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The Oxidation of Salicylates in Alkaline Solutions*.[†]

By E. A. Brecht[‡] and C. H. Rogers**

Salicylate solutions, which are colorless when freshly prepared, are rapidly discolored by the formation of a brown oxidation product resulting from the activity of atmospheric oxygen. Numerous past studies of this reaction have been concerned only with the rate of discoloration and the influencing factors (1-13). Reviews of this literature are available in references (6), (8) and (13). It was the purpose of this research to isolate and study the structure of the brown oxidation product obtained from salicylates.

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[†] Abstracted from the dissertation submitted by Dr. Brecht to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[‡] Instructor, School of Pharmacy, University of North Carolina.

** Dean of the College of Pharmacy, University of Minnesota.

A few oxidation reactions of salicylates have been characterized, but none of the products was similar to that from aged, brown salicylate solutions (14-17). The sodium salt of gentisic acid (2,5-dihydroxybenzoic acid) was obtained by the oxidation of sodium salicylate by magnesium persulfate in alkaline solution (14). Gentisic acid was obtained as a colorless compound. Solutions of gentisic acid rapidly turned brown when exposed to air (15). Gentisic acid was converted by manganese dioxide in sulfuric acid to an unnamed compound of the formula $C_{14}H_6O_6$. This compound was obtained as an ochre-yellow crystalline powder from *o*-cresol. It sublimed at 230° to sulfur-yellow needles, and melted above 360° (16). This compound is interesting because it is produced from an oxidation product of a salicylate, but it is a different compound than the brown substance obtained from alkaline solutions by atmospheric oxidation. Gentisic acid may be an intermediate product in all oxidations of salicylates.

For the purpose of reference, until a chemical name can be applied, it is proposed to refer to the brown oxidation product from salicylates, a trisodium salt of an organic radicle, as "sodium salicylate-brown." The acid form will be termed "acid salicylate-brown."

EXPERIMENTAL

The oxidation of sodium salicylate and other related compounds was studied in three types of media: (a) slightly acidic, (b) slightly alkaline, containing 2.5 per cent each of sodium bicarbonate and sodium carbonate and (c) strongly alkaline, containing 25 per cent of sodium hydroxide. Two oxidizing agents were used: air and hydrogen peroxide.

Slightly Acidic.—Atmospheric oxygen: Solutions of sodium salicylate, saturated with salicylic acid, showed no discoloration upon aging.

Hydrogen peroxide: One gram of salicylic acid, or a similar compound, was mixed with 1 cc. of water and 5 cc. of 30 per cent hydrogen peroxide solution in a capacious beaker. No reaction took place until 5 drops of ferric chloride test solution were dropped on different areas of the mixture. The reaction then took place immediately with the evolution of sufficient heat to cause boiling of the water. The reaction was complete in about fifteen seconds. The amount of brown product was deter-

mined by a colorimetric assay, to be discussed later. The following compounds were tested:

Compound	Yield of Brown Oxidation Product, Gm.	Speed of Reaction
Phenol	0.36	Very rapid
Benzoic acid	0.16	Slow
Salicylic acid	0.28	Very rapid
Catechol	0.43	Very rapid
Resorcin	0.41	Very rapid
Hydroquinone	0.44	Very rapid
Pyrogallol	0.08	Very rapid
Citric acid (control)	0.00	Heat on a steam bath required to start reaction

There were no tests available for proving that the brown products were acid salicylate-brown, but their color and solubilities were identical. Sodium salicylate reacted in the same way as salicylic acid. No reaction took place until the ferric chloride was added. When the reaction was retarded by dilution of the reaction mixture the yield of the brown product was greatly decreased due to increased oxidation of it to colorless compounds.

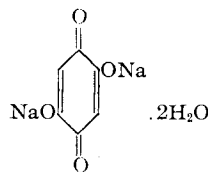
Strongly Alkaline.—Atmospheric oxygen: Neither sodium salicylate nor sodium salicylate-brown showed any change when dissolved in a 25 per cent sodium hydroxide solution. Atmospheric oxygen was not active in this medium.

