

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. VII. Molecular Rearrangements During Lithium Aluminum Hydride Reductions in the 3-Phenyl-2-butanol Series<sup>1</sup>

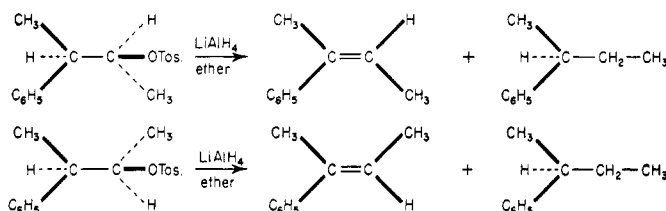
BY DONALD J. CRAM

Treatment of the *p*-toluenesulfonates of the optically pure isomers of 3-phenyl-2-butanol with lithium aluminum hydride resulted in the reduction of the compound to 2-phenylbutane. Evidence is presented that this reduction takes place with partial migration of the phenyl group. The accompanying elimination reaction is shown to be predominantly *trans* in its steric course. Treatment of the *p*-toluenesulfonate esters of the isomers of 3-phenyl-2-butanol with sodium ethoxide in ethanol results in an elimination reaction which is predominantly *trans* in its stereochemistry. The configuration of the four stereoisomers of 3-phenyl-2-butanol, the four stereoisomers of 3-phenyl-2-pentanol and the four stereoisomers of 2-phenyl-3-pentanol have been related to D-glyceraldehyde.

The observation by Karrer, *et al.*,<sup>2</sup> that the reduction of the *p*-toluenesulfonate of cholesterol with lithium aluminum hydride leads to the products cholestene and *i*-cholestane<sup>3</sup> suggested the present study of the reductions of the *p*-toluenesulfonates of the stereomers of 3-phenyl-2-butanol. The purposes of the present investigation are the following: (a) to obtain information regarding the stereochemistry of both the rearrangement and elimination reactions that occur during the reduction of *p*-toluenesulfonates with lithium aluminum hydride; (b) to acquire at least preliminary information regarding the mechanisms of these reactions; (c) to relate the configurations of the four isomers of 3-phenyl-2-butanol<sup>4</sup> and the eight isomers of 2-phenyl-3-pentanol<sup>5</sup> and 3-phenyl-2-pentanol<sup>6</sup> to that of D-glyceraldehyde.

## Results

The *p*-toluenesulfonates of IA and IIA<sup>4</sup> were submitted to the action of a homogeneous saturated solution of lithium aluminum hydride in ethyl ether. In each case a mixture of olefin<sup>6</sup> and (+)-2-phenylbutane<sup>6a</sup> was obtained. When the same



starting materials were treated with sodium ethylate in ethanol, the sulfonate ester of IA gave *trans*-2-phenyl-2-butene<sup>6a</sup> (VII) whereas the same ester of IIA produced *cis*-2-phenyl-2-butene<sup>6a</sup> (VIII).

(1) Parts of this paper were presented before the Organic Division of the American Chemical Society, Chicago Meeting, September, 1950.

(2) H. Schmidt and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

(3) These authors offered no evidence for the structure of this compound, but the good correspondence of properties of the substance (m.p. 76–78°,  $[\alpha]_D^{25}$  75.8°) with the compound (m.p. 78–79°,  $[\alpha]_D^{25}$  +78.5°) recently prepared by Riegel by a different route (F. Prout and B. Riegel, Abstract of the Meeting of the American Chemical Society, San Francisco, Calif., March, 1949) would indicate that *i*-cholestane was indeed produced by the action of lithium aluminum hydride on the *p*-toluenesulfonate of cholesterol.

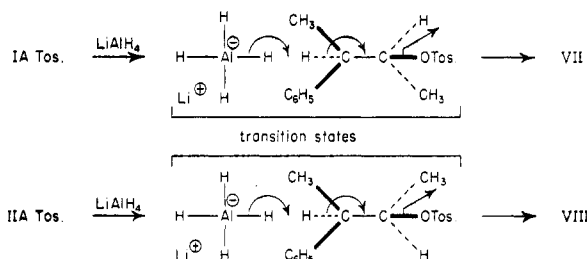
(4) (a) D. J. Cram, *THIS JOURNAL*, **71**, 3863 (1949); (b) D. J. Cram, *ibid.*, **74**, 2129 (1952). The numbering system for the various isomers of 3-phenyl-2-butanol is carried over into the present study.

(5) (a) D. J. Cram and R. Davis, *ibid.*, **71**, 3871 (1949); (b) D. J. Cram, *ibid.*, **71**, 3875 (1949).

