{11}H_{10}O_4$, one oxygen and two carbon atoms remain to be accounted for.

EXPERIMENTAL

Alkaline Degradation of Anhydrosepedonin

To anhydrosepedonin (100 mg), dissolved in *N* potassium hydroxide (0.25 ml) in a nickel crucible, pellets of potassium hydroxide (2 g) were added. The crucible was covered and placed for 5 minutes in a Woods metal bath preheated to 250°. After it had cooled, the reaction mixture was dissolved in water (10 ml), acidified carefully with concentrated HCl, while being stirred in an ice bath, and extracted with four portions (25 ml) of ether. The extracts were dried over anhydrous sodium sulphate and evaporated to dryness. The residue (70 mg) was heated in high vacuum at 160° C for 12 hours and the white sublimate (13 mg) collected. Paper chromatography using *sec*-butanol – 10% aqueous ammonia (4:1) showed two main components, R_f's 0.55 and 0.64, which gave orange-colored zones when the paper was sprayed with an aqueous solution of Fast Bordeaux Salt (9).

Similar fusions carried out at higher and lower temperatures, and for different periods of time, gave lower yields of the mixture of these two products.

The combined product (95 mg) from a number of experiments was dissolved in a small amount (1 ml) of the upper phase from an equilibrated mixture of *n*-butanol – toluene – 3% aqueous ammonia (5:1:3) and applied to a column (15 in. × $\frac{3}{4}$ in. diam.) of cellulose powder through which 1 liter of the upper phase of the solvent mixture had already been passed. The column was developed with the same solvent and 3 ml fractions collected. The desired compounds were located by paper chromatography of eluate fractions. Appropriate solutions were pooled and evaporated to dryness.

Fractions 34–42 gave on sublimation at 25×10^{-6} mm Hg and 95° C colorless needles (11 mg) m.p., 211–212° C. Found: C, 65.16; H, 6.01. Neutralization equivalent in 80% ethanol, 174. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%. Mol. wt. 166. This substance was indistinguishable in R_f values, color reactions, and absorption spectra from a specimen of 3,4-dimethyl-5-hydroxybenzoic acid (IX), and no depression of melting point resulted from admixture of the two compounds. It was esterified in ethereal solution at 4° C for 30 minutes with diazomethane. The product was sublimed at 70° C in high vacuum and crystallized from petroleum ether (b.p. 60–80°) as colorless cubes, m.p. 153.5°. Found: C, 66.63; H, 6.76; OCH_3, 16.43; CCH_3, 23.82%. Saponification equivalent 185. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; 1-OCH_3, 17.2; 2C—CH_3, 16.67%. Mol. wt. 180. A mixed melting point with methyl 3,4-dimethyl-5-hydroxybenzoate (VIII) caused no depression and the ultraviolet and infrared absorption spectra of the two substances were indistinguishable.

Fractions 55–80 gave on sublimation at 110° and 25×10^{-6} mm Hg colorless needles, m.p. 217° C. Found: C, 63.39; H, 5.22%. Neutralization equivalent in 80% ethanol, 155. Calc. for $C_8H_8O_3$: C, 63.15; H, 5.30. Mol. wt. 152. This substance had the same R_f values, color reactions, and absorption spectra as an authentic specimen of 3-hydroxy-5-methylbenzoic acid (I), m.p. 217° C. A mixed melting point also gave 217° C. Each compound was converted with diazomethane to the same methyl ester, m.p. 94°. Found for the product from anhydrosepedonin: C, 65.12; H, 6.18; C—CH_3, 9.6%. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07; 1C—CH_3, 9.04%.