Hydrogen peroxide: When a 30 per cent solution of hydrogen peroxide was added to a solution of sodium salicylate containing 25 per cent of sodium hydroxide, crystallization immediately took place. The same crystallization occurred without the presence of sodium salicylate. A microscopic examination showed the presence of well-defined, colorless needle crystals. Thirteen and five-tenths cubic centimeters of a 30 per cent solution of hydrogen peroxide (density 1.11) were added to a cooled solution of 62.5 Gm. of sodium hydroxide in 175 cc. of water. The crystals were collected on a filter, mixed twice with portions of alcohol and drained well on a filter after each washing. The product was then dried in a vacuum desiccator over sulfuric acid for three hours. A yield of 11.8 Gm. was obtained, theoretical 29.38 Gm. This yield indicated that the product was soluble to the extent of 8 Gm. in 100 Gm. of the mixture. The product was assayed by titration, with tenth-normal sodium thio-sulfate solution, of the iodine liberated from potassium iodide in acid solution. The product contained 33.5 per cent of Na_2O_2 , corresponding to a crystal with 8.1 mols of water for each mol of sodium peroxide.

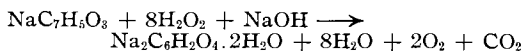
Other methods for the preparation of sodium peroxide octahydrate are given in references 18 to 26. Sodium peroxide octahydrate has been proposed as a reagent for the identification of polyphenols by the color reactions obtained in alcoholic solutions (27). Magidson, *et al.* (28) used sodium peroxide to oxidize phenol dissolved in sulfuric acid. After the separation of resinous

substances, 25 per cent yields of catechol and hydroquinone were obtained.

Sodium salicylate dissolved in a 25 per cent solution of sodium hydroxide was slowly oxidized by hydrogen peroxide to a dihydrated form of 2,5-disodoxyquinone.



This product was insoluble in the mixture, crystallizing as orange needle crystals. For a reaction mixture composed of 125 Gm. of sodium salicylate, 625 Gm. of sodium hydroxide and 1875 cc. of water it was found that not more than 15 cc. of 30 per cent hydrogen peroxide solution could be added at one time if the formation of sodium oxalate was to be prevented. After such a portion of hydrogen peroxide had been reduced, in about three days, another portion could be added. In this way as much as eighteen portions of hydrogen peroxide were added to one reaction mixture. The product was collected on a suction filter, washed twice with 25 per cent sodium hydroxide solution and then washed five or six times with alcohol.



Amount of 30 Per Cent Hydrogen Peroxide, Density 1.11	Actual Yield of Hydrated 2,5-Disodoxyquinone, Gm.	Theoretical Yield, Gm.	Per Cent Yield
Mixture 1			
45 cc.	6.4	12.11	52.8
45	9.7	12.11	80.0
45	9.1	12.11	75.2
Mixture 2			
45 cc.	8.9	12.11	73.4
75	14.0	20.19	69.4
45	11.7	12.11	96.6
45	8.4	12.11	69.3
60	10.2	16.15	63.2

From similar mixtures 2,5-disodoxyquinone was obtained from the sodium salts of *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, phenol, catechol resorcin and hydroquinone. Sodium benzoate was insoluble in a 25 per cent solution of sodium hydroxide and showed no reaction with hydrogen peroxide. These results have importance in showing a hitherto undemonstrated product from the oxidation of phenolic compounds.

The orange crystals of 2,5-disodoxyquinone dihydrate readily lost the water of crystallization when heated at 105° to yield a dull red powder. The water of crystallization was lost almost immediately when heated above 80° suspended in a 25 per cent sodium hydroxide solution; changing

crystalline form, to longer, thinner crystals. 2,5-Disodoxyquinone was readily soluble in water giving a red solution which turned yellow when acidified. Crystals of 2,5-dihydroxyquinone were formed in the acidified solution. Disodoxyquinone was insoluble in sodium hydroxide solutions of concentrations greater than ten per cent and in organic solvents.

The identity of 2,5-disodoxyquinone was proved through assay for sodium content and conversion to 2,5-dihydroxyquinone, m. p. 222° (corr.) with decomposition. Ultimate analysis of the dihydroxyquinone, best purified by vacuum sublimation, gave the following results:

	Carbon	Hydrogen
Actual	51.55%	2.76%
	51.60	3.17
	51.58	2.96
Theoretical, C ₆ H ₄ O ₄	51.4	2.87

The aqueous solution or suspension of 2,5-dihydroxyquinone darkened slowly at room temperature to give a dark brown amorphous precipitate. This reaction was accelerated by heat. This reaction was important because it gave a brown product very similar to acid salicylate-brown. (References on 2,5-dihydroxyquinone, its salts and derivatives: 29-47.)

