diene systems, and the stabilizing "push-pull" effect predicted by LCAO theory for 1,2-diphenylcyclobutadiene derivatives substituted in one phenyl ring by an electron-attracting group and in the other by an electron-donating group.[10]

We wish to thank Dr. Robert Nathan of the Institute Computing Center and Dr. John Christopher of the ElectroData Division of the Burroughs Corp. for their help in utilizing the institute's Datatron digital computer.

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Tetraphenylboron Derivatives of Amides

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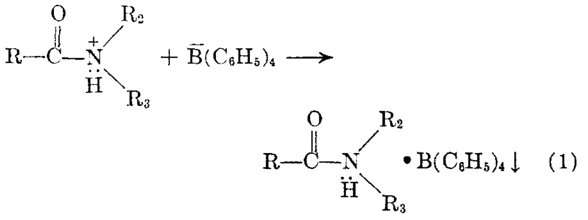
Sodium tetraphenylboron has received attention in recent years as a precipitant for potassium, ammonium, and organic nitrogen compounds.[1,2] Tetraphenylboron salts formed from an onium ion derived by protonation of a sufficiently basic organic nitrogen group are usually insoluble in water. Crane[3] suggested that an amine must have a basic dissociation constant of at least 1×10^{-11} to undergo qualitative precipitation as a tetraphenylboron salt. We have found that some organic acid amides, usually considered to be neutral, also give insoluble salts.

Amides are usually characterized by identification of their hydrolytic products. A limited number of amides have been identified by the direct formation of derivatives (mercury salts,[4] amide oxalates,[5] and xanthylamides).[6] The formation of tetraphenylboron derivatives of amides depends upon the weakly basic properties of the amide (*i.e.*, its ability to undergo protonation in an acidic medium); these salts may be used to identify amides for which suitable derivatives have been lacking. The stoichiometry of the reaction can be presented as follows:



$$\mathrm{R{-}C({=}O){-}\overset{+}{N}(\ddot{H})(R_2)(R_3)} + \overset{-}{\mathrm{B}}(\mathrm{C_6H_5})_4 \longrightarrow \mathrm{R{-}C({=}O){-}N(\ddot{H})(R_2)(R_3)} \bullet \mathrm{B(C_6H_5)_4}\downarrow \quad (1)$$

where R,R_2, or R_3 may be hydrogen, alkyl, aryl, or part of a ring system.

When electron-attracting groups which reduce the availability of the nitrogen electrons are introduced, no derivatives are formed as with *N*-vinyl or *N*-allyl pyrrolidone-2, and acrylamide. In *N*-allyl-γ-hydroxybutyramide the electron-attracting effect of the allyl group is balanced by the hydroxyl group operating in the opposite direction. Although the hydroxyl group exerts its effect over a greater distance, comparison of the *p*K value for glycolic and vinylacetic acids shows the greater effect of the hydroxyl group. Although monomeric *N*-vinyl pyrrolidone does not form a derivative, polyvinylpyrrolidone (mol. wt. 50,000) forms a derivative readily. The nitrogen analysis of the latter suggests that approximately 45% of the amide residues in the polymer form tetraphenylboron complexes. Polyvinylpyrrolidone structurally is more closely related to *N*-methyl pyrrolidone-2. This compound forms a derivative immediately whereas 5-methyl pyrrolidone-2 and the unsubstituted pyrrolidone-2 do not form derivatives. In the case of *N*-methyl pyrrolidone-2 the electron-release effect of the methyl group increases the electron density on the nitrogen atom and thus enhances onium ion formation as typified in Equation 1. In 5-methyl pyrrolidone-2 the methyl group is too far removed from the nitrogen to be effective.

It is noteworthy that tetraphenylboron derivatives are onium salts closely related to quaternary ammonium salts. In view of the antibacterial and antifungal activity of the latter class of compounds,

TABLE I

Tetraphenylboron Derivatives of Amides

Amide	M.P.[a] °C.	Nitrogen Theory	Nitrogen Found
Acetamide	180–182	3.69	4.08
Dimethylacetamide	119–120	3.44	3.09
Formamide	187–190	3.83	4.09
Dimethylformamide	117–121	3.56	3.54
N-methyl pyrrolidone-2	148–150	3.34	3.43
N-allyl-γ-hydroxybutyramide	127–130	3.02	3.10
Polyvinylpyrrolidone[b] (mol. wt. 50,000)	>250	3.25	8.41

[a] Variations in melting points of tetraphenylboron salts have been reported previously for derivatives of simple amines. The rate of heating is very important for duplication of results. In our experiments temperatures were raised 2° per min. in the vicinity of the melting point range. [b] The melting point of this derivative is too high for characterization studies. The theoretical nitrogen analysis given is that for the polymer in which every vinylpyrrolidone residue is complexed. The actual value (8.41% N) shows that 45% of the available amide groups have formed tetraphenylboron salts.

