and the reaction allowed to take place slowly. When the reaction was complete, the mixture was distilled at atmospheric pressure (630 mm.). Material boiling near 75° solidified in the condenser, and the plug of solid was pushed through into the receiver, which was cooled in a Dry Ice-bath. The weight of solid distillate was 0.63 g. The recovery of norbornene was 69%.

Competition of Norbornadiene and Cyclohexene for *p*-Thiocresol.—This experiment was carried out in essentially the same manner as that described above. To a mixture of 939 mg. (10.2 mmoles) of norbornadiene and 822 mg. (10.0 mmoles) of cyclohexene at Dry Ice temperature, 1.304 g. (10.5 mmoles) of *p*-thiocresol was added and the reaction allowed to take place as the reactants warmed to room temperature. The reaction mixture was distilled at 630 mm., and 591 mg. (74%) of a liquid, b.p. 69°, $n^{20}\mathrm{D}$ 1.4465, was collected. The refractive index of the starting cyclohexene, $n^{20}\mathrm{D}$, was 1.4465.

Dilution Experiments with the Addition of *p*-Thiocresol to Norbornadiene. First Experiment.—Norbornadiene, 4.49 g. (48.6 mmoles) was stirred with 6.0 g. (48.6 mmoles) of *p*-thiocresol in a flask cooled in an ice-bath. After one hour, the reaction mixture was submitted to vacuum distillation, yielding 8.97 g. (85.5%) of a light yellow oil, b.p. 110–120° (0.8 mm.). No solids or dark tarry residue were found in the distillation flask. The oil was distilled again, giving a final yield of 8.39 g. (80.2%) of colorless oil. In all distillations in this series, an electrically heated oil-bath was used to avoid overheating the products.

Second Experiment.—A solution of 6.0 g. (48.6 mmoles) of *p*-thiocresol in 50 ml. of chlorobenzene, $n^{20}\mathrm{D}$ 1.5252, was stirred with 4.49 g. (48.6 mmoles) of norbornadiene in a flask cooled with an ice-bath. After two hours, the reaction mixture was submitted to vacuum distillation. After removal of the solvent, 9.27 g. (88.3%) of a colorless oil, b.p. 88–122° (0.5 mm.), was obtained, which was redistilled to give 8.90 g. (84.8%) of colorless oil, b.p. 90–112° (0.5 mm.). No solids or dark tarry residue were found in the distillation flask in either of these distillations.

Third Experiment.—A solution of 4.49 g. (48.6 mmoles) of norbornadiene in 40 ml. of chlorobenzene was stirred in a flask cooled with an ice-bath, and 6.0 g. (48.6 mmoles) of *p*-thiocresol dissolved in 10 ml. of chlorobenzene was added dropwise over a period of two hours. After one additional hour the reaction mixture was submitted to vacuum distillation. After removal of the solvent, 9.22 g. (87.9%) of a colorless oil, b.p. 90–117° (0.5 mm.) was obtained, and this was redistilled to give 8.71 g. (83.2%) of colorless oil, b.p. 90–113° (0.4 mm.).

Fourth Experiment.—A solution of 6.0 g. (48.6 mmoles) of *p*-thiocresol in 50 ml. of chlorobenzene was heated in an oil-bath to 105°, and then 4.49 g. (48.6 mmoles) of norbornadiene was poured in rapidly. The temperature of 105° was maintained for two hours with stirring. The reaction mixture was immediately distilled under vacuum, yielding 9.37 g. (89.5%) of colorless oil, b.p. 110–136° (0.8 mm.) after removal of the solvent. No solid or dark tarry material was in evidence in the distillation flask. The products were distilled again, yielding 8.67 g. (82.4%) of colorless oil boiling at 100–110° (0.2 mm.).

