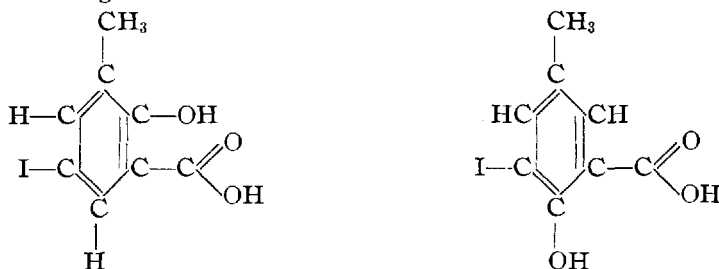


IODIZATION OF *o*- AND *p*-CRESOTINIC ACID.*

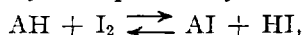
BY J. A. W. LUCK.

o-Cresotinic acid or 2-oxy-1-methyl-3-carboxyl-benzene and *p*-cresotinic acid or 4-oxy-1-methyl-3-carboxyl-benzene,¹ according to the Crum-Brown-Gibson rule, yield by direct iodization only mono-iodine derivatives. The directive influence of the hydroxyl group causes the introduction of iodine into the ortho and para position. The methyl group also influences the introduction of the iodine in the same manner, while the carboxyl directs the iodization to the meta position.

Since the ortho positions to the hydroxyl group are both occupied in the *o*-cresotinic acid, and since the combined directive influence of the hydroxyl and carboxyl groups outweigh the influence of the methyl group, substitution of iodine will only occur in the 5-position, methyl being 1, which is para to the hydroxyl and meta to the carboxyl group. Similarly, *p*-cresotinic acid will yield only 5-substitution of iodine, which is ortho to the hydroxyl and meta to the carboxyl groups. The configurations therefore are:



As shown by Kekulé,² the reaction between iodine and a carbon compound is a reversible one which may be expressed by



where A is a radicle. To bring the reaction to completion it is therefore necessary to remove the hydriodic acid as fast as it is formed. This can be accomplished by oxidizing the hydriodic acid to I_2 and H_2O . This method has been extensively used to iodize ring compounds which are not attacked by oxidizing agents. Kekulé³ used I_2 and HIO_3 to obtain phenyl iodide from benzene. Heating with concentrated H_2SO_4 and I_2 was used by Neuman⁴ to obtain the same substance. Terephthalic acid was iodized by Rupp,⁵ using fuming H_2SO_4 and I_2 , obtaining a mixture of tetra-iodo terephthalic acid and hexa-iodo benzene. Joraslawzew⁶ used $Na_2S_2O_8$ and I_2 to iodize benzene and its homologues.

The removal of the hydriodic acid in the form of metallic iodides has been extensively used in the iodization of hydroxy benzene derivatives. Messinger and Vortman,⁷ Kalle & Company,⁸ used a solution of I_2 in KI, which was added

* Contribution from the Chemical Laboratory of the University of California.

¹ M. M. Richter Verz.

² A. 131-122.

³ A. 137-162.

⁴ A. 241-84.

⁵ B. 29-1631.

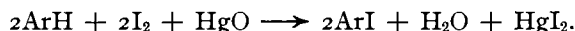
⁶ Giessen Thesis, 1914.

⁷ B. 22, 2312, 1889.

⁸ D. R. P. 106504.

to an alkaline solution of phenol, cresol, etc., which, upon acidification, yielded tri-iodo derivatives. Classen and Loeb⁹ used a borax solution of phenolphthalein obtaining tetra-iodophenolphthalein. This method has been used to detect benzoic acid in salicylic acid, the benzoic acid yielding no iodine derivative under these conditions. Haase¹⁰ treated an alkaline solution of *o*-cresotinic acid with a slightly less quantity than molal iodine dissolved in KI solution, and precipitated with a mineral acid. He obtained a mono-iodo derivative having a M. P. 204° C. This is listed by Stelzner¹¹ as 5-iodo-2-oxy-1-methyl-3-carboxylbenzene. By using this method, the writer obtained an iodine derivative having a M. P. 237° C.

