

## The Reaction of the Grignard Reagent from Neopentyl Chloride with Benzophenone. A Nuclear Magnetic Resonance Study<sup>1</sup>

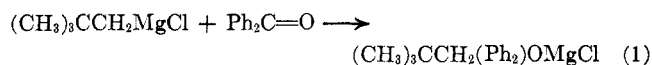
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A study has been made of the rate of change in the nuclear magnetic resonance spectrum of a mixture of the Grignard reagent from neopentyl chloride and benzophenone in tetrahydrofuran. The expected addition reaction was complicated by the simultaneous occurrence of a radical reaction to produce neopentane and benzopinacol. Furthermore these spectra are interpretable in terms of a reaction to give an initial product which in turn undergoes further reaction with the Grignard reagent to give a new reactive species. This reactive intermediate presumably is either the alkylmagnesium alkoxide (RMgOR') or a complex of the initial product with the Grignard reagent (RMgCl·R'OMgCl). This constitutes a direct observation of a process often postulated in the reaction of a Grignard compound. Qualitative generalizations could be made but because of these complications it was not possible to make a quantitative kinetic analysis of the data.

We have made an investigation of the reaction of the Grignard reagent from neopentyl chloride with benzophenone using an all-glass, stopcock-free system under rigorously anhydrous and oxygen-free conditions according to techniques already described.<sup>3</sup> These reactants were chosen in the hope that they would furnish a suitable system for studying the kinetics of the Grignard addition reaction (eq 1) by nuclear mag-

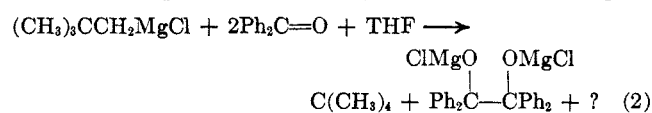


netic resonance (nmr) techniques. We reasoned that in this system (a) side reaction due to enolization would be precluded, (b) the reduction of benzophenone to benzhydrol by  $\beta$ -hydrogen transfer from the Grignard reagent would be impossible, (c) steric hindrance should cause the reaction to proceed at a convenient rate, and (d) the simple nmr spectra of reactants and product should permit the use of nmr techniques for following the progress of the reaction.

Figure 1A represents the 60-MHz nmr spectrum of neopentylmagnesium chloride in tetrahydrofuran.<sup>4</sup> The nmr spectrum of the magnesium bromide salt of diphenylneopentylcarbinol, prepared by treating the carbinol with a tetrahydrofuran solution of propylmagnesium bromide, Figure 1B, serves to locate the position for the *t*-butyl protons (a') and the methylene protons (b') of this alkoxide. The signal (a') for the *t*-butyl protons is characterized by a broad base which is unexpected and which will be discussed later.

Several complications were encountered during the nmr investigations of the reactions of neopentylmag-

nesium chloride with benzophenone. The first of these was an unexpected radical-type side reaction<sup>6</sup> (eq 2)



which gave neopentane and (on hydrolysis) benzopinacol. The 60-MHz nmr spectrum of a reaction mixture of equimolar amounts of neopentylmagnesium chloride and benzophenone in perdeuterated THF,<sup>7</sup> 24 hr after mixing, is shown in Figure 1C. The sharp singlet for the protons (e) of neopentane<sup>8</sup> was so close to the signal for the *t*-butyl protons (a) of the unreacted Grignard compound that neither could be used for accurate kinetic measurements (compare Figures 1A, 1C, 1D, and 2).

A second complication was that the change of the nmr spectrum of the reaction mixture during the progress of the reaction was considerably more complex than the simple stoichiometric eq 1 would indicate. This is very clearly illustrated in Figure 1D, which shows the 60-MHz nmr spectrum of a reaction mixture from diphenylneopentylcarbinol and excess neopentylmagnesium chloride in THF. This solution shows the signals for neopentane (e), the alkoxide of the carbinol (a', b'), and unreacted neopentylmagnesium chloride (a, b) as well as those for the solvent (c). This spectrum can not be reconstructed by adding together the spectra of Figures 1A and 1B and that of neopentane. The signal for the *t*-butyl protons (a') in the reaction product shows as three peaks instead of a singlet as is observed in the nmr spectrum of a solution of the magnesium bromide salt of diphenylneopentylcarbinol (Figure 1B).<sup>9</sup> In addition, the methylene protons in the excess Grignard reagent appear as two unequal and somewhat broad signals (Figures 1D and 2; b, 19 cps upfield from TMS, and bb, 29 cps upfield from TMS

(1) We gratefully acknowledge support of these studies by the National Science Foundation, Grant GP 6738.

