

Preparation of Geometrically Isomeric Grignard Reagents and the Stereochemical Courses of Their Reactions

Sir.

Previous stereochemical studies of carbon attached to magnesium, yielding nonracemic products, with one exception, have been restricted to olefinic^{1,2} and cyclopropyl³ systems. The various studies have provided information only regarding the net stereochemistry (retention) from alkyl halide to final products. The one exception in the type of system employed is found in the report by Reutov⁴ that optically active 2,5-dimethylcaproic acid is obtained in "low yield" and "weak optical purity" upon carbonation of the solution resulting from intermixing (\pm)-1,4-dimethylpentylmagnesium bromide and optically active di-1,4-dimethylpentylmercury.⁵ The observed stereochemistry in all these studies could result from two reactions which both occur by retention or by inversion of configuration.

In this report, the preparation of the *endo*-norbornyl Grignard reagent is described and the stereochemistry of reactions of both the *exo* and *endo* reagents with carbon dioxide and mercuric bromide is shown to be retention of configuration. Since there is no reason to expect abnormal reactions of these reagents, it is postulated that the normal course of the stereochemistry of electrophilic substitution of aliphatic Grignard reagents is retention of configuration.⁶

Each of the isomers in a mixture of *exo*- and *endo*-norbornyl Grignard reagents can readily be observed and identified by nmr spectroscopy.^{7,8} The signals of the α protons in the norbornyl Grignard reagents appear at high field well separated from the other resonances in the system. In Figure 1a is shown the nmr spectrum, taken on a Varian HA-100 instrument, of the protons α to magnesium for both isomers (diethyl ether solvent). The multiplet appearing at lower field (τ 10.12) is assigned to the *endo*-norbornyl Grignard reagent and the multiplet appearing at higher field (τ 10.48) is assigned to the *exo* Grignard reagent, in agreement with the reports of Hill⁷ and Krieghoff and Cowan.⁸ (The small peak at τ 9.95 is due to an impurity.)

Careful integration of the areas under the two multiplets in the nmr spectrum yielded a composition of 41% *exo* and 59% *endo* for the magnesium compounds. Carbonation of this mixture at -78° by bubbling carbon dioxide through the solution and by adding the mixture to a Dry Ice-ether slurry yielded *exo:endo*

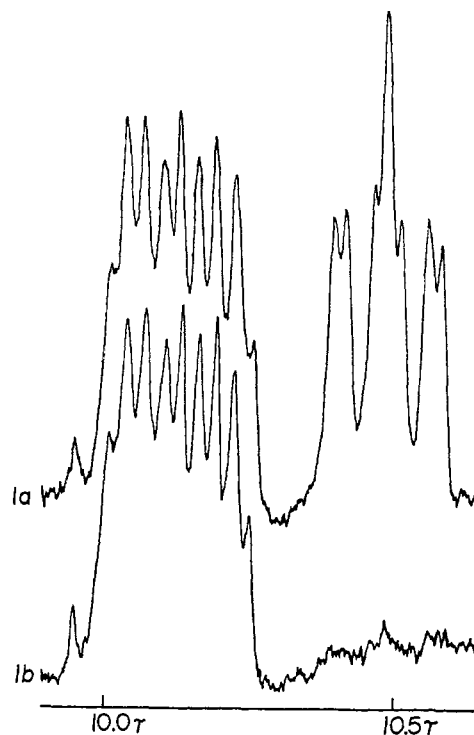


Figure 1. (a) Nmr spectrum of the 2-H resonances in a mixture of the *exo*- and *endo*-norbornyl Grignard reagents; (b) the spectrum after treatment with 57 mole % benzophenone (ca. 95% *endo* Grignard reagent). The above resonances appeared on the tailing of the large ether peaks and the phasing was adjusted to give level base lines.

ratios of acids of 40:60 and 44:56, respectively.⁹ Similarly, the alkylmercuric bromides obtained (*exo:endo* = 38:62) upon allowing the Grignard reagents to react with mercuric bromide were in agreement with the constitution of the reagent in solution.

