224. *Hydroxy-carbonyl Compounds. Part VIII. Some Derivatives of 2 : 6-Dihydroxytoluene.*

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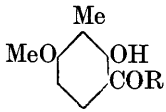
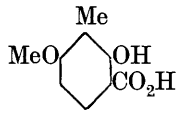
THE present investigation was undertaken (a) to establish the orientation of the compounds formed by the nuclear methylation of resacetophenone and β-resorcylic acid (Wechsler, *Monatsh.*, 1894, **15**, 239; Gregor, *ibid.*, p. 437; Perkin, J., 1895, **67**, 990; Crabtree and Robinson, J., 1918, **113**, 868) and (b) to attempt to obtain further independent evidence in support of the constitution of the benzophenonecarboxylic acid (III) recently used by us in the synthesis of rubiadin (J., 1930, 1699).



(I.)



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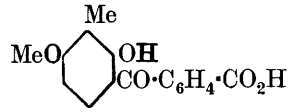

(III.)

Identical specimens of 2 : 6-dihydroxytoluene have now been obtained from 6-*amino*-o-*tolyl* p-*toluenesulphonate*, 6-methoxy-*o*-cresol, and from the acid (II) (compare Ullmann, *Ber.*, 1884, **17**, 1963; Heinrich and Herold, *Ber.*, 1927, **60**, 2053; Herzig and Wenzel, *Monatsh.*, 1903, **24**, 881).

The orientation of the *aldehyde* (I, R = H) and hence that of the acid (II), which it yields on oxidation, is established by the formation of 4′ : 7-*dimethoxy*-8-*methylflavylium ferrichloride*. Similarly the formula (I, R = Me) assigned to *C*-methylpæanol by Perkin (*loc. cit.*) follows from its conversion into 7-*methoxy*-2 : 8-*dimethyl*-1 : 4-*benzopyrone*.

We had hoped to convert the acid (III) into the *ketone* (I, R = Ph) by decarboxylation and to establish the orientation of the latter substance by ring closure with sodium acetate and acetic anhydride, but (I, R = Ph) could not be obtained from (III) and a specimen prepared by another method did not undergo ring closure in the usual manner.

EXPERIMENTAL.

6-*Amino*-o-*tolyl* p-*Toluenesulphonate*.—A mixture of 6-nitro-*o*-cresol (6 g.) (Nöelting, *Ber.*, 1904, **37**, 1020), *p*-toluenesulphonyl chloride (13 g.), and pyridine (14 c.c.) was heated on the steam-bath for 1 hour and poured into water (200 c.c.). Next day the p-*toluenesulphonate* of 6-nitro-*o*-cresol was collected and crystallised from alcohol (charcoal), forming elongated colourless laminæ (13·5 g.), m. p. 94° (Found : C, 54·9; H, 4·4. $C_{14}H_{13}O_5NS$ requires C, 54·7; H, 4·3%).

The nitro-compound was carefully reduced with stannous chloride (25 g.), acetic acid (25 c.c.), and concentrated hydrochloric acid (10 c.c.), the solution heated on the steam-bath for 1 hour and poured into water (300 c.c.), the solid collected, washed with 10% potassium hydroxide solution and then with water, and crystallised from alcohol, the *amine* being deposited in colourless prisms, m. p. 108° (Found: C, 60·6; H, 5·4. $C_{14}H_{15}O_3NS$ requires C, 60·7; H, 5·4%). The sulphate of this base is sparingly soluble in water.

2 : 6-*Dihydroxytoluene.*—(A) 6-Methoxy-*o*-cresol (J., 1930, 1699) (5 g.) was gently boiled with hydriodic acid (26 c.c. ; *d* 1·7) for 2 hours, the cooled mixture poured into 5% aqueous sodium bisulphite (200 c.c.), and the product isolated by means of ether. A hot benzene–ligroin extract of the crude material, filtered from insoluble coloured impurities, deposited 2 : 6-dihydroxytoluene, m. p. 112—115°, on cooling. Recrystallised from benzene, this formed colourless elongated prisms (3 g.), m. p. 117° (the melt cleared slowly) (Found : C, 67·8; H, 6·5. Calc. for $C_7H_8O_2$: C, 67·7; H, 6·5%) (Ullmann, *loc. cit.*, gives m. p. 63—66°). The compound is readily soluble in ether, alcohol, and water and insoluble in ligroin. With ferric chloride its aqueous solutions give a faint dark violet coloration which fades on the addition of an excess of the reagent. The dibenzoate separated from warm methyl alcohol in fern-like clusters of needles, m. p. 105—106° (Found : C, 76·0; H, 4·8. Calc. for $C_{21}H_{16}O_4$: C, 75·9; H, 4·8%) (Herzig and Wenzel, *loc. cit.*, record m. p. 101—103°).

