

112. *The Retardation of Chemical Reactions. Part VIII. The Darkening of Alkaline Solutions of Sodium Salicylate.*

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The object of this investigation is to examine the dark brown colour which develops rapidly in alkaline solutions of sodium salicylate (used in the treatment of muscular rheumatism and similar complaints), to survey the means already suggested for retarding the development of the dark colour, and if possible to discover other means.

It is found that the darkening of these solutions is due to absorption of atmospheric oxygen, and not of ammonia. Retardation by anti-oxygens has been investigated. Sodium thiosulphate (0.1%) and thiourea (0.04%) are suggested as the most suitable retarders when the salicylate solutions are to be used for medicinal purposes.

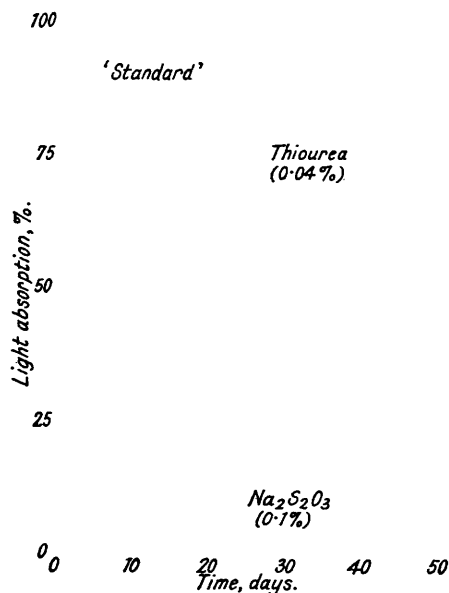
The Cause of the Darkening.—The “standard” alkaline salicylate solution used contained 5% of sodium salicylate and 2.5% of sodium bicarbonate in water.

That the change in colour is due to auto-oxidation of the salicylate seems probable, in view of the ready oxidation, with colour change, of alkaline solutions of pyrogallol and other phenolic materials. This has been the opinion of most workers (Greenish and Beesley, *Pharm. J.*, 1915, **94**, 201; Grill, *J. Amer. Pharm. Assoc.*, 1932, **21**, 763; Beukema-Goudsmit, *Pharm. Weekblad*, 1934, **71**, 196; Liberalli, *Boll. Assoc. brasil. farm.*, 1935, **16**, 154). On the other hand, Macadie (*Pharm. J.*, 1915, **94**, 355) attributed the darkening to the absorption of traces of ammonia from the air. Addition of ammonia to an alkaline salicylate solution certainly causes a fairly rapid darkening, even when the solution is sealed off from the air, but the colour is redder than the normal. The authors have found that (a) a solution of salicylate and bicarbonate in air-free water, exposed to nitrogen, does not darken, and (b) a solution of the same reagents in ammonia-free water (checked with Nessler’s reagent), and exposed only to air freed from any traces of ammonia by passage through sulphuric acid, darkens at a normal rate. It seems certain that oxygen, not ammonia, is responsible for the change.

Martins (*Tribuna farm.*, 1934, **3**, 8, 30) suggests that the oxidation is brought about by

an oxidase, pointing out that, although certain substances (see later) retard the normal darkening, they do not prevent oxidation by hydrogen peroxide. He concludes that their action is antiseptic rather than anti-oxygenic. This reasoning is unsound, for anti-oxygens of the usual types, although very effective in checking oxidation by oxygen gas, are generally unable to arrest oxidation by more vigorous oxidising agents. A solution of sodium salicylate and carbonate which has been boiled for some time, saturated with carbon dioxide to form bicarbonate, and kept in a tube plugged with cotton-wool, darkens normally, although oxidase-producing organisms are likely to have been destroyed or greatly reduced in number by this treatment.

The darkening is not very sensitive to illumination. No obvious difference in rate was detected between solutions kept (a) in the dark and (b) in diffused daylight, although both Grill and Liberalli (*loc. cit.*) record an acceleration by light. The rate of oxidation rises with temperature, and with increase in the ratio of exposed area to volume. The actual volume of oxygen absorbed is by no means negligible, for in one experiment 70 c.c. of the "standard" solution at atmospheric temperature and pressure absorbed 5.5 c.c. of oxygen in 3 months.



Retardation of the Darkening.—Retardation of the development of colour was achieved by Greenish and Beesley (*loc. cit.*), using sulphites, bisulphites, and thiosulphates as retarders, by Liberalli (*loc. cit.*), using reducing agents (not specified in the abstract, which alone was available), by Martins (*loc. cit.*), using iodides, potassium cyanide, copper sulphate, and formaldehyde, and by Beukema-Goudsmit (*loc. cit.*), who first boiled the water with calcium carbonate. The effect of sodium thiosulphate was confirmed by Rossi (*Rev. farm., Buenos Aires, 1933, 75, 303*).

