established specific dynamic effect, associated especially with glycine and alanine, investigated so carefully by Lusk.

102–111 Second Avenue, Southwest,
Rochester, Minnesota

[Contribution from the Baker Laboratory of Chemistry of Cornell University]

ORTHO-CRESOLBENZEIN AND SOME OF ITS DERIVATIVES

By W. R. Orndorff and S. Alice McNulty[1]

Received August 12, 1926 Published April 7, 1927

In connection with the chemical and spectrographic study of the phthaleins and sulfonephthaleins in this Laboratory, it was thought desirable to investigate *o*-cresolbenzein.

o-Cresolbenzein was first made in Doebner's Laboratory by Schroeter,[2] who found that it melted at 220–225° and gave results on analysis which agreed with the formula for dimethyldihydroxytriphenyl carbinol, similar to the dihydroxytriphenyl carbinol formula given to benzaurin (phenolbenzein) by Doebner. Schroeter concludes that like benzaurin, *o*-cresolbenzein is formed in two stages. It seemed highly probable that owing to the color of *o*-cresolbenzein the carbinol formula for it is not correct. Baeyer has shown that all carbinols are colorless and that color appears only when the carbinols lose water and the quinoid condition is established. It will be shown in this paper that the formula for the stable, colored form of *o*-cresolbenzein differs from the carbinol formula by one molecule of water, that is, that it is in the quinoid condition.

Experimental Part

***o*-Cresolbenzein (Quinoid Form)**.—*o*-Cresol and benzotrichloride (2.1 moles:1 mole) were heated at 150° under reduced pressure until the evolution of hydrogen chloride ceased. The dark red material was dissolved in 5% sodium hydroxide solution, the benzein precipitated with hydrochloric acid, and the excess of *o*-cresol removed by steam distillation. The benzein, dissolved in sodium hydroxide solution, was treated with sulfur dioxide until a clear, brownish solution formed in the presence of considerable resinous material. (Phenyl-*o*-hydroxytolyl ketone was later recovered from these residues.) Acidification of the solution with hydrochloric acid decomposed the bisulfite compound, liberating the benzein. Repetition of this process produced a small amount of benzein which was boiled with water to remove traces of acid or sodium salts. Crystallization from absolute ethanol produced minute, red-orange crystal fragments which melted with decomposition at 260–262°.

Anal.[3] Subs., 0.1763, 0.1624: CO_2, 0.5379, 0.4968; H_2O, 0.0972, 0.0923. Calcd. for $C_{21}H_{18}O_2$: C, 83.41; H, 6.00. Found: C, 83.21, 83.43; H, 6.17, 6.36.

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[1] From a dissertation presented to the Faculty of the Graduate School, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, by S. Alice McNulty, holder of the Grasselli Fellowship in Chemistry at Cornell University, **1923–1924.**

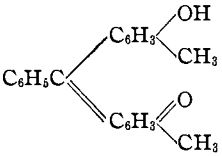
[2] Schroeter, *Ann.*, **257**, 68 (1890).

[3] The values used for the atomic weights are those given in the 1925 International Table of Atomic Weights.

o-Cresolbenzein was more satisfactorily prepared by adding small portions of benzotrichloride to *o*-cresol (1 mole:2.1 moles) over a period of several hours. The flask was warmed at 80° until evolution of hydrogen chloride ceased. Water was added to the brittle, dark red solid, which had a green surface color, and the excess of *o*-cresol removed by steam distillation. Yellow, needle-shaped crystals of phenyl-*o*-hydroxytolyl ketone separated from the cooled filtrate. The benzein, dissolved in dil. sodium hydroxide solution, was poured with stirring into water containing enough acetic acid to neutralize the alkali. The benzein separated as a red-orange powder, was filtered off, washed with water, dried at 110° and then repeatedly extracted with boiling ether in which phenyl-*o*-hydroxytolyl ketone dissolved. The benzein, crystallized from glacial acetic acid, produced dark spots on the walls of the melting-point tube at about 255° and melted with decomposition at 260–262°.