(B) 2-Hydroxy-4-methoxy-3-methylbenzoic acid was prepared from β-resorcylic acid and crystallised from dilute methyl alcohol, forming slender needles, m. p. 215—216° (Perkin and Herzig and Wenzel, *locc. cit.*, give m. p. 210°). Treatment of this acid (2 g.) with boiling hydriodic acid (12 c.c.) for 3 hours gave 2 : 6-dihydroxytoluene, m. p. and mixed m. p. 117°; the dibenzoate had m. p. and mixed m. p. 105—106°.

(C) A solution of the *O*-*p*-toluenesulphonate of 6-amino-*o*-cresol (15 g.) in boiling 10% sulphuric acid (50 c.c.) was rapidly cooled to 0°, a slight excess of sodium nitrite (5 g.) introduced, and the mixture stirred until the small crystals of the sulphate had disappeared (3—4 hours). The excess of nitrous acid was destroyed with urea, the filtered diazonium solution heated on the water-bath for 1·5 hours, and the *p*-toluenesulphonate of 2 : 6-dihydroxytoluene quickly separated. The crude ester, which partly solidified on cooling, was hydrolysed by boiling with 12% aqueous potassium hydroxide (100 c.c.) for 4 hours and after neutralisation with dilute sulphuric acid the solution was cooled, treated with charcoal, filtered, and saturated with ammonium sulphate. 2 : 6-Dihydroxy-

toluene, isolated by five extractions with ether, crystallised from benzene in colourless prisms (3·5 g.), m. p. and mixed m. p. 117°.

2 : 4-*Dihydroxy*-3-*methylbenzaldehyde*.—The condensation of 2 : 6-dihydroxytoluene (2 g.) and hydrogen cyanide (2 c.c.) in ethereal solution was effected with zinc cyanide (2 g.) and excess of hydrogen chloride. A solution of the resulting aldimine in water (35 c.c.), heated on the steam-bath for 20 minutes, gave the *aldehyde*, which crystallised from water in almost colourless, rhombic prisms, m. p. 150° with slight sintering at 147° (Found : C, 63·2; H, 5·4. $C_8H_8O_3$ requires C, 63·2; H, 5·3%). The substance, which is readily soluble in alcohol, acetone, or ether, separates from warm benzene in rectangular plates, forms an orange solution with aqueous calcium hypochlorite, and gives a wine-red coloration with alcoholic ferric chloride.

2-*Hydroxy*-4-*methoxy*-3-*methylbenzaldehyde* (I, R = H).—Zinc cyanide (5 g.) and hydrogen cyanide (5 c.c.) were added to a solution of 6-methoxy-*o*-cresol (5 g.) in ether (90 c.c.) and the mixture was saturated with hydrogen chloride. Next day the crystalline solid was collected, washed with ether, and hydrolysed with water (100 c.c.) during 1 hour on the water-bath, yielding a brown oil which solidified. A solution of the solid in ether was washed with 10% aqueous sodium carbonate and then with water, and after the removal of the solvent the *product* (4·5 g.) was distilled in steam and crystallised from dilute methyl alcohol, forming colourless, elongated, rectangular plates, m. p. 64°, easily soluble in alcohol or benzene (Found : C, 65·1; H, 6·1. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%). With alcoholic ferric chloride it gives a reddish-brown coloration and with aqueous calcium hypochlorite a lemon-yellow coloration.

Partial methylation of 2 : 4-dihydroxy-3-methylbenzaldehyde (0·7 g.) with methyl iodide (1 c.c.) and excess of potassium carbonate in boiling acetone during 1·5 hours gave an almost quantitative yield of the 4-methyl ether, which crystallised from dilute methyl alcohol in plates, m. p. and mixed m. p. 64° (Found : C, 65·3; H, 6·0%).

4′: 7-*Dimethoxy*-8-*methylflavylium Ferrichloride*.—The condensation of the foregoing aldehyde (0·75 g.) and *p*-acetylanisole (0·5 g.) was effected in dry ethyl acetate by means of hydrogen chloride and after 3 days the chloride was isolated and crystallised from 9% hydrochloric acid, forming slender reddish-brown needles. The *ferrichloride* separated from hot acetic acid in glancing, dark-red, rhombic plates, m. p. 177—178° (Found : C, 45·0; H, 3·5. $C_{18}H_{17}O_3Cl_4Fe$ requires C, 45·1; H, 3·5%).

2-*Hydroxy*-4-*methoxy*-3-*methylbenzoic Acid* (II).—2-Hydroxy-4-methoxy-3-methylbenzaldehyde (1 g.) was dissolved in warm

acetone (20 c.c. at 50°) and oxidised by the gradual addition of a solution of potassium permanganate (1·6 g.) in water (27 c.c.). After 15 minutes the cooled reaction mixture was cleared with sulphur dioxide, and the acetone evaporated in a vacuum. A solution of the solid in aqueous sodium bicarbonate was filtered from unchanged aldehyde and on acidification with hydrochloric acid gave 2-hydroxy-4-methoxy-3-methylbenzoic acid, which crystallised from methyl alcohol in clusters of needles (0·5 g.), m. p. and mixed m. p. 215—216° (Found : C, 59·5; H, 5·4. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). With alcoholic ferric chloride the acid gave a purple coloration and with aqueous calcium hypochlorite a bright yellow coloration.

