

SUGGESTED REASONS FOR COLOR CHANGES IN PRESCRIPTIONS CONTAINING SALICYLATES.

BY FREDERICK GRILL.*

INTRODUCTION.

An aqueous solution of sodium salicylate and sodium bicarbonate containing suspended magnesium hydroxide is given as an "incompatibility" in a course in prescription compounding, because this preparation is white in color when first prepared and gradually darkens in color to almost black after standing a few days in a cork-stoppered glass container. The solution of salicylate and bicarbonate containing the magnesium hydroxide suspended is not agitated while standing. The reasons for color change in the above preparation and in preparations similar to it are not explained satisfactorily in the literature consulted. The object of this paper is to offer some suggestions for these color changes under the conditions which have been described above.

Pharmaceutical literature gives little or no information concerning the color change which has just been described, and is equally non-informative concerning color changes similar to it.

Ruddiman¹ gives a prescription that contains salicylic acid and sodium bicarbonate, each one ounce, and water a sufficient quantity to make six fluidounces as an "incompatibility." He remarks that carbon dioxide is evolved when the ingredients are mixed and the resulting solution is alkaline in reaction. On standing for two or three days this preparation changes color from light brown to dark brown. Ruddiman explains this color change as being due, probably, to the aqueous alkaline solution of a salicylate absorbing air, causing the oxidation of the salicylate. He does not indicate what compound or compounds are formed that give color to the solution and how the reaction (oxidation) proceeds.

Krantz² offers the suggestion that color changes which occur with salicylates in the presence of alkali bicarbonates are due to the absorption of atmospheric oxygen. He does not attempt to explain how the reaction between the salicylates and atmospheric oxygen proceeds in order to produce color.

The United States Dispensatory³ reports the following colored compounds of iron and salicylic acid: "ferric disalicylate, black; ferric ferri-salicylate, blackish; basic ferric ferri-salicylate, rust-colored; and ferrous ferro-salicylate, yellow," but does not show which of these have been isolated in a pure state and found to be colored. Hence, it is not very definite and correspondingly unreliable, especially, as it does not seem to take into consideration the hydrolysis of salts of weak bases and weak acids.

To show more definitely under what conditions the color change noted in preceding paragraphs takes place and also to suggest further reasons for the development of color in the preparations given, the following experimental work was carried out.

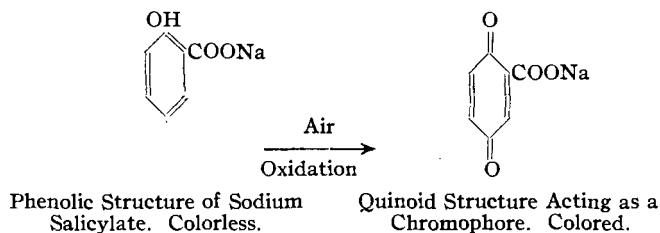
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¹ Ruddiman, "Incompatibilities in Prescriptions," 4th Edition, pages 127 and 187 (1917).

² John C. Krantz, Jr., "Pharmaceutical Chemistry," page 105 (1928).

³ "United States Dispensatory," 21st Edition, page 53 (1926).

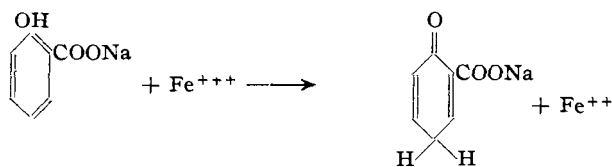
The solution of sodium salicylate formed by the above reaction was alkaline to litmus. Due to the evolution of carbon dioxide and diffusion of air into the container the atmosphere above the solution was probably a mixture of carbon dioxide and air. The color change noted in Table I may be accounted for by the oxidation of the phenolic structure of sodium salicylate by atmospheric oxygen producing a rearrangement to the quinoid structure, in the presence of alkali.



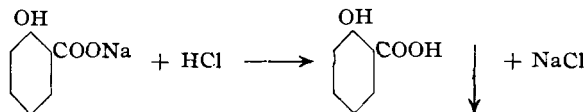
This reaction may be hastened by the action of light. Equal volumes of the colored salicylate solution and fifty per cent sodium hydroxide in water gradually produces a colorless solution. This suggests the reaction of phenolphthalein with concentrated sodium hydroxide in which the quinoid structure of the colored compound of phenolphthalein is changed to the benzoid structure. The reaction of the sodium hydroxide on the colored salicylate probably breaks the parallel arrangement of the quinoid structure forming a colorless compound. This strongly suggests the phenolic structure of the salicylate.