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comparison with cetyl pyridinium chloride (CPC) is of interest. *N*-Methyl-pyrrolidinium tetraphenylboron, our most biologically-active amide derivative, compares favorably with CPC in activity against gram-positive bacteria and fungi (Active at 1–10 µg./ml.).

EXPERIMENTAL

Preparation of derivatives. Approximately 250-mg. samples of each compound were dissolved or suspended in 20 ml. of water that was then adjusted to *p*H 2.0 with dilute hydrochloric acid. Several drops of 0.1% aluminum chloride solution were added to aid in the final precipitation. To the solutions heated at 60° in a water bath, an excess of 0.6% sodium tetraphenylboron solution was added. The precipitate was allowed to settle at room temperature; was filtered and washed with water, and dried at 60° *in vacuo*, and the melting point of the derivative was determined.

Melting points were determined on a Kofler micro hot stage with a calibrated thermometer. Dumas nitrogen determinations were made on all derivatives.

Starting materials. 5-Methyl-2-pyrrolidone was kindly supplied by the Quaker Oats Company; *N*-vinylpyrrolidone, polyvinylpyrrolidone (mol. wt. 50,000), and *N*-methylpyrrolidone-2 were supplied by the General Aniline and Film Corporation. Acrylamide was furnished by the American Cyanamid Company. *N*-Allyl-γ-hydroxybutyramide and *N*-allyl-pyrrolidone-2 were synthesized from butyrolactone and allylamine according to the method of Spath and Lintner.[7] The other amides were purchased from commercial sources.

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An Attempt to Form a Grignard Reagent in Phenyl Ether

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During the course of some studies of the Grignard reagent, an attempt was made to prepare the reagent in phenyl ether by the usual methods. The attempt failed in a rather interesting fashion. A reaction took place, but it was not a Grignard reaction.

EXPERIMENTAL

Twelve and two-tenths grams of "Grignard-grade" magnesium (0.5 mole) was placed in a two-necked flask containing 348 g. of phenyl ether (2 moles). An addition funnel containing 75.0 g. of *n*-amyl bromide (0.5 mole) was placed on one neck and a Dry Ice–acetone trap on the other. Stirring was provided by a magnetic stirring apparatus and a Teflon covered stirring bar. A small amount of amyl bromide was added to the flask, which was then warmed. No reaction was observed. The flask was warmed further, more amyl bromide being added, until all the amyl bromide had been added and a temperature of about 65° was reached. Heating was continued until a reaction started at about 110–115°, as evidenced by the appearance of a white precipitate, and foaming. Since the possibility of Grignard formation was still being considered at that time, the reaction vessel was quickly cooled with an ice water bath kept handy for the purpose. The reaction stopped, and would continue only at elevated temperatures. The temperature was held at about 110–120° for 24 hr., until no amyl bromide could be refluxed. It was observed that only about half of the magnesium, originally present in stoichiometric amount based on the Grignard, had reacted.

The solution was centrifuged, the supernatant decanted, and the precipitate was washed three times with portions of dry benzene and dried. The precipitate was then treated with sufficient dilute HCl to react with all the magnesium, the reaction flask being separated from the atmosphere at all times by a cold water condenser topped by a Dry Ice–acetone trap. Only a trace of pentane could be collected. Attention was then turned to the supernatant fluid.

The next most likely possibility seemed to be that a Wurtz-type reaction had taken place, forming *n*-decane. (B.P. 174°) The fluid was heated past 174°. No decane distilled off.

Since all possibilities except direct addition to the ether seemed to have been eliminated, the fluid was vacuum-distilled at 13 mm. About three fourths of the fluid distilled over at 124°, after which the temperature rose to about 155°, remaining there for the remainder of the distillation. Infrared analysis of this latter cut showed a strong C—H peak. Several peaks in the 800–900 cm.$^{-1}$ region indicated the possibility of para substitution. Analysis by means of hyperfine proton magnetic resonance techniques indicated the presence of a sec-amyl group, again suggesting para substitution. Elemental analysis of the product gave C, 84.6%, and H, 8.7%. Theoretical analysis for an amylated phenyl ether is C, 84.6%, H, 8.8%. Yield was about 60%. The density was 1.073 gm./cm.^{3}; the index of refraction was 1.5771. An examination of recent literature failed to reveal data on this compound.

Later runs involving smaller quantities resulted in the evolution of about the correct amount of H_2 according to the overall reaction

$$2(C_6H_5)_2O + 2AmBr + Mg \longrightarrow 2\ C_6H_5O\text{—}C_6H_4Am + MgBr_2 + H_2$$

Recovery of excess magnesium was also made here. Magnesium was used according to the above reaction.

It seems clear that what actually happened was not a Grignard reaction, but a Friedel-Crafts alkylation of the ether. The Lewis acid here was $MgBr_2$, initially formed in trace quantities by some side reaction. The reaction itself produced more catalyst, so that once initiated, it proceeded smoothly.

The implications of this and certain other experiments with Grignard systems will be discussed in a forthcoming publication.

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