However, when the mixture was allowed to react with a deficiency of benzophenone an entirely different phenomenon was observed. Upon treatment with about 50 mole % benzophenone, the *exo*-norbornyl Grignard reagent disappears, as evidenced by the nmr spectrum of the solution (Figure 1b). The principal products of this rapid reaction are norbornene and benzhydrol (as the magnesium salt) and are typical of reduction reactions of Grignard reagents. Evidently, normal additions are slow, and the *endo* Grignard reagent is sufficiently hindered that it reacts slowly by a reduction procedure. Reaction of the remaining reagent (95–100% *endo*) with carbon dioxide and mercuric bromide gives respectively 95% *endo* acid and 94% *endo*-norbornylmercuric bromide. Since the reactions of the mixtures yielded products reflecting the isomer distribution of the mixtures and the *endo* isomer reacts with retention of configuration, both isomers must undergo

(9) These carbonation values are in contrast to the *exo:endo* ratio of 90:10 reported by Sauers and Kwiatkowski (R. R. Sauers and G. T. Kwiatkowski, *J. Org. Chem.*, **27**, 4049 (1962)). These workers used boron trifluoride in methanol solution to convert the 2-norbornane-carboxylic acids to esters and then analyzed the resulting mixture by vpc. Their results appear to be questionable since with known acid mixtures using their procedure we obtained variable analyses. The difficulty in this analytical procedure is that the *endo*-acid is esterified very slowly by the reagents. In our analytical procedure, the acids were converted to esters with diazomethane and the esters were analyzed by vpc. This method was found to be reliable for quantitatively analyzing known mixtures of the acids.

(1) E. A. Braude, J. A. Coles, and C. J. Timmons, *J. Chem. Soc.*, 2078, 2085 (1951).

(2) T. Yoshino and Y. Manabe, *J. Am. Chem. Soc.*, **85**, 2860 (1963).

(3) H. M. Walborsky and A. E. Young, *ibid.*, **86**, 3288 (1964).

(4) O. A. Reutov, *Bull. Soc. Chim. France*, 1383 (1963).

(5) Similar studies were carried out some time ago in our laboratory, and because of the nature of our findings we believe that a final conclusion regarding the significance and validity of Reutov's results should be held in abeyance until his experimental details are fully disclosed. Our results were similar to those reported by Reutov, i.e., "low yield" and "weak optical purity." Because of the marginal nature of our results we concluded that they probably were not meaningful.

(6) Cyclopropyl reagents do not in some cases give representative reactions of aliphatic compounds. For example, there is evidence that cyclopropyl carbanionic species have a larger tendency to maintain their stereochemical integrity: H. M. Walborsky, *Record Chem. Progr.*, **23**, 75 (1962).

(7) E. A. Hill, *J. Org. Chem.*, **31**, 20 (1966).

(8) N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.*, **88**, 1322 (1966).

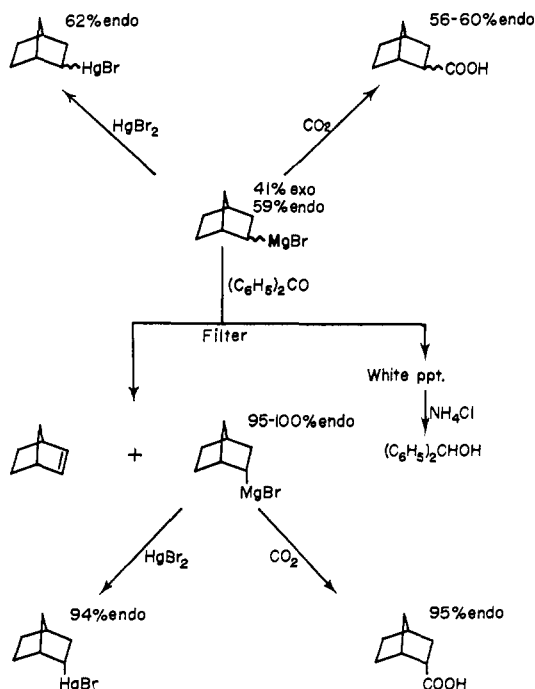
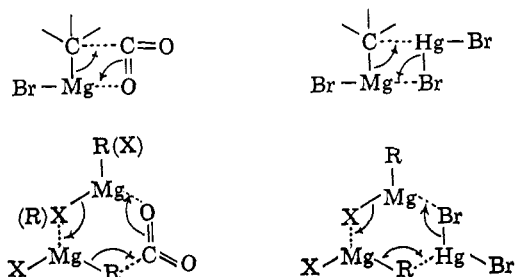


Figure 2. Reaction of carbon dioxide and mercuric bromide with the 2-norbornyl Grignard reagent with and without prior treatment with benzophenone.

substitution with retention of configuration. The results are summarized in Figure 2.