Sodium oxalate was obtained in satisfactory yields from the same reaction mixture used for the production of 2,5-disodoxyquinone by maintaining the reaction near 100° C. At this temperature none of the quinone was found in the product of sodium oxalate, which crystallized from the reaction mixture. At temperatures ranging between room temperature and 100°, a mixed product was obtained. When a product of sodium oxalate was desired it was found most effective to add the hydrogen peroxide very slowly from a dropper funnel dipping below the surface of the hot reaction mixture. Yields of sodium oxalate ranging from 44.3 to 92.4 per cent of the theoretical were obtained. If the hydrogen peroxide was added too rapidly no sodium oxalate was obtained as the oxidation was carried to ultimate completion, the production of sodium carbonate.

Sodium salicylate-brown was stable in 25 per cent sodium hydroxide solution, even when boiled. The decolorization noted by Grill (8) must have been due to oxidation, as the addition of hydrogen peroxide quickly decolorized the solution.

concentration of 2.5 per cent each of sodium bicarbonate and sodium carbonate has been shown to allow maximum oxidation by air.

Previous investigators did not realize that the brown product from salicylates was also oxidized by air in mildly alkaline solutions. Three solutions of sodium salicylate-brown were prepared and the rate of color decrease was measured by means of a colorimeter using a standard brown solution made from coal-tar dyes.

At the end of the three-day period one drop of 30 per cent hydrogen peroxide solution was added to solution III. The amount of color remaining was decolorized to the extent of 88.8 per cent when the solution was assayed one day later, although the access of air had not been increased.

Mildly alkaline resorcin solutions were discolored by atmospheric oxygen as readily as sodium salicylate.

Hydrogen peroxide: The addition of 10 cc. of 30 per cent hydrogen peroxide solution to 150 cc. of a solution containing 5 per cent of sodium salicylate and 2.5 per cent each of sodium bicarbonate and sodium carbonate produced a delayed brown discoloration. The color darkened slowly for three days, and then finally, gave a very good color formation. The addition of a second 10-cc. portion of hydrogen peroxide completely decolorized the solution, after which discoloration again took place.

Acid salicylate-brown was suspended in water and treated with small portions of hydrogen peroxide at room temperature. After six days the precipitate was completely oxidized, decolorized. A positive test for the oxalate ion was obtained with calcium sulfate test solution. The identity was confirmed by the insolubility of the crystalline precipitate in acetic acid, its solubility in hydrochloric acid and its reduction of potassium permanganate.

Acid Salicylate-Brown and Sodium Salicylate-Brown.—Three methods were used for the production of a brown oxidation product from salicylates.

Atmospheric oxidation in mildly alkaline solution: Seven liters of a solution containing 5 per cent of sodium salicylate and 2.5 per cent each of sodium bicarbonate and sodium carbonate were aerated for four weeks. A maximum color was obtained in two weeks, but the aeration was continued longer for the possible precipitation of an excess of the sodium salicylate-brown. However, such was not the case, probably because an equilibrium was ob-

Solution number:
Weight of acid salicylate-brown in 100 cc. of solution, with 2 Gm. Na ₂ CO ₃ , H ₂ O
Volume of solution
Volume of air in container
Total loss of color in 98 min.
Total loss of color in 3 days

I	II	III
0.0204 Gm.	0.0102 Gm.	0.0108 Gm.
50 cc.	100 cc.	100 cc.
75 cc.	150 cc.	5 cc.
...	23.1%	...
75.6%	77.7%	29.3%

Mildly Alkaline.—Atmospheric oxygen: The oxidation of salicylates by air in these media has been discussed by previous writers (1-13). The

tained in which the sodium salicylate-brown was converted to sodium oxalate as rapidly as it was formed. Small amounts of the above reaction mix-

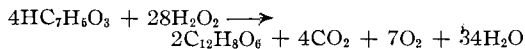
ture have often yielded precipitates of sodium salicylate-brown when allowed to age in stoppered containers. For this reason the seven-liter mixture was allowed to stand for an additional month. No precipitate was obtained. The sodium salicylate-brown was obtained from the solution by two methods.

A 1400-cc. portion of the solution was rendered acid by an excess of hydrochloric acid, sufficient to decompose all of the sodium salicylate. The precipitated salicylic acid and acid salicylate-brown were collected on a filter and washed with alcohol. The alcohol dissolved most of the salicylic acid and only a little of the acid salicylate-brown. The acid salicylate-brown was then purified by washing with hot 5 per cent hydrochloric acid. The hydrochloric acid prevented the acid salicylate-brown from becoming colloiddally suspended. A yield of 2.8 Gm. of acid salicylate-brown was obtained from the 1400 cc. of brown salicylate solution.