(6) (a) D. J. Cram, *ibid.*, **71**, 3883 (1949); (b) D. J. Cram, *ibid.*, **74**, 2137 (1952).

## Discussion

The results of the base-induced (sodium ethylate) elimination reaction offer further substantiation of the stereochemical structures assigned to the four stereomers of 3-phenyl-2-butanol,<sup>4a</sup> and hence provide further evidence that the Chugaev reaction in these systems described in Paper V<sup>6a</sup> of this series assumes a predominantly *cis* course. Furthermore, the configurational relationships between the starting materials and products indicate



that a *trans* elimination has taken place when the sulfonate esters of the isomeric alcohols are treated with lithium aluminum hydride. The stereochemical course of this elimination reaction appears to be the same as that observed with sodium ethylate. Although both the  $\text{E}_2$  and the simple  $\text{E}_1$  reaction appear to give the same steric results,<sup>6b</sup> since lithium aluminum hydride is a base it is probable that the olefin arises in this experiment by the bimolecular mechanism. The reason for the *trans* character of the  $\text{E}_2$  reaction has been discussed by Hückel<sup>7</sup> and Ingold<sup>8</sup> in some detail.

In regard to the reduction that accompanies the elimination reaction, the fact that the *p*-toluenesulfonates of IA and IIA give (+)-2-phenylbutane of almost the same rotation indicates that the *major* reaction is that of simple nucleophilic displacement of the *p*-toluenesulfonate group by the aluminum hydride ion. The stereochemistry of this reaction cannot be determined in the present investigation, but Eliel<sup>9</sup> demonstrated that the reaction of lithium aluminum deuteride with 1-chloro-1-phenylethane is at least partially stereospecific, whereas Brown<sup>10</sup> provided evidence that suggested that ethylene oxide rings are opened with

(7) W. Hückel, W. Tapp and G. Legutke, *Ann.*, **543**, 191 (1940).

(8) M. Dhar, E. D. Hughes, C. K. Ingold, A. Mandour, G. Maw and L. Woolf, *J. Chem. Soc.*, 2117 (1948); see also S. J. Cristol, *THIS JOURNAL*, **69**, 338 (1947).

(9) E. Eliel, *ibid.*, **71**, 3970 (1949).

(10) L. Trevoy and W. Brown, *ibid.*, **71**, 1675 (1949).

inversion by lithium aluminum hydride. Kenyon<sup>11</sup> prepared (+)-2-phenylbutane and reported a rotation of  $\alpha^{20}_D +23.6^\circ$  ( $l = 1$  dm.); the enantiomer also has been reported,<sup>6b</sup>  $\alpha^{23}_D -24.3^\circ$  ( $l = 1$  dm.). The value of the rotation obtained in the present investigation for this hydrocarbon from the sulfonate ester of IIA amounted to about the same as the above values, whereas the rotation of the 2-phenylbutane produced from IA had a rotation about 10% lower in magnitude.

The simple reduction of IA without involvement of the phenyl group should produce optically pure (+)-2-phenylbutane.<sup>12</sup> The loss of some activity in the product suggests that some migration of the phenyl group occurred during the reduction, and that the product of this migration possessed a configuration enantiomeric to that of the starting material, thus producing partially racemic material. Since it has already been demonstrated that the *p*-toluenesulfonate of IA can isomerize to the sulfonate ester of I (racemic material) through an internally compensated phenonium sulfonate ion-pair,<sup>4b</sup> it seems probable that an analogous isomerization reaction can also occur in ether containing substantial amounts of lithium aluminum hydride.<sup>13</sup>

Two general reaction paths by which racemic 2-phenylbutane can arise from IA *p*-toluenesulfonate seem probable, both of which involve the phenonium sulfonate ion-pair as an intermediate. In path A, the reduction occurs through an exchange reaction of the *p*-toluenesulfonate anion in the ion-pair for an aluminum hydride anion to form a new ion-pair which collapses to racemic hydrocarbon.<sup>14</sup> In path B the phenonium sulfonate ion-pair collapses to racemic sulfonate ester which then is reduced by a simple displacement reaction. A choice between these two paths must await further work.

Although an analogous rearrangement probably also occurs in the II series, it cannot be detected because the stereochemical structure of the ion-pair is such that 2-phenylbutane of the same configuration results regardless of which way the ion-pair collapses. Therefore it is impossible to distinguish between material that arises by simple reduction or that produced by a rearrangement reaction.