When a sample of the *endo* Grignard reagent was placed in the HA-100 probe at 37°, the multiplet due to the *exo* isomer slowly increased with time. Similarly, the equilibrium composition was obtained upon allowing a sample to stand at room temperature for 1 day. Whitesides and Roberts¹⁰ have reported that typical secondary Grignard reagents interconvert slowly if at all on the nmr time scale. Thus, the norbornyl Grignard reagent appears to behave as a normal secondary aliphatic compound.

Reasonable S_Ei and S_E2 type mechanisms can be written for these reactions. Because of the Lewis acid nature of magnesium(II), the S_Ei processes seem more likely. Plausible transition states are



Detailed kinetic, stereochemical, and interconversion rate studies are contemplated for these compounds.

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(10) G. M. Whitesides and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 4878 (1965).

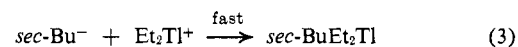
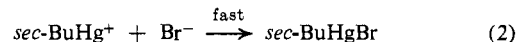
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A Reinvestigation of the Purported S_Ei Reaction of Di-*sec*-butylmercury

Sir:

Of importance to theoretical studies of electrophilic substitution would be the availability of a simple process for generating alkyl carbanions. Recently, Hart and Ingold¹ reported that carbanions are formed upon admixing di-*sec*-butylmercury and diethylthallium bromide, and they drew broad generalizations from their findings. This reaction has been reinvestigated and not only is the mechanism not of the type reported but the reaction which occurs is air oxidation of the mercurial.

These workers determined the kinetics of the reaction between di-*sec*-butylmercury (optically active) and diethylthallium bromide at 70° in dimethylformamide (DMF) solution in the presence of small amounts of water and cyclohexene which were thought to suppress kinetic disturbances. The atmosphere was not stated. First-order in mercurial and zero-order in thallium compound kinetics were observed, and an identical rate constant was obtained by following the rate of disappearance of titrable bromide, formation of base, or disappearance of optical activity in the solution. No products were isolated, but upon the kinetic results the following reaction scheme was proposed.



The experimental work and conclusions appeared to be questionable on many grounds, but two particularly puzzling facets were that the carbanions were postulated to react faster with the thallium compound than with water and eq 1 is contrary to the established behavior of dialkylmercurials. A much more reasonable and simpler postulate appeared to be that the reaction which was observed was the well-known air oxidation of dialkylmercurials.²

The reaction was restudied in a thermostated gas buret under the exact specified conditions, except that both air and inert atmospheres were utilized. When the reagents were brought together in the gas buret under an air atmosphere a reaction occurred, but an uptake of gas (oxygen) resulted rather than the gas evolution expected from Hart and Ingold's conclusions. The products of this reaction were also inconsistent with the scheme proposed by the previous workers and included 1-butene, butane, *cis*- and *trans*-2-butene, 2-butanone, and 2-butanol. *sec*-Butylmercuric bromide and diethylthallium hydroxide were obtained in the work-up consistent with the postulate of Hart and Ingold. The rate of reaction, the total amount of oxygen uptake (0.5 to >2 molar amounts), and the distribution of products depends on the partial pressure

(1) C. R. Hart and C. K. Ingold, *J. Chem. Soc.*, 4372 (1964); C. K. Ingold, *Helv. Chim. Acta*, **47**, 1191 (1964), *Record Chem. Progr.*, **25**, 145 (1964).

(2) Recent examples are Yu. A. Aleksandrov, O. N. Druzhkov, S. F. Zhil'tsou, and G. A. Razuvaev, *Dokl. Akad. Nauk SSSR*, **157**, 1395 (1964); *Zh. Obshch. Khim.*, **35**, 1440 (1965).