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(3) A. D. Vreugdenhil and C. Blomberg, *Rec. Trav. Chim. Pays-Bas*, **82**, 453 (1963).

(4) Recently House, Latham, and Whitesides,<sup>5</sup> in an extensive paper on nmr spectra of several organomagnesium compounds, reported (in their Experimental Section) some of their results obtained with diethyl ether solutions of neopentylmagnesium chloride and of dineopentylmagnesium. The authors did not undertake further investigations on these solutions "because of apparent presence of alkoxide impurities." From Table XII in their paper it follows that at 60 MHz in diethyl ether solution the *t*-butyl absorption peak appears at 70 cps downfield from internal TMS standard (50 cps in THF as shown in Figure 1A, signal a, according to our studies) whereas methylene proton absorption occurs at 18 cps upfield for the Grignard compound and at 20.0–20.5 cps upfield for the dialkylmagnesium compound (29 cps, Figure 1A–b) and 31 cps, Figure 3B–b, respectively, in THF according to our studies).

(5) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).

(6) C. Blomberg and H. S. Mosher, *J. Organometal Chem.*, **13**, 519 (1968).

(7) The solvent signals (c) in Figure 1C are due to a small amount of THF-*d*<sub>7</sub> and isotopically normal THF which was incompletely removed from the original Grignard reagent which was prepared in isotopically normal THF, the solvent removed under high vacuum, and perdeuterated THF added.

(8) Identified<sup>6</sup> by comparison with the nmr spectrum of an authentic sample; also see Figure 1D. Mass spectral analysis of a sample of gas isolated from this reaction showed an incorporation of deuterium, which establishes the origin of the additional hydrogen in the neopentane.

(9) During preliminary investigations of several other reactions of aliphatic Grignard compounds with ketones this same phenomenon was observed. Namely, the signals for the protons of the alkoxy group and the Grignard reagent were more complicated than expected based upon the stoichiometric eq 1 alone.