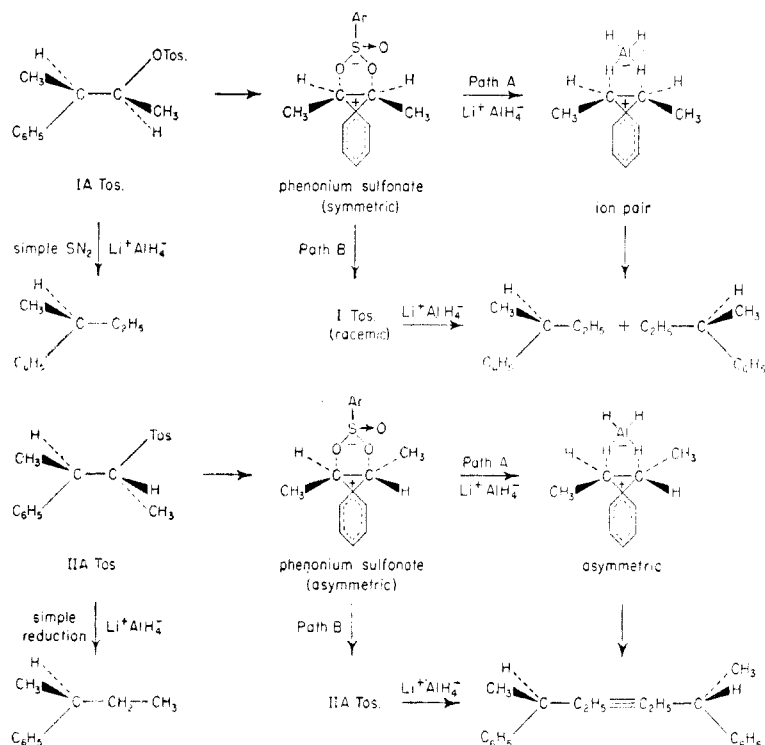
The above results make possible an assignment

(11) P. Harrison, J. Kenyon and J. Shepherd, *J. Chem. Soc.*, 658 (1928).

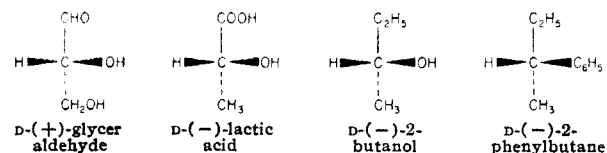
(12) Evidence for the optical purity of the starting materials is presented in Paper I of this series (ref. 5a).

(13) Although pure lithium aluminum hydride is soluble in ether to the extent of 25–30 g. per 100 g. of solvent [A. Finholt, A. Bond, and H. Schlesinger, *This Journal*, 69, 1201 (1947)], a much lower concentration was obtained in the present investigation by warming an excess of the commercial reagent (Metal Hydrides, Inc.) with ether (~6.4 g. per 100 ml. of solution). Even at this concentration the ionizing power of this solution must be vastly superior to that of ether.

(14) That the phenonium sulfonate ion-pair can exchange its anion has been demonstrated in Paper V of this series (ref. 4a).



of configuration to all the stereomers of 3-phenyl-2-butanol, the stereomers of 2-phenyl-3-pentanol and 3-phenyl-2-pentanol relative to D-glyceraldehyde. Wolfrom<sup>15</sup> has recently carried out a series of reactions confirming the configurational correlation of L-(−)-glyceraldehyde with L-(+)-lactic acid. Levene<sup>16</sup> correlated the configuration of L-(+)-lactic acid with that of L-(+)-2-butanol.<sup>17</sup> Kenyon<sup>18</sup> reported that treatment of the *p*-toluenesulfonate of L-(+)-2-butanol with phenylmagnesium bromide produced (−)-2-phenylbutane, having a rotation slightly lower than the optically pure material prepared in the present investigation. Since this reaction must go with inversion,<sup>18,19</sup> the configuration of the product relative to that of D-(+)-glyceraldehyde can be inferred and is designated below. The conversions of the derivatives



of the isomers of 3-phenyl-2-butanol to 2-phenylbutane together with the already established relative

(15) M. Wolfrom, R. Lemieux, S. Olin and D. Weisblat, *This Journal*, 71, 4057 (1949). The earlier literature is summarized by these authors.

