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.

HENRY W. BENNETT
FRANK T. HESS

Miles Laboratories, Inc.
Elkhart, Ind.

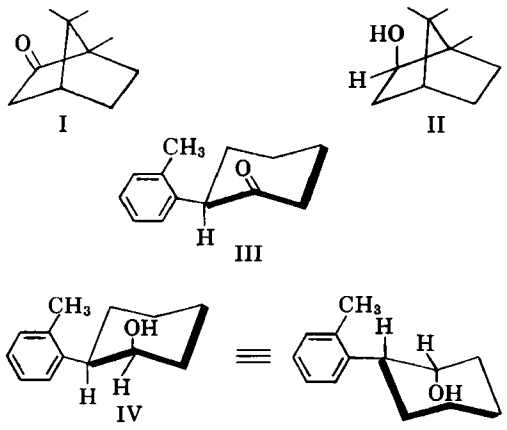
Received August 14, 1962.
Accepted for publication April 10, 1963.

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-

figuration of the optically active *cis*-2-*o*-tolylcyclohexanol obtained from the stereoselective reduction. This is consistent with the mechanism for stereoselective reduction by isobornyloxymagnesium bromide proposed by Streitwieser and co-workers (3) based on structure I being the absolute configuration of (+)camphor (3, 5) from which the isoborneol was prepared.

The isoborneol prepared by lithium aluminum hydride reduction of (+)camphor according to the method of Noyce and Denney (6) had $[\alpha]_D^{25} = -23.0°$ (*c* 5 in ethanol) compared to $-26.0°$ reported by these authors for a product which was reported contaminated with about 10% borneol (6). It has been shown (1, 3) that the presence of this amount of borneol does not affect the course of reduction by isobornyloxymagnesium bromide because borneol reacts so much slower under the same conditions. We have purified the isoborneol by elution chromatography on alumina to give $[\alpha]_D^{25} = -30.0°$ (*c* 5 in ethanol) (reported value (7) for pure isoborneol, 8% in ethanol, is $[\alpha]_D^{19} = -33.5°$) and have found no apparent difference in the stereospecificity of the reduction by the magnesium bromide salt of the purified isoborneol compared to that obtained from isoborneol contaminated with some borneol. A solution of racemic 2-*o*-tolylcyclohexanone in anhydrous benzene was added to a benzene solution of isobornyloxymagnesium bromide, prepared by the method of Streitwieser (3), and the mixture was heated to reflux. The progress of the reaction was followed by periodic work-up of small portions of the reaction mixture and analysis of the product by gas chromatography in comparison to the known *cis*- and *trans*-2-*o*-tolylcyclohexanols (8). Two conditions, referred to as *Methods A* and *B*, were used. In *Method A* slightly over two equivalents of the racemic ketone were used and the refluxing was carried on until practically all the isoborneol was depleted (about 45 hours of refluxing). In *Method B* two equivalents of isobornyloxymagnesium bromide were used and the reaction carried out until the ketone was practically depleted (about 60 hours of refluxing). The 2-*o*-tolylcyclohexanol obtained by *Method B* consisted of about 92% *cis* isomer and 8% *trans*. This ratio appeared to remain constant during the course of the reactions. The product of *Method A* consisted of about 91.5% *cis* after 23 hours of refluxing and about 89% *cis* and 11% *trans* at the end of 45 hours of refluxing. The *cis* isomer was recovered by preparative gas chromatography, using a 5-ft. column packed with 18% Carbowax 20M on acid-washed Chromosorb W. The *cis* product of reaction *A* had $[\alpha]_D^{24} = -2.88°$ and that from reaction *B* $-2.95°$. Resolution of *cis*-2-*o*-tolylcyclohexanol is in progress in order to establish the optical purity of the product of the asymmetric synthesis. The unreacted ketone recovered from reaction *A* was not optically active. This fact and the fact that complete reduction of the racemic ketone yielded optically active *cis* alcohol in reaction *B* indicates isomerization of the ketone through enolization. If isomerization did not occur, the remaining ketone in reaction *A* would be richer in the mirror image of structure III.

In a (Meerwein-Pondorff)-Oppenauer reaction of the type used, many species can be in equilibrium. The initial reaction between the isobornyloxymagnesium bromide and the 2-*o*-tolylcyclohexanone could be reversible, and the magnesium bromide salts of the 2-*o*-tolylcyclohexanols could possibly equilibrate with unreacted 2-*o*-tolylcyclohexanone. The apparent constant ratio of *cis* and *trans* products in reaction *B* and the apparent increase in *trans* isomer, with time, in reaction *A* suggest a tendency toward equilibrium between products and unreacted ketone. It is of interest that from molecular models and Streitwieser's mechanism (3) the reaction of the optically active product (salt of IV) with 2-*o*-tolylcyclohexanone is predicted to be faster with the enantiomorph shown by structure III, and that the most rapid reaction will yield IV as the product. This possibility is being investigated further.

Steric control of the reduction of certain cyclanones by diisopinocamphenylborane has been reported by Brown and Bigley (9).

(1) Vavon, G. A. and Antonini, A., *Compt. Rend.*, **232**, 1120(1951).
(2) Streitwieser, A., Jr., and Wolfe, J. R., Jr., *J. Am. Chem. Soc.*, **79**, 903(1957).
(3) Streitwieser, A., Jr., Wolfe, J. R., Jr., and Schaeffer, W. D., *Tetrahedron*, **6**, 338(1959).
(4) Belleau, B., and Burba, J., *J. Am. Chem. Soc.*, **82**, 5751(1960).
(5) Jacob, G., Ourisson, G., and Rassat, A., *Bull. Soc. Chim. France*, **1959**, 1374.
(6) Noyce, D. S., and Denney, D. B., *J. Am. Chem. Soc.*, **72**, 5743(1950).
(7) von Huckel, W., *Ann.*, **549**, 95(1941).
(8) Huitric, A. C., and Carr, J. B., *J. Org. Chem.*, **26**, 2648(1961).
(9) Brown, H. C., and Bigley, D. B., *J. Am. Chem. Soc.*, **83**, 3166(1961).

Alain C. Huitric
Thomas R. Newell

College of Pharmacy
University of Washington
Seattle

Received March 6, 1963.
Accepted for publication April 11, 1963.
This investigation was supported by a PHS research grant No. HE-03843-04 from the National Heart Institute, Public Health Service, Bethesda, Md.