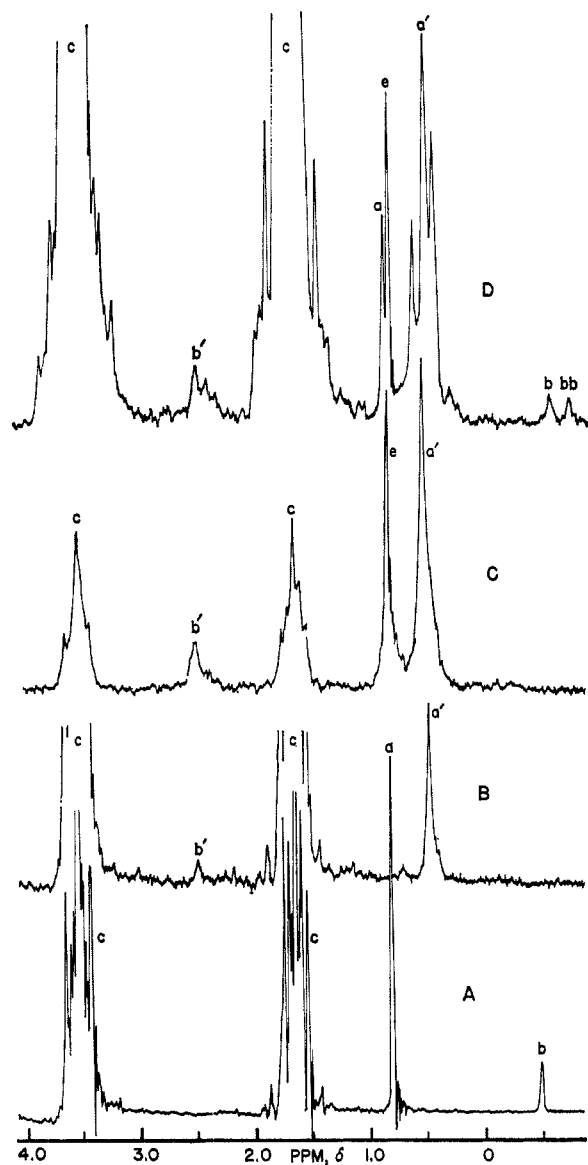


Figure 1.—A is the nmr spectrum of 0.74 *N* neopentylmagnesium chloride in THF. The *t*-butyl protons [(CH<sub>3</sub>)<sub>3</sub>C-] are designated as a, the methylene protons [-CH<sub>2</sub>Mg-] as b, and the solvent protons as c. Aromatic signals are not shown. B is the nmr spectrum of the magnesium bromide salt of diphenylneopentylcarbinol in THF, 1.0 *N*, prepared by the reaction of propylmagnesium bromide with the carbinol. The *t*-butyl protons [(CH<sub>3</sub>)<sub>3</sub>C-] are designated a', the methylene protons [-CH<sub>2</sub>CPh<sub>2</sub>-] as b'. C is the 60-MHz spectrum of a reaction mixture from equimolar amounts of neopentylmagnesium chloride and benzophenone in perdeuterated THF, 0.74 *N*, 24 hr after mixing. The neopentane protons [(CH<sub>3</sub>)<sub>3</sub>C] are designated as e. Designation of signals a', b', and c are the same as in A, B, and D. D is the 60-MHz spectrum of a reaction mixture from equal volumes of neopentylmagnesium chloride (0.74 *N*) and diphenylneopentylcarbinol (0.67 *N*) in THF.

standard) compared with the lone signal shown in Figure 1A.<sup>10</sup>

Figure 2 represents part of several nmr spectra of a reaction mixture of molar equivalents of neopentylmagnesium chloride and benzophenone in THF at 20° taken at different time intervals. Several trends are evident. (1) Peak a, due to the *t*-butyl protons of unreacted Grignard reagent, slowly decreases. (2)

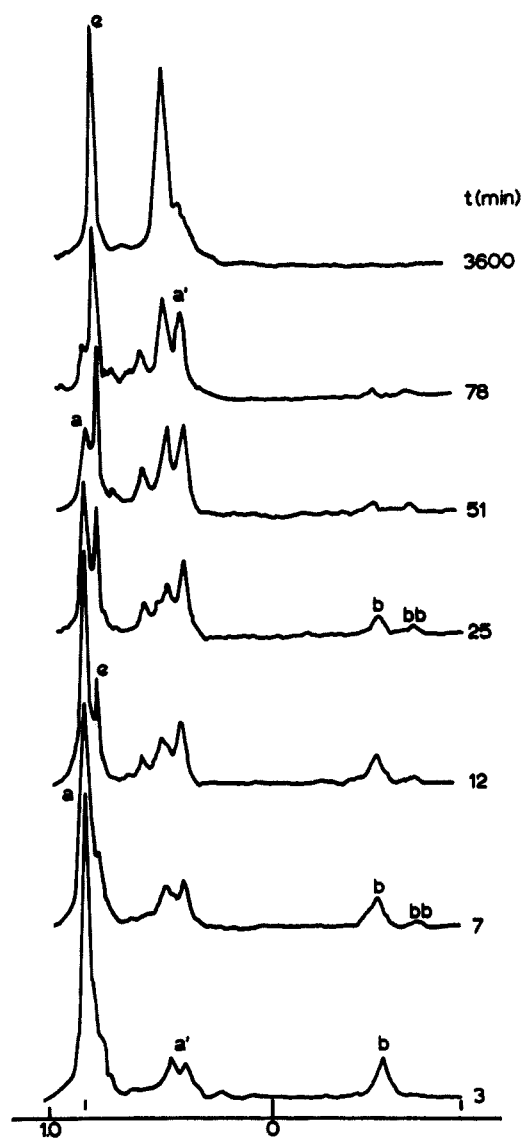


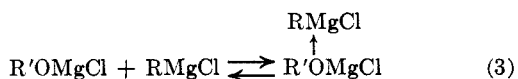
Figure 2.—Change of 60-MHz nmr spectra with time; equimolar mixture of neopentylmagnesium chloride and benzophenone in THF, 0.74 *N*, 20°. Designation of signals is as in Figures 1 and 3.

At the same time peak e, due to the protons in neopentane, increases. (3) The broad peak b, due to the methylene protons of the Grignard reagent, decreases and at the same time a second broad peak, bb, forms and ultimately disappears. Three minutes after mixing, peak b has broadened (*cf.* Figures 1A and 2), probably owing to fast complexation with the ketone. (4) A doublet peak, a', is evident 3 min after mixing and as the reaction proceeds the signals in this region increase in intensity and become more complex but finally change back to a single major peak with a broad base after several hours time.