The color change in Nos. 3 and 4 may be explained in the same manner as the color change in No. 2.

Preparation No. 5 contained ferric chloride and the color change can be explained by the oxidation of the phenolic structure of sodium salicylate to a quinoid structure by ferric iron in the presence of light and atmospheric oxygen.



In preparation No. 6 salicylic acid was precipitated as a white crystalline precipitate in an excess of hydrogen ion as follows:

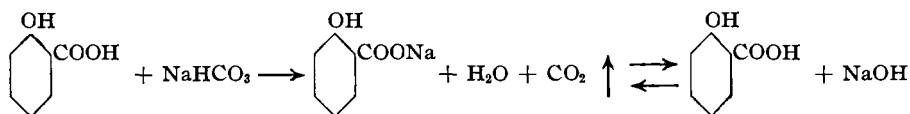


The color change observed here is probably again due to the oxidation of the phenolic structure of salicylic acid to a quinoid structure by ferric iron. The purple color of the solution was dispelled by concentrated sodium hydroxide solution indicating that the parallel arrangement of the quinoid structure (chromophore) of the salicylate is changed to the benzoid structure (colorless).

Preparation No. 7, alkaline to litmus, contained ferric iron. The color change here may be explained in the same way that the color change in No. 6 has been explained.

From Table I it is seen that the solutions containing the salicylate changed color. The solution (No. 1) of sodium bicarbonate containing suspended magnesium hydroxide did not change in color. It reasonably follows that the salicylate is the compound that is responsible, in part, for the color changes in the above preparations. In general, the color production in the six preparations can be explained by the oxidation of the phenolic structure of the salicylate to the quinoid structure by atmospheric oxygen, impurities of iron and light.

In order to show that iron is not alone responsible for any color change with a salicylate a qualitative solution of salicylic acid and sodium bicarbonate was made. This solution was alkaline to litmus because of hydrolysis.



Hydrogen sulphide was passed through the liquid under atmospheric pressure for fifteen minutes. The solution was filtered, the filtrate boiled to free of hydrogen sulphide as shown by lead acetate and transferred to a glass-stoppered bottle allowing only one to two cc. of air above the surface of the liquid. The solution was colorless when first prepared and turned in color to dark brown after standing for five days under varying daylight conditions. No precipitate was formed. This experiment indicates other agents besides iron effect color change with the salicylate, because ferric iron must be present in less quantities than the solubility product of ferrous sulphide, 3.7×10^{-19} .¹

To show the effect of daylight and atmospheric oxygen on preparations containing salicylates in alkaline solution four solutions were made, each containing the following amounts:

Salicylic acid	10 Gm.
Sodium bicarbonate	10 Gm.
Water	200 cc.

The compounds were mixed separately with a portion of the water and placed into a bottle (similar to those used for solutions of magnesium citrate) and capped after the reaction between the salicylic acid and sodium bicarbonate had subsided to some extent. This would allow most of the air to be displaced by the carbon dioxide in the bottle above the surface of the liquid. The solutions were alkaline to litmus for reasons previously given. This did not insure a complete elimination of air because there was no attempt to free the solution of dissolved air and there remained a small amount of air in the neck of the bottle that had not been displaced by the evolved carbon dioxide. From the results that are shown later this amount of air did not materially interfere with the purpose of the experiment. Two of the solutions made in this manner were protected from daylight by wrapping in three thicknesses of photographic black paper and one thickness of ordinary wrapping paper and stored in very diffuse daylight. The other two solutions were subjected

¹ Handbook of Chemistry and Physics: 16th Edition, page 581 (1931).

to varying daylight conditions. The four preparations were kept in this manner for ninety days. At the end of this time the solutions that had been protected from daylight were unwrapped and color changes compared with freshly prepared solutions made in the manner described above. The four bottles were unstoppered and exposed to daylight and air for a period of another thirty days. The results are summarized in Table II.

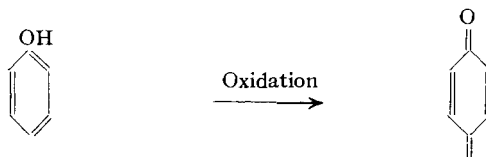
TABLE II.

