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Reduction of Olefins Using Sodium–Hexamethylphosphoramide–*t*-Butyl Alcohol[1]

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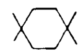
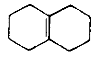
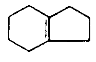
Nonconjugated alkenes and polyalkylated aromatic compounds are resistant to reduction by dissolving metals in liquid ammonia.[3–6] Solutions of lithium in certain alkylamines reduce some nonconjugated monoolefins and alkylbenzenes, but reaction is slow and yields are variable.[7] During the course of other work, we found that solutions of sodium hexamethylphosphoramide (HMPA) containing *t*-butyl alcohol were capable of effecting reduction of hexamethylbenzene not only to 1,2,3,4,5,6-hexamethylcyclohexa-1,4-diene, but also to the corresponding hexamethylcyclohexene and -hexane.[8,9] The observation of the latter products suggested that HMPA–sodium–*t*-butyl alcohol might be effective in reducing other unactivated alkenes. Here we wish to describe experiments indicating that this reducing mixture provides a convenient and general method of saturating even tetraalkyl substituted carbon–carbon bonds.[11]

Table I lists the yields of products detected on reaction of several representative unsaturated compounds with ~2–4 equiv of sodium in HMPA–*t*-butyl alcohol at room temperature over periods of 6–24 hr. The yields of reduced product in these reactions are generally high. The relatively low yields observed for the reduction of norbornene and 3,3,6,6-cyclohexa-1,4-diene represent isolated yields, and should be considered minimum values: with attention to detail during the work-up procedures, it should be possible to increase these numbers significantly. Similarly, the conversion

TABLE I
REDUCTION OF OLEFINS WITH
SODIUM–HEXAMETHYLPHOSPHORAMIDE–*t*-BUTYL ALCOHOL

Starting material	Product	Yield, %[a]
1-Hexene	*n*-Hexane	98
Methylenecyclohexane	Methylcyclohexane	100
trans-3-Hexene	*n*-Hexane	97
Cyclohexene	Cyclohexane	99
Norbornene	Norbornane	73[b]
		>40[b,c]
1-Methylcyclohexane	Methylcyclohexene	100
	*trans*-Decalin	91
	cis-Decalin	3
	*trans*-Hexahydroindan	(73)[d]
	cis-Hexahydroindan	(27)[d]
3-Hexyne	Hexane	79
	trans-3-Hexene	14
Norcarane	1-Methylcyclohexane	Trace[e]

[a] Unless noted otherwise, yields were determined by glpc using internal standard techniques. Products were identified by comparison of mass spectra with those of authentic samples. [b] Isolated yield. [c] No effort was made to maximize this yield (see Experimental Section). [d] Relative yields. [e] >95% norcarane was observed at the end of the reaction. 1-Methylcyclohexane (<1%) was identified by glpc retention time only.

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[2] National Science Foundation Trainee, 1965–1966; National Institutes of Health Predoctoral Fellow, 1966–1969.

(3) A. J. Birch, *Quart. Rev. (London)*, **4**, 69 (1950); A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958).

(4) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 3.

(5) T. J. King, *J. Chem. Soc.*, 898 (1951).

(6) H. Boer and P. M. Duinker, *Recl. Trav. Chim. Pays-Bas*, **77**, 346 (1958); J. D. Brooks, R. A. Durie, and H. Silberman, *Aust. J. Chem.*, **17**, 55 (1964).

(7) For examples, see (a) R. A. Benkeser, C. Arnold, R. F. Lambert, and O. H. Thomas, *J. Amer. Chem. Soc.*, **77**, 6042 (1955); (b) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *ibid.*, **77**, 3230 (1955); (c) R. A. Benkeser, *et al.*, *J. Org. Chem.*, **29**, 1313 (1964); (d) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *ibid.*, **28**, 1094 (1963); (e) R. A. Benkeser, J. J. Hazdra, R. F. Lambert, and P. W. Ryan, *ibid.*, **24**, 854 (1959).

(8) G. M. Whitesides and W. J. Ehmann, *J. Amer. Chem. Soc.*, **91**, 3800 (1969).

(9) The initial stimulus to examine sodium–HMPA–*t*-butyl alcohol as a reducing system originated in studies of the reduction of α,β-unsaturated ketones carried out by Dr. Roger Giese and Professor H. O. House in this department.[10] We are indebted to Drs. Giese and House for advice concerning this system.