Oxides of the heavy metals PbO, HgO have also been used. Weselsky¹² dissolved salicylic acid in 90 percent alcohol, heated under reflux condenser and added small portions of I₂ and HgO, obtaining di-iodo salicylic acid,



The constitution of the iodine derivatives may be determined by replacing the iodine by other groups, forming compounds whose constitutions are known. Of the halogens both Br and Cl have been replaced by NO₂, by treating the halogen derivatives dissolved in glacial acetic acid with NaNO₂, see Zincke.¹³ In a similar manner, I can be replaced by NO₂.



By fusing the iodine derivatives with KOH or NaOH replacement of I by OH occurs. The procedure depends upon the stability of the substance used. The iodo cresotinic acids resinify readily upon heating with alkali. This can be partially prevented by fusing at low temperatures and the addition of PbO or Pb(OH)₂ freshly prepared.

During the fusion oxidation of side chains frequently occurs, Barth.¹⁴ This is accelerated by the presence of MnO₂, CuO, Fe₂O₃, Oppenheim & Plaff,¹⁵ Koenig & Heyman.¹⁶ Ag₂O behaves similarly, the methyl group being oxidized to COOH yielding derivatives of isophthalic acid from cresotinic acid. This is expressed in the simplest manner by the equation



EXPERIMENTAL.

(1) *o*-Cresotinic Acid.—Dissolve 6 Gm. of *o*-cresotinic acid in 100 Cc. of 95 percent alcohol, add 10 Gm. of I₂ and heat to boiling under reflux condenser, gradually add in small quantities of 4.3 Gm. HgO, vigorously rotating flask after each addition. Soon after the last portion of HgO has been added the liquid has a pale yellow color, the HgO combines with the HI liberated, forming HgI₂. The total time is from 20 to 30 minutes. Filter the liquid into a solution of KI, to remove the HgI₂ which is slightly soluble in alcohol; wash the HgI₂ on the filter paper

⁹ B. 28, 1609, 1895.

¹⁰ D. R. P. 224536 C. 1902 (2) 700.

¹¹ *Verz. Org. Verb.*, 1910-11, page 437.

¹² A. 174-103.

¹³ Jp. (2) 61, 564, 1900, compare Rayford & Heyl, *A. Chem. J.*, 43, 393.

¹⁴ A. 154-360.

¹⁵ B. 8, 887.

¹⁶ B. 19, 704.

with alcohol and dilute the solution with water, bringing the total volume to 500 Cc. Filter on suction pump. Redissolve the precipitate in hot alcohol and dilute with boiling H₂O to twice the volume. Upon cooling the iodized cresotinic acid crystallizes in long, shining needles. Recrystallize from dilute alcohol. Yield, 90 percent of theory.

Faintly yellow, long, shining needles sublime at 140° C., without decomposition. Soluble in alcohol, acetone, ether, chloroform, hot glacial acetic acid; slightly soluble in H₂O. M. P. 237° C. with decomposition, losing iodine at 225° C. The alcoholic and aqueous solutions give with FeCl₃ solution a violet color. The analysis for iodine by Pringsheim's method, Weyl,¹⁷ Lassar-Cohn,¹⁸ yielded:

I found: 46.04 percent

I theory: 45.66 percent

(2) *Ethyl Ester*.—2 Gm. of the iodized acid were dissolved in 100 Cc. absolute alcohol, adding 20 Cc. H₂SO₄ and heated on water bath under reflux condenser for three hours. Pour into cold water, cool and filter. Recrystallize from alcohol. Short needles. M. P. 78° C. Soluble in NaOH solution. Nearly insoluble in solution of sodium carbonate.