No.	Ferric Iron Added.	Whether or Not Exposed to Light.	Color Change after 90 Days.	Color Change after 120 Days. Exposed to Light and Air for 30 Days.
1	0.5 cc. <i>Nl</i> FeCl ₃	+	Colorless to brown	Dark brown
2	No iron	+	Colorless to dark brown	Black
3	0.5 cc. <i>Nl</i> FeCl ₃	-	Colorless to very light brown	Dark brown
4	No iron	-	No color change	Black


Preparations Nos. 1 and 2 as compared to preparations Nos. 3 and 4 would indicate light affects positively the speed of the reaction producing color. Comparing preparations Nos. 3 and 4 the results would indicate ferric iron in the absence of light and a minimum concentration of air affects positively the speed of reaction producing color. The presence of air is shown in the last column of Table II. When the bottles containing the salicylate solutions were opened to the air, preparations Nos. 1 and 2 deepened in color more rapidly than when not exposed to air. Preparations Nos. 3 and 4 show the effect of light and air. In both the latter solutions the color changed more rapidly after exposure to light and air. The constriction of the neck of the bottle would allow for a minimum concentration of air over the surface of the liquid and it might have been better to transfer the solutions to beakers.

CONCLUSIONS.

(1) The color change in each of the preparations of Tables I and II can be explained by the oxidation of the phenolic structure of the salicylate to a quinoid structure.



The rate of oxidation is affected positively by (1) light, (2) air and (3) ferric iron when the salicylate is in alkaline solution.

(2) Porter¹ states that the quinoid structure of the ring  acts as a chromophore.

(3) Krantz² explains the color change of phenol to pink and red somewhat as follows: Phenol is oxidized by air (this oxidation being influenced by heat and light) to quinol, quinone and catechol and the color is probably given by condensa-

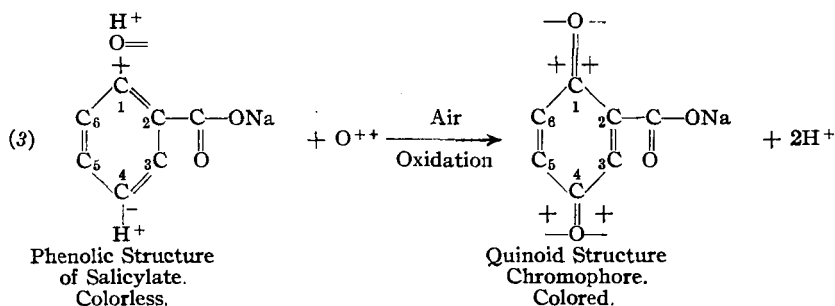
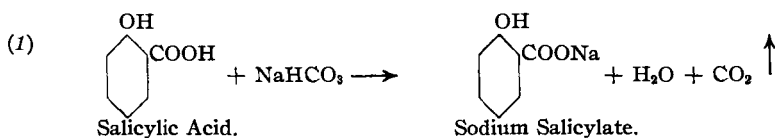
¹ C. W. Porter, "The Carbon Compounds," 2nd revised Edition, page 288 (1931).

² John C. Krantz, Jr., "Pharmaceutical Chemistry," page 118 (1928).

tion products of quinone. Krantz has apparently overlooked the fact that ferric iron¹ also produces a color with phenol, this being a general reaction for the aromatic compounds that have the hydroxyl group in the ring. Salicylic acid and its salts contain the hydroxyl group in the ring and it is thus related definitely to the phenols. The oxidation of the phenolic structure of salicylates to a quinoid structure by atmospheric oxygen will explain more fully the color change noted by Ruddiman and Krantz—see page 765.

(4) The experiments show that visible light affects positively the production of color in alkaline solutions of salicylates under the conditions described. It is not the purpose of this paper to account for the structural change in the salicylate molecule as produced by light energy.

(5) The action of air on salicylates producing color may be shown by the following equations.



Equation No. 3 (a) No. 1 carbon, sum of valencies plus one, is oxidized to carbon with a sum of valencies equal to plus two.

(b) No. 4 carbon, sum of valencies minus one, is oxidized to carbon with a sum of valencies of plus two.

(c) The total gain of valence of the two carbon atoms is equal to four.

(d) Oxygen with a valence of plus two is reduced to oxygen with a valence minus two.

(e) The total loss of valence for oxygen is equal to four.