Fifth Experiment.—A mixture of 6.0 g. (48.6 mmoles) of *p*-thiocresol and 4.49 g. (48.6 mmoles) of norbornadiene was stirred vigorously with 50 ml. of reagent-grade ethylene glycol in a flask cooled with an ice-bath. The temperature of the reaction mixture was maintained at 5–15° for 30 minutes, and then at 20–25° for two hours, after which the mixture was extracted four times with petroleum ether, b.p. 59–61°. The organic layer was dried over magnesium sulfate, and the solvent was removed. The residue was subjected to vacuum distillation, yielding 9.58 g. (91.3%) of a colorless oil, b.p. 115–134° (0.4 mm.). The residue from this distillation consisted of 0.68 g. (6.4%) of an impure solid, m.p. 58–90°, which was recrystallized six times from acetone and from petroleum ether to give an analytical sample, m.p. 116–117°. This material took up no hydrogen over a 10% palladium-on-charcoal catalyst, and analyzed for the addition product of two moles of thiocresol and one of diolefin.

Anal. Calcd. for $C_{21}H_{24}S_2$: C, 74.05; H, 7.12; S, 18.83. Found: C, 74.25; H, 6.97; S, 18.57.

In three other experiments in which water instead of ethylene glycol was used as the coolant, the crude yields of solid residue ranged from 19.2–24.8%.

The oil obtained above was redistilled, yielding 8.92 g. (85.0%) of colorless oil, b.p. 110–125 (0.4 mm.).

Estimation of Unsaturation.—In a typical experiment, 100 mg. of 10% palladium-on-charcoal catalyst was weighed into a hydrogenation flask, 15 ml. of 95% ethanol was added, and the flask was shaken on a quantitative (atmospheric pressure) hydrogenator for 10–15 minutes, during which time 2.2 ml. of hydrogen was taken up. The flask was taken off and the hydrogen atmosphere in it removed. Then 0.1140 g. (0.5253 mmole) of the oil from dilution experiment 1 was washed into the flask with 25 ml. of 95% ethanol in small portions. The flask was then shaken on the quantitative hydrogenator for 15 minutes, at which time a constant value of 6.70 ml. of hydrogen had been taken up. This volume was corrected to standard conditions by the use of the ideal gas law, and gave a value of 5.08 ml., or 43.2 mole percentage of hydrogen uptake.

BOULDER, COLORADO

[CONTRIBUTION FROM RESEARCH DEPARTMENT, HOWARDS OF ILFORD, LTD.]

Chemical Reductions of Substituted Cyclohexanones

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Substituted cyclohexanones have been chemically reduced with four different reagents and the stereoisomeric composition of the products determined. The results obtained do not support any of the generalizations made by previous workers as to the differing effects of the reagents used.

Although a considerable number of examples of the proportions of *cis* and *trans* isomers produced by chemical reduction of substituted cyclohexanones have been reported in the literature, much of the work is of little value since the methods used in establishing the stereoisomeric compositions of the products of reduction are not reliable.[1]

Noyce and his co-workers have carried out a number of hydride reductions recently[2,3] and have developed a theory to account for their results.[3] Their analytical procedure was sound and was based on the determination of the densities of the products they obtained.

We have reduced 2-, 3- and 4-methylcyclohexanones, dihydroisophorone and 4-cyclohexylcyclohexanone with lithium aluminum hydride, potassium borohydride, sodium and alcohol, and aluminum isopropoxide, and determined the isomeric composition of the products by either density measurements or thermal analysis. The results of the present work are given in Table I, together with the results of previous workers where these are based on reliable analytical methods.

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[1] E. G. Peppiatt and R. J. Wicker, *Chemistry & Industry*, 747 (1955).

[2] D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

[3] W. G. Dauben, G. J. Fonken and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

TABLE I

THE PERCENTAGE OF STABLE ISOMER IN REDUCTION PRODUCTS OF SUBSTITUTED CYCLOHEXANONES

	Reducing reagent						
Compound reduced	$LiAlH_4$	KBH_4 in aq. EtOH	$NaBH_4$ in aq. MeOH	$NaBH_4$ in pyridine	Na and EtOH	Al isopropoxide	Method of product analysis
2-Methylcyclohexanone	64,[2,5] 82,[3] 60	41	69[3]	56[3]	72	42,[2] 50,[4] 63	Density
3-Methylcyclohexanone[a]	92,[2] 89	58	..	..	80	45,[4] 55	Density
4-Methylcyclohexanone	81,[2] 75	65	75[3]	60[3]	83	67,[4] 68	Density
Dihydroisophorone	50	47	..	..	63	75	Thermal
4-Cyclohexylcyclohexanone	43	50	..	..	50	28	Thermal
4-Isopropylcyclohexanone	...	..	..	..	..	60[4]	
Methone	71[2]	..	49[3]	..	..		Opt. rot.