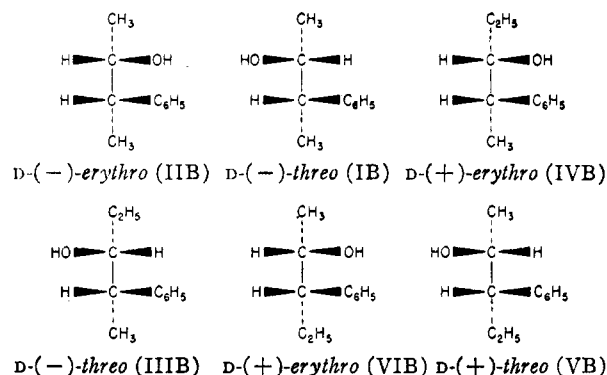
(16) (a) P. Levene, A. Walti and H. Haller, *J. Biol. Chem.*, 71, 465 (1926–1927); (b) P. Levene and H. Haller, *ibid.*, 65, 49 (1925); 67, 331 (1926); 79, 475 (1928).

(17) In this series of interconversions the methyl group as well as the asymmetric carbon atom to which it was attached remained intact. It would seem logical to give the compound an L-designation, thus leaving the  $\text{CH}_2\text{OH}$  group in this substance and the  $-\text{CH}_2\text{OH}$  group of glyceraldehyde analogously oriented.

(18) J. Kenyon, H. Phillips and V. Pittman, *J. Chem. Soc.*, 1080 (1935).

(19) The results of R. L. Letsinger [*This Journal*, 70, 407, 3342 (1948)] indicate that at least some of the product results from an  $\text{S}_\text{N}2$  reaction accompanied by inversion of configuration.

configurations of all of the isomers of 3-phenyl-2-butanol,<sup>4,6</sup> 2-phenyl-3-pentanol<sup>5</sup> and 3-phenyl-2-pentanol allow assignments of configuration to be made based on the Freudenberg convention<sup>20</sup> for the configuration of D-(+)-glyceraldehyde. Thus the various isomers can be given the names indicated below.



### Experimental

**Elimination of *p*-Toluenesulfonic Acid from the *p*-Toluenesulfonate of IIA (L-(+)-*erythro*-3-Phenyl-2-butanol) with Sodium Ethoxide.**—To a solution of sodium ethoxide (6 g. of Na was allowed to react with 45 ml. of absolute alcohol) held at 120° was added 17.5 g. of *p*-toluenesulfonate of IIA (m.p. 35–36°, made from alcohol IIA,  $[\alpha]^{25}_D +0.69^\circ$ ). The resulting mixture was held at 110° for four hours and overnight at 80°. The product was steam distilled, extracted with pentane, and the organic layer was washed with water, dried and concentrated. The residue was flash distilled under reduced pressure to give 7.3 g. of a colorless oil,  $\alpha^{25}_D +1.25^\circ$  ( $l = 1$  dm.),  $n^{25}_D 1.5373$ . Fractionation of 7.1 g. of this material through a center rod column at atmospheric pressure produced four fractions of equal amounts boiling from 188.8° to 193.5° and with indices of refraction varying continuously from  $n^{25}_D 1.5348$  for the lowest boiling to  $n^{25}_D 1.5390$  for the highest boiling fraction. A total of 5.4 g. was collected with 0.8 g. of polymerized material left in the pot. The combined fractions had a slight rotation,  $\alpha^{25}_D +0.75^\circ$  ( $l = 1$  dm.), indicating contamination with optically active material, probably 3-phenyl-1-butene. The fractions were combined and 0.500 g. of the olefin was mixed with 0.875 g. of 2,4-dinitrobenzenesulfonyl chloride according to the procedure recorded in paper IV of this series<sup>20</sup> to produce 0.90 g. of recrystallized product, m.p. 81–82°, m.m.p. with an authentic sample of the adduct of *cis*-2-phenyl-2-butene, 81–82°. The yield of olefin adduct obtained in a parallel experiment with pure *cis* olefin<sup>20</sup> (b.p. 193.5°,  $n^{25}_D 1.5402$ ) amounted to 0.94 g. from 0.50 g. of olefin. A parallel distillation of 7.1 g. of pure *cis* olefin in the same column produced 5.66 g. of pure product, the remainder having polymerized or been lost on the column.

**Elimination of *p*-Toluenesulfonic Acid from the *p*-Toluenesulfonate of IA (L-(+)-*threo*-3-Phenyl-2-butanol) with Sodium Ethoxide.**—The *p*-toluenesulfonate of IA (18.5 g. m.p., 62–63°, made from alcohol having the rotation,  $[\alpha]^{25}_D$