2,3-Dimethyl-5-nitrobenzonitrile (XII)

o-Xylene was nitrated and the products separated by the procedure of Crossley and Renouf (10). Reduction of 3,5-dinitro-*o*-xylene (II) with 4 equivalents of stannous chloride in ethanolic hydrogen chloride (11) gave mainly 3-amino-5-nitro-*o*-xylene (XI) which, when purified by chromatography on alumina and crystallized from ethanol or benzene, had m.p. 113° C. This product (19.3 g) was dissolved by warming in concentrated sulphuric acid (35 ml) and water (175 ml) added. The solution was cooled rapidly with stirring and the fine suspension diazotized at 0° C with sodium nitrite (8.83 g) in water (40 ml). The diazonium salt was neutralized with calcium carbonate and the filtered solution added to a well-stirred mixture of toluene (100 ml) and potassium cuprocyanide (100 ml water, 20 g cuprous cyanide, and 40 g potassium cyanide) at 10° C (12). The temperature was allowed to rise to ambient and the mixture stirred vigorously at 60° C

until gas evolution ceased. The toluene layer was separated and extraction of the product from the aqueous phase completed with ether (3 × 100 ml). The combined extracts were washed successively with 4 *N* hydrochloric acid, *N* sodium hydroxide, and water, dried, and evaporated to dryness. The crude product was purified by chromatography on alumina and crystallized from ethanol as needles (10.6 g), m.p. 131–131.5° C, $\lambda\lambda_{max}^{KBr}$ 4.44, 6.54, 7.36 μ. Found: C, 61.37; H, 4.45; N, 16.13%. Calc. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90%.

3,4-Dimethyl-5-nitrobenzonitrile (IV)

5-Amino-3-nitro-*o*-xylene (III) was obtained from 3,5-dinitro-*o*-xylene by reduction with ammonium polysulphide as described by Noelting and Thesmar (13), or more simply with sodium hydrogen sulphide (14). It was separated from (XI) by fractional crystallization of the crude product from 4 *N* hydrochloric acid. The free base crystallized from ethanol as orange-red prisms, m.p. 69–71° C. The product (14 g) was diazotized and reacted with potassium cuprocyanide as above to give the nitrile as needles (7.6 g), m.p. 118.5–121° C, $\lambda\lambda_{max}^{KBr}$ 4.43, 6.52, 7.36 μ. Found: C, 61.31; H, 4.55; N, 16.08%.

2,3-Dimethyl-6-nitrobenzonitrile (XXIII)

3-Amino-4-nitro-*o*-xylene (XXII), prepared from 3,4-dinitro-*o*-xylene by the method of Burton and Kenner (15) was obtained as orange prisms, m.p. 120° C. The amine (14 g) was diazotized and treated with potassium cuprocyanide as in the preceding experiments to give the nitrile as needles (9.0 g), m.p. 111° C, $\lambda\lambda_{max}^{KBr}$ 4.46, 6.52, 7.41 μ. Found: C, 61.40; H, 4.54; N, 15.73%.

Hydrolysis of Nitriles

2,3-Dimethyl-5-nitrobenzonitrile (9.3 g) and 3,4-dimethyl-5-nitrobenzonitrile (7.0 g) were each hydrolyzed by heating in 100% phosphoric acid (50 ml) at a bath temperature of 150° C for 2 hours. The reaction mixture, which had set to a crystalline mass was diluted with water and filtered. The residue was separated into neutral and acidic fractions by distribution between chloroform and 5% sodium carbonate solution. Acidification of the aqueous layer yielded a crystalline product which was recrystallized from aqueous ethanol. The yield of 2,3-dimethyl-5-nitrobenzoic acid (XIII), m.p. 199–200° C, $\lambda\lambda_{max}^{KBr}$ 5.90, 6.58, 7.40μ, was 6.39 g. Found: C, 55.39; H, 4.68; N, 7.10%. Calc. for $C_9H_9O_4N$: C, 55.38; H, 4.65; N, 7.18%. The yield of 3,4-dimethyl-5-nitrobenzoic acid (V), m.p. 205–205.5° C, $\lambda\lambda_{max}^{KBr}$ 5.86, 6.50, 7.35 μ, was 5.0 g. Found: C, 55.46; H, 4.62; N, 7.11%.

