# Rapid Detection of Excess Glucose in Coloring Syrups Used in Tablet Production

*Sir:*

When more than 2% glucose is present in the coloring syrup applied in tablet coating, the resulting tablets may be inelegant and exhibit a blotchy, wrinkled, or leathery surface. Such unmarketable tablets represent a substantial loss in material, labor, and time. This loss can be avoided if the offending batches of coloring syrup can be detected before they are used on the tablets.

We have found a simple procedure using a dip-and-read stick test, Clinistix,[1] to identify batches of coloring syrup that contain excess glucose. The stick test contains the enzyme glucose oxidase and so is specific for glucose. To use the test, the reactive area of the stick is dipped in a solution and removed. If glucose is present in the solution, the reactive area (originally red) turns purple. The purple can be compared with the color chart provided to determine if a little or a lot of glucose is present. The test was originally designed to detect glucose in urine.

To identify unsatisfactory batches of coloring syrup, we use a different procedure from that suggested by the manufacturer for the detection of glucose in urine. We prepare two dilutions of the coloring syrup, one of 2 drops in 10 ml. of water (1:110 dilution) and one of 5 drops in 10 ml. of water (1:44 dilution). (Under the conditions of this study there were 22 drops of coloring syrup in 1 ml.) One stick is dipped in each of these dilutions, removed, and the color allowed to develop for 30 seconds. The stick dipped in the 2-drop dilution is compared with the light color on the color chart and the stick dipped in the 5-drop dilution is compared with the medium color on the color chart. If either of the sticks is darker than the color it is compared with, the batch of syrup is discarded as containing too much glucose. Our experiments indicate that sticks dipped in the above dilutions of clear syrup (without dye) containing more than 2% glucose will give colors darker than the control colors on the chart. Sticks dipped in the same dilutions of clear syrup containing less than 2% glucose will give colors lighter than the control colors on the chart.

We have also carried out the stick procedure on some syrups containing dyes. We found the procedure as described satisfactory with syrups containing FD&C Yellow No. 5, FD&C Red No. 4, and an orange made by combining these two dyes. The procedure as described was not satisfactory with syrups containing FD&C Blue No. 1 and Hercules Mint Green. In both of these colored syrups, sticks dipped in dilutions of syrup which originally contained 1% glucose gave colors darker than the control colors on the chart. It is clear that the procedure would have to be modified to detect excess glucose in syrups of these colors. It is our opinion that for any particular operation the investigator should develop his own procedure with the stick test. The material presented here is only meant to illustrate that a practical system for detecting batches of coloring syrup containing excess glucose can be developed simply.

Our coating operation has been helped by the stick test control procedure. From the time we first encountered the excess glucose problem until we began testing all batches of coloring syrup, 21% of the tablets were rejected for discoloration resulting from excess glucose in the coloring syrup. Since we began testing all batches, no tablets have been rejected for discoloration related to the excess glucose.

When the cause of irregular coloring on tablets is obscure, the stick test can be used to determine if excess glucose in the coloring syrup used was a factor. To use the test for this purpose, three of the irregularly colored tablets are placed in 30 ml. of water in a small beaker. The tablets are left in the water until their color has been washed off, then are quickly removed. If the tablets are left in the water longer, sugar from subcoatings is washed off and the test results are not valid. A stick is dipped in the water in which the tablets were washed. At 30 seconds the color on the stick is compared with the color chart. If excess glucose is present in the tablet coloring, the stick will give a reaction darker than the medium color on the chart. This procedure is satisfactory for our coating operation; others who might want to use the test for this purpose would probably have to establish their own procedure empirically.

The undesirable glucose apparently is produced in the coloring syrup under normal production conditions. To determine how glucose might be produced, a simple experiment was carried out. One sample of freshly prepared coloring syrup was refrigerated for 3 days and a second sample of the same syrup was put in a small flask and heated in an oven at about 70° for 3 days.

[1] Marketed by the Ames Co. Inc., Elkhart, Ind.

