THE SYNTHESIS OF TRANS-TRANS-2,5-DI-T-BUTYLCYCLOHEXANOL VIA HYDROBORATION OF 1,4-DI-T-BUTYLCYCLOHEXENE

Daniel J. Pasto and Francis M. Klein (1)

Department of Chemistry, University of Notre Dame

Notre Dame, Indiana

The synthesis of substituted cis-di-t-butylcyclohexane derivatives usually relies on the catalytic hydrogenation of the appropriately substituted benzene derivatives in which the all cis reduction product predominates (2,3). In a study of the steric effects of variously positioned alkyl substituents in the cyclohexene system, the hydroboration of 1,4-di-t-butyl-cyclohexene (1) differed substantially from the results obtained with other systems. Hydro-boration of 1 at $0°$ with borane in tetrahydrofuran (externally generated) in a 1:1 mole ratio followed by basic hydrolysis and oxidation produced predominantly trans-trans-2,5-di-t-butyl-cyclohexanol (2), along with lesser amounts of the cis, trans- and trans, cis-2,5-di-t-butyl-cyclohexanols (3 and 4). The structures of the three alcohols were determined by chemical interconversions, spectral properties, and by comparison of alcohols 3 and 4 with authentic samples kindly provided by Prof. R. Stolow of Tufts University. The formation of 2 represents the formation of a system, not readily available by other means, in which a twist-boat confor-mation is formed as well as providing a trans relationship between the functional group and the alkyl groups.

The crude mixture (82% yield) of alcohols was separated by careful chromatography on neutral Woelm activity II alumina by elution with hexane-benzene mixtures. Alcohol 2 (77% of the crude alcohol mixture) was recrystallized from pentane giving m.p. 72-73° (Anal. Calcd. for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found:C, 79.45; H, 12.92). The NMR spectrum displayed a relatively narrow, unresolved band for the ring hydrogens and a multiplet at -4.04 ppm characteristic of a secondary alcohol. Oxidation of 2 with chromic acid produced a mixture of two ketones as shown by GLC, the predominant isomer cis-2,5-di-t-butylcyclohexanone (5) being formed in 90-95% yield. The amount of the isomeric trans-2,5-di-t-butylcyclohexanone (6) varied from one experiment to another and arises by a facile acid-catalyzed isomerization

of $\underset{\sim}{5}$ during the oxidation. We have been unsuccessful in preparing $\underset{\sim}{5}$ in pure form under a
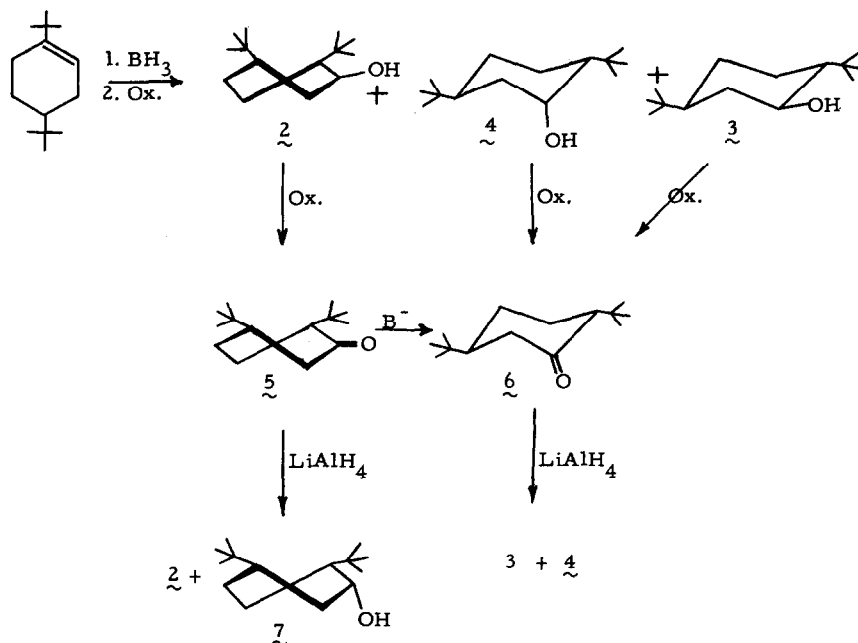
variety of oxidizing conditions. Ketone $\underset{\sim}{5}$ was isomerized quantitatively to ketone $\underset{\sim}{6}$ (m. p.

75-75. 5; <u>Anal</u>. Calcd. for $C_{14}H_{26}O$: C, 79. 94; H, 12. 46. Found: C, 79. 48; H, 12. 39) by

refluxing with dilute sodium ethoxide in ethanol for 15 minutes. The facile isomerization of $\underset{\sim}{5}$

to $\underset{\sim}{6}$ indicates that the <u>t</u>-butyl groups in $\underset{\sim}{5}$ are <u>cis</u>, and hence $\underset{\sim}{2}$ must be either <u>trans</u>, <u>trans</u>- or

<u>cis</u>, <u>cis</u>-2, 5-di-<u>t</u>-butylcyclohexanol. As the hydroboration reaction proceeds <u>via</u> a <u>cis</u> addition

of BH to the double bond, and the oxidation proceeds with retention of stereochemistry, the

predominant product formed on the hydroboration of $\underset{\sim}{1}$ must be the <u>trans</u>, <u>trans</u>-isomer $\underset{\sim}{2}$.