A 5200-cc. portion of the oxidized salicylate solution was treated with an equal volume of alcohol. The mixture separated into two layers. The bottom layer, predominately aqueous, contained nearly all of the brown product. The upper layer was decanted and discarded. Some water was added to the bottom layer, and the alcoholic precipitation was repeated. This procedure was repeated many times. The bottom layer was always of less volume than the upper, measuring from one-fourth to one-twentieth of the total volume. It was found important not to add the aqueous solution to the alcohol as a permanent suspension usually resulted. It was also found important to add all of the alcohol in one portion for the same reason. For the final purification it was precipitated in the form of acid salicylate-brown by the addition of an excess of hydrochloric acid. The precipitate was collected by centrifuging for ten minutes. The supernatant liquid was decanted and discarded. The precipitate was then freed of impurities by repeatedly washing with 5 per cent hydrochloric acid and separation in a centrifuge. By this method of collection 16.0 Gm. of acid salicylate-brown was obtained.

Rapid oxidation of salicylic acid with hydrogen peroxide: 10 Gm. of salicylic acid were rubbed to a smooth paste with 10 cc. of water in a one-liter beaker. Then 21.25 cc. of a 30 per cent hydrogen peroxide solution were added. No reaction took place until ferric chloride test solution was added. Five drops of the test solution were distributed on different areas of the mixture. The reaction took place vigorously causing the temperature to rise from 25° to 95° within a half minute. There was a rapid evolution of oxygen and steam. The reaction was complete in three minutes. Water was added to the mixture, and the bulk of the excess of salicylic acid was removed by extraction with a mixture of equal volumes of ether and petroleum ether. Ether alone had a tendency to extract some of the acid salicylate-brown. The purifica-

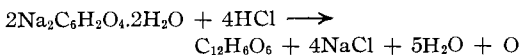
tion was completed by washing with 5 per cent hydrochloric acid by the centrifuge method.



The following yields were obtained:

Hydrogen Peroxide, 30 Per Cent, Density 1.11	Yield		
	Actual	Theoretical	Per Cent
21.25 cc.	1.3 Gm.	3.69 Gm.	35.3
42.5	2.9	7.37	39.4

Conversion of 2,5-dihydroxyquinone: 20 Gm. of 2,5-disodoxyquinone were dissolved in 250 cc. of boiling water. The solution was filtered. The addition of 20 cc. of concentrated hydrochloric acid produced immediate crystallization of 2,5-dihydroxyquinone. This mixture was heated on a steam bath for 90 minutes. The color rapidly changed from yellow to dark brown, and acid salicylate-brown was precipitated. The brown precipitate was collected on a filter, and washed with 5 per cent hydrochloric acid.



A yield of 5.3 Gm. was obtained which was 47.3 per cent of the theoretical.

Acid salicylate-brown was the final product of the above methods of preparation because it could be purified more readily than its sodium salt. When a pure sodium salicylate-brown was required it was prepared from acid salicylate-brown by the following method. Three grams of acid salicylate-brown were dissolved in 350 cc. of alcohol by the application of heat. The solution was filtered, and a slight excess of concentrated sodium hydroxide solution was added. Sodium salicylate-brown was immediately precipitated. Alcohol was used to wash the product free of sodium hydroxide. A yield of 2.95 Gm. was obtained, 77.7 per cent of the theoretical.

Physical and chemical properties: Both acid salicylate-brown and sodium salicylate-brown are dark brown amorphous solids. Acid salicylate-brown was soluble in alcohol, absolute alcohol and melted urethane and was insoluble in water, other organic solvents and melted phenol. Sodium salicylate-brown was soluble only in water. Acid salicylate-brown did not melt, even when heated to 400°. Acid salicylate-brown was subjected to vacuum sublimation for four hours at a temperature of 400° and a partial pressure of less than 2 mm. of mercury. This treatment produced about 10 mg. of a shiny black sublimate. Microscopic examination showed that the sublimate was amorphous. The sublimate was chemically changed because it was no longer soluble in sodium hydroxide solution. Acid salicylate-brown gave negative tests for nitrogen, halogens, sulfur and metals.

A colorimetric method was devised for the quantitative determination of salicylate-brown compounds. A standard brown solution was defined as

containing 0.003 Gm. "S. F. Yellowish Light Green, 435," 0.035 Gm. "85 Orange I" and 0.10 Gm. sodium benzoate. (The dyes were the products of F. Kohnstamm and Co., Inc., Chicago.) The same color intensity was given by 0.0133 Gm. of sodium salicylate-brown or 0.0105 Gm. of acid salicylate-brown in 100 cc. It was necessary to add 2 Gm. of monohydrated sodium carbonate to 100 cc. of the salicylate-brown solution to assure complete solution. This colorimetric assay was not completely reliable as the color of the salicylate-brown solutions was gradually reduced by atmospheric oxidation of the brown product.