(10) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970); H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *ibid.*, **92**, 2800 (1970).

(11) For reviews of HMPA as a solvent for reductions, see H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967); H. Normant, *Bull. Chim. Soc. Fr.*, 791 (1968); H. Normant, T. Cuvigny, J. Normant, and B. Angelo, *ibid.*, 1561 (1965); and ref 10.

of 3-hexyne to *n*-hexane could have been improved by the use of additional sodium. However, reduction of the cyclopropyl ring of norcarane does not appear to be practical under these reaction conditions.

The ratios of products containing *cis* and *trans* ring junctures obtained on reduction of $\Delta^{9,10}$-octalin and 4,5,6,7-tetrahydroindan indicate that, at least in these cases, the reductions are nonstereospecific. For comparison, the equilibrium ratio of *cis*- to *trans*-decalin at room temperature is 5:95,[12] and the corresponding ratio for hexahydroindan is 39:61.[13] Hence, the product mixtures formed in these two reductions lie close to equilibrium mixtures. It seems unlikely that *cis* and *trans* isomers of decalin or hexahydroindan interconvert under these conditions. Thus, the carbanions or organosodium compounds that are presumed to be intermediates in the reductions react, either by virtue of the stereochemistry of their formation or of their subsequent equilibration, to give directly a nearly thermodynamic product distribution.

These reductions in HMPA offer a potentially attractive method of incorporating deuterium into organic molecules. The reduction of olefins using a deuterated alcohol (*e.g.*, *t*-butyl alcohol-O-*d*) should permit deuteration without the isomerization and scrambling common to catalytic reductions or the expense of deuterated diborane and similar reducing agents. To test the practicality of deuterium incorporation by reduction in HMPA, $\Delta^{9,10}$-octalin and 3,3,6,6-tetramethylcyclohexadiene were allowed to react with sodium–HMPA–*t*-butyl alcohol-O-*d* (93% d_1, 7% d_0). The observed deuterium incorporation into the *trans*-decalin and 1,1,4,4-tetramethylcyclohexane were 1.71 and 1.80 deuterium atoms per olefinic bond, respectively; after correction for the isotopic purity of the *t*-butyl alcohol-O-*d*, these incorporations become 1.84 and 1.94 deuterium atoms per olefinic bond. Although the hydrogen incorporated into these products may indicate that attack of carbanion or radical on HMPA occurs to some extent, it seems more probable that it reflects isotopic fractionation resulting from a kinetic isotope effect in protonation of intermediate carbanions by alcohol.[14] Regardless, reduction by sodium–HMPA–*t*-butyl alcohol-O-*d* holds clear promise as a method of introducing deuterium into certain classes of molecules.

Experimental Section[15]

General Methods.—All reactions were carried out in flame-dried glassware under an inert atmosphere of prepurified nitrogen using standard techniques for handling oxygen- and water-sensitive compounds.[16] Tetrahydrofuran was dried by distillation from lithium aluminum hydride under a nitrogen atmosphere. Hexamethylphosphoramide (Fisher Scientific Company) was purified by stirring with sodium at room temperature until a dark blue color persisted and distilling [65° (0.2 Torr)] through a 10-cm Vigreux column. Reagent grade *t*-butyl alcohol was dried by distillation from calcium hydride. Unless otherwise specified, all reagents were obtained commercially and used without further purification.

Reductions. General Procedure.—Similar procedures were used for all of the small-scale reductions described in Table I. A representative procedure is that for 1-hexene. A mixture of 150 mg (6.5 mg-atoms) of sodium cut into small pieces, 18 ml of HMPA, and 0.1141 g (1.4 mmol) of 1-hexene, containing 0.148 g of cyclohexane as an internal glpc standard, was stirred at room temperature until a blue color appeared. To the blue solution was added a 0.3-ml portion of *t*-butyl alcohol; two additional 0.3-ml portions were added at 1.5 hr intervals. After the blue color vanished, (~6 hr) the solution was poured into 80 ml of water and extracted with 5 ml of decane. The decane was washed with 50 ml of water and dried ($MgSO_4$). Analysis by glpc using a β,β'-oxidipropionitrile on Chromosorb W column showed 0.115 g (98%) of hexane and 0.0052 g (4%) of 1-hexene.