(f) The valence gained is equal to the valence lost, as must be the case in every chemical change.

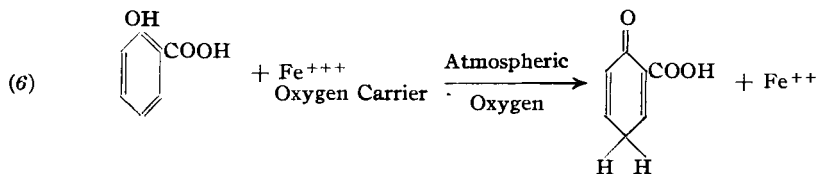
(6) The action of iron on salicylates producing color may be shown by the following equations.



The oxidation of ferrous iron to ferric proceeds more readily in alkaline solution than in acid solution.²

¹ E. Emmet Reid, "College Organic Chemistry," page 508 (1929).

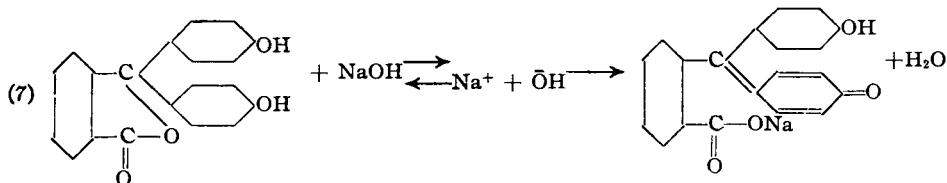
² Latimer and Hildebrand, "Reference Book of Inorganic Chemistry," page 308 (1929).



Phenolic Structure of Salicylate.
Colorless.

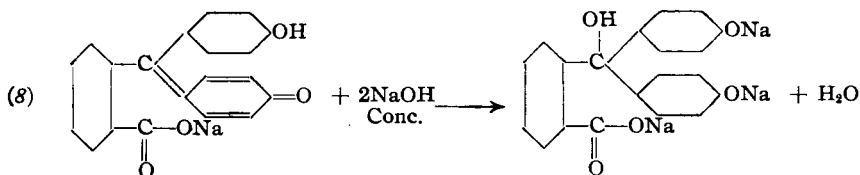
Quinoid Structure Acting as a
Chromophore. Colored.

(7) Preparation No. 2 (Table I) was decolorized when a fifty per cent solution of sodium hydroxide was added as described. As suggested before, the reaction between phenolphthalein and strong sodium hydroxide is very similar and the two reactions may be described by the following equations.

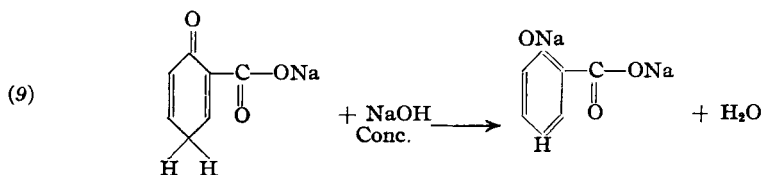


Lactone, Colorless, Acid.

Quinone, Red, Weakly Alkaline



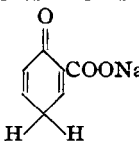
Sodium Salt of Carboxylic Acid, Colorless,
Strongly Alkaline.^{1,2}



Sodium Salicylate, Quinoid,
Colored.

di-Sodium Salicylate,
Benzoid, Colorless.

(8) Porter³ states that the groups $=C=C$ and $-CO-CO-$ act as chromophores. This suggests further reasons for the quinoid structure of sodium

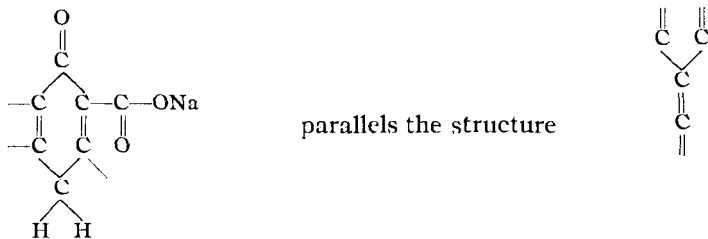
salicylate  being colored. The carbonyl group in the side chain is di-

¹ Richter's "Organic Chemistry," Trans. D'Albe, E. E. Fournier, 11th German Edition, Vol. 2, page 597 (1922).