I found: 41.2 percent

I theoretical: 41.48 percent

(3) *Nitro Derivative*.—Dissolve 5 Gm. of iodized cresotinic acid in 50 Cc. glacial acetic acid by heating on the water bath; add 2.5 Gm. of solid NaNO₂. When reaction subsides pour into cold H₂O and let cool. Filter, to filtrate add 10 Cc. 6 N NaOH followed by H₂SO₄; a solution of Na₂SO₄ will do as well; filter and dissolve the two crystallized nitro acids in a 1 N NaOH solution. Dilute to twice the volume and add a solution of 3 percent H₂O₂ to oxidize nitroso derivatives. Heated to boiling, the solution becomes faintly yellow. Let cool and acidify with H₂SO₄, recrystallize from dilute alcohol. M. P. 198° C. Long, faintly yellow needles; soluble in alcohol, ether, and slightly soluble in water. The aqueous and alcoholic solutions give a cherry-red color with FeCl₃ solution. Einhorn & Phyl¹⁹ nitrated *o*-cresotinic acid and obtained a nitro derivative M. P. 199° C.; see Kostanecki and Niementowski.²⁰ Borshe and Beckhout²¹ condensed 5-nitro-2-oxy-1-methylbenzene with formaldehyde in the presence of H₂SO₄. The condensation product upon hydrolysis yielded 5-nitro-2-oxy-1-methyl-3-carboxylbenzene. M. P. 199° C.

(4) *Replacement of I by OH*.—5 Gm. of the iodized cresotinic acid and 50 Gm. KOH were fused in a silver evaporating dish at 175° C. and kept at this temperature for two hours. After cooling the melt was dissolved in cold water, acidified with H₂SO₄, and cooling the liquid carefully so that the temperature did not rise above 20° C. Let stand for six hours and filter. Extracting the filtrate with ether, the ethereal solution upon evaporation yielded a brown mass. The brown mass was dissolved in hot alcohol, diluted with an equal volume of water and filtered. Heating this solution on the water bath, until nearly all the alcohol had evaporated, it was cooled, filtered, and extracted with ether. The residue from the ether extract gave by heating a white sublimate melting at 123° C. The

¹⁷ Vol. 1, page 52.

¹⁸ Vol. 1, page 325.

¹⁹ A. 311-47-48.

²⁰ B. 18, 254.

²¹ A. 311-47-48.

aqueous solution of this sublimate gives with FeCl_3 a brown-red color. It dissolves in a solution of NaOH with a green color which turns brown when exposed to air. Toluhydrochinon melts at 124°C . and behaves similarly.

(5) 5 Gm. of the acid dissolved in 150 Cc. of 6 N KOH solution and evaporated in a silver evaporating dish until the temperature reached 135°C . After maintaining the temperature of the melt between 135° and 140°C . for three hours, it was cooled and treated as previously described. The residue of the ether extract was dissolved in alcohol and diluted with water, evaporated to half the volume on the water bath and cooled in a freezing mixture. The solution was filtered and extracted with ether. After the ether had evaporated, a yellow crystalline mass of indefinite melting point was obtained. By repeating this three times a white crystalline substance was obtained, which was recrystallized from a mixture of ether and alcohol. White needles, M. P. 215°C . The alcoholic solution gives a blue color with FeCl_3 which turns green upon further addition of FeCl_3 . The analysis for carbon and hydrogen gave:

Found: C, 57.5	Theoretical: 57.14
H, 4.4	$\text{C}_8\text{H}_8\text{O}_4$: 4.79

The analysis corresponds to a dioxytoluic acid,²² 2,5-dioxy-1-methyl-3-carboxylbenzene. M. P. 215°C ., Schering.²³

(6) Repeating the fusion but adding 15 Gm. freshly precipitated $\text{Pb}(\text{OH})_2$ to the fused mass at 135°C ., and observing conditions as described under (5). Less resin is formed and a larger yield of dioxytoluic acid is obtained. This acid can be readily separated from toluhydrochinon and *o*-cresotinic acid by heating on a hot plate at 110°C . Toluhydrochinon and *o*-cresotinic acid sublime. No decomposition of the dioxytoluic acid occurs at this temperature. When using Ag_2O instead of $\text{Pb}(\text{OH})_2$, three substances were obtained with melting points at 163°C ., 215°C ., and 238°C ., respectively. *o*-Cresotinic acid melts at 163° - 164°C . The substance melting at 215°C . behaves as previously described and yielded on combustion:

Found: C, 56.94 percent	Theoretical: C, 57.14 percent
H, 4.84 percent	$\text{C}_8\text{H}_8\text{O}_4$: H, 4.79 percent