[a] The results for the 3-isomers have been revised where necessary to conform with the recently reversed configurations. Of 2- and 4-substituted cyclohexanols the more stable isomer is the *trans*, whereas it is the *cis* isomer that is the more stable of the 3-substituted cyclohexanols.

Noyce and his co-workers[3] consider that two factors control the ultimate proportions of isomers obtained in a hydride reduction. One is the degree of steric hindrance operating between the ketone and the reducing agent, and the other is the relative stabilities of the two alcohols that are ultimately formed. They consider that $LiAlH_4$ is less bulky than $NaBH_4$ and that therefore reductions with $LiAlH_4$ are less subject to steric requirements than those with $NaBH_4$. Thus the products from $LiAlH_4$ reductions should contain a preponderance of the more stable equatorial alcohol, whereas those with $NaBH_4$ will depend far more on steric interactions which are estimated from considerations of the possible conformations of the ketone. Application of these ideas to menthone and 2- and 4-methylcyclohexanones, led Noyce and his co-workers to the conclusion that a greater preponderance of the more stable alcohol should result from reductions with $LiAlH_4$ than with $NaBH_4$, and they point out that their experimental results conform with those predictions.[3] However, in an earlier paper,[2] Noyce reports that the reduction of 2-methylcyclohexanone with $LiAlH_4$ gives a product containing 64% of *trans* isomer, whereas in the later paper a figure of 82% is given, without comment. Since the figure of 64% was independently confirmed by Macbeth and Shannon,[5] and in the present work a figure of 60% is obtained, the higher figure of 82% would appear to be incorrect. If the lower figures of 60 and 64% are used instead of the figure of 82% then the results for this particular ketone do not then support the hypotheses of Noyce's later paper.[3]

Examination of the results for other ketones obtained in our work by means of the concepts of Noyce and his co-workers leads to the following observations. 4-Cyclohexylcyclohexanone should give similar results to 4-methylcyclohexanone, whereas in fact the opposite results of those expected are obtained, and more of the stable *trans* isomer results from borohydride reduction than from $LiAlH_4$ reduction.

The examples with dihydroisophorone are particularly valuable since in this ketone one of the *gem*-methyl groups must occupy the axial position, and so offers considerably more 1:3 steric interaction to the reducing agent attacking the carbonyl group than does the axial hydrogen on C_3 in the methylcyclohexanones. The axial 3-methyl isomer can be ignored since this is very unstable.[6]

Examination of the equatorial 3-methyl form leads to the prediction that steric requirements should lead to a preponderance of the *trans* isomer. Consideration of the stability of the alcohols produced suggests the preferential formation of the stable *cis* isomer.[6] Thus $LiAlH_4$, which is less sensitive to steric requirements should give considerably less of the unstable *trans* isomer than borohydride. In fact no significant difference in the proportion of isomers is found experimentally (50 and 53%, respectively).

The results with 3-methylcyclohexanone will be found on similar considerations to conform with the hypotheses of Noyce and his co-workers. It is interesting to note that less of the stable isomer is formed with this ketone with both lithium aluminum hydride and potassium borohydride than is formed in the case of the other 3-substituted ketone examined, namely, dihydroisophorone.

Thus, although it can be seen from the results that there may be a general tendency for borohydrides to give a lower proportion of the stable alcohol than lithium aluminum hydride, the considerable effects caused by the change of solvent used and also the cation in the case of the borohydrides suggest that it is probably not possible at this stage to consider any mechanisms other than from a purely speculative point of view.