2-*Hydroxy*-4-*methoxy*-3-*methylacetophenone* (I, R = Me).—6-Methoxy-*o*-cresol (2 g.) and acetonitrile (1 g.) were condensed by means of zinc chloride (2 g.) and excess of hydrogen chloride in dry ether (50 c.c.) and 24 hours later the crystalline solid was collected, washed with ether, and hydrolysed by boiling with water (30 c.c.) for 1 hour. The product (1·2 g.), which was insoluble in 1% aqueous sodium hydroxide or in 10% aqueous sodium carbonate, appeared to consist entirely of 2-hydroxy-4-methoxy-3-methylacetophenone. Crystallised from 80% methyl alcohol, it formed colourless prismatic needles, m. p. 83° (Found : C, 66·4; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%). The ketone gave a brownish-purple ferric chloride reaction.

2-*Hydroxy*-4-*methoxy*-3-*methylbenzoylacetone*.—A mixture of the foregoing ketone (2 g.), sodium (1 g. in small pieces), and ethyl acetate (15 c.c.) was heated on the steam-bath for 2 hours; a bright yellow solid quickly formed and after 1 hour further quantities of sodium (1 g.) and ethyl acetate (10 c.c.) were added. The resulting thick brown oil was poured into water (200 c.c.), and the solution acidified with acetic acid. Next day the *diketone* was collected, dried, and crystallised from benzene–ligroin, forming almost colourless needles, m. p. 118° (Found : C, 65·1; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). The compound is readily soluble in alcohol, acetic acid, or benzene, and gives a dull purple ferric chloride reaction.

7-*Methoxy*-2 : 8-*dimethyl*-1 : 4-*benzopyrone*.—The diketone just described was quantitatively converted into the 1 : 4-*pyrone* by boiling with acetic acid (4 c.c.) containing one drop of concentrated hydrochloric acid for 3 minutes. The cooled solution was diluted with water (50 c.c.) and the compound was collected and crystallised from benzene–ligroin, forming squat prisms. Recrystallised from dilute alcohol, it separated as a hydrate in long colourless prisms, m. p. 142° (Found in material dried at 110° : C, 70·6; H, 5·9.

$C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The colourless solution of the pyrone in concentrated sulphuric acid exhibits a bluish-green fluorescence.

2 : 4-*Dihydroxy*-3-*methylbenzophenone*.—(A) A solution of 2 : 6-dihydroxytoluene (2 g.) and excess of benzonitrile (3 g.) in ether (30 c.c.) was saturated with hydrogen chloride in the presence of zinc chloride (2 g.), and a reddish viscous layer gradually separated. Two days later ether (100 c.c.) was added, the ethereal layer decanted, and the viscous liquid twice washed with this solvent (30 c.c.). A solution of the residual material in water (50 c.c.) was boiled for ½ hour, and, on cooling, the *ketone* was collected and crystallised from 60% alcohol, forming pale straw-coloured plates (2·5 g.), m. p. 177° (Found : C, 73·6; H, 5·5. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%). With alcoholic ferric chloride the compound gives a dark red coloration which becomes red-brown on dilution with water.

(B) To a cooled solution of 6-methoxy-*o*-cresol (1 g.) and benzoyl chloride (1·1 g.) in carbon disulphide (10 c.c.), anhydrous aluminium chloride (3 g.) was added in three portions. The mixture was warmed on the steam-bath for 1 hour, the product decomposed with ice and dilute hydrochloric acid, an ethereal solution of the solid produced was extracted with 5% aqueous sodium hydroxide, and the extract acidified with hydrochloric acid giving the hydroxy-ketone, m. p. and mixed m. p. 177° after crystallisation from benzene.

2-*Hydroxy*-4-*methoxy*-3-*methylbenzophenone* (I, R = Ph).—A mixture of the foregoing ketone (2 g.), methyl iodide (3 c.c.), acetone (20 c.c.), and powdered potassium carbonate (3 g.) was refluxed for 2 hours. Acetone (50 c.c.) was added, the solution filtered from potassium salts, the solvent evaporated in a vacuum, and the solid residue triturated with 1% aqueous sodium hydroxide. The insoluble *monomethyl* ether was collected, washed with water, and crystallised from alcohol, forming bright yellow, rhombic plates, m. p. 125° (Found : C, 74·3; H, 6·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). This substance sometimes separates from alcohol in needles which change in the course of a few hours into rhombic plates. The ferric chloride reaction is identical with that of the dihydroxy-compound.

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