BIS-3-METHYL-2-BUTYLBORANE AS A SELECTIVE REAGENT FOR THE REDUCTION OF REPRESENTATIVE FUNCTIONAL GROUPS

Sir:

Bis-3-methyl-2-butylborane is a highly selective reagent for the hydroboration of olefins and dienes. We now report that this reagent exhibits remarkable selectivity in its reducing action toward representative functional groups, permitting selective reductions not otherwise feasible.

The groups listed are reduced at 0°C in 0.5 M solution in tetrahydrofuran (products in parentheses): aldehydes and ketones (alcohols), unhindered olefins and acetylenes (organoboranes), y-lactones (hydroxyaldehydes) and N,N-dimethylamines (aldehydes). Nitrobenzene and nitriles react only slowly under these conditions.

These groups react to evolve hydrogen, but do not undergo reduction: carboxylic acids, amides, and sulfonic acids. No reactivity occurs under these conditions with esters, acid chlorides, acid anhydrides, azobenzene, sulfones and sulfonyl chlorides.

The failure of bis-3-methyl-2-butylborane to reduce carboxylic acids is unexpected in view of the very fast reaction with diborane. It makes possible both selective reductions and hydroboration in the presence of unprotected carboxylic acid groups, as illustrated by the following conversion of 10-undecenoic acid to 11-hydroxyundecanoic acid.

Undecenoic acid, 25 mmoles, was treated with a solution of 50 mmoles of bis-3-methyl-2-butylborane in tetrahydrofuran at 0°C. Hydrogen (24 mmoles) was rapidly evolved. After 30 minutes, the reaction mixture was treated with alkaline hydrogen peroxide and the product was recrystallized from water. There was obtained 20.6 mmoles, 82% yield, of 11-hydroxyundecanoic acid, m.p. 68-69°C.

Acknowledgment.—This study was made possible by a grant from the American Cyanamid Company. This support is gratefully acknowledged.

(3) P. Chuit and J. Hauser, Helv. Chim. Acta, 12, 403 (1929), report m.p. 70-70.5°C.

HYDROBORATION AS A CONVENIENT PROCEDURE FOR THE ASYMMETRIC SYNTHESIS OF ALCOHOLS OF HIGH OPTICAL PURITY

Sir:

We wish to report a new asymmetric synthesis which permits the conversion of olefins into optically active alcohols with optical purities in the neighborhood of 90%.

We previously observed that the hydroboration of hindered olefins proceeds rapidly to the dialkylborane stage and these compounds exhibit a remarkable selectivity for the hydroboration of olefins...
of varying structure. Accordingly, it appeared possible that dialkylboranes derived from optically active terpenes or steroids might convert olefins into organoborane moieties capable of being transformed into optically active derivatives.

α-Pinene was hydrosorated to form di-isopinocamphenylborane, and the product utilized for the hydrosorbtion of a number of representative olefins.

\[
\begin{align*}
\text{C} & + \text{BH}_3 \rightarrow \text{C} \quad \begin{array}{c}
\text{H} \quad \text{H} \\
\text{H} \quad \text{H}
\end{array} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Oxidation of the resulting organoborane with alkali hydrogen peroxide produced the corresponding alcohols with exceptionally high optical purities—in the range of 83-91%. Since the optical purity of the α-pinene ([α]_D^20 +47.6°) is probably no better than 90%, it appears that this procedure achieves nearly complete asymmetric stereoreactivity.

A representative procedure is given: α-Pinene, 27.2 g. (0.200 mole) was dissolved in 75 ml. of a 1.0 M solution of sodium borohydride in diglyme and the mixture, cooled to 0°, was treated with 14.2 g. (0.100 mole) of boron trifluoride etherate to form the di-isopinocamphenylborane. To the reagent at 0° was added 6.1 g., 0.100 mole, of cis-2-butene and the reaction mixture maintained at 0° for four hours, then left overnight at room temperature. Oxidation at 30-50° with 31 ml. of 3 N sodium hydroxide followed by 31 ml. of 30% hydrogen peroxide produced 0.7 g. of 2-butanol, a yield of 90%; b. p. 98° at 744 mm.; n\text{D}^1 1.3975; [α]_D^1 +11.8°, indicating an optical purity of 87%.

Similarly, cis-3-hexene, readily synthesized via the hydrosorbtion reaction from 3-hexyne, was converted in 81% yield to 3-hexanol: b. p. 135-136°; [α]_D^1 +41.4°, indicating an optical purity of 89%.

Application of the procedure to norbornene produced exo-norborneol in a yield of 62%. The product, m. p. 125-126°, exhibited the rotation [α]_D^1 +2.0°; acetate, [α]_D^1 +7.9°, indicating an optical purity of 88%.

The results clearly demonstrate that a boron atom at the asymmetric center, RR'C*HBr, is capable of maintaining asymmetry without significant racemization over periods of several hours. The ease with which organoboranes may be converted into other derivatives with retention of configurational and the unusually high optical purity achieved should make this approach to optically active derivatives a most valuable one for the synthetic chemist.

(2) F. H. Thalmer and R. C. Thielke, ibid., 85, 1030 (1963), report [α]_D^1 +51.1° for α-pinene porduced via the nitrosocloride.
(3) P. J. Leroux and H. J. Lucas, ibid., 78, 41 (1951), report for I( )-2-butanol: b. p. 97.5-98° at 745 mm.; n\text{D}^1 1.4148; [α]_D^1 -6.5°, indicating an optical purity of 91.7%.

STUDIES ON POLYPEPTIDES. XIII. THE SYNTHESIS OF A TRICOSAPEPTIDE POSSESSING ESSENTIALLY THE FULL BIOLOGICAL ACTIVITY OF NATURAL ACTH-(1-39)

Sir:

As an outgrowth of our systematic studies relating structure and function of peptides possessing melanophoretic and adrenocorticotropic activity, we have prepared seryltyrosylsermionothionylglutamylhistidylphenylalanylarginyltyptophylglycyllysylprolylvalyglycyllicyllysyllysine amide and seryltyrosylsermionothionylglycyllysylprolylvalyglycyllicyllysyllysine amide and found these peptide derivatives which correspond to substantial portions of the N-terminal sequence of the corticotropins to possess, at best, a very low level of in vivo adrenocorticotropic activity (<0.1 IU/mg.). These results justify the conclusion that a sequence of more than 18 amino acid residues from the amino end of the corticotropin molecule is required for high adrenocorticotropic activity.

A recent communication by Li, et al., reporting in vivo adrenocorticotropic activity (29 IU/mg.) of a synthetic nonadecapeptide corresponding to the sequence of the 19 N-terminal amino acid residues of the corticotropins prompts us at this time to record further observations in this field. We have prepared the tricosapeptide amide (1) and find that this compound possesses in vivo adrenocorticotropic activity. The most highly purified samples of the synthetic hormone derivative obtained to date exhibit 103 ± 10.4 IU/mg. of both ascorbic acid depleting and plasma corticosterone elevating activity.

(1) Supported by grants from the U. S. Public Health Service, the National Science Foundation, the National Cancer Society and Armour and Company.
(2) The amino acid residues, except glycine, are of the L-configuration.
(3) Amino acid analyses were carried out with a model 120 Beckman-Spinco amino acid analyzer. Unless noted otherwise, the $R_\text{T}$ values refer to the Partridge system; S. M. Partridge, Biochem. J., 43, 238 (1948).