Since it is known that the less stable isomer of substituted cyclohexanols can be isomerized by heating with sodium in alcohol, it has often been assumed that reductions of substituted cyclohexanones with sodium and alcohol will lead to a preponderance of the more stable isomer, since isomerization will occur simultaneously. However, we have found that the less stable *trans* isomer of 3,3,5-trimethylcyclohexanol is not isomerized when treated with sodium and alcohol under the same conditions as used in its preparation by the reduction of dihydroisophorone with sodium and alcohol. Thus reduction with sodium and alcohol does not necessarily cause isomerization. This is no doubt due to the fact that much lower temperatures than the 200° usually used for the isomerization reaction were reached during the reduction of the ketone.

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(4) L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.* 2641 (1949).

(5) A. K. Macbeth and J. S. Shannon, *ibid.*, 2852 (1952).

(6) E. G. Peppiatt and R. J. Wicker, *ibid.*, 3122 (1955); R. J. Wicker, *ibid.*, 2165 (1956).

Although Jackman, Macbeth and Mills[4] found in the two examples they examined that no isomerization occurred during reductions of cyclic ketones with aluminum isopropoxide, we have found that 3,3,5-trimethylcyclohexanol containing 90% of *trans* isomer isomerizes to a mixture containing 80% of *trans*-alcohol when treated with aluminum isopropoxide under the same conditions as those used for reducing dihydroisophorone. We used the standard Meerwein–Ponndorf procedure as did Jackman, Macbeth and Mills.

Thus the proportions of isomers produced by chemical reduction will vary with the duration and conditions of the reaction if isomerization occurs, as it may do when aluminum isopropoxide or sodium and alcohol are the reducing reagents; isomerization with metal hydrides is less likely since the reductions are very rapid and are normally carried out at lower temperatures.

Noyce and Denney[2] consider that the use of aluminum isopropoxide in reduction leads to a preponderance of *cis* isomer due to steric hindrance to the reagent caused by substituents in the ketone, this being most marked in 2- and least in 4-substituted cyclohexanones. Jackman, Macbeth and Mills[4] make similar statements. In a later paper[3] the views of Noyce are modified to the statement that $LiAlH_4$, $NaBH_4$ and Al isopropoxide lead to increasing amounts of axial alcohol. Our results do not lend support to this generalization. We suggest that the assignment of configurations to substituted cyclohexanols should therefore not be based solely on arguments from generalized rules, such as those listed by Barton[7] regarding the proportion of stereoisomers produced on reduction with these reagents, and that any generalizations which can be made should be used solely as a guide to choice of reagent.

More experimental work is required before any further speculations as to the mechanism of these reductions are advanced.

Experimental

Melting points were determined by a standard cooling curve method and are corrected. *cis–trans*-Compositions of products were determined by thermal analysis in the case of 3,3,5-trimethylcyclohexanol and 4-cyclohexylcyclohexanol, and by density in the case of the three methylcyclohexanols. Corrections were made for any ketone present as determined by the hydroxylamine method. For details of experimental procedures see reference 6.

Reductions with Lithium Aluminum Hydride.—The ketone (0.1 mole) dissolved in anhydrous ether (50 ml.) was added dropwise to a stirred solution of lithium aluminum hydride (10% in excess of theory), in anhydrous ether (50 ml.) at a rate just sufficient to maintain gentle reflux. Stirring was continued for a further 15 min., and the excess of reagent destroyed by dropwise addition of water. The reaction mixture was then poured into ice-water and acidified with hydrochloric acid (2 *N*). The alcohol was ether extracted, washed with dilute sodium hydroxide, water, and dried with anhydrous sodium sulfate. Ether was removed on a steam-bath and the residue distilled.

Reductions with Potassium Borohydride.—To the ketone (0.1 mole) dissolved in ethanol (25 ml.) was added slowly with shaking a solution of potassium borohydride (100% excess of theory) in the minimum amount of water (about 20 ml.). The reaction was maintained below 40° with ice-bath cooling when necessary. After the addition of the reagent the reaction mixture was allowed to stand for several hours with occasional shaking and then poured into water (150 ml.). The precipitated product was extracted exhaustively with ether and the ethereal extracts dried with anhydrous sodium sulfate. Ether was removed by evaporation on a steam-bath and the residue distilled.