The chloroform layers were evaporated and the products purified by sublimation in high vacuum followed by crystallization from ethanol. 2,3-Dimethyl-5-nitrobenzamide (XX) was obtained as needles (2.87 g) m.p. 198–199° C, $\lambda\lambda_{max}^{KBr}$ 2.88, 3.01, 3.11, 6.04, 6.17, 6.55, 7.45 μ. Found: C, 55.44; H, 5.06; N, 14.48%. Calc. for $C_9H_{10}O_3N_2$: C, 55.66; H, 5.19; N, 14.43%. 3,4-Dimethyl-5-nitrobenzamide (XIX) was obtained as prisms (2.15 g), m.p. 185–186° C, $\lambda\lambda_{max}^{KBr}$ 2.87, 3.14, 5.94, 6.15, 6.53, 7.46 μ. Found: C, 55.56; H, 5.06; N, 14.36%.

Attempts to hydrolyze 2,3-dimethyl-6-nitrobenzonitrile with phosphoric acid under these conditions caused extensive decarboxylation of the acid formed. Other vigorous methods of hydrolysis were similarly unsuccessful in converting the nitrile directly to the acid. The reaction was carried out in two steps. The nitrile (1.82 g) was heated for 3 hours at a bath temperature of 160° C in a mixture of glacial acetic acid (15 ml), sulphuric acid (15 ml), and water (15 ml). The cooled solution was diluted with water and the product extracted into chloroform. The residue from evaporation of the extract crystallized from ethanol as prisms (1.55 g), m.p. 182.5–183.5° C, $\lambda\lambda_{max}^{KBr}$ 2.96, 3.12, 6.03, 6.58, 7.40 μ of 2,3-dimethyl-6-nitrobenzamide (XXIV). Found: C, 55.66; H, 5.19; N, 14.43%.

2,3-Dimethyl-6-nitrobenzoic Acid (XXV)

2,3-Dimethyl-6-nitrobenzamide (1.83 g) was dissolved in 25% (v/v) aqueous sulphuric acid at a bath temperature of 160° C. Sodium nitrite (1.30 g) in water (25 ml) was then added slowly through a narrow funnel reaching to the bottom of the solution (16). On cooling, the reaction mixture deposited long needles (1.64 g), m.p. 175.5°, $\lambda\lambda_{max}^{KBr}$ 5.90, 6.58, 7.39 μ, after recrystallization from aqueous ethanol. Found: C, 55.38; H, 4.65; N, 7.18%.

Methyl Dimethylnitrobenzoates

The acids, suspended in ether, were each treated with excess of an ethereal solution of diazomethane, crystallized from aqueous ethanol and sublimed in high vacuum to give the following compounds.

(*a*) Methyl 2,3-dimethyl-5-nitrobenzoate (XIV), m.p. 76–76.5° C, $\lambda\lambda_{max}^{KBr}$ 5.80, 6.59, 7.45 μ. Found: C, 57.54; H, 5.43; N, 6.82%. Calc. for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70%.

(*b*) Methyl 3,4-dimethyl-5-nitrobenzoate (VI), m.p. 59–60° C, $\lambda\lambda_{max}^{KBr}$ 5.82, 6.51, 7.39 μ. Found: C, 57.31; H, 5.26; N, 6.67%.

(*c*) Methyl 2,3-dimethyl-6-nitrobenzoate (XXVI), m.p. 86.5–87.5° C, $\lambda\lambda_{max}^{KBr}$ 5.77, 6.58, 7.43 μ. Found: C, 57.4; H, 5.30; N, 6.75%.

Methyl Aminodimethylbenzoates

The nitrobenzoates were each dissolved in 2.5% (w/v) methanolic hydrogen chloride and reduced with

hydrogen over palladium on charcoal catalyst at atmospheric pressure and room temperature. After hydrogen uptake ceased the filtered reaction mixtures were concentrated to a small volume under reduced pressure and neutralized with sodium bicarbonate solution. The product was extracted into ether and the dried ethereal solution evaporated to give three compounds.

(*a*) Methyl-5-amino-2,3-dimethylbenzoate (XV) as needles, m.p. 72°, $\lambda\lambda_{max}^{CHCl_3}$ 2.90, 2.96, 5.84, 6.17 μ, after crystallization from benzene – petroleum ether (b.p. 60–80° C). Found: C, 66.94; H, 7.23; N, 7.90%. Calc. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82%.