Quantitative kinetic analysis of these complex changes based on the 60-MHz nmr spectra was not feasible. The situation was improved but not resolved at 100 MHz. Qualitatively, however, we interpret the changes in the following manner. Simultaneous reactions, represented by eq 1 and 2, are taking place. The unusual free-radical nature of the reaction leading to neopentane and benzopinacol has been discussed.<sup>6</sup> The initial addition reaction, represented by eq 1 (in which coordinated ether molecules are not shown),

(10) In their paper on nmr spectra of organomagnesium compounds, House, Latham, and Whitesides<sup>11</sup> also recorded a second absorption peak for methylene protons vicinal to a carbon-magnesium bond when alkoxides were present in the solution.

produces an alkoxide,  $R'OMgCl$ . This initial alkoxy product reacts with the Grignard reagent,  $RMgCl$ , either by complexing as in eq 3 or by disproportionation as in eq 4 (or by both) to give a second form of a reactive organomagnesium reagent as revealed by the developing signal *bb*; the methylene protons of the carbon attached to magnesium, in either or both products of eq 3 and 4, must give a signal (*bb*) different



from that of the unreacted initial Grignard reagent. The products from reaction 3 and/or 4 compete with the original Grignard reagent in the reactions with benzophenone.

House, Latham, and Whitesides<sup>5</sup> have observed similar phenomenon in the nmr spectrum of the diethyl ether solution of dineopentylmagnesium, containing alkoxide impurities as well as in the nmr spectra of the diethyl ether solution of the methylmagnesium alkoxide of 3-methyl-3-pentanol. In the latter case these authors observed collapse of the two signals after the addition of 0.5 mol equiv of magnesium bromide or after dilution with "the better solvating solvent, tetrahydrofuran." Considering these and our own observations, one is struck by the difference in behavior of the two alkoxides: whereas the presence of magnesium bromide or THF catalyzes the exchange of alkyl or alkoxy groups or breaks complexes between organometallic reagents and magnesium alkoxides among the methylmagnesium species, such an exchange is not observed among neopentylmagnesium species, at least not catalyzed by magnesium chloride and/or THF. Furthermore, from the spectra given in Figure 2 it may be concluded that the alkoxy products, represented in eq 3 and 4, must give absorption for the *t*-butyl protons of the carbinol moiety which are not identical with those of the alkoxy product, represented in eq 1.

An additional alkoxy species which may further contribute to the complexity of the signal *a'* of the *t*-butyl group in the alkoxide may be formed by the disproportionation of the initial alkoxy group according to eq 5 to give a dialkoxymagnesium. The nmr spec-



trum of the reaction mixture of benzophenone and dineopentylmagnesium (containing 12 mol % magnesium chloride) sheds some light on the problem of complexation and equilibration of different alkoxides species (Figure 3). Figure 3A is the nmr spectrum of the reaction mixture from 1 mol of dineopentylmagnesium and 2 mol of benzophenone. It is seen that the spectrum for the *t*-butyl protons [*a'* in  $(RO)_2Mg$ ] made in this manner is very different than that for the corresponding alkoxide (*a'* in Figures 1B and 1C) made from the usual Grignard reagent. It should be noted again that neopentane is formed in this reaction mixture, signal *e*.

A peculiar observation was made concerning the nmr spectrum of the reaction mixture of neopentylmagnesium chloride with 2 molar equiv of benzophenone. The spectrum originally observed differed only slightly