Reductions with Sodium and Alcohol.—To the ketone (0.1 mole) dissolved in ethanol (25–30 ml.) was slowly added sodium (twice the theoretical requirement) with shaking and cooling in an ice-bath to maintain control over the vigorous reaction. The final additions of sodium were made whilst heating on a steam-bath. The solution was cooled and poured into water (150 ml.), acidified with hydrochloric acid and exhaustively extracted with ether. The ether extracts were dried with anhydrous sodium sulfate and ether evaporated on a steam-bath and the residue distilled.

Reductions with Aluminum Isopropoxide.—The ketone (0.1 mole) was mixed with aluminum isopropoxide solution (90 ml. of 10% solution in isopropyl alcohol) and isopropyl alcohol (90 ml.) and distilled slowly until acetone was no longer detectable in the distillate. The isopropyl alcohol was then removed by vacuum distillation and the residue mixed with water, and sulfuric acid added until all precipitated solid dissolved. The mixture was then steam distilled and the distillate exhaustively extracted with ether, washed, dried with anhydrous sodium sulfate and the ether evaporated on a steam-bath and the residue distilled.

The following results were obtained: reagent, $LiAlH_4$ (Compound, d^{30}_{4}, m.p., ketone (%)): 2-methylcyclohexanone, 0.9214, —, nil; 3-methylcyclohexanone, 0.9079, —, nil; 4-methylcyclohexanone, 0.9073, —, nil; dihydroisophorone, —, 20°, 0.95 (duplicate, —, 20°, 1.6); 4-cyclohexylcyclohexanone, —, 89.5°, nil.

Reagent, KBH_4: 2-methylcyclohexanone, 0.9233, —, 0.4; 3-methylcyclohexanone, 0.9099, —, nil; 4-methylcyclohexanone, 0.9087, —, nil; dihydroisophorone, —, 27.5°, 2.6 (duplicate, —, 22.7°, 0.35); 4-cyclohexylcyclohexanone, —, 92.5°, 0.6.

Reagent, Na and Alcohol: 2-methylcyclohexanone, 0.9202, —, 0.6; 3-methylcyclohexanone, 0.9085, —, nil; 4-methylcyclohexanone, 0.9062, —, nil; dihydroisophorone, —, 25.2°, 1.2 (duplicate, —, 26.3°, 1.5); 4-cyclohexylcyclohexanone, —, 90°, 6).

Reagent, Al isopropoxide: 2-methylcyclohexanone, 0.9211, —, nil; 3-methylcyclohexanone, 0.9101, —, 0.4; 4-methylcyclohexanone, 0.9083, —, 1.3; dihydroisophorone, —, 29.7°, 1.0 (duplicate, —, 28.2°, nil); 4-cyclohexylcyclohexanone, —, 82.5°, 1.3.

Attempted Isomerization of *trans*-3,3,5-Trimethylcyclohexanol with Sodium and Alcohol.—3,3,5-Trimethylcyclohexanol (10 g. containing 89% *trans* and 11% *cis* isomer and 0.6% ketone) was dissolved in ethanol (25 ml.) and treated with metallic sodium (1 g.) under the exact conditions used in the reduction of dihydroisophorone with sodium and alcohol. The initial starting material was recovered unchanged.

Isomerization of *trans*-3,3,5-Trimethylcyclohexanol with Aluminum Isopropoxide.—3,3,5-Trimethylcyclohexanol (10 g. containing 89% of *trans* and 11% *cis* isomer) was treated with aluminum isopropoxide solution (80 ml.) and isopropyl alcohol (80 ml.) under the exact conditions used in the reduction of dihydroisophorone with aluminum isopropoxide. The final product contained 79% *trans*- and 21% *cis*-3,3,5-trimethylcyclohexanol.

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(7) D. H. R. Barton, *J. Chem. Soc.*, 1027, footnote 23 (1953).