(*b*) Methyl-5-amino-3,4-dimethylbenzoate (VII), as fine needles, m.p. 80.5° C, $\lambda\lambda_{max}^{CHCl_3}$ 2.87, 2.94, 5.88, 6.17 μ after crystallization from benzene – petroleum ether (b.p. 60–80° C). Found: C, 66.99; H, 7.27; N, 7.97%.

(*c*) Methyl-5,6-dimethylanthranilate (XXVII) as a liquid $n_D^{25°\ C}$ 1.5626, $\lambda\lambda_{max}^{CHCl_3}$ 2.86, 2.94, 5.87, 6.19 μ after distillation *in vacuo*. Found: C, 67.12; H, 7.40; N, 7.65%.

Methyl Dimethylhydroxybenzoates

The aminobenzoates (1–2 g) suspended in *N* sulphuric acid (25 ml) were each diazotized at 0° C under vigorous stirring by the dropwise addition of a solution of sodium nitrite (0.41 g) in water (5 ml). Urea was added to destroy excess nitrite and the solution added slowly to a boiling solution of copper sulphate (100 g) in water (100 ml). The reaction mixture was then diluted with two volumes of water, cooled, and extracted with ether. The ether was washed with sodium bicarbonate solution, dried, and evaporated to give three compounds.

(*a*) Methyl-2,3-dimethyl-5-hydroxybenzoate (XVI) as prisms, m.p. 104–105° C, $\lambda\lambda_{max}^{CHCl_3}$ 2.79, 5.83 μ after crystallization from benzene – petroleum ether (b.p. 60–80° C) (yield 77%). Found: C, 66.80; H, 6.72%. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

(*b*) Methyl-3,4-dimethyl-5-hydroxybenzoate (VIII), m.p. 153.5°, $\lambda\lambda_{max}^{CHCl_3}$ 2.79, 5.85 μ after crystallization from benzene followed by sublimation in vacuum (yield 92%). Found: C, 66.81; H, 6.78%.

(*c*) Methyl-5,6-dimethylsalicylate (XXVIII) as needles, m.p. 26–27° C, $\lambda\lambda_{max}^{CHCl_3}$ 3.23–4.17, 5.78 (w), 6.00 (s) μ, by spontaneous crystallization of liquid obtained when the crude product was distilled in vacuum (yield 94%). Found: C, 66.81; H, 6.81%. The absorption maximum at 5.78 μ did not disappear on dilution of the chloroform solution and was present at the same intensity in a sample purified by saponification, recrystallization of the acid to constant melting point (147.5–148° C) and re-esterification with diazomethane.

Dimethylhydroxybenzoic Acids

The esters were each saponified by heating with *N* potassium hydroxide at 50° C for 5 hours to give three compounds.

(*a*) 2,3-Dimethyl-5-hydroxybenzoic acid (XVII), $\lambda\lambda_{max}^{CHCl_3}$ 2.79, 3.20–4.21, 5.83 μ after crystallization from benzene followed by sublimation in high vacuum. The sample melted and resolidified at 189–190° C, and gave a second m.p. at 196–197.5° C. Found: C, 65.06; H, 6.02%. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%.

(*b*) 3,4-Dimethyl-5-hydroxybenzoic acid (IX), m.p. 212° C, $\lambda\lambda_{max}^{CHCl_3}$ 2.77, 3.32–4.27, 5.86 μ after crystallization from benzene followed by sublimation in high vacuum. Found: C, 65.11; H, 6.06%.

(*c*) 5,6-Dimethylsalicylic acid (XXIX), m.p. 147.5–148°, $\lambda\lambda_{max}^{CHCl_3}$ 2.86–4.27, 6.03 μ, after sublimation in high vacuum. Found: C, 65.09; H, 6.11%.

Acetoxydimethylbenzoic Acids

The hydroxy acids were acetylated by heating with acetic anhydride and anhydrous sodium acetate on a steam bath for 3 hours. Excess acetic anhydride was decomposed with ice. The product was separated and recrystallized from aqueous ethanol to give four compounds.