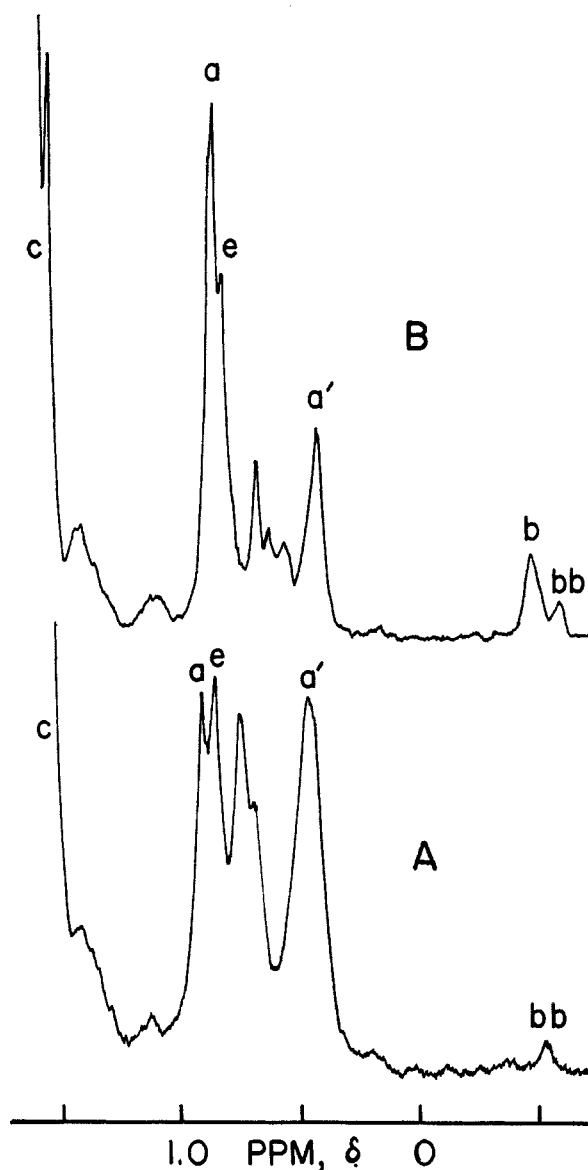


Figure 3.—Spectra of mixtures of dineopentylmagnesium, 0.57 *M*, and benzophenone; molar ratio 1:2 in A and 2:1 in B. Designation of signals is same as in Figures 1 and 2.

from the usual spectrum such as given in Figure 1C (or Figure 2 after 3600 min). However, 31 days after mixing the two reactants, a sharp signal, a few cycles per second upfield from the neopentane absorption *e*, had appeared at the expense of the original signal *a'*. This new signal *a''* is located at almost the same position as a peak in the region of the nmr spectrum of the reaction mixture of dineopentylmagnesium with benzophenone irrespective of the molar ratios of these two reagents (Figure 3A and 3B). It is presumed that under the influence of excess benzophenone the equilibrium, represented by eq 5, is shifted to the right. This phenomenon was not observed in reaction mixtures of equivalent amounts of neopentylmagnesium chloride and benzophenone after 120 days.

The reactivity of products such as represented by eq 3 and/or 4 should differ appreciably from that of the initial Grignard reagent.<sup>11</sup> Thus kinetic analysis of a reaction such as this will be complicated unless limited

(11) M. S. Singer, R. M. Salinger, and H. S. Mosher, *J. Org. Chem.*, **32**, 3821 (1967); J. Billet and S. G. Smith, *J. Amer. Chem. Soc.*, **90**, 4108 (1968) and references therein.

to initial rates or to reactions in which one reagent is in considerable excess. The present nmr analysis therefore has uncovered complexities to this reaction that kinetic studies, based upon product analysis, could not hope to reveal.

### Experimental Section

**Preparation of Organomagnesium Compounds.**—Preparation and handling of the organomagnesium compounds was performed in a glass-to-glass sealed high vacuum apparatus as described previously.<sup>3</sup> Transfers were made *via* break-seal arrangements and samples were removed by sealing off side arms without use of stopcocks.

Neopentyl chloride, 100 mmol, was magnetically stirred with magnesium crystals,<sup>12</sup> 110 mg-atom, in 100 ml of tetrahydrofuran; no reaction took place during 4 days of continuous stirring although a cloud of powdered magnesium made the solution gray. On the addition of 6 mmol of 1,2-dichloroethane a slow reaction took place. The yield of neopentylmagnesium chloride was 85% after 7 days. The solution contained 5 mol % magnesium chloride and unreacted organic halides. After standing a few weeks a clear water-white solution was obtained which was freed from the sediment by decanting in the sealed vacuum system into another vessel and from which all volatile material was removed by cooling one arm of the apparatus with liquid nitrogen while gradually increasing the temperature in the other from 100 to 150° during a 5-hr period. New tetrahydrofuran was distilled onto the glassy residue. The nmr spectra of the solution, which was 0.85 M in RMgX and which contained 5 mol % magnesium chloride, showed that no unreacted halides were present. Small ampoules, *ca.* 2 ml, were filled with this solution for use in nmr work.