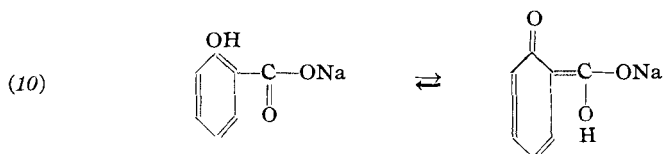
² I. M. Kolthoff and N. H. Furman, "Indicators," Trans., 2nd German Edition, page 238 (1926).

³ C. W. Porter, "The Carbon Compounds," 2nd revised Edition, page 288 (1931).

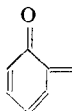
rectly attached to a carbon in the ring having a double bond and the arrangement



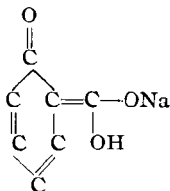
This is not strictly the chromophore group as given by Porter but may exert an influence in the formation of color with the quinoid structure of the salicylate. Also the possibility of a keto-enol equilibrium existing may add to the production of color because:



(a) existence of a quinoid structure.



(b) two adjacent carbon atoms in the ring having double bonds paralleling



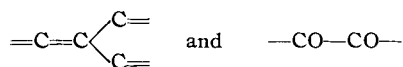
the structure —CO—CO— given by Porter as a chromophore.

(9) From the experimental work and the theoretical considerations suggested the "incompatibility" magnesium hydroxide, sodium bicarbonate, sodium salicylate and water is due to an oxidation of the salicylate. The oxidation will take place in the presence of atmospheric oxygen and impurities of ferric iron to form the quinoid structure of the phenolic group in the salicylate as illustrated in Equations 1 to 10. The experiments would indicate that visible light affects the formation of color.

(10) An "incompatibility" of this type is rather difficult for the dispenser to correct. However, the production of color in similar preparations might be reduced somewhat by observing: (1) The use of chemically pure materials, more especially iron free; (2) the use of tightly stoppered containers to prevent excessive diffusion of air; (3) the use of freshly boiled water; and (4) the use of colored glass containers.

SUMMARY.

- (1) Colorless solutions of salicylates in the presence of an alkali change in color to dark brown to almost black.
- (2) The reasons suggested for this color change are:
- (a) Salicylates have a phenolic structure;
 - (b) Because of this they are oxidized by:
 - (1) atmospheric oxygen
 - (2) light
 - (3) presence of ferric iron.
- (3) The oxidation products are probably compounds having quinoid structure.
- (4) A keto-enol equilibrium may affect the production of color, because of the existence of the structures paralleling the chromophore structures



- (5) The "incompatibility" magnesium hydroxide, sodium bicarbonate, sodium salicylate and water which changes in color to a dark brown to almost black can be explained by the reactions as indicated in Paragraphs 2 to 4.
- (6) The color change may be controlled to some extent by using:
- (a) chemically pure materials, more especially those which are iron free
 - (b) recently boiled water
 - (c) colored glass containers.

EARLY METHODS OF DISEASE PREVENTION.

The British Pharmaceutical Conference will meet in Aberdeen in September and this prompts the following quotation by our esteemed contemporary, *The Chemist & Druggist*, in reviewing Dr. John D. Comrie's "History of Scottish Medicine," now in its second edition, wherein it states—"It is recorded in 1578 that rats could not live in Aberdeen; and to this fact (if it is a fact) is attributed the comparative immunity of the northern city from plague. Whether or not this is so, the authorities of the city were the first to order (in 1647) that poison should be laid down for rats and mice, from which it may be inferred that vermin could find subsistence there in the seventeenth century if not in the sixteenth. With equal fullness the author has treated Edinburgh, Glasgow and St. Andrews, the other three cities which were the sites of universities at a time when England had only two. The scale on which this sumptuously printed work is planned has involved the recording of the rise and progress of medicine in the Scottish universities in considerable detail. The contribution to medicine of such typical figures as James Gregory, James Young Simpson, Robert Christison and Joseph Lister is described in a style both readable and authoritative. In addition, the footnotes and the index have the value that is expected in a history written on this scale. The plan of the work has involved slight overlapping; but this is a minor matter, and Dr. Comrie is to be congratulated on bringing a laborious task to a successful issue."

Al Mansur Gilafun said of the hospital which he founded at Cairo in 1283: "I have founded this institution for my equals and for those beneath me. It is intended for rulers and subjects, for soldiers and for the emir, for great and small, freeman and slaves, men and women."