The molecular weight of acid salicylate-brown was determined by the depression of the freezing point of urethane (48). An accurate determination was prevented by the slow solution of the acid salicylate-brown. Two determinations gave molecular weights of 206 and 260.

Acid salicylate-brown was ethylated in solution in anhydrous methyl alcohol with diazomethane (49). Two portions of the methylated acid salicylate-brown were assayed for methoxy content by the method of Viebock and Schwappach (50) as modified by Clark (51). The methylated product contained 31.33 per cent of methoxy, which corresponds to an equivalent weight of 85. Identical results were obtained with samples of acid salicylate-brown prepared by the rapid oxidation of salicylic acid with hydrogen peroxide and by conversion of 2,5-dihydroxyquinone.

The sodium content of sodium salicylate-brown was determined by the gravimetric sulfate method. Sodium salicylate-brown contained 22.5 per cent of sodium, corresponding to an equivalent weight for acid salicylate-brown of 80.

Samples of purified acid salicylate-brown from all three methods of preparation were analyzed for carbon and hydrogen by a semi-micro method:

Source of Acid Salicylate-Brown:	Carbon	Hydrogen	Oxygen
Atmospheric oxidation of salicylates	59.4%	3.24%	37.36%
Rapid oxidation of salicylic acid by hydrogen peroxide	56.4 ^a 56.6 ^a 56.6 ^a	3.03 3.42 3.06	— — —
Conversion of 2,5-dihydroxyquinone	56.5 56.5 ^a	3.17 2.44 2.29	40.33 — —
	56.5 58.4 58.4	2.36 2.42 2.58	41.14 — —
	58.4	2.50	39.10
Theoret., C ₁₂ H ₆ O ₆ , 246	58.5	2.44	39.06
C ₁₂ H ₈ O ₆ , 248	58.1	3.22	38.68

^a Slight colorless ash remained in the combustion boat. It was a chloride, probably sodium chloride which had not been completely removed from the product.

The reduction of sodium salicylate-brown was attempted with sodium amalgam in aqueous solution. Reduction was also tried with stannous

chloride in concentrated hydrochloric acid. In neither case was there a change in the product.

No acetylated product could be obtained sufficiently pure for a quantitative determination.

The formula C₁₂H₈O₆ is isomeric with 3,5,3',5'-tetrahydroxy-diphenylquinone-4,4'. This compound was first prepared by Liebermann and Burg (52) and its chemistry was studied by Liebermann and Herrmuth (53). This compound produces a violet-colored aqueous solution. This compound differs from acid salicylate-brown in producing a tetramethoxy derivative and in being readily reduced by stannous chloride.

SUMMARY

The brown product formed in the discoloration of salicylate solutions is an intermediate product because it is further oxidized to colorless compounds: oxalates and carbonates.

Three methods are given for the preparation of this compound.

The brown product has the formula C₁₂H₈O₆ and contains three hydroxyl groups which are easily methylated and form metallic salts with alkalis. When made from 2,5-dihydroxyquinone a dehydro compound results having the formula C₁₂H₆O₆ and the same chemical and physical properties.

A new method is given for the preparation of 2,5-disodoxyquinone and 2,5-dihydroxyquinone. The sodium compound is a general intermediate product in the oxidation of phenolic compounds under certain conditions.

A rapid method is given for the preparation of pure sodium peroxide octahydrate.

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A Study of the Assay of Strychnine in Tincture of Nux Vomica*

By Gertrude M. Horn,† K. L. Kaufman‡ and
S. G. Mittelstaedt**

Various assay methods for the determination of strychnine have resulted from investigations conducted with a view to improving the official processes. Such factors as the presence of fixed oil, resins and coloring matter tend to cause considerable variation in results when assaying the drug. Controversy has centered around the nitric acid method for destroying brucine. The elimination of emulsions during the extraction of the alkaloids is worthy of consideration. It has been suggested that certain agents might be used which would quanti-

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† Teaching Fellow, State College of Washington, School of Pharmacy, 1938-1939.

‡ Assistant Professor of Pharmacy, State College of Washington.

** Teaching Fellow, State College of Washington, School of Pharmacy, 1937-1938.