The refrigerated sample showed no buildup of glucose; the heated sample developed about 2% glucose. In another experiment, one sample of freshly prepared coloring syrup was allowed to stand for 3 days at room temperature; a second sample of the same syrup was heated for 3 days at 70° in steam kettles used in preparing the syrup. The syrup allowed to stand at room temperature contained about 1% glucose after the 3 days. The heated sample contained about 8% glucose (higher than the sample heated in the oven, probably because the inner surface of the steam kettle has a higher temperature than the 70° of the oven). It appears that glucose can be produced by the hydrolysis of sucrose in coloring syrups that are heated for some time.

Excess glucose probably causes the unacceptable tablet surface by retarding the drying of the coating material. The moist tablets tend to be sticky and adhere to one another and to the pan. In this state the surface is subject to tiny "pulls," eruptions, and general surface disfigurement as a result of repeated sticky collisions. Coloring syrups with excess glucose are much more likely to result in disfigured tablets with inexperienced coaters than with experienced coaters who can recognize the trouble and modify their procedure to allow proper drying of the tablets.

The stick control procedure has been very useful in our coating operation. The stick test is simple enough that modifications in procedure are practical. We think the test might be useful to others for whom the determination of glucose in some phase of tablet manufacture is important.

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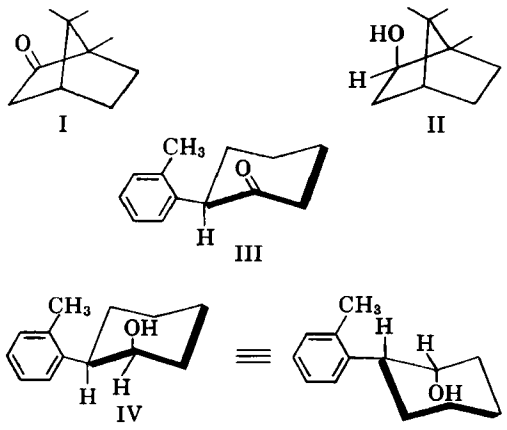
# Asymmetric Synthesis in the Stereoselective Reduction of 2-*o*-Tolylcyclohexanone by Isobornyloxymagnesium Bromide

*Sir:*

Subsequent to the synthesis of optically active mandelic acid by the reduction of phenylglyoxylic acid with isobornyloxymagnesium bromide by Vavon and Antonini (1) other investigators (2–4) have used the same reducing agent for the asymmetric synthesis of optically active deuterated primary alcohols of known absolute configuration from symmetrical aldehydes and deuterio-isobornyloxymagnesium bromide or from isobornyloxymagnesium bromide and symmetrical 1-deuterio-aldehydes.

We wish to report the synthesis of optically active *cis*-2-*o*-tolylcyclohexanol by the reduction of racemic 2-*o*-tolylcyclohexanone with isobornyloxymagnesium bromide. The high degree of stereoselectivity of the reaction is indicated from the fact that the 2-*o*-tolylcyclohexanol obtained consist of about 92% *cis*-2-*o*-tolylcyclohexanol, $[\alpha]_D^{24} = -2.9$ (0.1 Gm./ml. in ethanol) (optical purity unknown), and only about 8% of the *trans* isomer. The *trans* isomer was not recovered in sufficient amount for optical rotation measurements. Nonspecific reduction of racemic 2-*o*-tolylcyclohexanone would of course yield the four optical isomers of 2-*o*-tolylcyclohexanol in equal quantities. Since *cis* alcohol is formed preferentially, the energy of activation for the transfer of the hydride ion to the carbonyl carbon of 2-*o*-tolylcyclohexanone is lower when the transfer leads to an equatorial C—H bond. Because the resulting *cis* alcohol has optical activity, the energy of activation is lower for the formation of the *cis* alcohol from one enantiomorph of 2-*o*-tolylcyclohexanone than from the other. Molecular models indicate that the least hindered of the four possible transition states is the one resulting from the interaction of II and that enantiomorph of 2-*o*-tolylcyclohexanone shown by structure III to give product IV.




Structure IV is suggested as the absolute con-