(12) The authors gratefully acknowledge the gift of sublimed magnesium from the Dow Chemical Co. It had the following maximum limits of elemental impurities in parts per million: Al, 1; Cu, 1; Fe, 4; Mn, 2; Ni, 4; Pb, 10; Si, 10; Zn, 100; Ba, 1; Ca, 18; K, 5; K, 5; Na, 6; Sn, 1.

On cooling of the neopentylmagnesium chloride solution in a carbon dioxide-acetone bath, beautiful crystals were obtained which contained mainly magnesium chloride. When the mother liquors were decanted and cooled anew, again crystals were formed which contained an excess of magnesium chloride over dineopentylmagnesium. This second mother liquor was again decanted from the crystals and found to contain 0.60 mmol of dineopentylmagnesium and 0.15 mmol of magnesium chloride/ml (total volume was 7 ml). To precipitate the total amount of 1.1 mmol of magnesium chloride 2.2 mmol of dioxane was added. After 3 weeks a solid white precipitate was formed from which the mother liquor (4.5 ml) was decanted; it contained 0.57 mmol of dineopentylmagnesium and 0.07 mmol of magnesium chloride/ml and was used without further purification.

**Nmr Measurements.**—Use was made of nmr tubes provided with a glass constriction to make sealing possible. Filling of the tubes was performed under high vacuum as usual and no special difficulties were encountered during such manipulations. Benzophenone was distilled from a side tube into the nmr tube containing the Grignard solution which was cooled to -80° (causing the formation of beautiful crystals). The distillation path was no longer than 10 cm and use was made of a "hot air gun" to control the distillation and solidification of the benzophenone on to the cooled glass wall above the THF solution. The tube was sealed, and the mixing of the reagents was done immediately before nmr measurements were started. In all cases reddish brown color appeared which changed to orange-yellow during the course of the reaction.

**Registry No.**—Neopentylmagnesium chloride, 13132-23-5; benzophenone, 119-61-9; magnesium bromide salt of diphenylneopentylcarbinol, 19978-29-1; diphenylneopentylcarbinol, 19978-30-4; dineopentylmagnesium, 19978-31-5.

**Acknowledgment.**—We thank Dr. Lois Durham for her cooperation and advice in collecting the nmr spectral data.

## The Oxidative Coupling of Phenols Using Vanadium Tetrachloride and Vanadium Oxytrichloride

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The oxidation of most simple phenols and some aniline derivatives with vanadium tetrachloride or vanadium oxytrichloride affords dimeric products which are coupled predominantly at the *para* position. For example, admixture of equimolar quantities of phenol and vanadium tetrachloride in an inert solvent followed by hydrolysis led to the isolation of 4,4'-diphenyl, 2,4'-diphenol, and 2,2'-diphenol in an approximate ratio of 8:4:1 and an over-all yield of 55-65%. The remainder of the product mixture was composed of unreacted phenol and <5% of chlorinated diphenols. Phenol itself was not oxidized by vanadium oxytrichloride, under the condition of vanadium tetrachloride oxidation; however, those phenol derivatives with lower oxidation potentials were coupled by this reagent. Thus, 1- and 2-naphthol reacted smoothly with vanadium oxytrichloride to produce 4,4'-dihydroxybinaphthyl and 2,2'-dihydroxybinaphthyl in 56 and 65% yields, respectively. The oxidative coupling reaction is believed to occur by a rearrangement of electrons in a complex containing at least two phenoxide (or phenol) residues and at least one metal center. Evidence in support of the existence of vanadium phenoxides has been obtained. The selectivity of the coupling reaction may be interpreted in terms of a polar or ionic transition state in which charges are developed in the aromatic ring.

The oxidative coupling of phenolic compounds has received considerable attention owing both to its utility as a synthetic reaction and its proposed involvement in the biosynthesis of a number of classes of natural products.<sup>1</sup> To date, the oxidation of the most of the simple phenols and naphthols has been studied with a variety of reagents and, in general, the products are complicated mixtures of dimeric, polymeric, and

quinonoid compounds.<sup>2</sup> In most cases, both carbon to carbon and carbon to oxygen coupling occurs, although, depending on the oxidant and on the experimental conditions, some selectivity can be attained.<sup>3</sup> We wish to report here results on two unique oxidizing agents, vanadium tetrachloride and vanadium oxytrichloride, which couple phenols and some aromatic amines predominantly at the *para* position and afford

(1) A recent survey of phenol oxidations is available: "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1967.

(2) Leading references can be found in H. Musso, ref 1, Chapter 1.

(3) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966).