Reduction of ketone $\underset{\sim}{5}$ with lithium aluminum hydride produced a mixture of $\underset{\sim}{2}$ and a new alcohol

$\underset{\sim}{7}$. Alcohol $\underset{\sim}{7}$ was identical gas chromatographically (by retention time comparison of individual

samples and an admixture employing a 30 ft. 20% Carbowax 20M on firebrick column) with

authentic <u>cis</u>, <u>cis</u>-2, 5-di-<u>t</u>-butylcyclohexanol prepared by the catalytic reduction of 2, 5-di-<u>t</u>-

butylphenol and provided by Prof. R. Stolow. Reduction of ketone $\underset{\sim}{6}$ with lithium aluminum

hydride produced a mixture of alcohols $\underset{\sim}{3}$ and $\underset{\sim}{4}$ as shown by GLC comparison with authentic

samples (see later discussion).

Alcohol 3 (20% of the crude alcohol mixture) was recrystallized from aqueous-ethanol

giving m.p. 103-104°. The NMR spectrum of 3 displayed a broad band for the ring hydrogens

and a multiplet at -3.72ppm indicative of a secondary alcohol. Chromic acid oxidation of 3

produced only 6. Alcohol 3 was identical gas-liquid chromatographically with an authentic

sample of trans, cis-2,5-di-t-butylcyclohexanol provided by Prof. R. Stolow.

Alcohol 4 (3% of the crude alcohol mixture), m.p. 117-119°, displayed broad, unresolved

absorption for the ring hydrogens and an unresolved multiplet at -4.18 ppm indicative of a

secondary alcohol. Chromic acid oxidation of alcohol 4 produced only 6. Alcohol 4 was gas-

liquid chromatographically identical with authentic cis, trans-2,6-di-t-butylcyclohexanol

provided by Prof. R. Stolow.

Analysis of the above results indicates that the hydroboration of 1 proceeds to introduce

80% of the boron trans to the 4-t-butyl group. This is in distinct contrast to the results with

other 1-alkyl-4-t-butylcyclohexenes in which 62-75% of the boron is introduced cis with

respect to the 4-t-butyl group (4). This reversal in the mode of attack is not completely un-

expected in that Garbisch (5) has observed that the diimide reduction of 1,5-di-t-butylcyclo-

hexene gives a 48:52 mixture of cis- and trans-1,3-di-t-butylcyclohexanes whereas similar

reductions of 1-alkyl-4-t-butylcyclohexenes leads to the predominant formation of the trans

products (cis addition of H_2 with respect to the 4-t-butyl group). The interpretation of these

results will be presented in greater detail in the full publication.

The predominant formation of 8 in the hydroboration of 1, available in quantity by the

lithium in ethylenediamine reduction of 1,4-di-t-butylbenzene (6), provides an excellent

synthetic entry into the general system 9 in which the functional group Y is OH, NH_2 (7) or

Cl (8). Such compounds are not readily available by hydrogenation of the corresponding

substituted benzene systems.
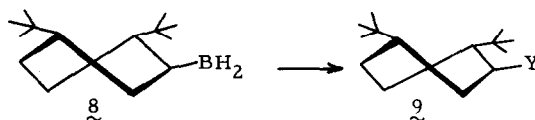
REFERENCES

1. National Science Foundation Predoctoral Fellow 1963-1965, Lubrizol Fellow 1965-1966.
    Acknowledgment is made to donors of the Petroleum Research Fund (PRF No. 1225-Al, 3),
    administered by the American Chemical Society, for partial support of this research.

2. N. L. Allinger, H. M. Blatter, L. A. Freiberg and F. M. Karkowski, J. Am. Chem. Soc.,
    88, 2999 (1966); M. Hanack, and K. W. Heiny, Ann., 682, 79 (1965); H. Feltkamp,
    N. C. Franklin, M. Hanack and K. W. Heiny, Tet. Letters, 3535 (1964); R. D. Stolow and
    M. M. Bonaventura, J. Am. Chem. Soc., 85, 3636 (1963).

3. R. D. Stolow, private communication.

4. D. J. Pasto and F. Klein, unpublished results.

5. E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson and C. M. Sprecher, J. Am.
    Chem. Soc., 87, 2932 (1965).

6. R. D. Stolow and J. A. Ward, J. Org. Chem., 31, 965 (1966).

7. H. C. Brown, W. R. Heydkamp, E. Breuer and W. S. Murphy, J. Am. Chem. Soc., 86,
    3565 (1964).

8. J. G. Sharefkin and H. D. Banks, J. Org. Chem., 30, 4313 (1965).