(*a*) 5-Acetoxy-2,3-dimethylbenzoic acid (XVIII) as needles, m.p. 162.5–163° C. Found: C, 63.35; H, 5.93%. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%.

(*b*) 5-Acetoxy-3,4-dimethylbenzoic acid (X) as needles, m.p. 162–163° C. Found: C, 63.35; H, 5.84%.

(*c*) Acetyl-5,6-dimethylsalicylic acid (XXX) as plates, m.p. 138–140° C. Found: C, 63.18; H, 5.79%.

(*d*) Acetyl-3,4-dimethylsalicylic acid (XXXIII) as needles, m.p. 143–145° C. Found: 63.21; H, 5.82%.

3,4-Dimethylsalicylic Acid (XXXII)

Kolbe–Schmitt carbonation of 2,3-xylenol (6.1 g) by the Marassé procedure (4) yielded a product which, after sublimation in high vacuum and crystallization from water, gave needles, m.p. 200–202° C, $\lambda\lambda_{max}^{CHCl_3}$ 2.86–4.17, 6.06 μ. Found: C, 65.05; H, 6.24%.

Methyl-3,4-dimethylsalicylate (XXXIV)

3,4-Dimethylsalicylic acid in ether was treated with a slight excess of ethereal diazomethane. The product, purified by sublimation in high vacuum, had m.p. 49.5° C. Found: C, 66.53; H, 6.77%.

Tiemann–Riemer Reaction with 3,4-Xylenol

The reaction was carried out according to the directions of Clayton (6). The main product separated from the steam distillate as long needles, m.p. 97° C (18% yield). Auwers (7) reported m.p. 102–103° C for 4-dichloromethyl-3,4-dimethylcyclohexa-2,5-dienone. Found: C, 52.45; H, 5.02; Cl, 33.91%. Calc. for $C_9H_{10}OCl_2$: C, 52.70; H, 4.91; Cl, 34.57%.

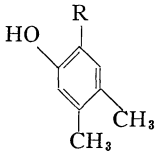
The material regenerated from the bisulphite derivative was crystallized from petroleum ether (b.p. 60–80° C) in 4% yield and the crystals sorted mechanically into two groups.

(*a*) Pale yellow needles, m.p. 67.5°, $\lambda\lambda_{max}^{CHCl_3}$ 2.8–3.7, 6.10 μ after several recrystallizations from petroleum ether and methanol. Found: C, 71.95; H, 6.76%. Calc. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%. Clayton reported m.p. 72° for 5,6-dimethylsalicylaldehyde (XXXI).

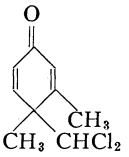
(*b*) Colorless plates, m.p. 69.5–70° C, $\lambda\lambda_{max}^{CHCl_3}$ 2.8–3.7, 6.04 μ after several recrystallizations from petroleum ether. Found: C, 72.13; H, 6.84%. Clayton reported m.p. 71° for 4,5-dimethylsalicylaldehyde (XXXVI).

Oxidation of Dimethylsalicylaldehydes

When the plates, m.p. 69.5–70° C, were heated in a fusion mixture of sodium hydroxide – potassium hydroxide at 180° C for 1.5 hours (6) an acid, m.p. 202° C, was obtained in 84% yield. This was indistinguishable from the 4,5-dimethylsalicylic acid (XXXV), isolated as the sole product after carbonation of 3,4-xylenol (4).



XXXV R = COOH
XXXVI R = CHO



XXXVII

Oxidation of the needles, m.p. 67.5° C under the same conditions, gave only unchanged starting material. More vigorous conditions (210° and 4 hours) gave a small yield (1%) of an acid, m.p. 146° C, separated from unreacted aldehyde by solubility in sodium bicarbonate solution, followed by fractional crystallization from aqueous ethanol. This product was spectroscopically indistinguishable from and did not depress the melting point of a sample of 5,6-dimethylsalicylic acid synthesized from 3-amino-4-nitro-*o*-xylene. Attempts to improve the yield by increasing the temperature and reaction time, or by using the procedure of Pearl (17) were not successful.

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