The substance melting at 238°C . gives in alcoholic solution a red color with FeCl_3 ; this is characteristic of oxyisophthalic acids. Analysis for carbon and hydrogen:

Found: C, 52.76 percent	Theoretical: C, 52.73 percent
H, 3.8 percent	$\text{C}_8\text{H}_6\text{O}_5$: H, 3.32 percent

An acid melting at 239°C . having a composition $\text{C}_8\text{H}_6\text{O}_5$ is listed as 2-oxy-1,3-dicarboxylbenzene.²⁴

(7) Para-cresotinic acid was iodized as described under ortho-cresotinic acid. The acid crystallizes in long, shining needles. M. P. 210°C .; loses iodine at 203°C . Soluble in alcohol, ether, acetone, chloroform, glacial acetic acid and slightly soluble in H_2O . The alcoholic solution gives a violet-blue color with FeCl_3 , which is changed by traces of OH^- to a purple color. Analysis for iodine gave:

I found: 45.71 percent	I theoretical: 45.66 percent
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²² Beilstein, II, 1033.

²³ D. R. P. 81297.

²⁴ Beilstein, II, 1936.

(8) *Ethyl Ester*.—Preparation as under ortho. Crystallizes from alcohol in small plates. M. P. 94° C.

Analysis for iodine:

I found: 41.43 percent

I theoretical: 41.48 percent

(9) *Replacement by NO₂*.—By method described under (3). It crystallizes from dilute alcohol in long, yellow needles. M. P. 174° C. Gives in alcoholic or aqueous solution a cherry-red color with FeCl₃. Einhorn and Pfy²⁵ obtained an acid melting at 175° C. by nitrating *p*-cresotinic acid.

(10) *Replacement by OH*.—Fusing in presence of Pb(OH)₂ and following directions as described under *o*-cresotinic acid, an acid crystallizing in needles and melting at 204° C. was isolated. The alcoholic solution of this acid gives a blue color with FeCl₃ which turns green on further addition of FeCl₃. The analysis for carbon and hydrogen yielded:

Found: C, 57.08 percent
H, 4.85 percent

Theoretical: C, 57.14 percent
C₈H₈O₄: H, 4.79 percent

This corresponds to a dioxytoluic acid, described in Beilstein²⁶ as 4,5-dioxy-1-methyl-3-carboxylbenzene, Schering.²⁷

Using Ag₂O in place of Pb(OH)₂, two substances were isolated, one melting at 152° C. and the other at 300° C. The acid melting at 152° C. gives a violet color with FeCl₃. *p*-Cresotinic acid melts at 151° C. The acid melting at 300° C. gives a red color in alcoholic solution with FeCl₃. The analysis of carbon and hydrogen gave:

Found: C, 53.2 percent
H, 4.04 percent

Theoretical: C, 52.73 percent
C₈H₆O₅: H, 3.32 percent

4-Oxyisophthalic acid melts at 304° C. to 306° C.²⁸

SUMMARY.

The iodine derivatives obtained by the method described are: 5-iodo-2-oxy-1-methyl-3-carboxylbenzene, M. P. 237° C. from *o*-cresotinic acid, and from *p*-cresotinic acid 5-iodo-4-oxy-1-methyl-3-carboxylbenzene; M. P. 210° C. This is proved by the conversion of the iodine into nitro and hydroxyl derivatives.

The nitro derivative made by Einhorn and Pfy²⁹ by direct nitration of *p*-cresotinic acid is 5-nitro-4-oxy-1-methyl-3-carboxylbenzene.

The presence of Ag₂O in alkali fusions causes oxidation of side chains and has the tendency to prevent the replacement of the iodine by the hydroxyl group, the iodine being largely replaced by hydrogen.

The ethyl ester of 5-iodo-2-oxy-1-methyl-3-carboxylbenzene melts at 78° C. and the ethyl ester of 5-iodo-4-oxy-1-methyl-3-carboxylbenzene melts at 94° C.

²⁶ *Loc. cit.*

²⁸ II*, 1031.

²⁷ D. R. P. 81298.

²⁸ Beilstein II, 1936; *Ost. Jp. Ch.*, XIV, 103.

²⁹ *Loc. cit.*