Anal. Subs., 0.1728, 0.1962: CO_2, 0.5271, 0.6001; H_2O, 0.0917, 0.1089. Calcd. for $C_{21}H_{18}O_2$: C, 83.41; H, 6.00. Found: C, 83.19, 83.42; H, 5.94, 6.21.

These analyses and the color of the compound show that this stable form of *o*-cresolbenzein does not have the carbinol formula given to it by Schroeter, but has the quinoid structure



The benzein crystallizes in tiny plates from acetone and benzene, in both of which it is very difficultly soluble. It is practically insoluble in ether. In solutions of the alkalies the benzein dissolves with a violet-red color, forming the monosodium or potassium salt. Heat intensifies the color of the solution, but the color fades on allowing the solution to cool. In an excess of alkali the benzein forms colorless solutions of the dialkali salts of the carbinol. When sulfur dioxide is passed into a dilute solution of the purified benzein in a 5% solution of sodium hydroxide, a clear solution forms, no resinous material being present.

Dry ammonia gas has no action on *o*-cresolbenzein.

Dry *o*-cresolbenzein absorbs between one and two molecules of hydrogen chloride.

Professor Gill[4] found that crystals of *o*-cresolbenzein from glacial acetic acid occur "in rhomboidal, tabular crystals, probably triclinic. Crystals about 0.05 mm. thick show moderately strong pleochroism, from clear chrome yellow to red-orange."

***o*-Cresolbenzein (Carbinol Form).**—Purified *o*-cresolbenzein was dissolved by boiling in 5% sodium hydroxide solution. Ether was added to the solution, and the alkali neutralized by the addition of an ammonium chloride solution, so that as fast as the carbinol formed it went into solution in the ether. The ether solution was dried over anhydrous calcium chloride, and benzene was added. On allowing the solvents to evaporate in a desiccator under reduced pressure, the carbinol form of the benzein crystallized slowly in almost colorless cubes which turned orange on standing in a desiccator containing concd. sulfuric acid.

The carbinol was readily soluble in ether, and much less soluble in benzene and in carbon bisulfide.

A sample of the air-dried carbinol was heated for five hours at 80–90° in a drying tube, the vapors passing out through a calcium chloride tube which absorbed the water

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[4] We wish to acknowledge our indebtedness to Professor A. C. Gill of the Department of Mineralogy at Cornell University for crystallographic data in this paper.

liberated. The sample came to constant weight and the resulting product gave the melting point of the benzein (260–262°). The carbinol had lost one molecule of water, although the total loss in weight was 20.35%, the rest of the loss being due to benzene of crystallization.

Anal. Subs., 0.1312: total loss in wt., 0.0267 (20.35%); wt. of H_2O lost, 0.0065. Calcd. loss for one molecule of H_2O, 0.0062.

Dibromo-*o*-cresolbenzein (Quinoid Form).—When dibromo-*o*-cresolbenzein, in combination with hydrobromic acid, was dissolved in boiling toluene, hydrobromic acid was given off. From the cool solution, red crystals containing toluene of crystallization were obtained. They are "pleochroic, triclinic crystals, twinned parallel to a longitudinal face." When heated to constant weight at 107° they lost half a molecule of toluene of crystallization, became opaque, orange in color, and melted with decomposition at 238°.

Anal. Subs., 0.1670, 0.1902: AgBr, 0.1366, 0.1560. Calcd. for $C_{21}H_{16}Br_2O_2$: Br, 34.75. Found: 34.81, 34.91.

ACTION OF AMMONIA GAS.—On passing dry ammonia gas over dry dibromo-*o*-cresolbenzein, the original orange product became deep blue and absorbed somewhat more than a molecule of ammonia gas.

Anal. Subs., 0.1043: NH_3 absorbed, 0.0045. Calcd. for $C_{21}H_{16}Br_2O_2.NH_3$: NH_3, 3.57. Found: 4.14.

When placed in a desiccator containing concd. sulfuric acid, and allowed to come to constant weight, none of the ammonia was retained by the sample.