+30.9°) was treated by the procedure outlined for the same derivative of IIA. A total of 7.4 g. of initially distilled product was obtained,  $\alpha^{25}_D -3.09^\circ$  ( $l = 1$  dm.). Careful fractionation of this material produced 4.7 g. of fraction 1, b.p. 171–172° (atmospheric pressure),  $n^{25}_D 1.5190$  for the first drop and  $n^{25}_D 1.5193$  for the last drop of the fraction,  $\alpha = 0.00$  (total sample). A second fraction, b.p. 172–183° (0.83 g.) proved to be slightly optically active,  $\alpha^{25}_D +0.18$  ( $l = 1$  dm.). The polymeric material left in the pot amounted to 0.83 g. From 0.500 g. of fraction 1 and 0.875 g. of 2,4-dinitrobenzenesulfonyl chloride was obtained 0.95 g. of adduct, m.p. 93–94°, m.m.p. with an authentic sample of adduct of *trans*-2-phenyl-2-butene, 93–94°. The yield of adduct obtained in a parallel experiment with pure *trans* olefin (b.p. 172°,  $n^{25}_D 1.5192$ ) amounted to 0.97 g. of recrystallized material from 0.50 g. of olefin. A parallel distillation of 7.4 g. of pure *trans* olefin through the same column produced 5.73 g. of olefin, the remainder being lost in holdup and as polymerized material.

**Treatment of the *p*-Toluenesulfonate of IA (L-(+)-*threo*-3-Phenyl-2-butanol) with Lithium Aluminum Hydride.**—A mixture of 6.3 g. of the *p*-toluenesulfonate of IA (prepared from optically pure alcohol,  $[\alpha]^{25}_D +30.2^\circ$ ) and 199 ml. of a clear, filtered, solution containing 6.4 g. of lithium aluminum hydride in ether was allowed to stand overnight and decomposed on a mixture of a 10% solution of NaOH and ice. The resulting mixture was extracted with pentane, the organic layer was washed with water, dilute acid, dilute base and again with water. The solution was dried, concentrated, and the product was distilled, to give 2.13 g. of an oil,  $n^{25}_D 1.5041$ ,  $\alpha^{25}_D +11.36^\circ$  ( $l = 1$  dm.).

A mixture of 1.5 g. of this oil was mixed with 0.90 g. of 2,4-dinitrobenzenesulfonyl chloride and 2 ml. of glacial acetic acid. The product that separated was recrystallized from ethyl acetate and pentane to give 0.76 g. of adduct, m.p. 92–93°, m.m.p. with the adduct of *trans*-2-phenyl-2-butene, 92–94°.

The filtrate from the original crystallization of the derivative was diluted with glacial acetic acid to a 10-ml. volume, mixed with 1.5 g. of 2,4-dinitrobenzenesulfonyl chloride and heated to 100° for one-half hour. This solution was then cooled and shaken with a mixture of pentane and water. The hydrocarbon layer was washed with water six times, dried and passed through a short column of alumina. The column filtrate was evaporated and distilled to give 0.52 g. of (+)-2-phenylbutane,  $n^{25}_D 1.4879$ ,  $\alpha^{25}_D +21.64^\circ$  ( $l = 1$  dm.).

To prove that the above procedure resulted in the complete removal of olefin, a 1.0-g. sample of 2-phenylbutane ( $n^{25}_D 1.4878$ ) was mixed with 0.5 g. of pure *cis*-2-phenyl-2-butene ( $n^{25}_D 1.5402$ ), 0.5 g. of pure *trans*-2-phenyl-2-butene ( $n^{25}_D 1.5192$ ), 3 g. of 2,4-dinitrobenzenesulfonyl chloride and 10 ml. of glacial acetic acid. This mixture was submitted to the same procedure and 0.7 g. of pure 2-phenylbutane was recovered,  $n^{25}_D 1.4879$ .

**Treatment of the *p*-Toluenesulfonate of IIA (L-(+)-*erythro*-3-Phenyl-2-butanol) with Lithium Aluminum Hydride.**—When submitted to the same treatment with lithium aluminum hydride as that recorded for the *p*-toluenesulfonate of IA, the same derivative of IIA (7.0 g.) gave 2.45 g. of a mixture of olefin and alkylbenzene,  $n^{25}_D 1.5121$ ,  $\alpha^{25}_D +12.01^\circ$  ( $l = 1$  dm.). From 2.2 g. of this mixture was isolated 1.10 g. of recrystallized (glacial acetic acid) adduct of olefin with 2,4-dinitrobenzenesulfonyl chloride, m.p. 82°, m.m.p. with an authentic sample of the same adduct with pure *cis*-2-phenyl-2-butene, 82°. The 2-phenylbutane isolated (1.6 g.) had the following properties,  $n^{25}_D 1.4878$ ,  $\alpha^{25}_D +24.2^\circ$  ( $l = 1$  dm.).

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(20) K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig and Wien, 1933, pp. 662.