Reduction of norbornene illustrates the procedure used for larger scale reactions. A mixture of 5.8 g (0.25 g-atom) of sodium and 100 ml of HMPA was stirred until a blue color appeared and 20 g (0.27 mol) of *t*-butyl alcohol was added in one portion. After the sodium–HMPA–alcohol solution had been allowed to stir for 5 min at room temperature, a solution of 9.4 g (0.10 mol) of norbornene in 10 ml of HMPA was added slowly over a period of 6 hr at such a rate that the blue color of the HMPA solution never completely disappeared.[17] After completion of the addition, the mixture was stirred for 12 hr, poured into 400 ml of ice water, and extracted with two 20-ml portions of pentane. The organic phase was then distilled through a 10-cm vacuum-jacketed column to yield 7.0 g (73%) of norbornene having bp 105.5–106.5° and mp 86.5–87.5°, and ir spectrum identical with that of an authentic sample. Glpc analysis of the pentane extract, using UC-W98 on Chromosorb W column, showed no trace of unreacted norbornene.

2,2,5,5-Tetramethylcyclohexa-1,3-dione.—A mixture of 60 g (0.43 mol) of 5,5-dimethylcyclohexa-1,3-dione (dimedone), 100 g (0.72 mol) of potassium carbonate, and 500 ml of methanol was heated at reflux temperature until carbon dioxide evolution had ceased (*ca.* 30 min). The mixture was cooled to 0° and 140 g (0.99 mol) of iodomethane was added slowly over 1 hr. The mixture was heated at reflux temperature for 1 hr, cooled, and poured into 1 l. of water. The water was extracted three times with 500-ml portions of ether and the ether solution dried ($MgSO_4$) and concentrated under vacuum. The residue was crystallized from hexane to yield 40 g (55%) of 2,2,5,5-tetramethylcyclohexa-1,3-dione having mp 96–97°, lit.[18] mp 98°.

2,2,5,5-Tetramethylcyclohexa-1,3-diol.—To a slurry of 16 g (0.42 mol) of lithium aluminum hydride in 500 ml of dry tetrahydrofuran was added 33 g (0.2 mol) of 2,2,5,5-tetramethylcyclohexa-1,3-dione in 250 ml of tetrahydrofuran over a period of 1 hr. After the addition was complete, the solution was heated to reflux for 1 hr, cooled, and excess LAH was decomposed by cautious addition of ethyl acetate. The mixture was made acidic with 20% aqueous hydrochloric acid, the layers were separated, and the solvent was removed under vacuum. The residue was dissolved in 1 l. of ether, washed with 500 ml of water, dried ($MgSO_4$), and the ether was removed under vacuum to yield 30 g (90%) of 2,2,5,5-tetramethylcyclohexa-1,3-diol having mp 185–190°; lit.[19] mp for the *trans* isomer 105–107°; for the *cis* isomer 201–206°.

3,3,6,6-Tetramethylcyclohexadiene.—A solution of 25 g (0.15 mol) of 2,2,5,5-tetramethylcyclohexa-1,3-diol and 150 g (0.79 mol) of *p*-toluenesulfonyl chloride in 450 ml of pyridine was refluxed for 20 hr, poured over ice, and extracted with three 100-ml

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(12) G. Chiurdoglu and J. L. Jaminet, *Bull Soc. Chim. Belges*, **62**, 448 (1953).

(13) K. R. Blanchard and P. von R. Schleyer, *J. Org. Chem.*, **28**, 247 (1963).

(14) Y. Pocker and J. H. Exner, *J. Amer. Chem. Soc.*, **90**, 6764 (1968).

(15) Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Nmr spectra were run on a Varian T-60 spectrometer. Infrared spectra were taken in sodium chloride cells using a Perkin-Elmer Model 237B grating spectrophotometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Product mixtures were analyzed by glpc on an F & M Model 810 flame ionization instrument. Products were identified by collecting samples by glpc using an F & M Model 720 instrument equipped with a thermal conductivity detector, and comparing the mass spectra of the collected samples with the spectra of authentic compounds. Microanalysis was performed by Midwest Microlab, Inc., Indianapolis, Ind.

(16) D. F. Shriver, "The Manipulation of Air-sensitive Compounds," McGraw-Hill, New York, N. Y., 1969.