ACTION OF HYDROGEN CHLORIDE.—On passing dry hydrogen chloride over dry dibromo-*o*-cresolbenzein the original product became red, and finally developed a dark green surface color when it had absorbed two molecules of hydrogen chloride.

Anal. Subs., 0.1614: HCl absorbed, 0.0248. Calcd. for $C_{21}H_{16}Br_2O_2.2HCl$: HCl, 13.69. Found: 13.32.

When placed in a desiccator containing sodium hydroxide and concd. sulfuric acid, and allowed to come to constant weight, the sample lost the hydrogen chloride.

HYDROBROMIDE.—A cooled solution of *o*-cresolbenzein in glacial acetic acid was brominated by the addition of an excess of bromine dissolved in glacial acetic acid. Crystals with a green surface color separated. They melted at 230° and, after standing in a vacuum desiccator over calcium chloride, analyzed as the hydrobromide of dibromo-*o*-cresolbenzein.

Anal. Subs., 0.2725: AgBr, 0.2859. Calcd. for $C_{21}H_{16}Br_2O_2.HBr$: Br, 44.33. Found: 44.65.

Usually dibromo-*o*-cresolbenzein was obtained in combination with more than one molecule of hydrobromic acid, as bromine determinations showed. On very long standing in a desiccator or in the air the green surface color disappeared and the hydrobromic acid was lost.

The hydrobromide of dibromo-*o*-cresolbenzein forms "red, tabular, monoclinic crystals with extremely strong pleochroism, from orange-yellow to dark red."

Dibromo-*o*-cresolbenzein (Carbinol Form).—The orange crystals of dibromo-*o*-cresolbenzein became dark blue and remained undissolved when dropped into a 5% aqueous sodium hydroxide solution, forming the monosodium salt of dibromo-*o*-cresolbenzein. On diluting the solution with water the crystals dissolved, forming a blue-violet solution, which became practically colorless on standing, as the disodium salt of the carbinol formed. Acidification with carbonic acid or acetic acid produced a very light yellow precipitate. Almost colorless crystals of this carbinol were obtained, using the same method as that for preparing the carbinol form of the benzein, except that a mixture of ether and petroleum ether was used as the crystallizing solvent.

Anal. Subs., 0.1249: AgBr, 0.0976. Calcd. for $C_{21}H_{18}Br_2O_3$: Br, 33.44. Found: 33.26.

Reduction Product of *o*-Cresolbenzein, Di-*p*-dihydroxydimethyltriphenylmethane.—*o*-Cresolbenzein was dissolved in a large volume of glacial acetic acid. The solution was kept at 80–90° and stirred, while small portions of zinc dust were added from time to time until the red solution became colorless. The solution was filtered, water added until a slight turbidity appeared, and on standing, colorless crystals formed. After several crystallizations from a mixture of benzene and ligroin, a colorless product, m. p. 107–109°, was obtained.

"Clear, colorless, monoclinic rods or tablets" were obtained from dil. acetic acid. They were dried in a vacuum desiccator over phosphorus pentoxide, and dry hydrogen was then passed over them.

Anal. Subs., 0.1777, 0.1803; CO_2, 0.5377, 0.5460; H_2O, 0.1063, 0.1072. Calcd. for $C_{21}H_{20}O_2$: C, 82.85; H, 6.63. Found: C, 82.52, 82.59; H, 6.69, 6.65.

The reduction product dissolves without color in dilute alkaline solution. Addition of acid precipitates a gummy material which turns pink and then dissolves in alkali with the characteristic violet-red color of the benzein in alkali. The benzein remained unchanged in trying to prepare the reduction product from it according to Schroeter's method of boiling it in an aqueous solution of sulfurous acid. The melting point, 170°, which he gives for the reduction product, is the melting point of phenyl-*o*-hydroxytolyl ketone, for the true reduction product melts at 107–109°. This ketone, and not the reduction product as Schroeter states, can be recovered from the resinous material which remains after the purification of the benzein by means of sulfur dioxide.