About 40 other substances were examined as possible retarders, with only one positive result. Most of the best-known anti-oxygens were useless. Polyhydroxyphenols such as quinol and pyrogallol caused immediate coloration, and alcohols, sugars, glycerol, sulphur, acetamide, hexamine, phenol, and urea were ineffective. Thiourea, on the other hand, had marked anti-oxygenic action, even

when present in very low concentration.

Most of the substances mentioned as retarders are obviously unsuitable for inclusion in medicine, and sodium thiosulphate and thiourea, both being of low toxicity (U.S.P.; Nicolas and Lebduska, *Compt. rend.*, 1928, **186**, 1441), seem to be the only two which might find practical application.

With the "standard" salicylate solution, the greatest retardation was obtained with the following concentrations: potassium iodide 1%, thiourea 0.04%, sodium thiosulphate 0.1%. With 1% iodide as retarder the colour is of the same brown shade as in the absence of a retarder, but develops about 50 times more slowly. With thiourea and sodium thiosulphate the colours are greener and yellower respectively, the reaction presumably following a different path.

The figure shows light-absorption curves obtained with a Lange photoelectric colorimeter. The curves show that the colour develops much more slowly in presence of thiourea or thiosulphate. The diminution in light absorption in the latter case after about 30 days is due to precipitation of the coloured compound. Thiourea, to the eye, appears a much better retarder than the curve would suggest, since the reading of the colorimeter is dependent on the nature, as well as on the depth, of the colour of the solution. A commonly prescribed mixture (80 grains each of sodium bicarbonate and salicylate to 8 oz. of distilled water) becomes dark brown and forms a considerable precipitate in a fortnight,

while the same solution protected by thiourea (0.04%) or sodium thiosulphate (0.1%) is still almost colourless.

Some Points of Interest.—It has been established that in many cases of retarded oxidation, the inhibitor is itself oxidised in the act of retardation. This is notably so in many cases where a chain mechanism exists, the products of oxidation of the inhibitor being apparently unable to propagate the reaction chain. For example, Bäckström and Alyea (*Trans. Faraday Soc.*, 1928, **24**, 601; *J. Amer. Chem. Soc.*, 1929, **51**, 90) showed that when the oxidation of sodium sulphite was retarded by isopropyl, butyl, or benzyl alcohol, the retarder was oxidised to the corresponding aldehyde or ketone. Again, Wagner and Brier (*Ind. Eng. Chem.*, 1931, **23**, 40) showed that the period of induction produced in the oxidation of linseed oil is proportional to the amount of quinol added, and that at the end of the induction period the reaction proceeds as if no retarder had been present. At this point, presumably, oxidation of the retarder is complete. These are only two out of many examples which might be cited.

A search was made for evidence of oxidation of sodium iodide used as a retarder, but neither free iodine nor iodate could be detected, even after some weeks. A similar experiment with sodium thiosulphate did not yield very conclusive results, since the iodine titre of a mixture of sodium thiosulphate and bicarbonate increases with time, probably owing to formation of sulphide and trithionate (a change which takes place rapidly on heating; cf. Bassett and Durrant, *J.*, 1927, 1418). The alteration in iodine titre was practically unaffected by sodium salicylate, which suggests that oxidation of the thiosulphate, or its decomposition products, incidental to its action as a retarder, did not take place to any great extent.

Another aspect of the problem deserves mention. A solution of sodium salicylate to which no alkali has been added does not suffer auto-oxidation, whereas the ordinary medicinal solution, containing bicarbonate, oxidises rapidly. Greenish and Beesley (*loc. cit.*) observed that replacement of the bicarbonate by sesquicarbonate (*i.e.*, by equimolar concentrations of carbonate and bicarbonate) resulted in much more rapid darkening. That the sesquicarbonate is peculiarly efficient in promoting darkening is now confirmed. As it seemed likely that this was so because the p_H of the sesquicarbonate-salicylate solution happened to be particularly good for the oxidation concerned, an attempt was made to test this point.

The p_H of a solution containing sodium salicylate (5%), carbonate (1.25%), and bicarbonate (1.25%) is about 10.3. A number of solutions was prepared containing salicylate (5%), bicarbonate (2.5%), and various amounts of sodium hydroxide, to give p_H values from 9 to 13. Darkening was most rapid with 0.70% of the hydroxide, which gave a solution of p_H close to 10.3. This result seems to strengthen belief in the importance of p_H . It is not, however, the only factor concerned, for little or no darkening was obtained with salicylate solutions containing (*a*) sodium hydrogen phosphate, sodium hydrogen phthalate, sodium acetate, or other salt, in place of sodium bicarbonate, and (*b*) sufficient sodium hydroxide to raise the p_H to 10.3. The present work, therefore, does not contradict the suggestion of Beukema-Goudsmit (*loc. cit.*) that the bicarbonate radical plays a specific part in the oxidation, but this aspect of the matter would repay further investigation.