(17) If the norbornene were added too rapidly to the reducing mixture, the blue color would vanish temporarily, but would return shortly after the addition of norbornene was stopped. If the addition of norbornene were continued after the blue color had vanished, the solution would eventually turn yellow and the blue color would not return, even upon stirring for several days. Sodium did not dissolve appreciably in this yellow solution and the reduction proceeded very slowly, if at all. The same phenomena were noted when the reaction was carried out by the addition of *t*-butyl alcohol to sodium in a solution of norbornene in HMPA.

(18) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).

(19) F. W. Grant, R. W. Gleason, and L. H. Bushwellen, *J. Org. Chem.*, **30**, 290 (1965).

portions of ether. The ether was washed with 150 ml of 10% aqueous hydrochloric acid, dried ($MgSO_4$), and concentrated by distillation through a 50-cm Vigreux column. The residue was then distilled through a 50-cm Teflon annular spinning-band column to yield 5.0 g (27%) of 3,3,6,6-tetramethylcyclohexadiene. The ir spectrum was in agreement with that of an authentic sample;[20] nmr ($CDCl_3$) δ 5.38 (s, 4, vinyl CH) and 1.01 ppm (s, 12, CH_3).

_t_-Butyl Alcohol-O-_d_.—To 33 g (0.25 mol) of potassium *t*-butoxide under nitrogen was added very carefully 7.0 ml (0.35 mol) of deuterium oxide (Columbia Organic Chemicals, 99.8% *d*). The crude *t*-butyl alcohol-O-*d* was removed by bulb to bulb distillation under vacuum and was then distilled from calcium hydride to yield 15 g (82%) of *t*-butyl alcohol, having isotopic composition[21] 93.0% d_1 and 7.0% d_0.[10,22]

1,1,4,4-Tetramethylcyclohexane-2,3,5,6-_d_$_4$.—A mixture of 1.0 g (44 mg-atom) of sodium and 25 ml of HMPA were stirred at room temperature until a deep blue color appeared. To the solution was then added 0.55 ml (*ca.* 0.5 g, 3.7 mmol) of 3,3,6,6-tetramethylcyclohexadiene and 4 ml of *t*-butyl alcohol-O-*d*. The mixture was stirred overnight and poured into 100 ml of an ice water slush. The aqueous phase was immediately extracted with 25 ml of fluorotrichloromethane and the organic layer was separated, dried ($MgSO_4$), and concentrated by distillation of the solvent through a 20-cm Vigreux column. The 1,1,4,4-tetramethylcyclohexane in the residue was collected using glpc (UC-W98 on Chromosorb W) to yield 0.21 ml of pure product having mass spectral isotopic composition (10 eV) 66.2% d_4, 28.6% d_3, and 5.2% d_2.

Characterization was accomplished by preparation of undeuterated 1,1,4,4-tetramethylcyclohexane using $(CH_3)_3COH$ as the proton source: nmr ($CFCl_3$) δ 1.25 (s, 8, CH_2) and 0.88 ppm (s, 12, CH_3).

Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.68; H, 14.37.

Registry No.—Hexamethylphosphoramide, 680-31-9; *t*-butyl alcohol, 75-65-0; sodium, 7440-23-5.

Acknowledgments.—We are indebted to Dr. H. O. House for a sample of $\Delta^{9,10}$-octalin, and Drs. Jon Engstrom and F. D. Greene for a sample of tetrahydroindan.

[20] Sadtler Catalogue, spectrum no 30757.

[21] Benzene-free phenylmagnesium bromide was prepared by the addition of 50 ml of toluene to *ca.* 10 mmol of phenylmagnesium bromide in 5 ml of ether and distillation of the mixture until glpc analysis showed that no ether or benzene remained in the resulting toluene suspension of phenyl Grignard reagent. The isotopic composition of the *t*-butyl alcohol-O-*d* was determined by reaction of the Grignard reagent with *t*-butyl alcohol-O-*d*, isolation of a sample of the resulting benzene by distillation, further purification by collection from glpc, and mass spectral isotopic analysis. Less than 1 equiv of *t*-butyl alcohol-O-*d* per equivalent of phenyl Grignard reagent was used to minimize the influence of any deuterium kinetic isotope effect in the hydrolysis on the accuracy of the analysis.

[22] A superior preparation of *t*-butyl alcohol-*O-d* has been published recently: A. T. Young and R. D. Guthrie, *J. Org. Chem.*, **35**, 852 (1970).