ACTION OF BROMINE.—Bromination of the reduction product of *o*-cresolbenzein in glacial acetic acid solution served not only to brominate the product but also to oxidize it, resulting in the formation of the hydrobromide of dibromo-*o*-cresolbenzein. Crystallization of this product from boiling toluene produced dibromo-*o*-cresolbenzein which, after heating to constant weight, melted at 237°.

By brominating the reduction product Schroeter obtained yellowish-red needles; m. p., 130°.

Condensation of Benzaldehyde and *o*-Cresol.—The reduction product of *o*-cresolbenzein was also made by condensing benzaldehyde and *o*-cresol by means of zinc chloride. The crude material was converted into the acetate. Two crystallizations from methanol yielded colorless crystals with the melting point for the diacetate of the reduction product of *o*-cresolbenzein, 109°. A mixture of the two substances melted at the same temperature.

Phenyl-*o*-hydroxytolyl Ketone.—A small amount of crystalline product was obtained from the resinous material left in the first method of purifying the benzein by boiling the residues with water, filtering, and cooling the filtrate. Larger amounts were obtained from the filtrate of the steam distillation in the second method of preparing the benzein, and from the ether residues. The ketone was also obtained by decomposing the benzein in an aqueous potassium hydroxide solution, and by treating an alkaline solution of the benzein with hydroxylamine. It was purified by conversion into the acetate, followed by saponification. The ketone crystallized from dil. ethanol in "thin, colorless, rectangular or octagonal, rhombic plates"; m. p., 170–171°. This melting point agrees with that given by Bartolotti[5] for a compound of the same structure.

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[5] Bartolotti, *Gazz. chim. ital.*, 30 [II], 231 (1900).

TABLE I

PROPERTIES AND ANALYSES OF DERIVATIVES OF *o*-CRESOLBENZEIN AND RELATED COMPOUNDS

Derivatives of	Formula	Form	Crystallizing solvent	M. p., °C.	Anal. Calcd., %		Anal. Found, %			
o-Cresolbenzein (quinoid form)	$C_{21}H_{18}O_2$									
1. Hydrochloride	$C_{21}H_{18}O_2.HCl$	Red powder[a]			HCl 10.77		10.65	10.47		
		Red, crystalline powder[b]	Glacial acetic acid	222–223	HCl 10.77		10.79	10.66		
2. Sulfate[c]	$C_{21}H_{18}O_2.H_2SO_4$	Dark red, triclinic plates	Glacial acetic acid	231–232	S 8.01		8.22	8.20		
					C	H	C		H	
3. Dinitro-*o*-cresolbenzein[d]	$C_{21}H_{16}O_2(NO_2)_2$	Yellowish needles or elongated tabular plates	Benzene, ether and ligroin, ethanol	127	64.26	4.11	64.44	64.32	4.27	4.02
o-Cresolbenzein (carbinol form)	$C_{21}H_{20}O_3$									
1. Diacetate[e]	$C_{21}H_{18}O_3(COCH_3)_2$	Yellowish powder	Benzene and ligroin, ethanol, ethyl acetate	104–105	74.22	5.99	74.31	74.04	6.14	6.05
2. Dibenzoate[e]	$C_{21}H_{18}O_3(COC_6H_5)_2$	Colorless, triclinic needles	Ether	128–129						
			Ethanol	139–140						
Dihydroxydimethyltriphenylmethane	$C_{21}H_{20}O_2$		Benzene	144 (final)	79.51	5.34	79.78	79.38	5.74	5.56
1. Diacetate[f]	$C_{21}H_{18}O_2(COCH_3)_2$	Colorless, triclinic prisms	Methanol	109–110	77.28	6.23	77.55	77.22	6.33	6.18
2. Dibenzoate	$C_{21}H_{18}O_2(COC_6H_5)_2$	Colorless, triclinic needles	Ether	145 (final)	81.99	5.51	82.40	82.16	5.54	5.56
3. Dimethyl ether[g]	$C_{21}H_{18}(OCH_3)_2$	Colorless plates	Methanol	100	83.08	7.27	83.31	83.25	6.99	7.17
					OCH_3	18.68	OCH_3	18.83		
Phenyl-*o*-hydroxytolyl ketone	$C_{14}H_{12}O_2$									
1. Acetate	$C_{14}H_{11}O_2(COCH_3)$	Colorless, rhombic needles	Methanol, ethanol	66.5	75.56	5.55	75.24	75.56	5.45	5.84
2. Benzoate[h]	$C_{14}H_{11}O_2(COC_6H_5)$	Colorless, rhombic blades	Ethanol	96	79.72	5.10	80.05	79.78	5.10	5.02

[a] Benzotrichloride and *o*-cresol (1 mole : 2.1 moles) heated at 80° until evolution of hydrogen chloride ceased. Unchanged benzotrichloride and *o*-cresol, and phenyl-*o*-hydroxytolyl ketone removed by extraction with ether.

[b] Hydrogen chloride passed into a solution of the benzein in glacial acetic acid.

[c] Solution of *o*-cresolbenzein in glacial acetic acid heated with concd. sulfuric acid.

[d] Fuming nitric acid added to a cooled solution of the benzein in glacial acetic acid. Crystals separated on addition of water. Dissolve readily in dil. alkali with orange color, and are reprecipitated with hydrochloric acid.

[e] Prepared directly from quinoid form of *o*-cresolbenzein.

[f] Prepared directly by acetylating the reduction product, and by reducing *o*-cresolbenzein in acetic anhydride.

[g] *o*-Cresolbenzein boiled in methanol containing hydrochloric acid. First crystallizations from glacial acetic acid.

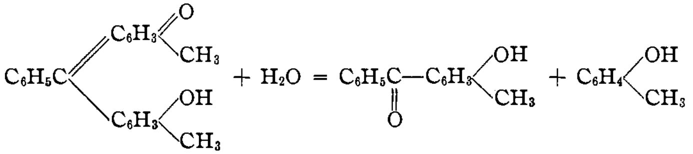
[h] Prepared from the ketone, and by condensing benzoyl chloride with *o*-cresol using zinc dust.

Anal. Subs., 0.1972, 0.1540: CO_2, 0.5733, 0.4485; H_2O, 0.1017, 0.0793. Calcd. for $C_{14}H_{12}O_2$: C, 79.21; H, 5.70. Found: C, 79.29, 79.43; H, 5.77, 5.76.

The formation of the ketone in making the benzein may be explained by the following reactions: $C_6H_5C{\equiv}Cl_3 + C_6H_4(OH)CH_3 = C_6H_5C({=}Cl_2)C_6H_3(OH)CH_3 + HCl$; $C_6H_5C({=}Cl_2)C_6H_3(OH)CH_3 + H_2O = C_6H_5C({=}O)C_6H_3(OH)CH_3 + 2HCl$.

Action of Potassium Hydroxide on *o*-Cresolbenzein.—When dissolved in 5% potassium hydroxide solution, *o*-cresolbenzein was decomposed by heating in a steam-bath for several hours while air was passed into the solution. The product was crystallized from hot water, dissolved in dilute alkali and precipitated with acid, and finally crystallized from dil. alcohol, giving the melting point of phenyl-*o*-hydroxytolyl ketone, 170°. The material yielded an acetate which, after crystallization from dil. alcohol, gave the melting point of the acetate of phenyl-*o*-hydroxytolyl ketone, 66.5°.

The benzein decomposes as follows.



Summary

1. This investigation has shown that the *colored*, stable form of *o*-cresolbenzein is the *quinoid* form. The intermediate product in its formation from *o*-cresol and benzotrichloride is the *colored* hydrochloride of *o*-cresolbenzein. The *colorless*, *carbinol* form of *o*-cresolbenzein has been made from the colored form.
2. Dibromo-*o*-cresolbenzein has been prepared in the quinoid and carbinol forms.
3. The action of certain reagents on *o*-cresolbenzein has been described.
4. The preparation and properties have been indicated of derivatives of both forms of *o*-cresolbenzein; of the reduction product, dihydroxydimethyltriphenylmethane; and of phenyl-*o*-hydroxytolyl ketone, a by-product in preparing *o*-cresolbenzein.

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